VALUE-BASED INSURANCE DESIGN

Spend a Little More On Selected Patients For Payoff Down the Line

Plans and payers are looking at a new insurance design that puts quality first. It might also save money.

By Martin Sipkoff
Contributing Editor

Health care costs are astronomical and premiums are rising. As a result, a basic question about private health plans is being asked by the public, payers, the federal government, and the media: What value do health plans offer?

In this country, health care is an industry. Its product is service, assessed in terms of value. Unfortunately, unlike other service industries, value in health care is difficult to define. Saving lives and relieving pain are of great value to consumers, but the industrial value of health care service in a free market lies in a somewhat vague area, in a seemingly endless battle between cost and performance.

As our society struggles with reforming health care, finding a functional definition of value is very important. And converting that definition to action may well be a matter of industry survival.

Quality, cost

Asked for his definition of health care value, Denis Cortese, MD, president and CEO of the Mayo Clinic, sounds exasperated. "It should be clear at this point to nearly everyone, but I suppose it's not," says Cortese. "Value is quality relative to cost. Right now plans do not pay for value. They pay for process. That's a reason value is hard to agree on, hard for some people to define. But the purpose of process should be to improve value, requiring a joint effort between insurers, providers, payers, and patients. It requires new models of care. Primarily it requires knowing outcomes, and acting on that knowledge."

A form of benefit design that is value oriented, endorsed by Cortese and others, is growing in popularity, especially among employers. Named value-based insurance design (VBID), it promotes the use of services when the clinical benefits exceed the cost and discourages the use of services when the benefits do not justify the cost. There are many proponents, including several payers and some health plan executives. The classic VBID example is lowering — even eliminating — the cost of treatment-related medications for diabetes patients. In fact, a recent study at the University of Michigan did find that lowering copayments does increase compliance.

The basic idea is to organize care delivery around medical conditions instead of uncoordinated, sequential visits to multiple providers, physicians, departments, and specialties — the existing and prevalent system that VBID advocates say works against value and increases costs. In the current system, everyone is required to pay the same out-of-pocket amount for health care services. But value depends on patient characteristics, so there is enormous potential for underuse and overuse of resources.

Acceptance of that idea relies on a practical definition of value. Cortese has such a definition: value = (outcomes + safety + service)/(cost + time).

That is a practical equation because:

- Cost and time are easily measurable. "The denominator is cost over a period," explains Cortese. "You determine the value of a service over time."
- Outcomes are generally measurable and comparable, especially for the chronic diseases that create so much cost. "Know your numbers" is the mantra of preventive care.
- Safety is lack of error, so medical errors are subtracted from value.

- Service is basically access, also measurable: No care is bad care.

"Value is absolutely measurable," says Cortese.

And value is very important to payers. The Business Roundtable recently issued a report, *The Health Care Value Comparability Study*, that took a critical look at whether our society is getting what we pay for. Using two spending measures (manufacturer-paid health benefits per hour and gross domestic product-adjusted per capita spending on health care) and 17 health measures (such as adult mortality, obesity prevalence, absenteeism, and cholesterol levels), the report found that "the U.S. is suffering from a significant health care value gap."

Workers and employers receive 23 percent less value from our health care system than the average of five leading competitors (Germany, Canada, Japan, the United Kingdom, and France). The future looks bad. Of the three emerging global competitors (Brazil, India, and China), we receive 46 percent less value from our system of care, according to this study.

What is the problem? "Providers are not being paid for providing value," says Cortese. "There is a wide variability in the quality of care because most plans do not pay for value. Medicare does not pay for it. There are some enlightened programs, Kaiser and Intermountain Healthcare in Utah, for example. But what we need is experimentation, a willingness to shift incentives to value, a concentration by insurance companies on outcomes, not just on costs. So VBID is a great idea. Absolutely in the right direction."

Good business sense

The cost and performance equation above makes determination of value concrete and communicable. Within that definition, VBID makes good business sense. It is geared toward improving outcomes over time, avoiding errors of omission through proven and simple processes, and encouraging service. The concept is gaining favor among pharmacy

Study demonstrates effectiveness of VBID

A study published in the April 7, 2009, issue of *Implementation Science*, titled "A controlled trial of value-based insurance design – The MHealthy: Focus on Diabetes (FOD) trial," found that a value-based insurance program with lower copayments significantly increased use of medications for, and improved secondary prevention among, people with diabetes, compared with traditional insurance coverage. Medications are the cornerstone of diabetes treatment, and because diabetes affects more than 20 million Americans, with substantial morbidity, mortality, and related costs, improved compliance has significant implications.

