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Thank You For Your Continued Support!
Opioid misuse/abuse is a major public health issue in the United States. Overdose deaths from prescription painkillers have increased significantly in recent years. There were 16,651 opioid-related deaths in 2010, which was three times the number of deaths that occurred in 1999.1 Almost one million people 12 years old and older reported nonmedical opioid use of greater than 200 days in 2009 to 2010; 4.6 million people reported such use for 30 days or more.2 The direct health care costs of nonmedical prescription painkiller use are estimated at $72.5 billion annually.

Opioids account for 43 percent of all fatal overdoses. The highest prescription painkiller overdose rates are in middle-aged adults with the highest rates in rural counties and among Caucasians, American Indians, and Alaska Natives. There are many more prescription opioid overdose deaths in men than women.

Reasons for opioid-related deaths include over-prescribing, nonadherence, and unanticipated or undiagnosed comorbidities. Over-prescribing by physicians includes starting doses too high, dose escalation too rapid, over reliance on conversion tables, and inadequate risk assessment. Patients contribute to deaths by nonadherence with prescribed medications by taking extra to control pain, “cope”, and straight out abuse. Unanticipated comorbidities include QT prolongation and sleep disordered breathing.

Prescriptions for immediate release and ER/LA agents increased significantly from 2000 to 2009 (164.8 million to 234 million, 9.3 million to 22.9 million, respectively). By and large, opioid abusers are not obtaining their supplies from drug dealers or purchasing them from friends. The majority are obtaining them from friends for free (Exhibit 1).3 Because of the issues with abuse and misuse, man-
Risk management for opioids is an evolving process. It initially started in 1970 with the Controlled Substances Act, which placed medications in different schedules based on potential for abuse. Extended-release and long-acting (ER/LA) opioids are classified as Schedule II. The most recent evolution was the introduction of Risk Evaluation and Mitigation Strategies (REMS) for ER/LA opioids in 2012. The REMS is part of a multi-agency federal effort to address the growing problem of prescription drug abuse and misuse. The REMS introduces new safety measures to reduce risks and improve safe use of ER/LA opioids, while continuing to provide access to these medications for patients in pain.

Per the FDA, ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risk of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. ER/LA opioid analgesics are not indicated for as-needed pain relief.

People can misuse or abuse opioids for medical and nonmedical reasons (Exhibit 2). In addition to
pain reduction, reinforcing effects of opioids include reduced anxiety, decreased boredom, decreased aggression, and increased self-esteem which can lead to self-medication. Addiction is a primary, chronic neurobiological disease with genetic, psychosocial and environmental factors influencing its development and manifestation. Addiction is out-of-control, compulsive drug use. Pseudoaddiction occurs because of inadequate analgesia.

It may be difficult to determine beforehand who could become problematic users of prescription medications. Assessment of risk must include all patients for whom prescribing is considered. Risk assessment considerations include social and psychiatric evaluation, presence of aberrant behaviors, and personal and family history of substance abuse/use.

Risk factors for aberrant medication taking behaviors and harm related to opioids are shown in Exhibit 3. Psychiatric diagnoses may account for aberrant behaviors. These include personality disorder (impulsive, entitled, chemical-coping behavior), bipolar disorder, and depression or anxiety. Additionally, people may be seeking opioids for criminal intent (diversion).

Based on risk factors, patients can be stratified into low-, moderate-, and high-risk groups. The high-risk group are those with active substance abuse, active addiction, and/or major untreated psychological disorder. People in this group are a significant risk to self and the practitioner. The moderate-risk group has a history of treated substance abuse, significant family history of substance abuse, or past/comorbid psychological disorder. The low-risk group has no identifiable risk factors. Patients don’t always fit nicely into these categories because there is a spectrum of risk. Screening tools such as the Opioid Risk Tool (ORT) may be helpful in everyday practice (Exhibit 4).

