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Senior Corporate Medical Director, Medicare
Humana
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</table>
**Important Safety Information**

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly.
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination.
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate.
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.
Indications and Usage

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo

- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy

Because of progression-driven events or at the physician’s discretion, patients randomized to placebo (COMFORT-II) or best available therapy (COMFORT-II) who crossed over to receive Jakafi continued to be grouped within their original randomized assignment for analysis purposes

All patients in the placebo group either crossed over or discontinued

When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations

Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia

The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache

A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy

Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about Jakafi, visit Jakafi.com/HCP.

starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 \( \times 10^9/L \)) and 20 mg twice daily. (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients

Risk of Infection

Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Tuberculosis. Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries where tuberculosis is endemic. Patients should consult a physician with expertise in the treatment of tuberculosis before initiating therapy with Jakafi. In patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi treatment during active tuberculosis should be based on the overall risk-benefit determination. (111) Pretreatment platelet counts (\( \geq 100 \times 10^9/L \)) has occurred with JAK inhibition for myelofibrosis. F PLM is suspected, stop Jakafi and evaluate. Herpes Zoster

ADVERSE REACTIONS

The most frequent adverse drug reactions in patients treated with Jakafi. Assess lip parameter elevations on a case-by-case basis with appropriate treatment and monitoring. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi in placebo-controlled studies. Additional Data from the Placebo-controlled Study

Study up to Week 32 of Randomized Treatment

Summary of Adverse Drug Reactions in the Phase 2 Clinical Studies. Median time to onset of first CTCAE Grade 2 or higher was approximately 6 weeks. One patient (<1%) discontinued treatment because of adverse events. In patients receiving Jakafi, mean decreases in hemoglobin concentration were observed in 15% of patients at 10 mg daily, 29% of patients at 20 mg daily and 36% of patients at 40 mg daily. (12.3)

In a randomized, placebo-controlled, study, 60% of patients treated with Jakafi and 36% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per patient was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients.

Thrombocytopения in the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopения, the median time to onset was approximately 8 weeks. Thrombocytopения was generally reversible with dose reduction or dose discontinuation. The median time to recovery of platelet counts above 50 \( X 10^9/L \) was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopения occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 \( X 10^9/L \) to 200 \( X 10^9/L \) before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 \( X 10^9/L \) (17% versus 7%).

Neutropenia in the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematologic abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=155)</th>
<th>Jakafi (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>70</td>
<td>9</td>
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<tr>
<td>Agranulocytosis</td>
<td>96</td>
<td>34</td>
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<tr>
<td>Neutropenia</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>
### Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in > 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
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<td></td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Abdominal Paina</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Dizzinessb</td>
<td></td>
<td></td>
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<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Fatigue</td>
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<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
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<td>Grade 3 (%)</td>
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<td>Pruritus</td>
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<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
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<td>All Grades (%)</td>
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<td>Grade 3 (%)</td>
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<tr>
<td>All Grades (%)</td>
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</tr>
<tr>
<td>Anemia</td>
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<td>All Grades (%)</td>
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<td>Metastatic Cancer</td>
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<td>All Grades (%)</td>
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<td>All Grades (%)</td>
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<td>Grade 3 (%)</td>
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<tr>
<td>Elevation of ALT</td>
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<td>13</td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
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### Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

#### Laboratory Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Jakafi (N=110)</th>
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<tr>
<td></td>
<td>All Grades (%)</td>
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<tr>
<td></td>
<td>Grade 4 (%)</td>
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<td>Grade 4 (%)</td>
<td>Grade 3 (%)</td>
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<tr>
<td>Hematology</td>
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<td>Anemia</td>
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<tr>
<td>Neutropenia</td>
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<td>3</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Elevated ALT</td>
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<td>15</td>
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<tr>
<td>Elevated CRP</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Elevation of ALT</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

### Drug Interactions

### Hormone Therapy

### Renal Imbalance

### Geriatric Use

### Pregnancy

### Nursing Mothers

### Risk Summary

### Use in Specific Populations

### Patient Information

### Incyte

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U.S. Patent Nos. 7,509,257; 7,413,582; 7,272,930; 8,224,041; 8,839,013; 9,079,812

Revised: March 2016 RU-X/178
EPILEPSY IS A DISEASE OF THE BRAIN defined as at least two unprovoked seizures occurring 24 hours apart or one unprovoked seizure and a probability of further seizure activity of greater than 60 percent or an epilepsy syndrome. Almost one in 15 people will experience an unprovoked seizure at some stage in their life.1 Approximately three million Americans and 65 million people worldwide have epilepsy. Epilepsy is considered to be resolved in patients who had age-dependent seizures but outgrew them or have been seizure free for 10 years, with no medication for the last five years.

Generalized-onset epilepsy, seizures produced by electrical impulses from throughout the entire brain, has the highest incidence in the first year of life. The incidence then decreases throughout childhood and modestly increases in the over 75 age group. In contrast to this pattern, the incidence of partial-onset epilepsy is a relatively constant rate throughout childhood and adult years (to age 65). Partial seizures are produced (at least initially) by electrical impulses in a relatively small part of the brain. In those over 75, there is a fivefold increase in incidence of partial seizures over that observed at earlier ages. In the older age groups, two-thirds of epilepsy is caused by cerebrovascular or degenerative causes.

Epilepsy profoundly affects all domains of life. Unemployment rates are higher in those with active epilepsy. Social isolation, especially in the younger age group, occurs more often than if someone does not have epilepsy. Social isolation is compounded by driving restrictions when seizures are not controlled. Lower levels of education and homeownership have also been found in those with epilepsy.2

The three major categories of treatment for seizure disorders include medications, surgery, and...
diet. Diet will not be covered in this article. Seizures are a disorder of balance where excitation forces outweigh the forces of inhibition (Exhibit 1). Anticonvulsants try to restore balance by working on at least one excitation or inhibition force.

Historically, antiepileptic drugs (AEDs) can be classified into three generations. The first generation, entering the market from 1857 to 1958, includes potassium bromide, phenobarbital, and a variety of drugs that were derived mainly by modification of the barbiturate structure, including phenytoin, primidone, trimethadione and ethosuximide. The second-generation AEDs, including carbamazepine, valproate, and the benzodiazepines, were introduced between 1960 and 1975 and differed chemically from the barbiturates. Following the introduction of valproate in the 1960s, no new AEDs entered the market for almost two decades, except some additional benzodiazepines. Carbamazepine is still widely used for partial-onset seizures and valproate is used for generalized seizures. The era of the third-generation AEDs started in the 1980s with drugs that were designed to selectively target a mechanism that is thought to be critical for the occurrence of epileptic seizures. Since 1993, 16 new AEDs have been approved and marketed. Only lacosamide, eslicarbazepine, brivaracetam, ezogabine, and perampanel, which are the newest approved medications, or those with new indications are discussed.

Lacosamide (Vimpat®) was first approved as adjunct treatment in 2008 and was approved as monotherapy in 2014 for focal seizures in adults. Both oral and intravenous dosage forms are available. Orally, this agent is given twice a day. It enhances slow activation of sodium channels. In electrophysiological in vitro studies, lacosamide stabilized hyperexcitable neuronal membranes and inhibited repetitive neuronal firing by selectively enhancing slow inactivation of voltage-gated sodium channels without affecting fast inactivation. In contrast with many older AEDs, it does not induce or inhibit CYP enzymes and there are no clinically relevant drug–drug interactions with other AEDs. Addition of lacosamide to other AEDs leads to a 40 percent median reduction in baseline seizure frequency, and 40 percent of patients have more than a 50 percent reduction in their seizures.³

Lacosamide is generally well tolerated; the most common adverse effects are similar to those seen with other AEDs – dizziness, headache, nausea, and diplopia. Higher doses and combination with other sodium channel blockers (such as phenytoin, carbamazepine, or oxcarbazepine) are more likely to cause these adverse effects. A small, dose-dependent elevation in PR interval—the time from the onset of the P wave to the start of the QRS complex on electrocardiogram—can occur; thus, lacosamide should not be combined with other agents known to be associated with PR prolongation (e.g., carbamazepine, lamotrigine, pregabalin) or Class I antiarrhythmic agents.

Brivaracetam (Briviact®) was approved as adjunct treatment for partial-onset seizures in adults in 2016. It is similar to levetiracetam (Keppra®). This agent is also available as oral and intravenous dosage forms and is dosed orally twice a day. The precise mechanism by which this agent exerts its anticonvulsant activity is not known. Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may modulate neu-

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**Exhibit 1: Seizures are a Disorder of Balance**

- Excitatory postsynaptic potential
- Na+
- Ca++ currents
- Paroxysmal depolarization

Seizure

- Inhibitory postsynaptic potential
- K+ efflux
- Cl- Influx

Na = sodium
K = potassium
Ca = calcium
Cl = chloride

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• Excitatory postsynaptic potential
• Na+
• Ca++ currents
• Paroxysmal depolarization

Exhibit 1: Seizures are a Disorder of Balance

• Inhibitory postsynaptic potential
• K+ efflux
• Cl- Influx
The most commonly reported adverse effects with brivaracetam are headache, dizziness, somnolence, irritability, fatigue, and nausea. Overall, the withdrawal rate for adverse effects in trials was not statistically different between brivaracetam and placebo groups, regardless of the dosage.

Patients treated with levetiracetam can have behavioral adverse events, including agitation, antisocial reaction, anxiety, apathy, depersonalization, depression, emotional lability, euphoria, hostility, nervousness, neurosis, and personality disorder. Thirteen to 20 percent of those on levetiracetam report behavioral symptoms versus 6 percent with placebo. Patients may get switched to brivaracetam and possibly greater in patients are levetiracetam-naïve than those who previously tried levetiracetam and possibly greater in patients who stopped levetiracetam because of adverse event rather than insufficient efficacy. One small trial examined switching and found 24 of 29 patients had improvement in adverse effects and two had worsening effects on brivaracetam. Seizure control was about the same as with levetiracetam.

Eslicarbazepine acetate (Aptiom®) is a prodrug of eslicarbazepine, which is the active enantiomer of oxcarbazepine (Trileptal®). The inactive enantiomer of oxcarbazepine is what tends to cause adverse effects such as headache. This agent, being the only active enantiomer, is thought to translate to improved efficacy and tolerability compared to carbamazepine and oxcarbazepine. Eslicarbazepine is approved as an adjunct and as monotherapy for partial-onset seizures in adults and is given once a day, which limits adherence. There is about a 30 to 45 percent median reduction in baseline seizure frequency and 30 to 45 percent of patients have greater than 50 percent reduction in their seizures.

Ezogabine (Potiga®) is FDA approved for adjunctive treatment of focal seizures in adults. Its mechanism of action is activation of neuronal M-current mediated by KCNQ (Kv7) voltage-gated potassium channels. The M current (outward potassium current) is the principle mechanism by which membrane repolarization occurs after action potential. Ezogabine does not significantly affect other AEDs, except a 22 percent increase in lamotrigine clearance. Unfortunately, this agent is dosed three times a day, which limits adherence. There is about a 30 to 45 percent median reduction in baseline seizure frequency. In trials, hyponatremia (< 125 meq/L) occurred more frequently in those treated with eslicarbazepine compared with placebo (2.2 % vs 0.2%). In the monotherapy trials, about 11.7 percent of the patients taking 1600 mg and 20.3 percent taking 1200 mg had reduction in plasma sodium concentration greater than 10 meq/L from baseline during an 18-week treatment period.

Switching from carbamazepine or oxcarbazepine is an option if a patient is having adverse effects on these, is non-adherent with twice daily dosing, or is on medications with drug interactions with carbamazepine. Eslicarbazepine is a weak enzyme inducer and thus does not cause significant drug–drug interactions.

Ezogabine has some unusual adverse effects. It can cause a blue pigmentation of the sclera, conjunctiva, lips, nail beds and scattered body areas with long-term exposure. As with other dyspigmentation-inducing drugs, the discoloration appears years after onset of ezogabine treatment. It occurs in 6.3 percent of patients after three years of therapy. Why this occurs is not known. Possible mechanisms include the medication may stimulate production of melanosomes or cause accumulation of a stable drug-melanin complex which may prevent melanin complex clearance in dermal macrophages. This accumulation is often exacerbated by sun exposure and the bluish gray tint is worse in sun-exposed areas.

Ezogabine has a black box warning for potential irreversible retinal toxicity. These changes may be permanent or partially reversible on stopping the drug. The FDA recommended in June 2015 that all patients taking ezogabine undergo periodic six months dilated examinations and imaging.

Urinary retention can also occur with ezogabine. Potassium channels are also present in the bladder and alteration may result in voiding dysfunction and urinary retention. Close monitoring is therefore recommended in patients who had medical con-
dions predisposing to retention, who are taking concurrent medications that may increase risk for urinary retention, or who may be unable to communicate clinical symptoms. Because of the significant adverse effects, this agent is not frequently used.

Perampanel (Fycompa) is the last new agent to discuss. It is approved as an adjunct treatment for primary generalized and partial-onset seizures in those ages 12 and over. It is an antagonist for the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) subtype of glutamate receptors. AMPA generates fast excitatory postsynaptic potentials. This is a once a day medication. This agent may decrease concomitant AED levels. In partial-onset seizures, there is about a 25 to 35 percent median reduction in baseline seizure frequency and 30 to 35 percent of patients have greater than a 50 percent reduction in their seizures with perampanel. A long-term study indicates seizure reduction increases gradually to 50 percent and remains stable after six months. In primary generalized epilepsy, there is about a 76.5 percent median reduction in baseline seizure frequency and 64 percent of patients have greater than a 50 percent reduction in their seizures. One-third of the patients are free of generalized tonic-clonic seizures on perampanel. Compare that to the fact that only 3 to 5 percent of those with partial-onset seizures become free of seizures on the previously discussed medications.

Perampanel causes typical AED adverse effects of dizziness and somnolence but also causes headache, falls, imbalance, mild weight gain (~1.2 kg), and psychiatric symptoms. Because this agent can cause significant drowsiness, it is given at bedtime, and the dose is titrated upwards every two weeks. Irritability (7-12%), aggression, and anger are the most common psychiatric symptoms.

The majority of people with epilepsy will have a good prognosis and their seizures will be controlled by a single AED. About 30 percent do not respond to medications and are considered resistant. The definition of drug-resistant epilepsy is failure of two appropriately chosen, tolerated AEDs (whether as monotherapy or in combination) to achieve sustained seizure freedom. Those patients with drug resistance should be referred to a comprehensive epilepsy center for additional management.

Surgery is an option for some types of epilepsy, including drug resistance. Patients with drug-resistant temporal lobe epilepsy are typically considered for surgery. Surgery has been proven to be superior to medication in patients who have temporal lobe epilepsy for both percentage of people seizure free and for quality of life. Fifty to 75 percent of patients report that they are seizure free five years after temporal lobe surgery.

Types of surgery include resection, neuroablation, and neuromodulation. Surgical resection requires an open craniotomy and can include temporal lobe, amygdala, or hippocampal resection. There are emerging surgical techniques in neuroablation and neuromodulation. Neuroablation surgeries include laser interstitial thermal therapy (LITT), radiofrequency thermocoagulation, MRI-guided focused ultrasound, and stereotactic radiosurgery (CyberKnife, Gamma Knife). Neuromodulation is done with vagus nerve, trigeminal nerve, deep brain, and closed loop stimulation.