The FOD trial includes 2,507 employees and dependents with diabetes insured by one large employer. Approximately 81 percent are enrolled in a managed care program. The control group included 8,637 patients with diabetes covered by other employers and enrolled in the same managed care organization.

Both groups received written materials about the importance of adherence to secondary prevention therapies, while only the intervention group received targeted copayment reductions for glycemic agents, antihypertensives, lipid-lowering agents, antidepressants, and diabetic eye exams.

Effective

The results were significant, and established the effectiveness of VBID, according to the authors, who were primarily from the University of Michigan. There was a nearly 5 percent increase in metformin use, an almost 9 percent increase in utilization of ACE inhibitors or angiotensin II receptor blockers (ARBs), and a greater than 9 percent increase in statin use among diabetics with value-based insurance, compared with a control group of diabetics with conventional insurance.

Although evidence-based medicine supports use of many secondary prevention agents for people with diabetes, underutilization remains a concern, says coinvestigator Allison Rosen, MD, of the University of Michigan, in a public statement about the results. High out-of-pocket costs are often cited as a culprit, and VBID might make a difference by linking patient copayments to value.

"When we talk about secondary prevention, we really mean preventing cardiovascular events — heart attacks and strokes. We include kidney disease in there because it's a vascular disease that is caused by diabetes," says Rosen. The study is available here: http://bit.ly/k3LS0.

benefit management companies and even consumer-directed health plans.

That's because, notwithstanding the perceived industry bias toward lowering employer cost through member cost-sharing, the rationale for VBID is maximizing clinical benefit by lowering member cost. Evidence exists that by doing so, overall health costs are lowered. So, in a nutshell, what is revolutionary about VBID is that one patient may pay less for a given service than another patient.

"Value-based design is a viable and compelling strategic approach that — when integrated with other employer initiatives such as focused employee communication, disease management, coaching and wellness programs — can better support and influence the interactions between patients and providers and enable positive patient behaviors while improving health outcomes," says Jennifer Boehm, a principal in Hewitt's Health Management Consulting practice.

While Hewitt's clients are primarily focusing on prescription drugs, the company believes that VBID will continue to evolve and become more complex and sophisticated.

A recent study by the American Academy of Actuaries looked at VBID and its implications for policy reform. The report states that "with VBID, health insurers are taking consumer-directed health care to the next level and lowering cost barriers to high-value services that otherwise might be delayed or avoided to save money. It is useful in grouping services into higher- and lower-value categories based on the cost of the service and the degree of clinical benefit. A higher-value service, for example, would have a clinical benefit commensurate with its cost."

A. Mark Fendrick, MD, of the University of Michigan and Michael Chernew, PhD, of Harvard University are the leading authorities on VBID. They designed the original concept several years ago and run the Center for Value-Based Insurance Design at the University of Michigan.

"We know what works, and we know how to make this work," says Fendrick. "The basic concept is irrefutable: With VBID you buy more health for the dollar spent. That is value. It entails redistribution. We want to lower financial barriers for patients and raise reimbursement for physicians if they are doing the things we want them to do. We believe the concept can become a standard in health plan product offerings."

It has that potential, although whether the kind of patient targeting VBID proposes saves in long-term costs remains an open question. "Does it make good business sense?" asks Chernew. "It depends on how it is designed. It certainly can. Lowering copayments itself does not necessarily save money, but the programs are designed to make people healthier. We do know that the long-term benefit still requires a comprehensive look."

Notwithstanding a lack — so far — in established long-term savings, the concept is most certainly gaining favor with large employers, including several members of the National Business Coalition on Health, who are pushing for VBID when they solicit vendors. Several plans, including Aetna and UnitedHealthcare, are responding. Humana has a program named RxPlus, which it markets to its ASO clients. It lowers copayments for members with diabetes and asthma.

"The value of an integrated program of insurer and PBM is that we have the data to target applicable populations," says Troy Koch, PharmD, of Humana Pharmacy Solutions.

Makes sense

"We believe it makes good business sense," says Troy Koch, PharmD, director of pharmacy sales support for Humana Pharmacy Solutions, the company's pharmacy benefit management company. "The value of an integrated program of insurer and PBM is that we have the data necessary to target applicable populations. Then we design their benefit specifically to their needs. The result is an increase in compliance, an improvement in overall health."