In addition to risk factors for aberrant behavior, risk factors for opioid adverse effects that are known to lead to deaths need to be considered in prescribing. Risk factors for respiratory depression include sleep apnea or a sleep disorder diagnosis, morbid obesity snoring, age greater than 60, no recent opioid use, post-surgery (particularly upper abdominal or thoracic), use of other sedating drugs [central nervous system (CNS) depressants], preexisting pulmonary or cardiac disease or major organ failure, and smoking. Respiratory depression is generally preceded by sedation and decreased respiratory rate. Overdose or death can occur if ER/LA opioids are used with other CNS depressants, including sedative-hypnotics, anxiolytics, and illegal drugs. Patients should be advised to use other CNS depressants, including other opioids, only under instruction of their prescriber.

Fatal opioid overdose is not typically instantaneous—there is usually time for remedial action. Naloxone can quickly reverse the effects so both patients and caregivers need to know how to identify an opioid overdose, as signs of an overdose are often missed. Opioid overdose signs include mental depression, hypoventilation, reduced bowel motility, and miosis.

Once the decision to prescribe an opioid is made, realistic individualized goal-setting between the clinician and patient is required for optimal pain management outcomes. Patient-specific goals should include pain reduction and/or improvement in select functional areas. A 30 percent reduction pain

<table>
<thead>
<tr>
<th>Biological</th>
<th>Psychiatric</th>
<th>Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 45 years</td>
<td>Substance use disorder</td>
<td>Prior legal problems</td>
</tr>
<tr>
<td>Gender</td>
<td>Preadolescent sexual abuse (in women)</td>
<td>History of motor vehicle accidents</td>
</tr>
<tr>
<td>Family history of prescription drug or alcohol abuse</td>
<td>Major psychiatric disorder (eg. Personality disorder, anxiety or depressive disorder, bipolar disorder)</td>
<td>Poor family support</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td>Involvement in a problematic subculture</td>
</tr>
</tbody>
</table>
is clinically significant. Patients need to understand that complete pain relief is rarely achieved. Some example improvements in functional areas include the ability to work full time at a previous or modified job, play golf once a week, or walk the dog daily. A patient-prescriber agreement can be used to outline these individualized goals and set expectations. A typical agreement, which is signed by the patient and prescriber, will include the risks and benefits of opioid therapy, taking the opioid exactly as prescribed, use of one prescribing doctor and one designated pharmacy, prescription refill policy, urine/serum drug testing when requested, how to safeguard opioid medication, and behaviors that may lead to discontinuation of opioids.

Once patients are started on opioids, the four “A’s” of pain treatment outcomes should be assessed at each visit. These are analgesia (pain relief), activities of daily living (psychosocial functioning), adverse effects, and aberrant behaviors (addiction-related outcomes).<sup>8</sup>

Patient adherence with their opioid plan needs to be monitored. The level of monitoring depends on the risk stratification level determined during initial screening (using ORT or other tools). Monitoring can include checking state Prescription Drug Monitoring Programs for doctor and pharmacy shopping, urine drug testing, and pill counts. Behavioral assessment should be done at each visit. If indicated, patients should be referred for substance abuse treatment.

A Patient Counseling Document (PCD) on ER/LA opioid analgesics is a tool unique to the ER/LA REMS designed to facilitate discussion with patients being prescribed an ER/LA opioid analgesic. The PCD should be provided to and reviewed with the patient and/or their caregiver at the time of prescribing. It contains important safety information about ER/LA opioids and can be used as a supplement to the patient-prescriber agreement. Printed copies of the PCD can be ordered at www.er-la-opioidrems.com.