LITT is a promising minimally invasive highly selective approach to epilepsy surgery for treating mesial temporal lobe epilepsy by thermally ablating with a laser the seizure onset zone. Compared with a temporal lobectomy, laser ablation reduces the risks associated with open craniotomy surgery. There are reduced surgical complications, minimal pain with a small incision site, a small scar, minimal post-op care, and limited time away from usual activities. Patients typically only have activity restrictions for one to two weeks compared with three to six months. There is also sparing of collateral damage to the functional cortex and an option of performing additional surgery. There does appear to be lower seizure free rates with LITT compared with resection (40-50% vs 70-80%).

Vagal nerve stimulation (VNS) is FDA approved as an adjunct treatment for partial-onset seizures in those over 12 years of age. It is for patients who are not candidates for or who fail intracranial surgery. It can also treat other neurological conditions including migraines, depression, and anxiety. The mechanism of action of VNS is not fully understood, but can be reasonably assumed to involve brainstem nuclei. The nucleus of the solitary tract, the main terminus for vagal afferents, has direct or indirect projections to the locus coeruleus, raphe nuclei, reticular formation, and other brainstem nuclei. These nuclei have been shown to influence cerebral seizure susceptibility; hence, vagal modulation of one or more of these nuclei could plausibly represent the mechanism for seizure suppression. The stimulator is implanted during outpatient surgery and has a five- to seven-year battery life.

VNS results in a 50 percent seizure reduction in 50 percent of patients with resistant epilepsy in the first year of therapy. The response rate tends to increase the first two years the stimulator is in place and then remains steady. VNS can also be used in patients with Lennox–Gastaut syndrome, with a 55 percent responder rate. Central nervous system side effects seen with AEDs are not reported with VNS.
There is no effect on cognitive motor performance and balance and no change in neuropsychological function. Patients have an improved quality of life and improved mood. Hoarseness occurs in about 19 percent and coughing in 5 percent, which improves with adjustments to the stimulation parameters. Three to 6 percent of patients will get infections which leads to device removal.

Deep brain stimulation is another neuromodulation option which has been studied for treating seizures. It is thought to interrupt the propagation of seizure activity or increase the overall seizure threshold. The current results with DBS for the treatment of epilepsy remain modest, even accounting for the difficult patient group with highly refractory epilepsy. Stimulation-related side effects have been reported, most commonly with psychiatric disturbances and depression. There is also the possibility of habituation to long-term stimulation.

These issues identified with deep brain stimulation have stimulated interest in more focused neurostimulation. Closed loop stimulation is a responsive form of neurostimulation which only administers stimulation if triggered by seizure activity. Seizure frequency was reduced by more than 50 percent with a responder rate of greater than 45 percent with closed loop stimulation.17

The efficacy of the new AEDs is still limited. Some of the new AEDs were designer drugs, formulated based on molecular mechanisms; however, we still do not have AEDs for specific epilepsy syndromes and seizure mechanisms, or for blocking epileptogenesis (how epilepsy develops). Medications which block epileptogenesis are particularly needed and could be given when patients have severe traumatic brain contusions or severe hemorrhages and are at risk for developing epilepsy. Some of the AEDs in the pipeline block kindling epilepsy models and perhaps will turn out to be useful prophylactic agents. AEDs without CNS and systemic side-effects are also needed.

There are also improvements on the horizon for surgical treatment of seizures. Advances in imaging will improve outcomes in resective surgery. Expanded treatment options are needed for those who are not candidates for resective surgery.

Conclusion
AEDs with new mechanisms of action that modulate sodium, potassium ion channels and AMPA receptors are now available. These newer AEDs have advantages over the older medications in terms of adverse effects but not necessarily increased efficacy. Surgery is superior to continued drug therapy in patients with drug-resistant temporal lobe epilepsy. Those with drug resistance should be referred to a comprehensive epilepsy center. Advances in epilepsy surgery are minimizing cognitive and surgical morbidity, but long-term efficacy remains to be understood.

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References
INFLAMMATORY BOWEL DISEASE (IBD) IS A chronic inflammatory condition of the GI tract that is typically diagnosed between ages 15 to 35, with a second peak between ages 50 and 70. Predisposing factors include genetics, gastrointestinal microbiome, and triggers such as gastrointestinal infections, heavy nonsteroidal anti-inflammatory use, and antibiotics. The microbiome has recently been implicated in the development of IBD; a lack of exposure to certain microbes early in life can predispose to autoimmune conditions.

IBD has traditionally been divided into two principal categories – ulcerative colitis (UC) and Crohn’s disease (CD) (Exhibit 1). Ulcerative colitis is a diffuse mucosal inflammation limited to the colon. Crohn’s disease, by contrast, is a patchy transmural inflammation that may affect any part of the gastrointestinal tract. Its most common distributions are either the small bowel alone (regional ileitis or enteritis), the colon (Crohn’s disease of the colon or colitis), or both the large and small bowel simultaneously (ileocolitis). Other chronic nonspecific colitides include microscopic colitis (either collagenous or lymphocytic); diversion colitis, which occurs when the colon is excluded from the intestinal stream; diverticular colitis; and pouchitis.

Approximately 1.6 million Americans have IBD; 780,000 have CD and 907,000 have UC. There are 71,000 new cases of IBD diagnosed in the United States (U.S.) each year. This includes 33,000 new cases of CD per year (10.7 per 100,000 people) and 38,000 new cases of UC per year (12.2 per 100,000 people).

UC severity can vary from mild to severe. It is characterized by bloody diarrhea, passage of mucus, significant rectal urgency, abdominal cramping, and tenesmus due to frequent involvement of the rectum. In more severe disease, weight loss, fever and anemia can occur. Up to 40 percent of patients with UC will require a colectomy.

CD symptoms will vary based on which part of the GI tract is involved. Typically, CD is character-
ized by more pain and less diarrhea than UC. This is due to the transmural inflammation, the typical locations affected, and development of strictures. Diarrhea with CD is typically not bloody. There may be an abdominal mass the patient can feel in the right lower quadrant if the terminal ileum/cecum is severely and transmurally inflamed. Weight loss occurs because patients stop eating as that causes pain. Fever occurs in the setting of abscess, but severe inflammation itself can also cause fever. Malnutrition occurs especially with involvement of the small bowel where nutrients are absorbed. Fatigue is due to chronic inflammation, malnutrition and anemia itself. Growth delay in pediatric patients is commonly seen.

CD can affect any part of the GI tract. Thirty-five percent of patients have ileal disease, 35 percent right-sided disease, 20 percent colonic only disease, 5 percent gastroduodenal disease, and 5 percent jejunal disease. Up to 30 percent of CD patients will suffer from perianal disease, including fistulas and abscesses. Up to 75 percent of patients will require at least one surgery.

Extra-intestinal manifestations can occur with colonic CD and UC. Peripheral arthritis, erythema nodosum, and episcleritis are related to the activity of the colitis. Ankylosing spondylitis, sacroiliitis, and primary sclerosing cholangitis (PSC) are independent of disease activity. Seventy to 80 percent of PSC patients have IBD (mostly UC). Those with PSC have a very high risk of colon cancer that persists even after liver transplantation. Pyoderma gangrenosum and iritis may or may not be related to the activity of IBD.

Currently, there is no cure for CD. The only “cure” for UC is taking out the colon. All but the patients with the mildest of disease will need to be on chronic lifelong therapy. Overall, the goals of therapy are to induce and maintain a clinical remission, minimize steroid exposure, avoid complications of the disease, achieve a good quality of life, and minimize short- and long-term toxicity. The major classes of medications used in IBD include 5-aminosalicylic acid agents, steroids, thiopurines, anti-tumor necrosis factor (anti-TNF) agents, and vedolizumab.

The 5-aminosalicylic acid (5-ASA) derivatives are well tolerated but can have a high pill burden, leading to noncompliance. These agents are used for induction and maintenance of remission in mild and moderate UC. There are mixed data on the effectiveness of the agents in CD because they only act superficially on the mucosa and do not penetrate transmurally. There are once a day products which can improve adherence but, because of costs, these are not always approved by managed care.

Corticosteroids are potent anti-inflammatory agents that are extremely effective in the induction of remission of both CD and UC. However, due to the significant long-term adverse effects, maintenance of remission with steroids is not appropriate. The two most commonly used agents are prednisone and budesonide. Budesonide is a newer form of steroids which has a high first pass metabolism...
in the liver, limiting the systemic side effects of the drug and having it work mostly topically. However, budesonide preparations are extremely expensive, which limits use despite a more beneficial side effect profile. Long-term use of corticosteroids in CD is associated with an increase in infections, penetrating disease, need for surgery, and death.

To best utilize corticosteroids in IBD, clinicians should minimize the dose and duration as much as possible, especially in CD. Budesonide formulations including Entocort®, which releases in the distal ileum/cecum for ileocolonic CD, and Uceris®, which releases throughout the colon for UC, should be considered. Concomitant calcium and vitamin D are recommended during steroid courses to maintain good bone health. Given that steroids are ulcerogenic, gastrointestinal protection with a histamine blocker or proton pump inhibitor should also be considered for those at high risk for ulcers.

Immunosuppressants (6-mercaptopurine, azathioprine) can be used as induction agents in mild to moderate CD. They are also effective in the maintenance of remission in about 50 percent of patients with UC and CD, as steroid-sparing agents, and in steroid refractory disease. The management of perianal fistula, abscess and fissure may also include immunosuppressants. These agents typically take two to four months to be effective.

Immunosuppressants can cause significant adverse effects. These include low white blood cell counts, elevated liver function tests, pancreatitis, fatigue, and nonmelanoma skin cancers. Treatment with these agents also increases risk for infection and lymphoma. The risk for lymphoma is increased four to five times over the general population.

Thiopurine methyltransferase or thiopurine S-methyltransferase (TPMT) is primarily responsible for metabolism of 6-mercaptopurine and azathioprine. TPMT activity level should be measured before starting therapy to identify poor metabolizers who have a high rate of severe cytopenias and should not receive an immunosuppressant. Patients started on an immunosuppressant will need close blood monitoring for adverse effects; monitoring is especially important when the medication is first started. Overall, about 10 percent of patients will need to stop the medication because of a reaction or adverse event.

Infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), and golimumab (Simponi®) are anti-TNF agents approved for treating IBD. Certolizumab is only FDA approved for CD and golimumab is approved for UC. Infliximab is an IV infusion, whereas the others are subcutaneous injections. Infliximab appears to be better than adalimumab for moderate to severe UC and fistulizing CD. Home injections are associated with a lower health care cost; however, compliance with treat-
ment cannot be as closely monitored. Because of the immunosuppressive effects of anti-TNF agents, these agents increase risk for infections, possibly lymphoma, and maybe skin cancers. All patients need a negative tuberculosis and hepatitis B screen before starting therapy.

Vedolizumab (Entyvio®), a selective monoclonal antibody against α4β7-integrin, is FDA approved for CD and UC. It targets leukocyte trafficking in the gastrointestinal tract and is related to natalizumab (Tysabri®), but it doesn’t affect the central nervous system or lead to progressive multifocal leukoen cephalopathy, a deadly adverse effect. Vedolizumab is effective for induction and maintenance of remission in UC and CD compared with placebo.1, 2 In the approval trials, all patients had active moderate to severe disease and about 50 percent had prior anti-TNF agent exposure. Patients with prior anti-TNF exposure had lower rates of response and remission. This agent has a very slow onset of response – typically 10 to 12 weeks.

Vedolizumab treatment can be considered for moderate UC disease; however, for severe disease, most clinicians are still using infliximab in combination with an immunosuppressant. Others indications may be primary non-responders of anti-TNF therapy, secondary non-responders of anti-TNF therapy, elderly patients that are at higher risk for infections, and patients with prior malignancy when anti-TNFs are contraindicated. This agent has no role for acute hospitalized patients due to delayed onset of action. Further studies are needed comparing infliximab and vedolizumab in UC. There are no data on efficacy in fistulizing CD yet. Data on post-operative CD patients is expected soon. Given its excellent safety profile, vedolizumab has largely replaced natalizumab.

Ustekinumab (Stelara®) is approved for moderately to severely active CD and plaque psoriasis and psoriatic arthritis. This is an IL-12/23 inhibitor. Its role in therapy is yet to be determined.

Traditionally, treatment of IBD has been done on a step-up basis, starting with 5-ASA derivatives and working toward more aggressive treatment. Because the more aggressive treatments such as immunosuppressants and biologics are targeting better the underlying inflammatory issues, therapy has been moving to step-down or top-down therapy – start aggressive and then back off therapy once stable. The benefits of step-down therapy are it modifies the natural progression of IBD by halting inflammation early in the disease course. Aggressive therapy at earlier stages improves clinical outcomes and increases the likelihood of mucosal healing. IBD patients who achieve mucosal healing require fewer hospitalizations, surgeries and intensive care unit admissions. There is an improved quality of life, decreased risk of relapse, and decreased risk of colorectal cancer. Overall, biologics appear to be more effective when given early in the disease course rather than later.

In deciding on top-down therapy, clinicians need to weigh the benefits and risks of combination therapy and determine who will have an aggressive course with complications and need for early surgery. This is typically the patient with earlier age at diagnosis, early need for surgery, early penetrating/fistulizing disease, and presence of anti-microbial antibodies. Thus, aggressive combination therapy is recommended as initial therapy for patients with more severe disease and an unfavorable disease course. In the future, we will be able to better predict on the basis of clinical, genetic, and laboratory factors.

Top-down therapy starts with the combination of...
an anti-TNF agent (infliximab, adalimumab, certolizumab, golimumab) and an immunomodulator (thiopurine or methotrexate). The addition of an immunomodulator decreases the immunogenicity of the anti-TNF agents and decreases the risk of antibody development and secondary non-response. Dual therapy, combining infliximab and 6-mercaptopurine, has been shown to be better than monotherapy.

There are risks with combination therapy. The patient is doubly immunosuppressed and has an even higher risk for lymphoma and skin cancers compared with monotherapy. There is especially concern for hepatosplenic T-cell lymphoma development in young men on combination therapy. To minimize risk, clinicians can consider use of methotrexate instead of a thiopurine. If the patient has severe and aggressive IBD, the benefits do outweigh the risks and one medication could be stopped after remission is achieved.

IBD management is moving toward personalized care. Exhibit 2 includes some of the biomarkers being investigated in IBD to allow better identification of aggressive disease and selection of therapy. At least one study has shown that the presence and magnitude of immune responses to microbial antigens are significantly associated with more aggressive disease phenotypes among children with CD.

Therapeutic drug monitoring is another way to personalize therapy. Azathioprine and 6-mercaptopurine serum levels can readily be measured to monitor for therapeutic response. Measuring levels of anti-TNF therapy are also possible.

Fecal calprotectin can be used to distinguish IBD from non-IBDs such as irritable bowel syndrome and furthermore predicts clinical relapse in IBD patients. Fecal calprotectin represents 60 percent of cytosolic proteins in granulocytes. The amount of calprotectin in feces is therefore proportional to the neutrophil migration to the gastrointestinal mucosa.

The American Gastroenterological Association quality improvement measures and selected Crohn’s & Colitis Foundation of America process measures are listed in Exhibit 3. These measures can be used to assess the quality of IBD care.