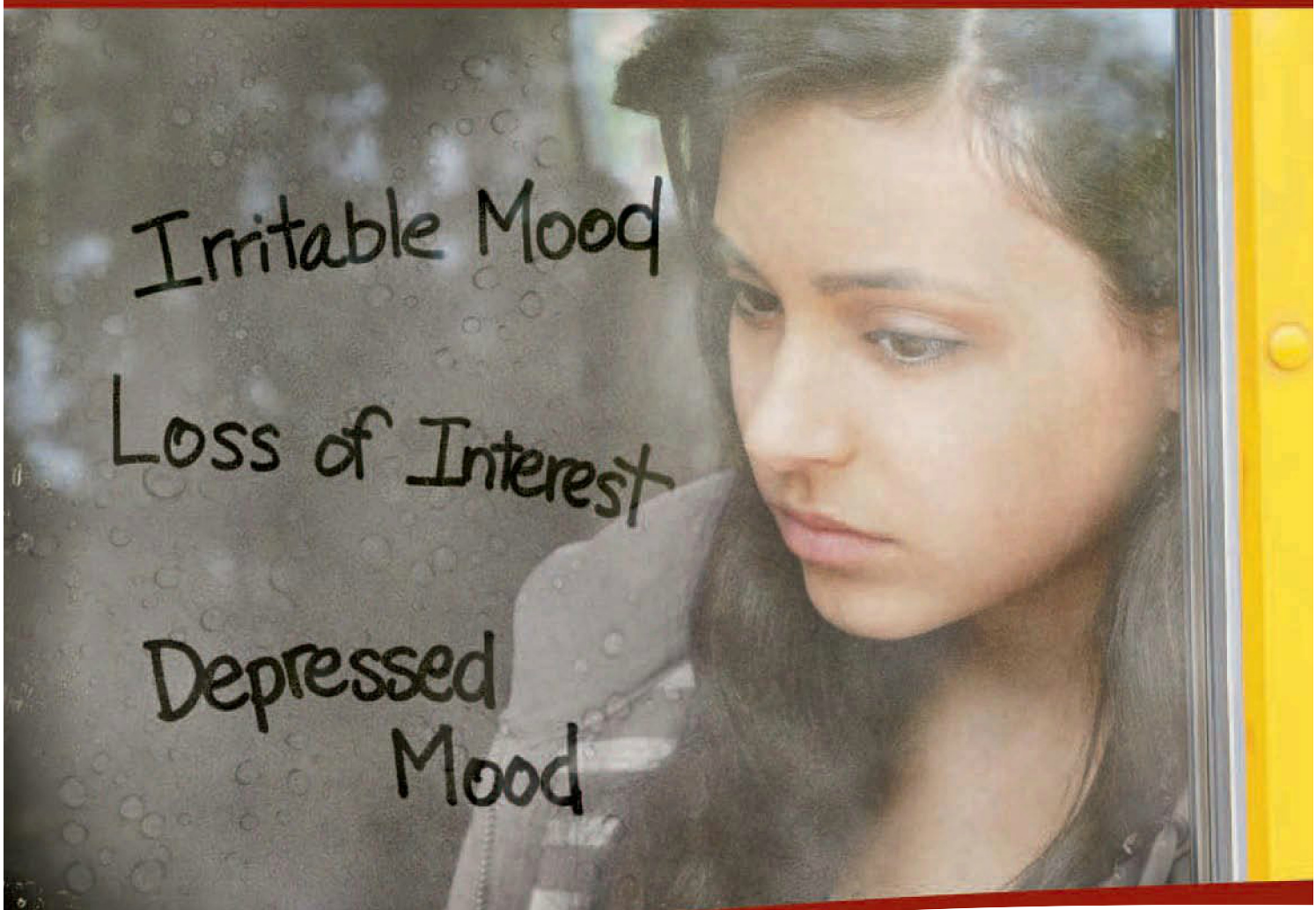
A couple of other PBMs have been pushing VBID in one form or another for a couple of years, although they don't always call it that. Several Blue Cross & Blue Shield plans (in Michigan and Pennsylvania, for example) have virtually eliminated copayments and coinsurance for many generic drugs, such as metmorfin for diabetes.

According to a Pharmacy Benefit Management Institute survey, "many multinational corporations are embracing value-based benefit design to meet business objectives while working to improve the health of the workforce."

Marriott is a good example. "We've been looking hard at solutions that provide reasonably priced

For Major Depressive Disorder (MDD)...

LEXAPRO IS NOW APPROVED for adolescents aged 12 to 17[1]