Several formulations with deterrents to abuse are now available (Exhibit 5). Importantly, dosing of these and all opioids depends on whether someone is naive or tolerant. Patients are considered opioid tolerant if they are taking, for one week or longer, at least oral morphine 60 mg daily, transdermal fentanyl 25 mcg/h, oral oxycodeone 30 mg daily, oral hydromorphone 8 mg daily, oral oxymorphone 25 mg daily, or an equianalgesic daily dose of another opioid. Some formulations are only indicated for

---

**Exhibit 4: Opioid Risk Tool<sup>6</sup>**

<table>
<thead>
<tr>
<th>Mark each box that applies</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Family history of drug abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Alcohol</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>- Illegal drugs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>- Prescription drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2. Personal history of drug abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>- Illegal drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>- Prescription drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3. Age (mark box if 16 - 45 years)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4. History of preadolescent sexual abuse</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5. Psychological disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ADD, OCD, bipolar, schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>- Depression</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

0 - 3: Low Risk
4 - 7: Moderate Risk
≥ 8: High Risk

ADD = attention deficit disorder
OCD = obsessive-compulsive disorder
people who are tolerant. Caution must be used when converting from one opioid to another. Cross-tolerance is a pharmacologic phenomenon whereby tolerance developed to the effects of one drug translates into tolerance to other drugs from the same class. Incomplete cross-tolerance occurs when complete cross-tolerance does not develop, increasing the likelihood of therapeutic effects as well as adverse effects and is known to occur among opioids.

**Conclusion**

Before prescribing opioids, clinicians need to consider the risks involved and balance those risks with potential benefits and stratify each patient. Clinicians need to understand opioid tolerance, dependence, and addiction because opioids can kill. Each patient’s risk of abuse, including substance use and psychiatric history, need to be assessed before prescribing an opioid. Screening tools may be beneficial and should be integrated into office-based protocols.

Steven Stanos, DO, is the Director of Corporate Pain Services and Attending Physician at the Center for Pain Management at the Rehabilitation Institute of Chicago. He is also an Associate Professor, Dept. of Physical Medicine and Rehabilitation at the Northwestern University Medical School Feinberg School of Medicine.

**References**


---

### Exhibit 5: Deterrent Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tamper-Resistance Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin (oxycodone CR)</td>
<td>• Matrix resists crushing with intention to prevent snorting</td>
</tr>
<tr>
<td>Opana ER (oxymorphone ER)</td>
<td>• Forms a viscous gel on dissolution with intention to prevent injection</td>
</tr>
<tr>
<td>Nucynta ER (tapentadol ER)</td>
<td></td>
</tr>
<tr>
<td>Oxecta (oxycodone IR)</td>
<td>• Aversive ingredients cause mucosal irritation with intention to prevent snorting</td>
</tr>
<tr>
<td>Embeda (Morphine ER/Naltrexone)</td>
<td>• Morphone ER beads with sequestered naltrexone • Deters injecting and snorting</td>
</tr>
</tbody>
</table>
Evaluating Prevention and Treatment Strategies in the Management of Osteoporosis

Ellen Hirschman Miller, MD
For a CME version of this, please go to www.namcp.org/cmeonline.htm which is supported by an educational grant from Amgen Inc.

Summary
Osteoporosis is a major risk factor for fractures. Current medications significantly reduce the risk of fracture but also cause some rare, but worrisome, adverse effects. Balancing the risk of fracture against medication adverse effects is leading to changes in treatment duration recommendations.

Key Points
• Management of osteoporosis includes ensuring basic bone health needs are met, screening for secondary causes of osteoporosis, and initiating pharmacologic therapy when appropriate.
• The need for continued pharmacologic therapy should be assessed annually.
• Osteoporosis medication should not be continued indefinitely.

OSTEOPOROSIS IS A DISEASE CHARACTERIZED by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures of the hip, spine, and wrist.1 Approximately one in three women 50 years and older will experience an osteoporosis-related fracture in her lifetime.2 By 2025, fracture rates in women over 50 years old in the United States are expected to grow 48 percent or more.3 Fractures, especially of the hip, are associated with substantial morbidity, disability, and mortality.4 Postmenopausal osteoporosis is a disease of unbalanced bone remodeling. Normal bone mass is maintained when there is balanced bone resorption and formation. When bone resorption exceeds bone formation at many sites within the skeleton, bone mass decreases and bone structure is compromised.