In addition to treatment aimed at the underlying pathophysiology in IBD, patients need preventive care. Patients with IBD are at increased risk for colon cancer. Risk is increased with longer duration of disease, greater extent of disease, increased activity of disease, family history of CRC, and presence of PSC, stricture, or pseudopolyps. Colorectal screening is recommended after eight years of colitis involving at least one-third of the colon. Colonoscopy is recommended every one to two years. Patients with PSC and UC should have screening yearly from time of diagnosis. Proctosigmoiditis does not increase the risk of colon cancer.

Smoking cessation is especially important in patients with CD. Smoking increases risk of small bowel CD and penetrating or stricturing CD. Additionally, continuing to smoke makes IBD medications less effective. If a patient has to have CD-related surgery, smoking afterwards increases the risk of needing additional surgery.

IBD patients have increased risk of venous thromboembolism (VTE) compared with those without this disease. IBD flares further increase the risk of VTE. VTE prophylaxis has been shown to be safe even in patients with current bloody diarrhea. Although guidelines recommend thromboprophylaxis during hospitalizations and post-operatively, the recommendations are not always followed because of concerns about safety and a lack of awareness of the magnitude of thrombotic risk in these patients.

Osteoporosis screening is recommended in certain IBD patients - postmenopausal women, those on ongoing corticosteroid treatment, those with cumulative use of steroids greater than three months, anyone with a history of low-trauma fractures, and patients greater than 60 years old. Osteoporosis prevention with calcium 1200 mg daily and vitamin D 800 mg daily is recommended if a steroid course is anticipated to last longer than three months.

The future holds several possible new biologics being available. The four agents that are closest to market include etrolizumab, tofacitinib, and ozanimod. Etrolizumab is a subcutaneous monoclonal antibody that binds β7 subunit of both α4β7 and αEF7 integrin and is in Phase III trials. Tofacitinib (Xeljanz®), an oral janus kinase 1 and 3 inhibitor, is already FDA approved for psoriasis treatment and is in Phase III trials for IBD. Ozanimod is an oral sphingosine-1-phosphate receptor inhibitor similar to fingolimod, which is already approved for multiple sclerosis treatment. This agent selectively retains activated lymphocytes in lymph nodes and has finished Phase II trials. Mongersen is an oral mothers against decapentaplegic homolog 7 (SMAD7) inhibitor in Phase III trials.

**Conclusion**

IBD is a complex, heterogeneous condition that affects patients for many decades. The exact pathogenesis is still unknown and there is no cure, so patients typically require lifelong therapy. Each therapy has its own risks and benefits that need to be carefully weighed for each patient. New therapies continue to be developed with the eventual hope for a cure.
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References
A BIOSIMILAR IS DEFINED AS A LEGITIMATE copy of a biopharmaceutical, which no longer is protected by patent, that has undergone rigorous analytical and clinical assessment, in comparison to its reference product, and has been approved by a regulatory agency according to a specific pathway for biosimilar evaluation. Clinicians and managed care plans have similar concerns about biosimilars. Will a biosimilar be as effective and as safe as the originally licensed biopharmaceutical? If a pharmacist substitutes a biosimilar for a prescribed biopharmaceutical, will the patient be adversely affected? Will the availability of biosimilars reduce the high cost of targeted biological therapies for our patients? This article addresses these concerns. In subsequent discussion, the originally licensed biopharmaceutical will also be referred to as the reference product.

According to the FDA, biosimilarity means “that the biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product”1. As shown in Exhibit 1, different regions and countries use different terminology to refer to biosimilars, which further adds to the complexity and potentially may lead to misinterpretations of the biosimilar concept.

Biosimilars are not second-generation biopharmaceuticals or generics. Second-generation biopharmaceuticals are structurally different from the originally licensed biopharmaceutical and are intended to improve performance while preserving mechanism of action. An example for an antitumor necrosis factor inhibitor is infliximab (Remicade®) which was the first tumor necrosis factor (TNF) inhibitor with adalimumab (Humira®) and golimumab (Simponi®), as subsequent second-generation agents. These three biologics are not biosimilars. Biosimilars are also not generics because small-molecule drugs can easily be identically manufactured, whereas the manufacturing process for biologics is

Summary
A few biosimilars are now available in the United States (U.S.) and many more are in the pipeline. Clinicians and managed care plans can be reassured of the efficacy and safety of biosimilars based on the rigorous evaluation process required by the FDA for marketing. There are still issues to be addressed related to the interchangeability of biosimilars.

Key Points
- Biosimilars undergo a rigorous regulatory approval process, with an abbreviated clinical package.
- Biosimilarity is demonstrated by the totality of evidence, with respect to physiochemical characteristics, biologic activity, pharmacokinetics, and clinical safety and efficacy.
- Opportunity exists to expand patient access through the availability of biosimilars.

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.
several orders of magnitude more complex and biosimilars are regulated through different statutes.

Biomimics, or “knock-offs,” are one thing clinicians worry about when considering biosimilars. A biomimic (or intended copy) is a replica of a biopharmaceutical that is not developed, assessed, or approved according to regulatory guidelines for biosimilars. Similarity is also not demonstrated by a stepwise and comprehensive comparability exercise, and there may be differences in the primary structure from the reference product. A biomimic may differ from the reference in formulation, available doses, dosing regimen, efficacy, safety, and immunogenicity, which may result in clinically significant differences. These agents are not legal in the U.S. Exhibit 2 shows some marketed examples from around the world. ² Some of these have been widely used in other countries.

The European Union (EU) leads the world in the number of biosimilars approved. There are erythropoietin-stimulating agents (ESA), granulocyte colony-stimulating factor (G-CSF), human growth hormone, TNF inhibitor, follicle stimulating hormone, and insulin glargine biosimilars approved in the EU. Regulatory authorities in Canada and Japan have approved a few biosimilars (3 and 7 respectively). In the U.S., four are currently approved, including three TNF inhibitors [etanercept-szss (Erelzi®,

| Exhibit 1: Varying Terminology for Biosimilars² |
|--------------------|----------------|
| Country/Organization | Terminology               |
| WHO                 | Similar biotherapeutic product (SBP) |
| EU and South Korea  | Similar biological medicinal product |
| Canada              | Subsequent-entry biological (SEB) |
| US and Australia    | Biosimilar               |
| Japan               | Follow-on biologic       |
| India               | Similar biologic         |
| Brazil              | Biologic product         |
| Mexico              | Biocomparable            |

| Exhibit 2: Marketed “Biomimics” Based on Biologic Agents used to Treat Inflammatory Diseases² |
|-----------------|-----------------------------|----------------|
| Drug*           | Manufacturer (location)     | Marketed In       |
| Rituximab biomimics                                    |
| Reditux™       | Dr. Reddy’s Laboratories (India) | Bolivia, Chile, Ecuador, India and Peru |
| Etanercept biomimics                                    |
| Yisaipu         | Shanghai CP Goujian Pharmaceutical Co. (China) | China |
| Etanar™         | Shanghai CP Goujian Pharmaceutical Co. (China) | Colombia |
| Etacept™        | Shanghai CP Goujian Pharmaceutical Co. (China) | India |
| Etart™          | Shanghai CP Goujian Pharmaceutical Co. (China) | Mexico |
| Infinitam™      | Probiomed (Mexico)          | Mexico |
Sandoz), adalimumab-atto (Amjevita®, Amgen), infliximab-dyyb (Inflectra®, Celltrion, Pfizer), and one G-CSF [filgrastim-sndz, Zarxio®, Sandoz]. The three TNF inhibitor biosimilars are not currently being marketed because of patent disputes. The addition of a modifier at the end of the biopharmaceutical name indicates that the agent is a biosimilar and which particular biosimilar. Biosimilars for erythropoietin, bevacizumab (Avastin®), and trastuzumab (Herceptin®) are the most likely to be approved next by the FDA.³

Filgrastim is a relatively small molecule and was the first biopharmaceutical for which a biosimilar was approved by the FDA. The efficacy of filgrastim-sndz was demonstrated in four clinical trials. Because of a patent dispute with Amgen, Sandoz was prohibited from marketing their agent for 180 days after approval, but this agent is now available.

Biopharmaceuticals are complex proteins with a complicated manufacturing process. Exhibit 3 illustrates where differences with biosimilars can occur in the manufacturing of these agents. For example, because the gene used to produce a biosimilar is reverse engineered based on the amino acid sequence of the final product, the gene sequence used to produce a biosimilar may be different but ultimately it produces the same amino acid sequence. Because of trade secrets, the manufacturing process for a biosimilar is similar, but not identical, to that of the originator product.

All biopharmaceuticals (originators and biosimilars) are subject to variability. Variability can occur because of protein folding, misfolding, aggregation, enzymatic cleavage, degradation, and numerous others.³ There are a range of structural relationships between biosimilars and their reference product. Proteins produced by recombinant DNA technology are highly similar to the original proteins and share the primary amino acid sequence but differ with respect to glycosylation and other post-translational modifications. Other nonrecombinant origin proteins that are purified from their natural sources are generally similar to the original biopharmaceuticals but, in addition to exhibiting different post-translational modifications, may have slightly different amino acid sequences.

Even among originator products there can be changes in the product over time because of manufacturing process changes. Small modifications may result in gradual changes. Chemical characterization of different commercial lots of etanercept and rituximab produced between 2007 and 2011 revealed variations in both C-terminal lysine content and glycosylation.⁶ There was a threefold increase in unfucosylated G0 glycans in later batches of rituximab, which resulted in more potent antibody-dependent cell-mediated cytotoxicity.⁶ Despite differences over time, when the originator products are within
a pre-specified acceptable range, the products are marketed with no change in label and the changes are not reported to clinicians or patients. If large alterations occur, analytical (and possibly additional clinical studies) are required to compare the post-change product with the existing pre-change product. For a product to demonstrate biosimilarity, the manufacturer must demonstrate equivalence within pre-specified margins (“goalposts”) in comparison to the current reference product.7 Biosimilars have to meet tighter reference standards over time because they are compared with the current version of the originator product and not the originally approved product.

Most large countries and the World Health Organization (WHO) have guidelines for biosimilar development.2 In the U.S., there are two pathways for medication approval by the FDA— the small-molecule and the biosimilar pathways. The small-molecule pathway through the new drug application (NDA) is the traditional drug approval pathway that uses a clinical trial pathway (preclinical through Phase III) for proving safety and efficacy. The abbreviated NDA process is used for generic approvals of small molecules where only bioequivalence and pharmacokinetic studies are required. Originator biopharmaceuticals undergo the same phases of development as a small molecule— analytical, nonclinical, clinical pharmacology, and then Phase I to III clinical trials to demonstrate efficacy and safety. The biosimilar pathway is different in that the biosimilar undergoes a very robust analytical process and a much smaller nonclinical and clinical pharmacology analysis. The analytical process requires over 100 analyses to prove structural similarity. Only one additional clinical trial is required, which is sort of a bioassay to prove that similar biologic effects are seen. The biosimilar application then relies on the accumulated clinical data with the reference product to extrapolate indications.

Overall, in demonstrating biosimilarity, clinical efficacy and safety of the reference biopharmaceutical have already been demonstrated. The biosimilar must demonstrate no significant difference from its reference product through robust analytical, toxicology, pharmacokinetic, pharmacodynamics (if applicable), and immunologic studies in comparison to the reference product and smaller comparative effectiveness clinical trial(s), which must be conducted in patients with a disease for which the reference product is licensed. The FDA has also suggested that it might be acceptable to conduct the efficacy trial for an indication for which the biologic is typically used but not necessarily currently FDA approved. There is no need to demonstrate efficacy in all indications and no differences in safety or efficacy are expected between an approved biosimilar and its reference product. In determining biosimilarity, the FDA uses a risk-based, totality-of-the-evidence approach to evaluate all available data and information submitted in support of the proposed product.8

The Biologics Price Competition and Innovation Act of 2009, as part of the Affordable Care Act, established an abbreviated Biological License Application (aBLA).9 This permits a biosimilar to be evaluated against only a single reference biological product. To be considered for an aBLA, the biosimilar and reference product must have the same presumed mechanism of action, route of administration, dosage form, and potency. Under an aBLA, a biosimilar may only be reviewed and approved for indications for which the FDA already has an approved reference product. The four approved biosimilars in the U.S. went through the aBLA process.

A biosimilar must be studied at the same dose that is licensed for the reference product; thus, doseranging studies are not needed for biosimilars.8 They have to demonstrate similar efficacy and safety, compared to the reference product through double-blind, parallel-group, active comparator trial design with patients with disease most responsive to the reference product and using the clinical endpoint most sensitive to detect product-related differences, if present. An active comparator clinical trial must demonstrate equivalence within a prespecified margin based on historical information obtained from placebo-controlled clinical trials of the reference product (difference in efficacy between active drug and placebo). A noninferiority trial design is not usually adequate to assess biosimilarity. If a proposed biosimilar is superior to the reference biopharmaceutical (‘bio-better’), it is not biosimilar. For inflammatory diseases, plaque psoriasis is probably the most sensitive disease for use in demonstrating biosimilarity. For the approval of infliximab-dyyb, the biosimilar was compared to the reference product (Remicade®) in a trial of 250 subjects with ankylosing spondylitis.10 Comparable pharmacokinetics, safety, and efficacy were demonstrated.

Demonstration of equivalent clinical responses during early, rapid rise phase of the time-response curves provides additional information on biosimilarity. The early portion of the time-response curve affords greater sensitivity to detect differences in efficacy between study drugs than does the plateau phase. Assessment of response to therapy over the first three months of treatment allows comparison of rapidity of onset. This tracking of multiple data points early in the course of therapy was done in one of the trials used to approve biosimilar etanercept.11
Manufacturing changes have resulted in altered immunogenicity of biopharmaceuticals. Interferon beta-1a (Avonex®), produced in a new cell line, had decreased immunogenicity compared to the interferon b-1a that had been produced in the original Chinese hamster ovary cell. Changes in formulation or packaging have resulted in increased immunogenicity with clinical consequences. A recombinant human erythropoietin product (rEPO, Eprex®, Ortho Biotech) had a formulation change of switching protein stabilizer from human serum albumin to polysorbate 80 and a new packaging system (pre-filled syringe with rubber plunger for subcutaneous administration). These changes resulted in formation of anti-EPO antibodies that cross-reacted with endogenous EPO. Between 1998 and 2004, 175 cases of pure red cell aplasia, as a result of these changes, were reported.13-15

The FDA expects one-year follow-up immunogenicity data for biopharmaceuticals intended for chronic administration. If extrapolating immunogenicity findings to other indications, the biosimilar manufacturer must use a study population and treatment regimen for which development of immune responses with adverse outcomes is most likely to occur (e.g., patients who are not immunosuppressed). Greater immunogenicity of a proposed biosimilar, compared to the reference product, would question biosimilarity, but lower immunogenicity of a proposed biosimilar would not preclude biosimilarity. Some of the approved biosimilars have lower immunogenicity.

Indications for biosimilars are extrapolated from the approved indications for the reference product. Extrapolation of data from a clinical trial of a biosimilar conducted in one disease is used to support approval for additional indications for which the reference product is already licensed. Factors to be considered in extrapolation of indications include clinical experience with the reference product, mechanism of action in each indication, target receptors, product structure and target/receptor interactions, pharmacokinetics and bio-distribution in different patient populations, and differences in the safety and immunogenicity profiles between indications. Extrapolation across indications cannot occur for indications that have different mechanisms of action. For example, rituximab works differently in rheumatoid arthritis and lymphoma. Extrapolation of data from a rheumatoid arthritis study could not be used to get a FDA approved indication for lymphoma treatment. Thus, approved indications for a biosimilar may be the same or different from the reference product. In the U.S., infliximab-dyyb and etanercept-szsz, filgrastim-sndz have the same indications as their reference products. Adalimumab-atto has slightly different indications from the reference product. It is not approved for pediatric Crohn’s disease and is for use in juvenile idiopathic arthritis in those ages 4 and up compared with 2 and up for the reference product.