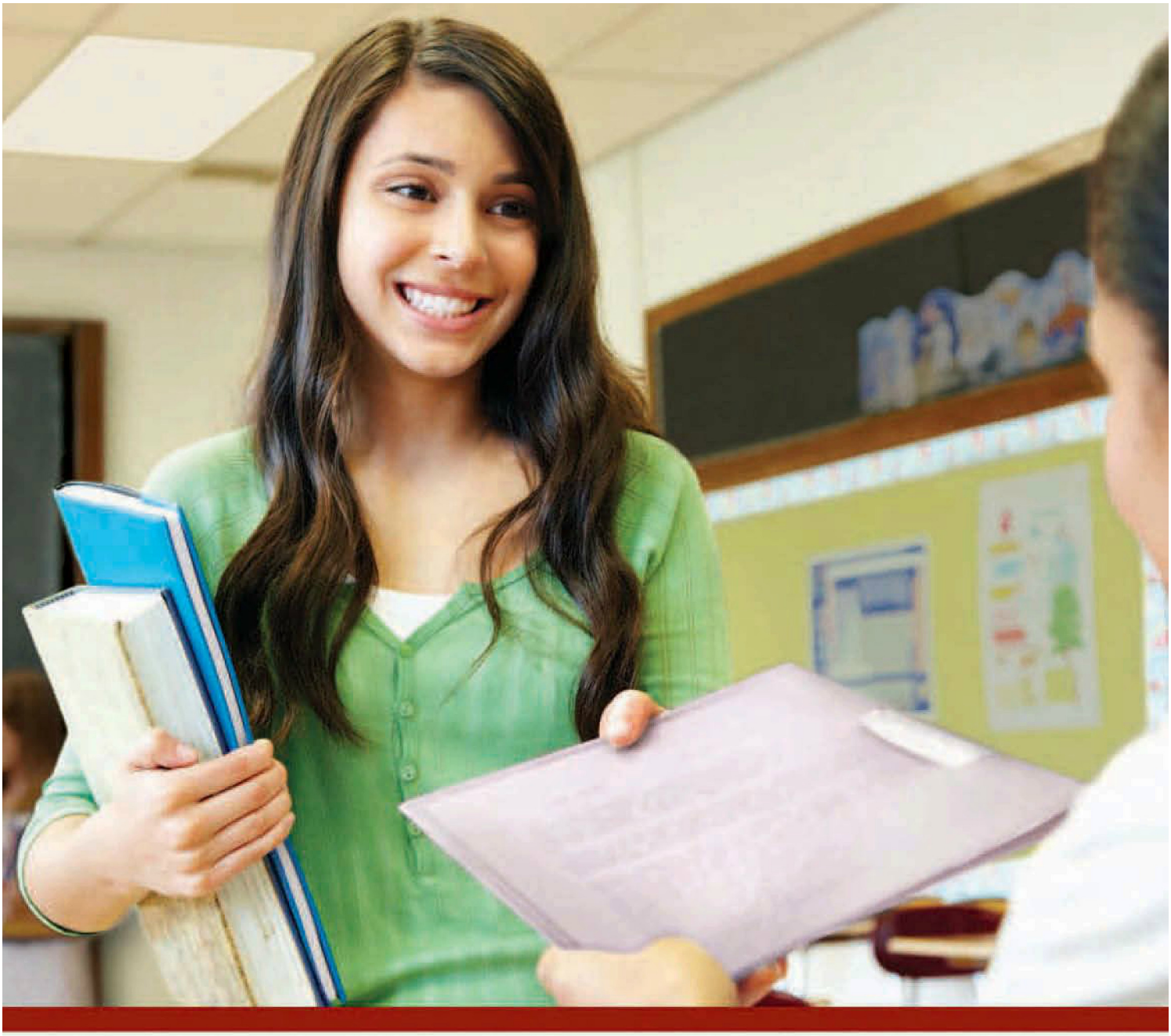
Lexapro® escitalopram oxalate

DSM-IV-TR criteria for Major Depressive Episode: Five or more symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure in nearly all activities. In children and adolescents, depressed mood can be irritable mood.[2]

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age.

Please see additional Important Safety Information on following pages.



IMPORTANT SAFETY INFORMATION (continued)

Contraindications

- Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). There have been reports of serious, sometimes fatal, reactions with some cases resembling neuroleptic malignant syndrome (NMS) and serotonin syndrome. Features may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Serotonin syndrome was reported for two patients who were concomitantly receiving linezolid, an antibiotic which has MAOI activity. Lexapro should not be used in combination with an MAOI or within 14 days of discontinuing an MAOI. MAOIs should not be initiated within 14 days of discontinuing Lexapro.
- Lexapro is contraindicated in patients taking pimozide or with hypersensitivity to escitalopram or citalopram.