Osteoporosis and osteopenia are defined by an individual’s bone mineral density (BMD) (Exhibit 1).5 BMD is measured in terms of a T-score; the T-score indicates the number of standard deviations above or below the average peak bone mass in young adults. A T-score between -1 and -2.5 indicates osteopenia, whereas osteoporosis is indicated by a T-score of -2.5 or lower. The diagnostic classification using T-scores allows the definition of osteoporosis based on dual-energy x-ray absorptiometry (DXA) only, is easy to understand and used worldwide, and identifies patients at high risk for a fracture. These criteria have increased the diagnosis and treatment of osteoporosis. The T-score influences therapy choice and can also be used for monitoring treatment efficacy. Using the T-score and other factors, an individual’s risk of fracture can be predicted by using the online FRAX Risk Assessment Tool (www.shef.ac.uk/FRAX). This is an algorithm that estimates 10-year risk of fracture and identifies high-risk patients who would benefit from treatment. The National Osteoporosis Foundation treatment guidelines recommend treatment based on T-scores and estimated fracture risk (Exhibit 2).6 It is important to note that a prior fragility fracture in women or men of any race 50 years of age and older “trumps” all other risk factors for predicting future fracture risk.
at any skeletal site. Those who have a fracture have a significantly increased risk for a second fracture in the first 12 to 18 months after the first fracture.

Because most vertebral compression fractures have no symptoms, it can be difficult to identify this type of fragility fracture. Medicare recently approved indications for performing an x-ray or vertebral fracture assessment (VFA) for detecting this high-risk group. VFA is a new technology using central DXA that permits imaging of the thoracic and lumbar spine. Images can be obtained at the same time as a BMD measurement at lower cost and radiation exposure than plain radiographs of the spine.

There are some universal management measures that apply for all people with low bone mass and include risk factor reduction, physical activity, and optimal nutrition. Risk factor reduction is geared toward preserving bone mass and fall prevention. For bone mass preservation, any medications contributing to bone loss should be stopped or the dose reduced if possible. Smokers should be encouraged to stop. Fall prevention includes stopping medications which may contribute to falls, environment changes such as good lighting and removal of tripping hazards, and balance training. Physical activity should be encouraged to continue to provide bone mass benefits and maintain muscle mass to prevent falls. Optimal nutrition should include adequate calcium and vitamin D. Getting adequate calcium and vitamin D through diet alone is better than using supplements. If a patient cannot get enough through diet, supplements can be used to reach the recommended daily amount.

FDA approved pharmacologic therapy falls into two categories: anabolic or antiresorptive. Teriparatide is an anabolic agent that increases bone turnover with bone formation more than bone resorption, increases bone mass, and improves bone architecture. The antiresorptive (anti-catabolic) agents lower bone turnover, maintain or improve bone mass, and stabilize bone architecture. Agents in this category include salmon calcitonin, estrogen/estrogen progestin combinations, raloxifene, denosumab, and bisphosphonates (alendronate, ibandronate, risedronate, zoledronate).

The pharmacologic treatment paradigm in osteoporosis is undergoing change because of discovered long-term effects of suppressing bone turnover with bisphosphonates (i.e., atypical fractures, osteonecrosis of the jaw). Patients need to be considered over their life span when considering a treatment plan. The goal is to factor in age and severity of disease to maximize benefit while minimizing the risk of fracture and risk of medication adverse effects. Treatment is moving to serial monotherapy with a limited treatment duration. Clinicians should be re-evaluating each patient’s treatment decision annually. Continuing osteoporosis medication indefinitely is no longer the standard.

Hormone therapy provides the highest benefit to risk profile early after menopause. In general, hormone therapy should be continued for a maximum of five years with as low of a dose as possible. Estrogen alone is safer and might allow a longer duration of treatment.Raloxifene is a good choice for women in their 50s to late 60s, especially if they have spine osteoporosis only, because hip fractures are rare in this age group. It can also be considered in women with low bone mass for prevention. In women in their 60s and beyond, bisphosphonates or denosumab would be the preferred choice because they reduce risk of hip and all nonspine fractures. Teriparatide can be used at any point in the life span but should only be used for 18 to 24 months because of potential sarcoma risk. It needs to be followed by antiresorptive therapy.