Interchangeability among biosimilars and reference products concerns many clinicians. The Biologics Price Competition and Innovation Act of 2009 addresses interchangeability. According to this act, the term interchange or interchangeability means that a biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the product. The approval for a biosimilar will designate interchangeability if the application for approval is sufficient to show that the biological product is biosimilar to the reference product, can be expected to produce the same clinical result as the reference product in any given patient, and the risk in terms of safety or diminished efficacy of alternating or switching between products is not greater than the risk of using the reference product without such alteration or switch.

If a patient is transitioned to a biosimilar, after initial treatment with the originator product, this is considered a switch. This requires a single switch study. Substitution is interchange of the two products (biosimilar and originator) at the time of original prescribing and can be initiated by the dispensing pharmacy without prescriber input. This is similar to the interchangeability for generic small-molecule medications. The Biologics Price Competition Act of 2009 affords one year of exclusive marketing rights to the first biosimilar approved as being interchangeable with a particular reference product. Proving interchangeability for biosimilars requires a repeated switching study, although a single switch study fulfills the statutory requirement. The FDA has not yet issued guidance on what studies will be required to have interchangeability and thus has not designated any of the approved biosimilars as interchangeable at the time of dispensing.

Pharmacovigilance, postmarketing safety monitoring, is important to ensure safety and effectiveness of all biopharmaceuticals, including biosimilars. Safety of a biosimilar in indications licensed for the reference product is monitored. Monitoring for rare adverse events already described for the reference product is also conducted. Lastly, there is monitoring for novel safety signals with the biosimilar. The Risk Management Plan (RMP)/ Risk Evaluation and Mitigation Strategies (REMS) for a given biosimilar product includes participation in existing registries, educational material for patients and/or
treated physicians, and requires a system of nomenclature to distinguish the biosimilar from the reference product.\textsuperscript{8}

For all biological products, specific nomenclature has to clearly identify biological products to improve pharmacovigilance and differentiate among biological products that have not been determined to be interchangeable. All biological products (originator biopharmaceuticals and biosimilars) have a proprietary name that includes a unique suffix composed of four lowercase letters that is devoid of meaning.\textsuperscript{10} For example, products sharing the core name replicamab, proper names may be replicamab-cznm and replicamab-hixf. The filgrastim-sndz name was assigned before this recommendation happened and may be updated to reflect the new standard.

A lower cost biosimilar can make medications more widely available to all members of society. The potential risk to the individual of switching to a lower cost biosimilar should be outweighed by the potential benefit to society of expanding access to care for all.\textsuperscript{17} The cost savings in the U.S. with filgrastim-sndz is approximately 15 percent. The newer approved, but not yet marketed agents, are expected to be significantly less expensive than the reference products. It will be interesting to see what happens with price as more biosimilars get FDA approved.

In answer to the original questions clinicians and managed care plans have, if a biosimilar is approved according to a regulatory pathway for biosimilars, it is as effective and as safe as the reference product. The designation of interchangeability is unlikely to be granted in the near future, but insurance carriers and pharmacy benefit managers likely will dictate switching from the originator to a biosimilar and between two biosimilars. To drive the move to biosimilars, higher tier copays for the originator may be granted in the near future, opportunity exists to expand patient access through the availability of biosimilars.

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References

PULMONARY ARTERIAL HYPERTENSION (PAH) is a deadly, progressive disease. The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) documents a 10 to 15 percent annual mortality, despite contemporary therapy. The median age of those affected is 50.

PAH is a disease of the pulmonary vasculature and primarily occurs in the small pulmonary arteries prior to the pulmonary capillary bed. Inflammation, fibrosis, and significant remodeling of the vasculature occur. Over time, the pulmonary vasculature is essentially obliterated. PAH is just one type of pulmonary hypertension (PH) and can be idiopathic, heritable, drug- and toxin-induced, persistent PH of the newborn or associated with connective tissue disease, HIV infection, portal hypertension, coronary heart disease, schistosomiasis, or chronic hemolytic anemia. Most drug-induced cases in the United States (U.S.) are from methamphetamine and cocaine.

PH is a general term used to describe elevated pressure in the pulmonary vascular bed and is defined as a mean pulmonary artery pressure \( \geq 25 \) mmHg as measured by right heart catheterization. The World Health Organization divides PH into five groups, which include PAH, PH with left heart disease, PH with lung disease, chronic thromboembolic pulmonary hypertension (CTEH), and everything else lumped into a final category.

Accurate diagnosis of PAH is important. It is estimated that 20 to 30 percent of those prescribed PAH therapy do not actually have this disease but may have another type of PH and will not benefit from the therapy.

Echocardiograms are used for screening for pulmonary hypertension but can only estimate pulmonary pressure. PH on echocardiogram is most commonly caused by left heart failure and not PAH. Obstructive sleep apnea and heart failure with preserved ejection fraction, both of which lead to PH,
are epidemic in the U.S. Overall, the echocardiogram is a great tool to evaluate dyspnea and screen for pulmonary hypertension but cannot be used to make the diagnosis. Unfortunately, many patients who are labeled as having PAH have been diagnosed based solely on this test.

Right heart catheterization is absolutely required for PAH diagnosis and ongoing PAH disease management. Managed care could significantly reduce costs by requiring that everyone has to have a right heart catheterization before receiving any PAH therapy.

CTEH is one type of curable PH that can be misdiagnosed as PAH. Ventilation–perfusion scans are the preferred test to evaluate for chronic embolic disease. Splenectomy is a key risk factor for CTEPH that many clinicians are not aware of, and many CTEPH patients do not remember an antecedent deep vein thrombosis or a pulmonary embolism event, or their events were not diagnosed. Pulmonary thromboendarterectomy surgery, a definitive treatment for CTEH, is akin to lung transplant in technical difficulty and should only be performed by those with real expertise. Outcomes are amazing for properly selected patients and, in expert hands, surgical risks are reasonable. Riociguat, which is discussed later, is approved for treatment of CTEH which is not operable.

PH from lung disease (chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis) also needs to be distinguished from PAH. Pulmonary function tests are mandatory before making a PAH diagnosis to eliminate PH from lung disease. CT imaging is also appropriate for people who have significant oxygen requirements or significantly abnormal pulmonary function tests. Resting hypoxemia is very unusual at initial PAH diagnosis (except secondary to scleroderma) and is a red flag for underlying emphysema or pulmonary fibrosis. Chronic hypercapnic respiratory failure is an increasing cause of right heart failure and PH.

In PH from lung disease, treatment for the primary conditions that led to the PH is key. Continuous positive airway pressure therapy (CPAP) is important for obstructive sleep apnea (OSA); OSA is often more clinically significant when people have comorbid cardiac and respiratory disease. Bilevel Positive Airway Pressure (BiPAP) is recommended for chronic hypercapnic respiratory failure. Compliance with oxygen for hypoxemia is especially important. Most, if not all, of these patients will also have heart failure with preserved ejection fraction and need aldactone-emphasizing diuretic regimens.

Medications approved for treating PAH may be appropriate for treating PH from lung disease when prescribed by experts. Endothelin blocking drugs are not indicated for PH associated with idiopathic pulmonary fibrosis (IPF) because of their mechanism of action. It is important to identify what is driving dyspnea in a patient; they can have both COPD and PAH. A short trial of PAH medications can be given to identify whether PH is driving their symptoms. No data exists that these PAH medications improve outcomes. The goals of therapy with PH from lung disease are to control right heart failure, relieve dyspnea, and improve exercise tolerance. Controlling right heart failure can be a very reasonable goal to facilitate transplant or reduce recurrent hospitalization.

Although PAH was initially described in 1891, the first targeted therapy was not developed until the 1980s. Synthetic prostacyclin (epoprostenol) was first administered in the early 80s and FDA approved in 1995. New understanding of the underlying mechanisms of this disease is leading to better treatments.

There are eight oral, three parenteral, and two inhaled PAH–specific therapies. These agents target the prostacyclin pathway, endothelin pathway, or the nitric oxide pathway to provide vasodilation and antiproliferative effects in the pulmonary vasculature.1,2

The prostacyclin analogues – epoprostenol, treprostinil, and iloprost – provide vasodilation, platelet inhibition, antiproliferative effects, and inotropic effects. Epoprostenol (Flolan®) is given as a continuous intravenous infusion because it has a half-life of minutes. It must be kept cold even during infusion. Importantly, abrupt withdrawal of epoprostenol is associated with clinical deterioration and death. Preparing this product is challenging for patients. Thermostable epoprostenol (Veletri®) has superior stability and can be given at room temperature, but the short half-life remains. Treprostinil (Remodulin®) is given as a continuous subcutaneous or intravenous infusion; it has a longer half-life of three to four hours. Adverse effects of prostacyclins are predominantly related to their vasodilatory action such as hypotension, headache, diarrhea, nausea, flushing, and dizziness. Parenteral therapy is highly effective with expert guidance, and the benefits in terms of outcomes outweigh the costs.

Inhaled iloprost (Ventavis®) is very difficult to use because it comes in individual glass vials that must be opened, put in the inhaling device, and inhaled six to nine times per day. Inhaled treprostinil (Tyvaso®) is a much better product which only requires once a day preparation and is administered four times daily. It has better efficacy data than iloprost and should be the preferred inhaled prostacyclin. Adverse effects...
are lower than with the parenteral versions. Overall efficacy with inhaled therapy varies with physician experience and individual patient features. Oral treprostinil (Orenitram®) is optimally given three time daily. There are reasonable data that this oral prostacyclin may be better a better choice than the parenteral prostacyclins in some patients. Clinicians are learning how best to use it and dosing is complex. Oral selexipag (Uptravi®) is the first-in-class nonprostanoid prostacyclin receptor agonist. Data for preventing clinical deterioration are strong with selexipag, but evidence for patients feeling better are lacking. It is the only approved PAH therapy that has not been shown to improve exercise tolerance. This agent has a less complex dosing regimen than oral treprostinil. Adverse effects are similar to other prostacyclins. Many PAH clinicians believe that use of oral prostacyclins early in the disease course will ultimately improve outcomes; data to support this are in its infancy.

Endothelin receptor antagonists (ERAs) target relative excess of endothelin-1 by blocking receptors on the endothelium and vascular smooth muscle. This leads to vasodilation and less proliferation. Oral bosentan (Tracleer®) was the first oral therapy approved for PAH. Its initial approval was based on improved exercise tolerance and delayed clinical worsening. This agent has a black box warning about hepatotoxicity and would not have been FDA approved if it had not been the first oral agent for PAH. Because of drug interactions and adverse effects, managed care should not be paying for this agent. Additionally, it should not be used with sildenafil. Oral ambrisentan (Letairis®) is once daily and does not cause hepatotoxicity. It also has a better drug interaction profile than

### Exhibit 1: Risk Assessment of PAH³

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Phosphodiesterase (PDE-5) inhibitors augment the bioavailability of nitrous oxide in the pulmonary arteries. This results in vasodilatory and anti-proliferative actions. Sildenafil (Revatio®) requires three times a day dosing and interacts with bosentan. Adherence is difficult with three times a day dosing. All the long-term outcomes data for this agent are with an 80 mg daily dose; unfortunately, only 20 mg daily is FDA approved. Clinicians routinely have to fight with managed care to get approval for 80 mg dosing. Generics are available, but most clinicians prefer to use tadalafil. Tadalafil (Adcirca®) is dosed once a day and has no relevant drug interactions. This agent will be going generic in 2017. It has been shown to provide a clear benefit in combination with ambrisentan and has a clear evidence base for dosing.

Unlike the PDE-5 inhibitors which prevent breakdown of cGMP, riociguat (Adempas®), the first-in-class soluble guanylate cyclase stimulator, promotes synthesis of cGMP. It has a theoretical advantage by being nitric oxide independent but unfortunately it requires three times a day dosing, and dose titration is an initial drawback. A clinical strategy some clinicians use is to start patients on tadalafil and then switch to riociguat if they do not respond.

The clinical trial design and endpoints for PAH targeting agents started out initially with showing differences in exercise tolerance by evaluating changes in the six-minute walk distance (6MWD). This was the path of initial approval for most currently registered drugs. Advantages for the 6MWD as an endpoint are ease of reproducibility, and it is an integrative assessment of functional ability. Conversely, musculoskeletal issues and motivation can affect the outcome. Additionally, it does not directly assay right ventricular function or hemodynamic improvement that experts consider most critical. The manufacturers of macitentan and selexipag have delayed studies demonstrating disease progression and tout their product as being better because of study design. A delay in disease progression is not the only endpoint to say that patients got better. Time to clinical worsening, which is a shorter endpoint, is used in some studies. NT-pro-BNP is emerging as a biomarker for right heart function. It is currently accepted lab surrogate in the ambrisentan label and is part of riociguat data but not in label. Right ventricular function is emerging as conceptually critical, but currently there is no clear measurement tool.

Risk assessment identifies patients at low, intermediate or high risk for progression (Exhibit 1). Therapy can be selected based on risk assessment. Oral therapies are reasonable choices for low and intermediate risk patients. Parenteral therapy should be an early consideration for anyone identified as high risk. With reasonable justification, short-term trials of inhaled or oral prostacyclins may be appropriate as long as there are clearly defined goals and easy movement to parenteral. Bosentan and sildenafil should not be used in combination because there are no data for efficacy, increased toxicity, and other choices are superior. There are compelling data for initial combination therapy, especially with ambrisentan and tadalafil. Compelling data are available for sequential combination therapy with three options. These include macitentan and sildenafil, riociguat and bosentan, and selexipag with bosentan and/or sildenafil. There are also reasonable data for ambrisentan and sildenafil and some people extrapolate to include macitentan and ambrisentan in combination with riociguat.

The costs of PAH therapies are significant. Individually, the therapies range from $18,000 to $210,000 per year and combination therapy, of course, is much more expensive.

Awareness of PAH has grown significantly, and those diagnosing and caring for these patients may not necessarily be experts. That can be an issue for managed care because non-experts may be using inappropriate medications. The Pulmonary Hypertension Association has established a program for accreditation of centers with special expertise in PH, particularly pulmonary arterial hypertension PAH, to raise the overall quality of care and outcomes in patients with this life-threatening disease. This is a rigorous, field-tested accreditation process with an extensive application and site review. There are currently at least 28 accredited adult centers across the U.S. Managed care can rely on this accreditation and can consider restricting care for PAH patients to an accredited center.

Conclusion
Pulmonary arterial hypertension is a deadly, progressive disease. The therapies are very expensive with compelling data for combination use, and these therapies clearly prolong life, further increasing the expense. There is no cure, although the long lives of some patients suggest that current
therapies arrest disease progression for some. Disease awareness is increasing faster than true expertise among clinicians, which is a very real risk for misuse of expensive therapy.

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References
OVERACTIVE BLADDER (OAB) IS OFTEN ignored and belittled; yet, it has a huge impact on quality of life and health. It is symptom complex, with urgency, frequency, and a large amount of urinary leakage in patients who have episodes of incontinence (urinary urge incontinence, UUI). Urgency is a strong, sudden desire to void, whereas frequency is defined as voiding more than eight times per 24 hours. Patients with OAB are often unable to reach the toilet in time after an urge to void and usually wake up to pass urine during the night. One in three adults in the United States (U.S.) over 40 years of age report symptoms of OAB at least “sometimes.”