Warnings and Precautions

- All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behavior, especially within the first few months of treatment or when changing the dose. Consideration should be given to changing the therapeutic regimen, including discontinuing medication, in patients whose depression is persistently worse, who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Families and caregivers of patients treated with antidepressants should be alerted about the need to monitor patients daily for the emergence of agitation, irritability, unusual changes in behavior, or the emergence of suicidality, and report such symptoms immediately. Prescriptions for Lexapro should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

NOW FDA APPROVED
for Major Depressive Disorder (MDD) in adolescents aged 12 to 17[1]

LEXAPRO provides symptom relief for adolescents with MDD

- **For acute and maintenance treatment[1]**
  - —Patients should be periodically reassessed to determine the need for maintenance treatment[1]
- **Significant improvement in CDRS-R scores starting at week 4[3]**
  - —Full antidepressant effect may take 4 to 6 weeks
- **Flexible dosing with a recommended dose of 10 mg/day[1]**
  - —Titration to 20 mg/day, if necessary, after a minimum of 3 weeks[1]

LEXAPRO is indicated as an integral part of a total treatment program for MDD. Drug treatment may not be indicated for all adolescents with this syndrome.

- A major depressive episode may be the initial presentation of bipolar disorder. In patients at risk for bipolar disorder, treating such an episode with an antidepressant alone may increase the likelihood of precipitating a mixed/manic episode. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. Lexapro should be used cautiously in patients with a history of mania or seizure disorder. Lexapro is not approved for use in treating bipolar depression.
- The concomitant use of Lexapro with other SSRIs, SNRIs, triptans, tryptophan, antipsychotics or other dopamine antagonists is not recommended due to potential development of life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Reactions have been reported with SNRIs and SSRIs alone, including Lexapro, but particularly with drugs that impair metabolism of serotonin (including MAOIs). Management of these events should include immediate discontinuation of Lexapro and the concomitant agent and continued monitoring.
- Patients should be monitored for adverse reactions when discontinuing treatment with Lexapro. During marketing of Lexapro and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania. A gradual dose reduction rather than abrupt cessation is recommended whenever possible.

Please see additional Important Safety Information on next page.

Lexapro®
escitalopram oxalate

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO: Proven efficacy in MDD in adolescents aged 12 to 17[1,3]

Warnings and Precautions (continued)

- SSRIs and SNRIs have been associated with clinically significant hyponatremia. Elderly patients and patients taking diuretics or who are otherwise volume-depleted appear to be at a greater risk. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.
- SSRIs (including Lexapro) and SNRIs may increase the risk of bleeding. Patients should be cautioned that concomitant use of aspirin, NSAIDs, warfarin or other anticoagulants may add to the risk.
- Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro does not affect their ability to engage in such activities.
- Lexapro should be used with caution in patients with severe renal impairment or with diseases or conditions that alter metabolism or hemodynamic responses. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day.
- For pregnant or nursing mothers, Lexapro should be used only if the potential benefit justifies the potential risk to the fetus or child.

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and supportive symptomatic treatment should be initiated. **Discontinuation of Treatment with Lexapro**-During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [*see Dosage and Administration*]. **Seizures**-Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. **Activation of Mania/Hypomania**-In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. **Hyponatremia**-Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Lexapro. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Lexapro was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Geriatric Use*]. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. **Abnormal Bleeding**-SSRIs and SNRIs, including Lexapro, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation. **Interference with Cognitive and Motor Performance**-In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. **Use in Patients with Concomitant Illness**-Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day [*see Dosage and Administration*]. Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients [*see Dosage and Administration*]. **Potential for Interaction with Monoamine Oxidase Inhibitors**-In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.

ADVERSE REACTIONS: Clinical Trials Experience-Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **Clinical Trial Data Sources; Pediatrics (6 -17 years)**-Adverse events were collected in 576 pediatric patients (286 Lexapro, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Lexapro in pediatric patients less than 12 years of age has not been established**. Adults**-Adverse events information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment; Major Depressive Disorder; Pediatrics (6 -17 years)**-Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Lexapro and 1% of 290 patients receiving placebo. The most common adverse event (incidence at least 1% for Lexapro and greater than placebo) associated with discontinuation was insomnia (1% Lexapro, 0% placebo). **Adults**-Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder; Adults**-Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials; Major Depressive Disorder; Pediatrics (6 -17 years)**-The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse reactions (excluding those which appear in Table 2 and those for which the coded terms were uninformative or misleading) were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion. **Adults**-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence. Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

TABLE 2
Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Major Depressive Disorder

Adverse Reaction (N=715)	Lexapro (N=592)	Placebo
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=225 Lexapro; N=188 placebo).
[3]Denominator used was for females only (N=490 Lexapro; N=404 placebo).

Generalized Anxiety Disorder; Adults-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia. Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

TABLE 3
Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Generalized Anxiety Disorder

Adverse Reactions	Lexapro (N=429)	Placebo (N=427)
Autonomic Nervous System Disorders		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal System Disorder		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Respiratory System Disorders		
Yawning	2%	1%
Urogenital		
Ejaculation Disorder[1,2]	14%	2%
Anorgasmia[3]	6%	<1%
Menstrual Disorder	2%	1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=182 Lexapro; N=195 placebo).
[3]Denominator used was for females only (N=247 Lexapro; N=232 placebo).