As an example bisphosphonate, intravenous zolendronic acid offers fracture protection throughout the skeleton over at least three years.6 Its effect on BMD and biochemical bone turnover persists even after discontinuation. Many people can and probably should stop bisphosphonate therapy after three

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**Exhibit 1: Bone Density Criteria**

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-score above or equal to -1</td>
<td>Normal</td>
</tr>
<tr>
<td>T-score between -1 and -2.5</td>
<td>Osteopenia (low bone mass)</td>
</tr>
<tr>
<td>T-score -2.5 or lower</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>T-score -2.5 or lower + fragility fracture</td>
<td>Severe established osteoporosis</td>
</tr>
</tbody>
</table>
years. The decision to continue a bisphosphonate beyond three years must be individualized. Women at high fracture risk, particularly for vertebral fracture, might continue therapy up to six years. Women at lower risk might take a drug holiday for up to three years and then be re-evaluated. Methods to identify subgroups who might benefit most from long-term therapy are being explored.

Denosumab, approved in 2010, is designed to inhibit RANKL (RANK ligand), a protein that acts as the primary signal for bone removal. In many bone loss conditions, RANKL overwhelms the body’s natural defenses against bone destruction. Studies have shown that subcutaneous denosumab offers fracture protection throughout the skeleton over at least three years. Its effect is rapidly reversed if medication is stopped. The optimal duration for denosumab therapy is still unknown.

A patient’s response to therapy should be assessed with BMD two years after starting pharmacotherapy for osteoporosis. A satisfactory response is when BMD is maintained or increased. If BMD declines, several issues should be considered before labeling the patient a treatment failure. Technical issues (e.g., validity of DXA comparison), medication adherence and dosing, and secondary causes need to be evaluated. Some patients are true nonresponders.

Several therapies are under investigation for osteoporosis treatment. Odanacatib (ODN) is an investigational once-weekly inhibitor of cathepsin K (Cat K), a cysteine protease expressed in osteoclasts. Cat K is responsible for bone matrix degradation. In a large Phase III trial in postmenopausal women, odanacatib significantly reduced the risk of osteoporotic hip, spine and nonvertebral fractures compared with placebo. In addition, treatment led to progressive increases over five years in BMD at the lumbar spine and hip. Compared to placebo, the change in BMD from baseline at five years with odanacatib for lumbar spine was 11.2 percent and for total hip was 9.5 percent.

Another area being targeted is sclerostin, an osteocyte-secreted protein, which negatively regulates osteoblasts and inhibits bone formation. Mutations in the gene for sclerostin are associated with disorders resulting in high bone mass (sclerosteosis and van Buchem disease). A sclerostin antibody, romosozumab, is being evaluated as an osteoporosis treatment. It increases BMD and appears to be a mixed antiresorptive/anabolic agent that might overcome the issue of long-term adverse effects from over suppression of bone resorption.

Conclusion
Osteoporosis-related fractures can dramatically affect the functional status of women who sustain them. These fractures represent a significant clinical burden; yet, they often go unevaluated and untreated. There are effective methods for estimating individual fracture risk and reducing risk with medication. Management strategies for patients with osteoporosis include ensuring basic bone health needs are met, screening for secondary causes of osteoporosis, and initiating pharmacologic therapy when appropriate. The concept that any osteoporosis medication should be continued indefinitely is no longer viable.

Ellen Hirschman Miller, MD, is an Associate Professor of Medicine at the Hofstra North Shore-LIJ School of Medicine. She also has a private practice in Internal Medicine, Endocrinology, and Reproductive Endocrinology in Hewlett, NY.