The most common risk factor for OAB is increasing age. Both men and women develop OAB; women are more likely to have incontinence. Other common risk factors include obesity, Caucasian race, depression, hormone replacement therapy, fibromyalgia, and altered bowel function. Neurogenic OAB may be secondary to multiple sclerosis, Parkinson’s disease, dementia, spinal cord injury, stroke, or diabetes.

Those affected by OAB tend not to want to admit they are having issues with incontinence and many, especially women, think it is just a part of getting older. It takes a sentinel event with major embarrassment before a woman, particularly, is willing to seek care. A negative response from a health care provider, such as telling a patient that incontinence happens to everyone as they age, may close the door to that patient getting appropriate treatment. Men have the option of coming into care under the guise of a prostate problem. Clinicians can give patients permission to discuss their issue with questionnaires or by asking a few simple questions about whether the patient is having problems with their bladder or holding their urine.

OAB is more than urinary frequency, urgency and incontinence. OAB has a significant impact on quality of life (QOL). QOL scores among people...
with OAB are worse than those of people with diabetes in several domains, including physical functioning, role–physical, vitality, social functioning, role–emotional, and mental health.\(^1\)\(^{-3}\) It affects day-to-day living. Those affected avoid going to places where there is not a bathroom, they may have to depend on someone else for shopping, intimacy can be impacted because of incontinence fear, and work can be affected by time spent in the bathroom.

OAB has significant economic impact. In 2007, the annual per capita cost of OAB was estimated to be $1,925 of which 75 percent was direct medical costs, 21 percent lost productivity, and 4 percent direct nonmedical costs.\(^10\) On an individual basis, the costs of incontinence supplies in OAB, estimated at $11 every week, can be significant. By 2020, the projected per capita cost of OAB is $1,970. Overall, OAB is estimated to cost $82.6 billion in 2020.

Management of OAB is multifaceted and should be individualized. Patients have to be educated regarding normal bladder function. They may have a goal of only voiding two times per day or being completely dry, but this may not be realistic. Getting to a normal voiding pattern (less than eight times daily) is the ultimate goal of treatment. Patients need to understand that OAB is not cured, it is managed. Although medication can start acting quickly, it may take several weeks for the patient to see changes in defensive behaviors such as frequent voiding.

The guidelines state clinicians should offer behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) as first-line therapy to all patients with OAB.\(^11\) The main type of behavioral modification is changing bladder function with bladder training. For someone with urgency as their primary problem, they can do a timed voiding regimen, such as visiting the bathroom every two hours. For someone with urgency and frequency but not incontinent, they can do delayed voiding and bladder contraction suppression strategies. Learning to tighten the correct muscles with Kegel exercises can suppress an involuntary bladder contraction which can be used to reduce the incidence of urge incontinence. A 25 percent reduction in fluid intake has been shown to reduce frequency and urgency. Similarly, reducing caffeine intake decreases voiding frequency. Dietary changes, such as avoiding spicy foods, citrus fruits and juices, tomato-based foods, and alcohol, may also help in the management of OAB. There are not strong data to support dietary changes, but sequential elimination of these problem foods may help some patients. An often forgotten behavioral intervention for OAB is weight loss. Generally, behavioral therapy is equivalent to medications in reducing incontinence episodes, improving voiding parameters, and enhancing quality of life.

Second-line therapy in managing OAB is pharmacologic therapy. Antimuscarinic and beta agonists are the two classes of therapy. Having two classes of therapy allows clinicians to individualize therapy.

In OAB, there can be overactivity of the detrusor muscle which leads to the urgency. People with frequency may have more neurologic activity going to the brain telling them they need to go. Antimuscarinic agents block the muscarinic (M3) receptor, which stabilizes the detrusor muscle. This increases bladder capacity, diminishes frequency of involuntary bladder contractions, and delays the initial urge to void by affecting the afferent pathways. Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride are all antimuscarinic agents and are all effective for treating OAB symptoms, but there are differences in metabolism and adverse effect profiles and thus tolerability (Exhibit 1). Also, there are now multiple different doses and dosage forms, including extended release oral, liquids, topical patches, topical gels, and bladder instillation which allow therapy individualization.

Finding an effective and tolerable antimuscarinic can require trying several different agents.

The antimuscarinic agents can have widespread effects throughout the body because they do not only affect the M3 receptors in the bladder. A preferable agent would have most effect on the M3 receptors. M1 receptors are in the brain and M2 receptors are in the heart and bladder. Exhibit 1 shows comparative selectivity of antimuscarinic agents.

There are not good comparative studies of the antimuscarinics; most are switch studies. The only head-to-head study was a comparison of fesoterodine 8 mg with tolterodine extended release 4 mg; as one would expect, the larger dose provided more efficacy in the reduction of UUI episodes.\(^12\) Given that they all have similar efficacy, the choice of an antimuscarinic should include the metabolism of a given agent related to a patient’s comorbidities, such as liver or kidney disease, ease of use, and dose flexibility. Tolterodine immediate release (IR) has reduced risk of dry mouth compared with oxybutynin IR. Extended-release oxybutynin and tolterodine both are preferable to IR formulations because of reduced risk of dry mouth. Solifenacin has better efficacy and less risk of dry mouth compared to tolterodine IR. Fesoterodine has superior efficacy compared to tolterodine ER but a higher risk of dry mouth.\(^13\)

Antimuscarinics may not be the best choice for elderly patients. Older patients experience more ad-
verse effects than younger patients because of age-related changes in their central cholinergic transmitter systems. Oxybutynin has been shown to adversely affect cognition in elderly patients, and they may not be aware of the resulting functional decline.\textsuperscript{14, 15} Older adults are also commonly on other prescribed medications with anticholinergic properties; the addition of an antimuscarinic agent

<table>
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<th>Generic Name</th>
<th>Dose</th>
<th>Hepatic/Renal Adjustment</th>
<th>M3 vs M1 Selectivity</th>
<th>M3 vs M2 Selectivity</th>
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<tr>
<td>Oxybutynin IR</td>
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<tr>
<td></td>
<td>10%: 1 gm sachet = 100 mg QD</td>
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<td></td>
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</tr>
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<td>1 - 2 mg BID</td>
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</tr>
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<td>Tolterodine ER</td>
<td>2 - 4 mg QD</td>
<td>Child-Pugh Class A-B or CrCl 10-30 mL/min: 2 mg daily; Not recommended: CrCl &lt; 10 mL/min or for Child-Pugh Class C</td>
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<td>Darifenasin</td>
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<td>7.5 mg daily for Child-Pugh Class B Not recommended for Child-Pugh Class C</td>
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<td>Solifenasin</td>
<td>5 - 10 mg QD</td>
<td>CrCl &lt; 30 mL/min: and Child-Pugh Class B: 5 mg daily; Not recommended: Child-Pugh Class C</td>
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<td>Fesoterodine</td>
<td>4 - 8 mg QD</td>
<td>CrCl &lt; 30 mL/min: 4 mg daily; Not recommended: Child-Pugh Class C</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
for OAB compounds their cumulative anticholinergic burden. The American Geriatrics Society states that antimuscarinics are potentially inappropriate medications and classes to avoid in older adults. 15

In general, the most bothersome adverse effects of antimuscarinic therapy are dry mouth and constipation. Clinicians should proactively manage these adverse effects. To treat constipation, patients can increase fluid intake, increase dietary fiber, and take an osmotic laxative. Many patients will fluid restrict without realizing the impact on their bowel habits and the bladder irritant effect of concentrated urine. If there is no improvement with these simple measures, clinicians should consider a gastrointestinal evaluation. Sipping cool water throughout the day, drinking milk to lubricate the oral mucosa, restricting caffeine and alcohol intake, chewing sugar-free gum to stimulate saliva flow, and utilizing saliva replacements can help dry mouth. The pearl with antimuscarinics is to start with a low dose and increase slowly. If patients get dry mouth from an initial high dose, they will not want to take the medication again. Only 18 percent of patients started on an antimuscarinic continue at six months. Also, nighttime dosing will decrease adverse effects, except tropism, which should not be given at bedtime.

Beta agonists are the other class of medications for OAB treatment. Mirabegron (Myrbetriq®) is a selective beta-3 adrenoceptor agonist. It activates beta-3 adrenoceptors on the detrusor muscle of the bladder to facilitate filling of the bladder and improved storage. Essentially, this is a bladder relaxant which does not affect detrusor muscle contractility. This reduces the risk of urinary retention. This agent is only available as a once a day extended-release tablet that cannot be crushed, which is a consideration if patients have difficulty swallowing. Unlike with the antimuscarinics, dry mouth and constipation are not major concerns with this agent, so it would be a good choice for the person who already has these issues. It does have several drug interactions and dosing adjustments need to be made for reduced kidney function. Overall, compared to antimuscarinics, mirabegron has a more favorable tolerability profile.16 In those greater than age 65, the efficacy of mirabegron is equal to antimuscarinics but with better tolerability.

Antimuscarinics have been the mainstay of OAB treatment, but persistence is often limited by insufficient efficacy and adverse effects. Mirabegron has a different mechanism of action and has been shown to significantly reduce micturition frequency and incontinence episode frequency compared to placebo with low incidence adverse effects. Combination with reduced doses of each agent may improve tolerability without compromising efficacy. Thus, an option to maximize therapy in those who are unable to tolerate higher doses of an individual agent is to use lower doses of mirabegron and an antimuscarinic. Two trials of combination therapy (mirabegron and solifenacin) found significantly reduced micturition frequency and reduced urgency episodes with the combination.17,18 Constipation is a little higher with combination pharmacotherapy, but other adverse effects were no worse than with monotherapy. In both trials, there was a significant improvement in efficacy without a significant increase in adverse effects with combination pharmacotherapy.

A patient’s quality of life is improved by OAB diagnosis and treatment.19,20 The key to successful OAB management is not always in the number of times a day urination occurs. Realistic treatment expectations with OAB treatment are a 90 percent reduction in UUI episodes and two to three fewer voids per day. Normal micturition is five to seven times per day. Dry rates (no UUI episodes) will vary with baseline severity—typically 50 to 64 percent. The rate is less with more severe UUI. Objective clinical improvement, treatment-related side effects, accessibility and convenience of treatment, education regarding the condition, and comorbidities all play a role in successful OAB management. Importantly, patient satisfaction with OAB therapy is associated with compliance with therapy.

Conclusion
OAB is a common, underdiagnosed condition which causes a major impact on quality of life. There are two classes of pharmacotherapy available to help patients. The future of treatment is likely the use of combination pharmacotherapy. The hope is that we can improve the balance between efficacy and tolerance to improve persistence, so individuals can continue to reap the benefits of treatment. Proper patient expectations of therapy and management of adverse effects are also key to improving persistence. Diagnosis and treatment of OAB has a positive impact on quality of life.

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References


PROSTATE CANCER IS A VERY COMMON condition. After initial definitive treatment, many men will develop recurrent or advanced cancer which will eventually become castration-resistant prostate cancer (CRPC).

For patients with metastatic prostate cancer on hormonal therapy, the median progression-free survival ranges from 12 to 30 months once treatment is initiated. Once the state of androgen independence occurs (castration-resistant prostate cancer, CRPC), historically the median overall survival was only eight to 16 months. That has increased somewhat with newer treatments.

Once metastatic (mCRPC), prostate cancer kills patients; it is the second leading cause of cancer deaths among American men.\textsuperscript{1,2} The goal is to figure out how to prolong survival in those with mCRPC because at this point it cannot be cured.

CRPC is defined by disease progression despite androgen deprivation therapy (ADT) and castrate levels of testosterone (\(< 20\text{ng/dL}\)).\textsuperscript{3} It presents as a spectrum of disease, ranging from rising prostate specific antigen (PSA) levels despite ADT without metastases or symptoms to mCRPC and significant debilitation from cancer symptoms.

CRPC does not necessarily imply hormonal resistance altogether. The tumor cells have adapted to a decreased hormonal milieu but still retain some sensitivity. There is a molecular basis underlying retained hormone sensitivity in CRPC. Amplification of the androgen receptor locus (AR) occurs in approximately 30 percent of CRPC tumors, but not in tumors prior to therapy. There is enhanced intracellular conversion of adrenal androgens to testosterone and dihydrotestosterone in tumor cells.\textsuperscript{4} The AR remains active in most patients with CRPC. Many groups including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and others recommend that ADT be continued in patients with CRPC and mCRPC.\textsuperscript{5-7}

In the past, chemotherapy was the first-line ther-
apy for mCRPC and is still used some. Docetaxel, a taxane-based chemotherapy, improves median overall survival (OS) by 1.9 to 2.4 months.\textsuperscript{8-9} Docetaxel causes significant adverse effects, including bone marrow suppression, hypersensitivity reactions, hepatic abnormalities, reversible cutaneous reactions, dyspnea, acute pulmonary edema, respiratory distress syndrome, and interstitial pneumonia. Cabazitaxel was the next evolution in chemotherapy for mCRPC. It is FDA approved for patients previously treated with docetaxel and does improve median OS by 2.4 months.\textsuperscript{10} Overall, chemotherapy is a $20,000 to $40,000 treatment for a median three-month increase in survival.

Sipuleucel-T (Provenge\textsuperscript{®}) was the first immunotherapy FDA approved for mCRPC. It is recommended as first-line treatment for asymptomatic or minimally symptomatic mCRPC, which is a very narrow window for appropriate treatment. A course of sipuleucel-T treatment consists of three basic steps. A patient’s white blood cells, primarily antigen-presenting cells (APCs), are extracted in a leukapheresis procedure. The blood product is incubated with a fusion protein (PA2024) consisting of two parts, the antigen prostatic acid phosphatase (PAP), which is present in 95 percent of prostate cancer cells, and the immune signaling granulocyte-macrophage colony stimulating factor (GM-CSF) that helps the APCs to mature. The activated blood product (APC8015) is returned to the infusion center and infused into the patient to cause an immune response against cancer cells carrying the PAP antigen. A complete sipuleucel-T treatment repeats three courses, with two weeks between successive courses. The cost is about $31,000 per infusion and $93,000 for a complete treatment. An acute infusion reaction is the most common adverse effect and was reported in 71.2 percent of clinical trial patients. Patients are premedicated with oral acetaminophen and an antihistamine to prevent the reaction. Sipuleucel-T provides a median of a 4.1-month OS benefit over placebo.\textsuperscript{11}

Addressing the underlying reason for castrate resistance including targeting androgen production and the androgen receptor are other treatment options in mCRPC. Abiraterone (Zytiga\textsuperscript{®}) and enzalutamide (Xtandi\textsuperscript{®}) target the androgen receptor in different ways and are FDA approved for treating CRPC. Abiraterone, an oral agent, is a CYP17 modulator that inhibits steroidogenesis. CYP17 is essential for biosynthesis of androgens and adrenal hormones and implicated in aberrant intratumoral androgen production. This agent provides more potent and durable androgen suppression than ketoconazole, another CYP17 inhibitor. It blocks two critical steps in testosterone biosynthesis – conversion of pregnenolone to 17 OH-pregnenolone and conversion of 17 OH-pregnenolone to dehydroepiandrosteredione. This agent is effective even in patients resistant to ketoconazole.