Dose Dependency of Adverse Reactions-The potential dose dependency of common adverse reactions (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse reactions that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group.

TABLE 4
Incidence of Common Adverse Reactions in Patients with Major Depressive Disorder

Adverse Reaction	Placebo (N=311)	10 mg/day Lexapro (N=310)	20 mg/day Lexapro (N=125)
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

Male and Female Sexual Dysfunction with SSRIs-Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to under-estimate their actual incidence.

TABLE 5
Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials

Adverse Event	Lexapro	Placebo
	In Males Only	
	(N=407)	(N=383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	3%	1%
Anorgasmia	3%	<1%

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes**-Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes**-Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes**-Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes**-Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Reactions Observed During the Premarketing Evaluation of Lexapro**-Following is a list of treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. The listing does not include those events already listed in Tables 2 & 3, those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Events are categorized by body system. Events of major clinical importance are described in the Warnings and Precautions section. Cardiovascular - hypertension, palpitation. Central and Peripheral Nervous System Disorders - light-headed feeling, migraine. Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis. General - allergy, chest pain, fever, hot flushes, pain in limb. Metabolic and Nutritional Disorders - increased weight. Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness. Psychiatric Disorders - appetite increased, concentration impaired, irritability. Reproductive Disorders/ Female - menstrual cramps, menstrual disorder. Respiratory System Disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache. Skin and Appendages Disorders - rash. Special Senses - vision blurred, tinnitus. Urinary System Disorders - urinary frequency, urinary tract infection. **Post-Marketing Experience; Adverse Reactions Reported Subsequent to the Marketing of Escitalopram**-The following additional adverse reactions have been identified from spontaneous reports of

escitalopram received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include: Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Ear and Labyrinth Disorders: vertigo Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma, mydriasis, visual disturbance. Gastrointestinal Disorders: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction, anaphylaxis. Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia. Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis. Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency. Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention. Reproductive System and Breast Disorders: menorrhagia, priapism. Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn. Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

DRUG INTERACTIONS: Serotonergic Drugs-Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort [*see Warnings and Precautions*]. The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended. **Triptans**-There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions*]. **CNS Drugs**- Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. **Alcohol**-Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. **Monoamine Oxidase Inhibitors (MAOIs)**-[*see Contraindications and Warnings and Precautions*]. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)**-Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Lexapro is initiated or discontinued. **Cimetidine**-In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. **Digoxin**-In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. **Lithium**-Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels shouldbe monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. **Pimozide and Celexa**-In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. **Sumatriptan**-There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. **Theophylline**-Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. **Warfarin**-Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. **Carbamazepine**-Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. **Triazolam**-Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. **Ketoconazole**-Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. **Ritonavir**-Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. **CYP3A4 and -2C19 Inhibitors**-*In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. **Drugs Metabolized by Cytochrome P4502D6**-*In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. **Metoprolol**-Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro and metoprolol had no clinically significant effects on blood pressure or heart rate. **Electroconvulsive Therapy (ECT)**-There are no clinical studies of the combined use of ECT and escitalopram.

USE IN SPECIFIC POPULATIONS: Pregnancy; Pregnancy Category C-In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis. In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses. In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy-Nonteratogenic Effects Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions*]. Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [*see Dosage and Administration*]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery**-The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers**-Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Lexapro is administered to a nursing woman. **Pediatric Use**-Safety and effectiveness of Lexapro has not been established in pediatric patients (less than 12 years of age) with Major Depressive Disorder. Safety and effectiveness of Lexapro has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder [*see Clinical Studies*]. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients. Safety and effectiveness of Lexapro has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder. **Geriatric Use**-Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Hyponatremia*]. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged [*see Clinical Pharmacology*]. 10 mg/day is the recommended dose for elderly patients [*see Dosage and Administration*]. Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence; Physical and Psychological Dependence-Animal studies suggest that the abuse liability of racemic citalopram is low. Lexapro has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Lexapro did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Lexapro patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience-In clinical trials of escitalopram, there were reports of escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. During the postmarketing evaluation of escitalopram, Lexapro overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported. Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose. **Management of Overdose**-Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered**.** Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Lexapro. In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

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Rev. 05/09

quality health care," says Marriott spokeswoman Stephanie Hampton, "and we've been piloting new ideas. Value-based design is one of those ideas and we think a successful one."

But in considering value as the core of its health coverage, Marriott goes further than drug costs. It provides free annual check-ups and immunizations to its 75,000 employees and their dependents. Pregnant employees get free monthly and, eventually, weekly checkups. "It's too soon to know whether this value-based approach is working the way it should, but the anecdotal evidence is very good. The reaction in focus groups has been extremely positive," says Hampton.