References

Exhibit 2: NOF Guidelines: When to Treat

Calcium/Vitamin D:

- For postmenopausal women and men age 50 and older,
  - Calcium: at least 1200 mg/d, including supplements if necessary
  - Vitamin D: 800 to 1000 IU per day of vitamin D3 for individual at risk of insufficiency

Pharmacological treatment:

- Postmenopausal women or men over age 50 with a prior hip or spine fracture
- Postmenopausal women or men over 50 with a BMD T-score of -2.5 or lower at the hip or spine
- Postmenopausal women or men over 50 with T-score between -1.0 and -2.5 at the femoral neck, total hip, or spine if:
  - 10-year probability (From FRAX) of hip fracture is ≥3%
  - 10-year probability of a major osteoporosis-related fracture is ≥20%
Important Safety Information

Neutropenia: Neutropenia is frequently reported with IBRANCE therapy. In the randomized phase II study, Grade 3 (57%) or 4 (5%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. Febrile neutropenia can occur. Monitor complete blood count prior to starting IBRANCE and at the beginning of each cycle, as well as Day 14 of the first two cycles, and as clinically indicated. For patients who experience Grade 3 neutropenia, consider repeating the complete blood count monitoring 1 week later. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Infections: Infections have been reported at a higher rate in patients treated with IBRANCE plus letrozole (55%) compared with letrozole alone (34%). Grade 3 or 4 infections occurred in 5% of patients treated with IBRANCE plus letrozole vs no patients treated with letrozole alone. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Pulmonary embolism (PE): PE has been reported at a higher rate in patients treated with IBRANCE plus letrozole (5%) compared with no cases in patients treated with letrozole alone. Monitor patients for signs and symptoms of PE and treat as medically appropriate.

Pregnancy and lactation: Based on the mechanism of action, IBRANCE can cause fetal harm. Advise females with reproductive potential to use effective contraception during therapy with IBRANCE and for at least 2 weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant or if pregnancy is suspected during treatment with IBRANCE. Advise women not to breastfeed while on IBRANCE therapy because of the potential for serious adverse reactions in nursing infants from IBRANCE.

Additional hematologic abnormalities: Decreases in hemoglobin (83% vs 40%), leukocytes (95% vs 26%), lymphocytes (81% vs 35%), and platelets (61% vs 16%) occurred at a higher rate in patients treated with IBRANCE plus letrozole vs letrozole alone.

Please see additional Important Safety Information and Brief Summary on the following pages.
Adverse reactions: The most common all causality adverse reactions (≥10%) of any grade reported in patients treated with IBRANCE® (palbociclib) plus letrozole vs letrozole alone in the phase II study included neutropenia (75% vs 5%), leukopenia (43% vs 3%), fatigue (41% vs 23%), anemia (35% vs 7%), upper respiratory infection (31% vs 18%), nausea (25% vs 13%), stomatitis (25% vs 7%), alopecia (22% vs 3%), diarrhea (21% vs 10%), thomboocytopenia (17% vs 1%), decreased appetite (16% vs 7%), vomiting (15% vs 4%), asthenia (13% vs 4%), peripheral neuropathy (13% vs 5%), and epistaxis (11% vs 1%).

Grade 3/4 adverse reactions reported (≥10%) occurring at a higher incidence in the IBRANCE plus letrozole vs letrozole alone group include neutropenia (54% vs 1%) and leukopenia (19% vs 0%). The most frequently reported serious adverse events in patients receiving IBRANCE were pulmonary embolism (4%) and diarrhea (2%).

General dosing information: The recommended dose of IBRANCE is 125 mg taken orally once daily for 21 days followed by 7 days off treatment in 28-day cycles. IBRANCE should be taken with food and in combination with letrozole 2.5 mg once daily continuously.

Patients should be encouraged to take their dose at approximately the same time each day. Capsules should be swallowed whole. No capsule should be ingested if it is broken, cracked, or otherwise not intact. If a patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Management of some adverse reactions may require temporary dose interruption/delay and/or dose reduction, or permanent discontinuation. Dose modification of IBRANCE is recommended based on individual safety and tolerability.

Drug interactions: Avoid concurrent use of strong CYP3A inhibitors. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg/day. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided.