The FDA approved abiraterone in 2011 for patients with progression after docetaxel. In late 2012, the FDA expanded approval to treat men with mCRPC prior to receiving chemotherapy. The cost of this agent is approximately $18,000 for 12 weeks of therapy. It also provides a three to four month improvement in median OS.\textsuperscript{12}

Because of the adrenal metabolic pathways altered by this agent, it must be given with daily prednisone. Adrenal insufficiency can occur if daily steroid

\begin{table}[h]
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\begin{tabular}{|l|c|c|}
\hline
 & Denosumab & Zoledronic acid \\
 & N=1,026 & N=1,020 \\
\hline\hline
Median time to first on-study skeletal-related event & Not yet reached (P<.001 for non-inferiority; P=.10 for superiority) & 26.4 months \\
Skeletal-related events/patient time at risk & 0.45 events/patient-year (P=.004) & 0.58 events/patient-year \\
Acute-phase ("flu-like") reactions & 10.4% & 27.3% \\
Renal toxicity & 4.9% (P = .001) & 8.5% \\
Osteonecrosis of jaw & 2% (P = .39) & 1.4% \\
\hline
\end{tabular}
\caption{Comparison Denosumab vs Zoledronic Acid\textsuperscript{15}}
\end{table}
dosing is interrupted, or during times of infection or stress. Common adverse effects with abiraterone include fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, anemia, hypercholesterolemia, hyperglycemia, increased liver function tests, hyperphosphatemia, and hypokalemia.

AR overexpression plays a critical role in CRPC. Enzalutamide, also an oral agent, is a second-generation AR antagonist with no agonist activity in the setting of androgen receptor overexpression which occurs with the first-generation agent, bicalutamide (Casodex®). Enzalutamide has high affinity binding to the AR-ligand binding domain with inhibitory activity. It was FDA approved in 2012 for patients with mCRPC with prior docetaxel treatment. It is now approved as first-line therapy for individuals failing ADT. It is a better androgen blocker than the currently used agents because it acts through three different pathways within a cancer cell to block the effects of testosterone. This agent costs approximately $7,400 per month. Unlike with abiraterone, patients do not need to take concomitant prednisone.

Compared with placebo in a randomized, double-blind study in mCRPC patients previously treated with at least two chemotherapy agents, enzalutamide resulted in a 4.8-month difference in median OS. Median OS was 18.4 months in the enzalutamide group and 13.6 months in the placebo group. At the time of pre-specified interim analysis, enzalutamide use resulted in a 37 percent reduction in risk of death as compared with placebo. The OS benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region and type of disease progression at entry. Enzalutamide was also better than placebo for all the secondary endpoints, which included PSA level response rate, soft-tissue response rate, quality of life, time to PSA progression, radiographic progression-free survival, and time to the first skeletal-related event.

In a randomized, double-blind, placebo-controlled, multi-national trial with more than 1,700 chemotherapy-naïve mCRPC patients, enzalutamide treatment was associated with significant reduction in risk of death by 29 percent, significant reduction in risk of radiographic progression by 81 percent, complete or partial response in soft tissue disease on imaging in 59 percent compared to 5 percent with placebo, and importantly delayed median time to chemotherapy initiation by 17 months compared to placebo.14

Enzalutamide does have significant potential for serious drug-drug interactions. Strong CYP2C8 inhibitors need to be avoided and so do CYP3A4, CYP2C9 and CYP2C19 substrates with narrow therapeutic index. The reported adverse effects of this agent include asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, muscular weakness, dizziness, insomnia, hematuria, paresthesia, anxiety, increased blood pressure, and seizures.

Bone effects of prostate cancer treatment and the disease itself is a major concern. The most common site of metastases in prostate cancer is bone. ADT leads to bone loss which increases risk of fracture. Greater than 90 percent of patients with mCRPC develop bone metastases and decreased bone integrity. These individuals have significant risk of developing skeletal-related events (SREs) including fracture, bone pain, and spinal cord compression. Quality of life is significantly affected by these bone-related events.

In addition to vitamin D and calcium, the NCCN guidelines recommend specific therapy to preserve bone health and to prevent SREs in patients with bone metastases.5 Zoledronic acid (Zometa®), a bisphosphonate given intravenously every three to four weeks, is recommended in men with mCRPC and bone metastases to prevent SREs. Denosumab (Xgeva®) is a RANK ligand inhibitor given subcutaneously every four weeks. Both have been shown to decrease SREs. The NCCN guidelines recom-

<table>
<thead>
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<th>Abiraterone</th>
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<td>Data set 3</td>
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</table>
mend denosumab as an alternative to zoledronic acid for prevention of SREs.6

Zoledronic acid is not recommended if the patient’s baseline kidney function is less than 30ml/min. To reduce risk of osteonecrosis of the jaw, good oral hygiene, a baseline dental evaluation for high-risk patients, and avoidance of invasive dental surgery during bisphosphonate therapy is recommended.

Denosumab has some advantages in efficacy and reduction in some adverse events (Exhibit 1).15 In a cost-effectiveness analysis from a United States (U.S.) payer perspective, denosumab resulted in fewer estimated SREs (~0.241), better quality of life, and lower SRE-related costs (~$2,340) than zoledronic acid.16 Those benefits came at a higher drug-related cost ($10,181) and higher total costs ($31,968 vs $24,127).

Bone pain is a significant effect of mCRPC. Strontium-89 (SR-89) is a targeted option for treating pain related to bone metastases. It is close to calcium in the periodic table and is a beta-emitter that has a higher affinity for tumor containing bone than normal bone. The half-life of Strontium-89 in normal bone is considerably shorter than in tumor containing bone (14 versus 50 days). The most frequently observed toxicities are associated with bone marrow suppression of 11 to 65 percent in more than 50 percent of patients. Blood counts return to normal within eight weeks after treatment and rarely does severe toxicity occur when given to patients with normal hematological parameters.17 Compared with external beam radiotherapy, it reduces bone pain similarly.18

Radium-223 (Xofigo®) is another option for treating bone metastases in patients with no known visceral metastatic disease. Radium-223 is an alpha-particle-emitting radionuclide that mimics calcium and is incorporated in osteoblastic bone lesions. It delivers short range, high energy which minimizes myelotoxicity. This is the first bone-targeted therapy to show an effect on OS; Radium-223 increased OS by 3.6 months compared to placebo.19 Significant OS benefit was demonstrated in both a chemotherapy-naïve and a post-docetaxel group (3.6 months). It also extends median time to first SREs by 5.8 months. Neutropenia occurred in 4 percent of study subjects and thrombocytopenia in 8 percent. The most common non-hematologic adverse effects include diarrhea, nausea, vomiting, and constipation.

There are numerous agents for mCRPC which provide incremental increases in survival, but there are unanswered questions of how best to use the various therapies. Optimal sequencing of the approved agents, duration of use of each agent, how to combine agents to maximize survival and minimize toxicity, and which patients will benefit the most (or the least) are questions to be answered. Head-to-head trials and prospective data for the new therapies are not available. Preclinical data suggest that some agents may influence the efficacy of subsequent agents.

In deciding how to sequence the various agents, there are not a lot of data. Prior abiraterone therapy may adversely impact docetaxel activity, but further data are needed. A recent retrospective review of 58 patients did not observe any differences in clinical outcomes based on alternative sequencing of abiraterone and docetaxel in men with mCRPC.20 No prospective data are available but retrospective cohort data suggest that cabazitaxel retains significant activity when used in a third-line setting.21

There are no direct comparisons of first- versus second-line abiraterone; the existing data are extrapolated from pre- and post-docetaxel studies. Abiraterone appears to lead to higher rates of PSA decline and soft tissue responses when administered to chemotherapy naïve patients.22 In the third line, activity of abiraterone appears to be reduced after exposure to both enzalutamide and docetaxel. A variety of studies are ongoing evaluating combination therapy with abiraterone.

Limited data are available evaluating sequential administration of enzalutamide after abiraterone and docetaxel. Like abiraterone, enzalutamide appears to have higher activity in docetaxel-naïve patients. For third-line therapy after prior docetaxel and abiraterone, a retrospective cohort analysis of 35 subjects demonstrated that complete cross-resistance was not observed; 16 percent of nonresponders to abiraterone had PSA declines of greater than 50 percent on enzalutamide.23 A multicenter study in patients who did not tolerate or progress on docetaxel combined with abiraterone found that 46 percent treated with enzalutamide had a greater than 30 percent PSA decline, 21 percent had a greater than 50 percent decline, and 3 percent had a 90 percent decline.24

The current American Urological Association (AUA) guidelines state that individuals who are asymptomatic or minimally symptomatic with mCRPC and have good performance status without prior docetaxel chemotherapy can receive abiraterone/prednisone, enzalutamide, docetaxel, or sipuleucel-T.25 The guidelines note that there are no direct studies comparing the agents that can be used to inform optimal sequencing. It is preferable to give the least toxic agent first, but clinicians must also consider ease of administration and other factors.
As experience has been gained with new agents, they are being used more frequently for first line therapy. Docetaxel was used 100 percent of the time for first-line therapy in 2011 and declined to slightly more than 20 percent use in 2014. Abiraterone increased to 40 percent and enzalutamide increased to about 20 percent in 2014. Sipuleucel-T and cabazitaxel use stayed essentially the same from 2011 to 2014, with less than 10 percent usage in the first-line setting. Overall, there has been a shift in the U.S. from chemotherapy as first- and even second-line therapy.

**Conclusion**

Several new agents are approved for the management of mCRPC that have unique mechanisms of action and indications. Once androgen independence occurs, patients will ultimately require multiple agents over time. Currently, new therapies are used in patients with metastatic disease, but many questions remain about their optimal sequential use. A better understanding of the impact of prior therapy on the efficacy of subsequent therapies is needed. The cost of management of CRPC is not without significant economic consequences.

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**References**


CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) is characterized by chronic airflow limitation and a range of pathologic changes in the lung, significant extra-pulmonary effects, and important comorbidities. Features of this disease may include chronic bronchitis (cough and sputum production) and emphysema (destruction of gas exchanging surfaces of the lung). An estimated 30 million Americans have COPD, of which about half are undiagnosed. Importantly, this is a preventable disease; avoidance of major risk factors such as smoking and workplace pollution can go a long way toward reducing the numbers of people with COPD.

The clinical practice guidelines from the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society, the European Respiratory Society, the Global Initiative on Chronic Obstructive Lung Disease (GOLD), and information from the COPD Foundation help guide screening, diagnosis, and treatment of COPD. Spirometry is a definitive way to screen for airflow limitations. Spirometry should not be used to screen for airflow obstruction in individuals without respiratory symptoms but should be obtained to diagnose airflow obstruction in patients with respiratory symptoms. An issue in the United States (U.S.) is that most people diagnosed with COPD have never had spirometry. In those already diagnosed with COPD but without spirometry, spirometry should be done to identify the extent of disease.

Various tools are available to help screen for possible COPD. One of these that is being evaluated in primary care settings in a NIH sponsored study is a simple questionnaire (CAPTURE, Exhibit 1). Some of the screening tools in the past only identified older smokers, but nothing elaborate is needed...
to identify this group at risk for COPD. The old tools missed a lot of people with significant respiratory symptoms. The CAPTURE tool does not even ask age or smoking history and has been shown to work well in the settings studied so far.

Like many diseases, the care of COPD is trying to move to more individualized care. There are a few newer classification strategies in COPD that are helping move care into the area of personalized medicine. The traditional classification of COPD, which relied solely on the amount of lung dysfunction on spirometry, fails to account for the complexity and heterogeneity of the disease. The GOLD guidelines now recommend classifying patients based on spirometry results, the number of exacerbations per year, a modified Medical Research Council (mMRC) Dyspnea Scale score, and a COPD assessment test (CAT) score. Patients will fall into four basic categories that range from mild disease/few exacerbations to very poor lung function/frequent exacerbations/almost constant symptoms. Therapy is then chosen based on this classification.

Exhibit 2 illustrates another way to classify patients and is from the COPD Foundation. This approach takes into account several domains to gauge severity and target therapy. Comorbidities, assessment tools, body weight, and other factors can be used to gauge severity. COPD is one disease where having extra body weight is beneficial; those who are overweight tend to do better than those who are underweight. The COPD Foundation recommends therapy based on severity domains.

It has been challenging to understand disease progression in COPD. The problem in COPD is that significant disease progression has already occurred before patients actually develop symptoms and get diagnosed (Exhibit 3). There is not a biomarker of early disease, such as cholesterol levels for atherosclerotic heart disease. It has been thought that patients progress in a straight line through the categories of mild, moderate, and severe disease. This may be true, but some patients can identify the event that provoked a move from health to a state of moderate to severe disease.

Traditionally, COPD has been divided into emphysema and chronic bronchitis, but it does appear to have several different manifestations or phenotypes. There appears to be significant overlap between chronic bronchitis, emphysema, reversibility of airflow obstruction, and asthma. There are people who have abnormalities on CT scan but whose spirometry results do not indicate airflow obstructions.

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**Exhibit 1: An Emerging Tool (CAPTURE™)**

For each question place an X in the box with the answer that is best for you. There are no right or wrong answers, only answers that are right for you.

<table>
<thead>
<tr>
<th>Please answer each question</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you ever lived or worked in a place with dirty or polluted air, smoke, second-hand smoke, or dust?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Does your breathing change with seasons, weather or air quality?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Does your breathing make it difficult to do things such as carry heavy loads, shovel dirt or snow, jog, play tennis or swim?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Compared to others your age, do you tire easily?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. In the last 12 months, how many times did you miss work, school, or other activities due to a cold, bronchitis or pneumonia?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you answered “Yes” to 2 or more questions, talk with your doctor about your breathing and ask about a quick and easy breathing test called “peak expiratory flow (PED). You may breathe easier with treatment.
There are also those who have significant symptoms but whose spirometry results do not indicate issues with lung function. Emerging subgroups/phenotypes include patients with normal airflow but with emphysema on CT scan, impaired diffusion, severe symptoms or exacerbation-like events.

Lung function does naturally decline from adulthood with aging, but how fast it declines varies based on childhood and adult exposures. Early childhood events including exposure to smoking, indoor and outdoor pollution, poverty, and prenatal exposures can impact the development of COPD.6 Biomarkers to identify the point where lung function starts to decline and to better identify different phenotypes are needed. Researchers are studying potential biomarkers using computed tomography scans, perfusion scans, and diffusing capacity.7 At this time, spirometry remains the best means of routinely classifying abnormalities in patients with COPD. In the near future, it is hoped that other biomarkers will be developed.

Nonpharmacologic therapy is a very important aspect of managing COPD. This includes smoking cessation, patient education, oxygen therapy, pulmonary rehabilitation, and surgery. Lung volume reduction is one of the surgical therapies, but is not done very often in the U.S.

There are numerous different pharmacologic treatment options available for treating COPD. These include short-acting beta agonists (SABAs) for managing acute symptoms, long-acting beta agonists (LABAs) and antimuscarinics (LAMAs), combinations of LABAs/LAMAs, inhaled corticosteroids (ICSs), ICS/LABA combinations, and phosphodiesterase-4 inhibitors (PDE-4, theophylline, roflumilast). Roflumilast is a more selective, long-acting inhibitor of PDE-4 than theophylline, but it is significantly more expensive. It is indicated for those with moderate to severe disease and who are at significant risk for exacerbations. There is a degree of inflammation in some patients with COPD, especially in those who have asthma/COPD overlap. These patients will benefit from an ICS. ICSs reduce the risk of exacerbations, but slightly increase the risk of pneumonia.8 Some COPD patients on ICSs can be withdrawn from the therapy once stabilized without risk of worsening the disease.9 Mild disease may only require an as needed SABA, whereas those with moderate to severe disease may require combinations of several medication classes. The reader should consult the various guidelines for recommended therapy at each classification of disease.