Aetna's approach

According to Fendrick and Chernew, there are two approaches to VBID targeting. The first approach targets clinically valuable services for copayment reduction (for example, beta-blockers). That provides substantial benefit for some users (such as patients with CHF or myocardial infarction), but provides less value for other patients (such as those with performance anxiety).

"Right now, the current system does not differentiate between these patients," says Fendrick. "That is an issue that has to be addressed."

The second approach targets patients with select clinical diagnoses (for example, CHF) and lowers copayments for specific high-value services (for example, beta-blockers and ACE inhibitors). It requires sophisticated data systems to implement, and creates different copayments based on patient characteristics. "Programs using this approach typically identify patients with specific diseases, such as diabetes or coronary heart disease, and reduce copayments for identifiable high-value services for those patients," says Fendrick.

Fendrick says that Pitney Bowes uses the first approach, reducing copayments for all users of drugs commonly prescribed for diabetes, asthma, and hypertension. ActiveHealth Management, an independent patient-management subsidiary of Aetna, also focuses on drugs, lowering copayments for ACE inhibitors and angiotensin-receptor blockers, beta-blockers, medications for glucose control, statins, and inhaled steroids used to treat asthma. Fendrick says that ActiveHealth has the technology to precisely target patients to gain the most from VBID.

Fendrick says that the second approach, which targets specific patients, is less common. Two examples are the municipality of Asheville, N.C., and the University of Michigan. Both of these employers implemented a program that lowered copayments for selected medications for employees with diabetes. The Asheville program is led by pharmacists and includes coached self-management.

UnitedHealthcare's incentives

UnitedHealthcare has a program named Diabetes Health Plan which combines VBID with wellness programs. Started in the large employer market, the program gives incentives, such as free services and medications, online monitoring, wellness coaches, and self-management programs, to diabetics and prediabetics who follow their treatment plans and evidence-based guidelines. Depending on the patient's condition, the compliance requirements include lab evaluations, exams, preventive care, and wellness program participation.

UnitedHealthcare officials say the program can save plan members from $250 to $500 a year by not paying for diabetes-related pharmaceuticals, and reduces the $22,000 that employers pay to care for the average diabetic annually — although by how much remains an open question.

Fendrick and Chernew list three ways VBID makes good fiscal sense:

- **Savings through improved health outcomes.** "This depends on successful targeting," says Fendrick. "The technology exists to target populations who will benefit the most. That is a measure of value."
- **Savings through increased productivity** (for example, less absenteeism and fewer disability claims).

"What would work is health plans that cover someone their entire life. Then value would make complete sense to insurers," says Denis Cortese, MD, president and CEO of the Mayo Clinic.

Senate looks at VBID — an idea with broad support

Recent U.S. Senate Finance Committee hearings on health care reform highlighted value-based insurance design (VBID) as a model to improve patient health outcomes and lower costs. As a result of recent hearings, Sen. Kay Bailey Hutchison (R-Texas) is co-sponsoring legislation, now in committee, that would instruct Medicare to conduct VBID pilot projects.

The purpose of the bipartisan bill, cosponsored by Sen. Debbie Stabenow (D-Mich.), is "to establish a demonstration program requiring the utilization of value-based insurance design to demonstrate that reducing the copayments or coinsurance charged Medicare beneficiaries for selected medications can increase adherence to prescribed medication, and for other purposes."

Aetna's chief

Testifying in favor of the legislation, Aetna Chairman and CEO Ron Williams said, "Based on evidence in the medical literature that copayments and/or coinsurance can create barriers to care, value-based insurance design eliminates or reduces copayments or coinsurance for certain medications or types of care that are demonstrated to be crucial in preventing or managing disease. In other words, insurance is designed so that costs are not a deterrent to individuals in seeking out the right kind of care. One important example is the various types of care that are provided with first-dollar coverage, including preventive care, routine physicals, gynecological exams, and medications for chronic care conditions."

- **Savings by shifting costs to lower-value interventions.** "As we make more effective use of evidence-based medicine and implement comparative effectiveness research, we are increasingly able to identify those services that yield less value, while identifying those that are of the greatest value," says Fendrick. "And that is a smart allocation of resources."

Problems

Fendrick says that VBID is not a panacea, of course. He lists several barriers to VBID implementation. One is about the cost of increased use of services. VBID involves lowering copayments for some underused, high-value services. Lower copayments are associated with higher costs and create concerns that VBID will increase spending, at least in the short term. As noted above, whether employers can capture long-term savings has yet to be determined.

Another concern is that implementation of VBID involves identification of high-value services.