Other pharmacologic treatments that help reduce exacerbations include vaccinations, management of comorbidities, and antibiotics. Everyone with COPD should receive a vaccination for influenza, pneumonia, and pertussis. Their comorbid conditions should be optimally managed to maintain as

---

Exhibit 2: The Future Classification of COPD?

Less Severe | More Severe
---|---
Lung Function | Target Therapy
Symptoms | 
Exacerbation |
Polymorbidity |
SGRQ/CAT |
Exercise Capacity |
Body Mass Index/Other Factors |

SGRQ = Saint George’s respiratory questionnaire
CAT = COPD assessment test

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good of health as possible. Antibiotics may have a role in those with high risk for exacerbations where they may be functioning as anti-inflammatories. The macrolides have been studied the most and are supported by the data. Azithromycin therapy, the typical choice, has been shown to delay time to an exacerbation.

All the COPD therapies have potential benefits and risks. The challenge is to maximize benefits while balancing the risk. Management of COPD is trying to move to personalized therapy that is not only driven by clinical phenotype (symptoms) but is also driven by endotype (biomarker). An example is the presence of alpha-1 antitrypsin deficiency. A patient with this biomarker is given replacement infusions of alpha-1 antitrypsin.

All COPD patients should have an action plan, similar to asthma action plans. Education can be used to improve adherence with nonpharmacologic and pharmacologic therapy. Patients especially need instruction on the various inhalers that are prescribed. Patients with normal lung function can easily use inhalers. Those with poor lung function and hand-eye coordination difficulties will have great difficulties with inhaler use.

Medication usage factors in nonadherence include difficulties associated with inhalers, complicated regimens, fears about/or actual side effects, cost, and distance to pharmacies. Various nonmedication factors are also involved in nonadherence. This includes misunderstanding or lack of information, fears about side effects, inappropriate expectations, underestimation of severity, attitudes toward ill health, cultural factors, and poor communication on the part of both the patient and clinicians.

**Conclusion**

COPD is a preventable and treatable disease for which treatments continue to evolve. Management of COPD is trying to move to personalized therapy that is not only driven by clinical phenotype (symptoms) but is also driven by endotype (biomarker). The future may bring better phenotypic characterization and more individualized therapies.

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**References**


Chemotherapy-Induced Nausea and Vomiting (CINV): Perceptions, Mechanisms, and Treatment Guidelines

Charles Loprinzi, MD

Summary
Chemotherapy-induced nausea and vomiting (CINV) is best prevented rather than waiting for it to occur. The understanding of the underlying pathophysiology of this process has led to effective medication combinations. There are numerous options for preventing both acute and delayed CINV. Evidence-based guidelines are available to guide therapy selection.

Key Points
• Acute, delayed, and anticipatory are types of CINV.
• Prevention is better than treatment.
• Therapy is guided by the emesis potential of the chemotherapy regimen.
• The most effective combination for preventing acute CINV is serotonin receptor antagonists and dexamethasone.
• Guidelines recommend agents to use which provide both acute and delayed coverage.

CHEMOTHERAPY-INDUCED NAUSEA AND vomiting (CINV) is treated better today than in the past, but it can still be a major issue for patients. CINV may be classified as acute (beginning within the first 24 hours after chemotherapy), delayed (beginning more than 24 hours after chemotherapy), or anticipatory (beginning before acute chemotherapy-related symptoms would be expected to occur). Some data suggest the delayed phase may begin as early as 16 hours after chemotherapy administration. An example of anticipatory CINV would be a patient throwing up in the parking lot before even entering the chemotherapy infusion center. Preventing CINV from the first administration of chemotherapy will help prevent anticipatory CINV.

Patient- and treatment-related risk factors exist for developing chemotherapy-induced nausea and vomiting. Patient-related risk factors include younger age, female gender, no prior history of alcohol use, and history of motion sickness. Treatment-related risk factors include high emetogenicity (compared with moderate or low emetogenicity) of the chemotherapy agent and high drug dose. Chemotherapy can be divided into emetic risk groups, ranging from high, where 90 percent or more of patients given this agent will have CINV, to minimal, where less than 10 percent of patients are at risk. This classification system serves as a framework for the development of antiemetic treatment guidelines.

Nausea and vomiting used to be two of the most concerning adverse effects of chemotherapy. As antiemetic regimens have improved, vomiting is much less of a concern, but nausea still impacts people. Unfortunately, even in the era of modern antiemetic therapy, health care providers can underestimates the impact of CINV on patients. In an international prospective observational study of 298 patients, 97 percent of patients received a serotonin (5-HT3) receptor antagonist and 78 percent received a corticosteroid prior to receipt of moderately
or highly emetogenic chemotherapy (78% received moderately emetogenic regimens). Physicians and nurses overestimated the efficacy of antiemetic treatment for the majority of patients. The greatest discrepancy between predicted and actual nausea and emesis occurred for the delayed period, with physicians and nurses underestimating the incidence of delayed CINV by nearly 30 percent. Even with treatment with antiemetics, 35 percent of patients experienced acute nausea and over 50 percent experienced delayed nausea.

CINV appears to occur via two different mechanisms—one is located in the central nervous system (central) and the other is mediated in the GI tract (peripheral). The central mechanism is hypothesized to occur by activation of the chemotherapy trigger zone (CTZ) by a chemotherapeutic agent. The CTZ is found within the area postrema of the brain, which lacks a blood-brain barrier and can be accessed through either the blood or cerebrospinal fluid. Once activated, the CTZ releases multiple neurotransmitters, which then activate the brainstem vomiting center. The peripheral mechanism is postulated to occur by a chemotherapeutic agent causing local GI irritation and damage to the GI mucosa, which results in the release of neurotransmitters. This then activates receptors in the GI tract, which are mediated by afferent fibers of the vagus nerve. The activated vagal afferent fibers send signals to the brainstem vomiting centers. In both instances, the neurotransmitters may act independently or in combination to induce vomiting. Some chemotherapeutic agents activate both the central and peripheral mechanisms.

Exhibit 1 illustrates the evolution of antiemetic therapy from the use of phenothiazines in the 1960s to the development of neurokinin-1 (NK1) receptor antagonists in the early 2000s. This evolution reflects advances in understanding the neuropharmacology of emesis. In the early 1960s, phenothiazines became the first class of agents demonstrated to reduce emesis associated with fluorouracil by targeting the neurotransmitter dopamine and the D2 receptor. During the late 1970s, the introduction of cisplatin provided stimulus for further antiemetic research because the inevitable side effect of nausea and vomiting threatened the use of this effective agent. Beginning in the 1980s, high-dose metoclopramide provided a new antiemetic option. High-dose metoclopramide is not used because better antiemetics with fewer adverse effects are now available. It is used in lower doses to treat breakthrough CINV. The first 5-HT3 receptor antagonist launched in 1991 and continued research led to its combined use with dexamethasone for improved results. This regimen became the standard of care. The extensive research regarding 5-HT3 receptor antagonists also clarified the existence and persis-
tence of delayed nausea and vomiting following che-
motherapy and helped fuel development of agents
active on other neurotransmitters and receptor sys-
tems, such as the NK1 receptors.

Because multiple neurotransmitters are thought
to be involved in CINV, antiemetic regimens can
be designed to target more than one neurotransmit-
ter. The antiemetic arsenal includes 5-HT3 receptor
antagonists, corticosteroids (dexamethasone), NK1
receptor antagonists, dopamine receptor antagonists
(prochlorperazine, metoclopramide), cannabinoids
dronabinol), and multiple receptor antagonists
(olanzapine). Benzodiazepines such as lorazepam
do not have antiemetic properties but are used to
decrease anxiety related to CINV, particularly antici-
patorny CINV.

The impact of blocking serotonin receptors in
preventing CINV was first recognized with high-
dose metoclopramide. The introduction of more
specific 5-HT3 antagonists offered an improved
treatment option. Four 5-HT3 receptor antagonists
are approved for use in the United States for che-
motherapy-induced emesis: palonosetron (Aloxi®),
donsetron (Zofran®), dolasetron (Anzemet®), and
granisetron (Kytril®). Clinical studies have shown
that a regimen containing a 5-HT3 receptor antago-
nist is highly effective in preventing acute vomit-
ing, but demonstrates variable efficacy for delayed
events. Based on the vast accumulated literature to
date, the primary mechanism of action for 5-HT3
receptor antagonists is thought to be blockade of
5-HT3 receptor activation mediated by serotonin
release in the gut.11,12

The 5-HT3 agents are similar in efficacy with
the exception of palonosetron, which is given in-
travenously and appears to have improved efficacy
for delayed CINV. The extended plasma half-life of
palonosetron, combined with its high binding af-
finity for the serotonin receptor, may contribute to
its prolonged effect. The first studies with palono-
setron did not include concomitant dexamethasone.
Because of this, palonosetron did not appear to be
more effective than the other 5-HT3s, so it was
given to each other so one can be picked based on cost.
Fosaprepitant probably should be avoided when che-

Evidence of the efficacy of dexamethasone in pro-
tecting against acute and delayed nausea and vomit-
ing in patients who received highly or moderately
emetogenic chemotherapy. A meta-analysis found
that dexamethasone was superior to placebo or to no
treatment for complete protection from acute and
delayed emesis and nausea.14 One in six patients
fected with dexamethasone avoided emesis com-
pletely.15 New studies have shown that dexametha-
sone can be discontinued after the first day of anti-
emetic therapy if the patient had no symptoms on
day one of chemotherapy with moderately emeto-
genic or an adriamycin/cyclophosphamide (highly
emetogenic) regimen when palonosetron and an
NK1 antagonist are given on day one.13,16

The NK1 pathway relays noxious sensory infor-
mation to the brain (i.e., modulates nociception).
There is a high density of substance P/NK1 recep-
tors located in brain regions implicated in the emetic
reflex; thus, the primary mechanism of NK1 recep-
tor blockade action appears to be central. The avail-
able NK1 antagonists include aprepitant (Emend®,
oral), fosaprepitant (Emend®, intravenous), netupi-
tant (Akynzeo® - oral combination with palono-
setron) and rolapitant (oral). Because of long half-
lives, all but aprepitant are only given on day one of
chemotherapy administration. Aprepitant is labeled
to be given on days one through three after che-
motherapy. These agents are effective for both acute
and delayed events.17,18 They reduce acute CINV
rates by about 10 percent and about 20 percent for
delayed. The combination of a 5-HT3 receptor an-
tagonist plus dexamethasone is the cornerstone of
therapy, and aprepitant adds to symptom control
in the acute and delayed phases after highly emetic
chemotherapy.

Fosaprepitant is an intravenous form of aprepi-
tant that can be given as a single dose which pro-
duces equivalent results to a three-day oral regimen
of aprepitant.18 The only differences between these
two regimens are the possible adverse effects of the
intravenous injection and possibly a lower cost with
the injectable form. Phlebitis can occur in addition
to pain on infusion.19 Two studies of phlebitis found
much higher rates with fosaprepitant given via pe-
ipheral intravenous access when highly emetic che-
motherapy was also given via the same route.19,20

Steroids also have an antiemetic effect. A meta-
alysis was performed to identify randomized

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motherapy is given peripherally.

Olanzapine is a thienobenzodiazepine antipsy-
chotic which interacts with many different recep-
tors in the brain, which is not necessarily ideal. It
increases appetite (like megestrol acetate), decreases
nausea and vomiting, and decreases anxiety. The
potential for this agent is how inexpensive it is. It
has been studied against aprepitant and fosaprepi-
tant in several trials.21-23 The data from these trials
support that olanzapine is as good as apreptiant for
preventing vomiting, if not a little better, and bet-
ter than apreptiant for preventing nausea at a much
lower cost. It has also been studied against placebo
and is better than placebo for no nausea (17% better
for acute and delayed) and complete response (21.1%
acute and 14.5% delayed). It does increase drowsi-
ness, which can be significant in some patients.

In controlling emesis, the strategy is prevention
rather than treatment. Thus, the goal is to prevent
CINV from occurring if at all possible. Evidence-
based guidelines are available to guide therapy.4,14,24, 25
Each guideline provides recommended regimens for
each category of emetogenic potential. The standard
regimen for highly emetogenic chemotherapy is a
combination of 5-HT3 antagonists, NK1 antago-
nists, and dexamethasone. The first two agents are
only given on day one, unless apreptiant is used, and
the dexamethasone is given for additional days. The
NCCN guidelines do suggest olanzapine as an op-
tion instead of a NK1 antagonist.4 The recommend-
ed regimen when moderately emetogenic chemo-
therapy is given is palonosetron and dexamethasone.
If a NK1 antagonist is used to prevent CINV with
moderately emetogenic therapy, any 5–HT3 can be
used. Low emetogenic chemotherapy only requires
a single dose of dexamethasone before therapy. No
routine antiemetic before or after chemotherapy is
recommended if a minimally emetogenic chemo-
therapy regimen is given.

Typically, institutions will use the available guide-
lines to develop their own specific guidelines, which
is what the Mayo Clinic does. They grade all their
chemotherapy regimens based on emetogenic poten-
tial and have recommended regimens for each
regimen. When chemotherapy is ordered, the ele-
tronic medical record automatically adds the recom-
manded antiemetic regimen which can be modified
by the oncologist. A study found that institutions
follow the recommended antiemetic guidelines 93
to 95 percent of the time.26 A prior adverse reaction
or other patient factors may lead to deviations from
the recommended antiemetic regimens.

Nausea or vomiting that occurs despite preventive
therapy is called breakthrough CINV. In these cases,
metoclopramide, olanzapine, megestrol, or another
antiemetic that was not used in the prevention regi-
nons can be used.

Conclusion
Preventing CINV from the very beginning of che-
motherapy treatment is key to success. Preventive
regimens are selected based on the emetogenic poten-
tial of the chemotherapy being given and patient-
related factors. The available evidence-based guide-
lines should be used to select therapy.

Charles Loprinzi, MD, is the Regis Professor of Breast Cancer Research
at the Mayo Clinic College of Medicine.

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LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C) reduction with statin therapy has been shown in numerous trials to be beneficial. Overall, the landmark statin trials have shown that the greater the risk of developing cardiovascular disease, the greater the benefit of lipid lowering with statins. Also, the lower that the LDL-C is achieved with statins, the greater the benefit in terms of risk reduction. Exhibit 1 illustrates some of the benefits of LDL-C lowering with statin therapy based on a meta-analysis of 14 of the large statin clinical trials. All cardiovascular events, revascularization procedures, stroke, and any vascular event are reduced by statin therapy.

The most evidence of cardiovascular benefits exists for statins, and they should be the first medication of choice for lipid lowering in patients with dyslipidemia. In the past, we have treated to an LDL-C goal, which is what the clinical trials did. There have been concerns about whether LDL-C could be lowered too much, but no adverse effects of very low LDL-C have been proven. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that an LDL-C of 40 mg/dl is an acceptable level without harm, but not everyone needs to have their LDL-C lowered to this level. The recommendations for lipid lowering have changed over time. As more clinical trial experience has been gained, LDL-C goals for high-risk patients have become more intensive over time. The original Adult Treatment Panel (ATP) guide-
lines recommended an LDL less than 130 mg/dl which was reduced eventually to less than 100 mg/dl and less than 70 for those with high risk in the 2006 ACC/AHA guidelines.4,5 The approach to lipid lowering radically changed with the publication of the updated ACC/AHA guidelines in 2013.3 The updated guidelines used a new perspective on LDL-C and/or non-high-density lipoprotein (HDL) goals. They stated that there is no randomized controlled evidence to support continued use of specific LDL-C and/or non-HDL-C treatment targets and that the appropriate intensity of statin therapy should be used to reduce atherosclerotic cardiovascular disease (ASCVD) risk in those most likely to benefit. The studies were never designed to achieve a particular LDL-C goal. Furthermore, the guidelines stated that non-statin therapies, whether used alone or in addition to statins, do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD. Exhibit 2 outlines the recommendations from the guidelines for each lipid typically measured. Therapeutic lifestyle changes (TLC) are still an integral part of therapy and should be the background for every patient who is started on a statin.

LDL-C reduction remains fundamental to all the major cholesterol treatment guidelines, but there is controversy because of the different recommendations among guidelines. For example, for patients with clinical ASCVD, the ACC/AHA and the American Diabetes Association recommend a percentage reduction in LDL-C, whereas the National Lipid Association, American Association of Clinical Endocrinologists, International Atherosclerosis Society and the European Society of Cardiology/European Atherosclerosis Society still recommend a goal LDL-C of less than 70 mg/dl.3, 6-11 Clinical ASCVD is defined as coronary heart disease (CHD), acute coronary syndrome, history of myocardial infarction (MI), stable or unstable angina (UA), coronary or other arterial revascularization, stroke or transient ischemic attack, or peripheral arterial disease.

Another controversy beyond LDL goals is what to do about treating those outside the age groups studied in the trials. There are no trials in the under age 40 population with diabetes, but the ADA guidelines recommend, based on expert opinion, that moderate to high-intensity dose statins should be used in those with ASCVD risk factors (LDL cholesterol $\geq 100$ mg/dL, high blood pressure, smoking, overweight or obesity, and family history of premature ASCVD) and diabetes. There is also not significant evidence in those older than 75. This age group has more problems tolerating high-intensity statins. The ACC/AHA guidelines recommend treatment based on risk factors in this age group.

In the guidelines, statins are recommended as either moderate or high intensity. High-intensity statins reduce LDL-C by 50 percent or more and include atorvastatin 40 to 80 mg daily and rosuvastatin 20 to 40 mg daily. Moderate intensity statins, which lower LDL-C by 30 to 50 percent include atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin 20 to 40 mg, pravastatin 40 to 80 mg, lovastatin 40 mg, fluvastatin extended release 80 mg, and pitavastatin 2 to 4 mg.

The National Lipid Association guidelines offer an alternative goal-directed strategy focusing on non-HDL-C as the primary target.9 The reality is, even if goals are recommended, 72 percent of those treated with lipid-lowering agents do not achieve their goal.12 For many years, combination therapy of statins and other lipid-lowering agents have been the

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**Exhibit 1: Meta-Analysis of 90,056 Subjects in 14 Randomized Clinical Trials of Statins**

For every 39 mg/dL (1 mmol/L) absolute reduction in LDL with Statin Rx

- 23% reduction in major cardiac events
- 20% reduction in CHD mortality
- 22% reduction in ischemic strokes
- Benefit entirely in proportion to LDL reduction
- No influence of baseline LDL on level of benefit
- No effect of sex, age, or other risk factors on benefit
- Similar relative risk reduction in all subgroups
- No increase in non-cardiovascular mortality
Exhibit 2: 2013 ACC/AHA Expert Panel

<table>
<thead>
<tr>
<th>TLC</th>
<th>Still an Integral part of CHD risk management</th>
</tr>
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<tbody>
<tr>
<td>LDL-C</td>
<td>No longer a primary target of lipid-modifying therapy</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>No longer a secondary target of therapy in patients with hypertriglyceridemia (≥ 200 mg/dL)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>No treatment goals are identified for HDL-C</td>
</tr>
<tr>
<td>- Low HDL-C (&lt;40 mg/dL) as positive CHD risk factor</td>
<td></td>
</tr>
<tr>
<td>- High HDL-C (≥60 mg/dL) as negative CHD risk factor</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>No treatment goals are identified for TG</td>
</tr>
<tr>
<td>- Treat if levels &gt;500 mg/dL where risk of pancreatitis is still high</td>
<td></td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology  
AHA = American Heart Association  
TLC = therapeutic lifestyle change  
LDL-C = low density lipoprotein cholesterol  
HDL-C = high density lipoprotein cholesterol  
TG = triglycerides  
CHD = coronary heart disease

norm. Monotherapy trials do exist for bile acid sequestrants (colesevelam cholestyramine), fibrates, and niacin showing benefit for particular instances. Unfortunately, there is no significant evidence supporting the addition of niacin, fibrates, fish oil, or bile acid sequestrants to statins. Even when the lipid fractions are improved by the addition, there is not an additional reduction in ASCVD. The ADA guidelines state that combination therapy with statins and a fibrate does not improve ASCVD outcomes and is generally not recommended. They do suggest considering therapy with statin and fenofibrate for men with both triglycerides ≥204 mg/dL (2.3 mmol/L) and HDL ≤34 mg/dL (0.9 mmol/L), but that is based on a retrospective analysis. Further, combination therapy with statin and niacin has not demonstrated additional cardiovascular (CV) benefit over statins alone, may raise risk of stroke, and is not generally recommended. The FDA recently came out with a forceful statement about combination therapy stating that scientific evidence no longer supports that a drug-induced reduction in triglycerides or an increase in HDL-C in statin–treated patients results in reduction in CV risk and that niacin and fibrates should not be combined with statins.

There is now a trial showing benefit of adding ezetimibe to a statin in patients who have had acute coronary syndrome (ACS) and who have an LDL-C of 50 to 125 mg/dL (or 50-100 mg/dL if prior lipid-lowering medication). Over seven years, there was about a 2 percent reduction in CV events with the combination compared with a statin alone. This was a number needed to treat of 50 to prevent one event. The trial only compared simvastatin to simvastatin/ezetimibe. Atorvastatin 80 mg may be equivalent to 10 mg of ezetimibe and 40 mg of simvastatin, but this has not been studied in any trials. High-sensitivity C-reactive protein (Hs-CRP) was 0.5 lower with combination Rx. There was no increase in adverse effect rates in those who achieved very low LDL-C values (less than 30 mg/dL) in this study. There was no difference in safety endpoints for cancer, myopathy, and liver side effects between statin–alone and statin/ezetimibe.

A trial is also underway with a prescription eicosapentaenoic acid (EPA) only fish oil product (Vascepa®) and a statin. REDUCE-IT is a global Phase III, randomized, multicenter, double-blind, placebo-controlled study designed to evaluate whether treatment with EPA reduces cardiovascular events in patients who, despite stabilized statin therapy, have elevated triglyceride levels and other cardiovascular risk factors. Publication of this study is anticipated in 2018.

Overall, the addition of nonstatin cholesterol-lowering drug(s) may be considered if the patient cannot tolerate higher doses of statins and the ASCVD risk–reduction benefits outweigh the potential for adverse effects. Preference should be given to ezetimibe, which has trial support. The bile acid sequestrants have the benefit of reducing A1C, so selecting one of these may be a consideration in those with diabetes.
The four adult groups who benefit the most from statin therapy include those with clinical ASCVD, those with an LDL-C \( \geq 190 \) mg/dL, those ages 40 to 75 with diabetes and LDL-C 70-189 mg/dL, and those ages 40 to 70 without diabetes but have a greater than or equal to 7.5 percent 10-year estimated risk (Exhibit 3). The group that only has the greater than or equal to 7.5 percent 10-year estimated risk requires risk discussion between the clinician and patient before statin initiation. Ten-year ASCVD risk for nonfatal or fatal MI; and nonfatal or fatal stroke can be calculated at [http://my.americanheart.org/cvriskcalculator](http://my.americanheart.org/cvriskcalculator) or by using a phone application that is available for free (AHA CV Risk Calculator). Other than those four groups, therapy should be individualized based on ASCVD risk. Patients should be monitored with a lipid panel and risk assessment every five years.

Coronary artery calcium (CAC) scores can be used in those where the decision to start statin therapy is not clear. On the basis of current guidelines from both the National Cholesterol Education Program and the ACC/AHA, patients with CAC scores less than the 75th percentile and less than 300 are to be treated with low- to moderate-dose statins. Those with CAC scores greater than the 75th percentile or \( \geq 300 \) are to be treated with high-dose statins. Lifestyle modification is indicated for those with CAC, unless a compelling indication for statins already exists. In one study, a CAC of zero resulted in the largest, most accurate downward risk reclassification of tests done.

There is significant inter-individual variation in response to statins. Subjects, participating in clinical trials of statin therapy, display impressive average reductions in LDL-C. An individual patient’s response to statin therapy, however, can be very variable given diet and medication adherence variability. It is important to check the LDL-C at some point to make sure the chosen statin is working. The guidelines recommend an initial fasting lipid panel, a second panel four to 12 weeks later to determine adherence to therapy, and then measurement every three to 12 months as clinically indicated.

An estimated 5 to 20 percent of people cannot tolerate statin treatment because of adverse effects. Statin intolerance is most commonly muscle pain, aching, and weakness which commonly...
Exhibit 4: Treatment Options for HoFH and HeFH

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Major Effect</th>
<th>LDL-Lowering Response HoFH</th>
<th>LDL-Lowering Response HeFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-fat Diet</td>
<td>↑ LDLR activity</td>
<td>&lt; 10%</td>
<td>10 - 25%</td>
</tr>
<tr>
<td>Statins</td>
<td>↑ LDLR activity</td>
<td>&lt; 10%</td>
<td>&gt; 25%</td>
</tr>
<tr>
<td>Resins</td>
<td>↑ LDLR activity</td>
<td>&lt; 10%</td>
<td>10 - 25%</td>
</tr>
<tr>
<td>Ezitimibe</td>
<td>↓ chol absorp + ↑ LDLRa</td>
<td>&lt; 10%</td>
<td>10 - 25%</td>
</tr>
<tr>
<td>Stanol Esters</td>
<td>↓ chol absorp + ↑ LDLRa</td>
<td>&lt; 10%</td>
<td>10 - 25%</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>↓ VLDL synthesis</td>
<td>&lt; 10%</td>
<td>25%</td>
</tr>
<tr>
<td>LDL apheresis</td>
<td>Removes LDL-C</td>
<td>&lt; 25%</td>
<td>25%</td>
</tr>
</tbody>
</table>

HoFH = homozygous familial hypercholesterolemia  
HeFH = heterozygous familial hypercholesterolemia  
LDLR = LDL receptor  
LDLRa = LDL receptor activity  
chol = cholesterol  
VLDL = very low density lipoprotein

leads to discontinuation. Intolerance may be the result of perception or expectation. Most statin-intolerant patients can be successfully re-challenged with the same or another statin. A small subset of patients are truly statin intolerant, but the exact number is unclear.

Familial hypercholesterolemia (FH), the most common inherited disorder, is characterized by strikingly high LDL-C, resulting from mutations in genes involved in LDL metabolism. In the United States (U.S.), FH is a clinical diagnosis, whereas in Europe genetic studies are done for identification. Clinical manifestations include severe hypercholesterolemia due to accumulation of plasma LDL that is often accompanied by cholesterol deposition in tendons and skin (xanthomas) and in the eyes (corneal arcus). Many FH patients have a family history of early CV disease. Heterozygous FH (HeFH) is found in 1:250-300 patients and is characterized by LDL-C greater than or equal to 190 mg/dL. Homozygous FH (HoFH) is a LDL-C greater than or equal to 500 mg/dL. Untreated, these patients develop CV disease on average by the age of 20.

FH is due to genetic mutations that result in decreased clearance of LDL particles from the plasma. There is usually a loss of function (LOF) mutation in the LDL receptor gene (FH1). Other mutations include LOF in apolipoprotein B (ApoB) gene (FH2) and gain of function mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene (FH3).

Exhibit 4 shows the treatment options for FH before the approval of three new classes of lipid-lowering agents. Apheresis was the only option that provided significant LDL-C reductions. Unfortunately, this procedure is not easily available in many areas of the U.S.

The new classes of lipid-lowering agents either block lipoprotein assembly or increase lipoprotein clearance. Those that block assembly include mipomersen (Kynamro®), an ApoB antisense agent, and lomitapide (Juxtapid®), a microsomal triglyceride transfer protein (MTP) inhibitor. PCSK9 inhibitors increase clearance. Two of these have been FDA approved and at least eight more are in development.

Mipomersen, an injectable given weekly, is FDA approved for use in homozygous FH. It produces a 25 to 37 percent reduction in LDL-C when added to statins with or without other lipid-lowering therapy. Adverse effects typically include gastrointestinal issues and transaminase elevations. Lomitapide, a daily, oral medication, produces a 40 to 50 percent LDL-C reduction in addition to standard therapy. The side effects are more common and severe with lomitapide. Both agents cause fatty liver and have black box warnings related to liver toxicity and are only available under a Risk Evaluation & Mitigation Strategies (REMS) program. These agents should only be prescribed by lipid specialists and endocrinologists.

PCSK9 is a protein secreted by the liver which acts as a chaperone for the LDL receptor targeting the receptor for degradation. Patients with hyper-active PCSK9 (gain of function mutations) have
fewer LDL receptors and higher circulating LDL-C levels, leading to premature atherosclerosis. Loss of function mutations are actually associated with low LDL-C. The PCSK9 inhibitors, monoclonal antibodies against the PCSK9 protein, lead to re-circulation and expression of a greater numbers of LDL receptors, thereby lowering LDL-C levels. These agents reduce the total atherogenic lipoprotein burden by reducing serum LDL-C, very low-density lipoprotein cholesterol (VLDL-C), non-HDL-C, apo B, Lp(a), and remnant lipoproteins.

The PCSK9 inhibitors are FDA indicated as an adjunct to diet and maximally tolerated statin therapy for those with clinical ASCVD who need additional LDL-C lowering. They have been studied as monotherapy, as add-on to low- or high-dose statins with and without ezetimibe, and in statin intolerance, HeFH, and most variants of HoFH. The studies have been large and have run for up to two years in duration. Alirocumab (Praluent®) and evolocumab (Repatha®) are the two approved agents and are injected subcutaneously every two weeks. Both are expensive, with wholesale costs of approximately $14,000 per year. These agents reduce LDL-C by 40 to 70 percent and triglycerides and lipoprotein little a [Lp(a)] by 30 percent when combined with a statin and alone. No dose-limiting toxicities have been seen; injection site reactions are the most common adverse effects. To date, over 10,000 patients have received these medications in clinical trials for up to one year.

The question, of course, is do these agents improve clinical outcomes beyond the effects of statins. In a retrospective analysis, evolocumab reduced clinical events by 50 percent and alirocumab reduced events by 48 percent. Randomized, double-blind studies designed to determine outcomes have not yet been published. Early post-hoc data on CVD events in ongoing outcomes studies are encouraging, but clinicians and managed care await the results of large outcomes trials to better know the place of these agents in therapy.

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References


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