Also, when a system targets specific patient groups, decisions about which groups would be eligible for lower copayments can be problematic. Therefore, "current patient-targeted VBID programs focus on diabetes because patients with diabetes can easily be identified using existing pharmaceutical data sets," says Fendrick.

Medicare roadblock

Perhaps the single biggest problem is that health systems as they now exist do not encourage value-based design. Medicare is a prime example, according to Cortese. "Public programs are not geared toward value," he says. "What would work is health plans that cover someone their entire life. Then value would make complete sense to insurers."

Universal American in Houston is a good example of what Cortese is talking about — and a good example of the barriers faced by VBID. Described by Patricia Salber, MD, the company's chief medical officer, as a "senior-focused health care company," Universal American has not implemented a full VBID because Medicare regulations do not support this approach. Salber has been part of the Center for Value-based Insurance Design since its inception. "We know it is the right thing to do, to try to lower the financial barriers to care. If Medicare develops pilot projects to look at VBID, we would love to be a part of that."

Fendrick is doing what he can to make that happen. Right now there is legislation being considered in the Senate to create such pilot projects.

"What we do know is the current system is unsustainable," says Cortese. "Solutions centered on value are a necessity." MC

Contributing Editor Martin Sipkoff can be reached at MSipkoff@ManagedCareMag.com

Use a Value-Based Strategy For Biotech Medications

Coverage often straddles the line between the pharmacy and medical benefit, but a properly constructed formulary can bridge the gap

By F. Randy Vogenberg, RPh, PhD

Specialty drugs and other new drug technologies are the fastest growing sector of the prescription drug market primarily because of price inflation and increased utilization.

Manufacturers have justified the high unit cost of these categories by using the pharmacoeconomic argument that the lower incidence of serious side effects and increased efficacy over traditional medications leads to reduced hospitalizations and reduces the need for medical visits. However, since the pharmacy benefit is managed independently of the medical benefit, the value of the specialty drug is unlikely to be seen from the viewpoint of the pharmacy benefit.

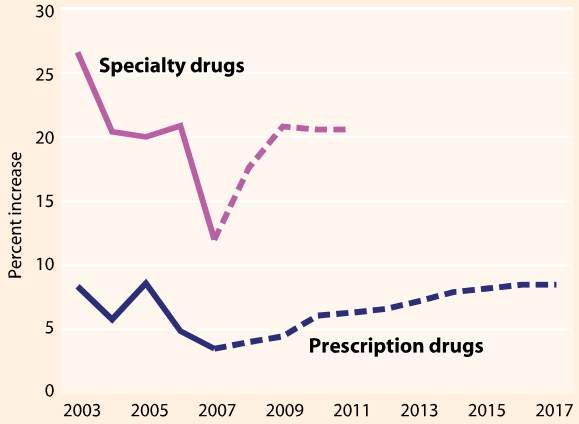
Bridging the gap requires a holistic approach to designing benefits. Stakeholders need to figure out how to assess the value of specialty drugs and other new drug technologies, given that the health care system is misaligned. A value-based formulary is one option for controlling specialty drugs.

Value-based insurance design aligns the goals and objectives of a business to increase the total value of health care to the business. In a value-based formulary, total medical costs determine whether the use of specialty drugs and new drug technologies save money. In specialty drug formularies based on value, decision-making should be based on total medical costs, and the impetus must come from plan sponsors.

In 2003, specialty drug spending increased 26.6 percent from the previous year, and in 2004 it jumped another 20.4 percent. The Express Scripts *2008 Drug Trend Report* projects that the specialty drug trend will continue to increase between 18 percent and 21 percent yearly through 2011. Of the 14 percent increase in 2007 for specialty pharmacy, 4.9 percent was because of new drugs, 34.7 percent was attributed to price inflation, and 60.4 percent was because of increased utilization.

F. Randy Vogenberg, RPh, PhD, is a principal in the Institute for Integrated Healthcare in Sharon, Mass., and executive director of the Biologic Finance & Access Council in Philadelphia. He can be reached at PO Box 433, Sharon, MA 02067; by telephone at 781-307-6247; or by e-mail at rvogenberg@bfaconline.org

FIGURE 1
Prescription drug spending projections % increase per year



SOURCE: Medco *Drug Trend Report 2004* and *2008*; Express Scripts *Drug Trend Report 2008*

Greatest utilization

Conditions with the greatest utilization and increase in use of specialty pharmacy include autoimmune disorders, primarily rheumatoid arthritis, multiple sclerosis, and cancer.

Figure 1 compares overall drug spending to specialty drug spending. The blue line represents actual growth of total prescription drug spending until 2007 and projected growth of drug spending after 2007. This is based on published data from the Centers for Medicare & Medicaid Services (CMS) for national health expenditure projections. The