Avoid concomitant use of strong and moderate CYP3A inducers. The dose of the sensitive CYP3A substrates with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

Hepatic and renal impairment: IBRANCE has not been studied in patients with moderate to severe hepatic impairment or in patients with severe renal impairment (CrCl <30 mL/min).

**Brief Summary of Prescribing Information**

**IBRANCE® (palbociclib) capsules**
Initial US Approval: 2015

**INDICATIONS AND USAGE**
IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This indication is approved under accelerated approval based on progression-free survival (PFS) [see Clinical Studies]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**DOSAGE AND ADMINISTRATION**

**General Dosing Information.** The recommended dose of IBRANCE is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. IBRANCE should be taken with food in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle. [see Clinical Pharmacology]. Patients should be encouraged to take their dose at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

**Dose Modification.** Dose modification of IBRANCE is recommended based on individual safety and tolerability. Management of some adverse reactions [see Warnings and Precautions] may require temporary dose interruptions/delays and/or dose reductions, or permanent discontinuation.

If dose reduction is required the first recommended dose reduction is 100 mg/day and the second dose reduction is 75 mg/day. If further dose reduction below 75 mg/day is required, discontinue the treatment.

**Dose Modification and Management – Hematologic Toxicities**

<table>
<thead>
<tr>
<th>CTCAE Grade</th>
<th>Dose Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>No dose adjustment is required.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Consider repeating complete blood count monitoring one week later.</td>
</tr>
<tr>
<td>Grade 3 ANC (&lt;1000 to 5000/mm³) + Fever ≥38.5°C and/or infection</td>
<td>Withhold initiation of next cycle until recovery to Grade 2. Resume at next lower dose.</td>
</tr>
<tr>
<td>Grade 3 ANC (&lt;1000 to 5000/mm³)</td>
<td>Withhold IBRANCE and initiation of next cycle until recovery to Grade 2 ≤1000/mm³. Resume at next lower dose.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Withhold IBRANCE and initiation of next cycle until recovery to Grade 2. Resume at next lower dose.</td>
</tr>
</tbody>
</table>

Grading according to CTCAE Version 4.0:
- ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events.
- Monitor complete blood count prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first two cycles, and as clinically indicated.
- Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

**Dose Modification and Management – Non-Hematologic Toxicities**

<table>
<thead>
<tr>
<th>CTCAE Grade</th>
<th>Dose Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>No dose adjustment is required.</td>
</tr>
<tr>
<td>Grade 3 ≥ non-hematologic toxicity (if persisting despite medical treatment)</td>
<td>Withhold until symptoms resolve to:</td>
</tr>
<tr>
<td>Grade 4 ≤</td>
<td>• Grade 5</td>
</tr>
<tr>
<td>Grade 4 ≤ (if not considered a safety risk for the patient)</td>
<td>Resume at the next lower dose.</td>
</tr>
</tbody>
</table>

See manufacturer’s prescribing information for the coadministered product, letrozole, dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

**Dose Modifications for Use With Strong CYP3A Inhibitors.** Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be coadministered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg once daily. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor [see Drug Interactions and Clinical Pharmacology].

**DOSAGE FORMS AND STRENGTHS**

125 mg capsules: opaque hard gelatin capsules, size 0, with caramel cap and body, printed with white ink “PBC” on the cap, “PBC 125” on the body.

100 mg capsules: opaque hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink “PBC” on the cap, “PBC 100” on the body.

75 mg capsules: opaque hard gelatin capsules, size 2, with light orange cap and body, printed with white ink “PBC” on the cap, “PBC 75” on the body.

**CONTRAINDICATIONS:** None

**WARNINGS AND PRECAUTIONS**

Neutropenia. Decreased neutrophil counts have been observed in clinical trials with IBRANCE. Grade 3 (57%) or 4 (5%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole in the randomized clinical trial (Study 1). Median time to first episode of grade 3 neutropenia per laboratory data was 15 days (13-117 days). Median duration of Grade 3 or 4 neutropenia was 7 days [see Adverse Reactions]. Febrile neutropenia events have been reported in the IBRANCE clinical program, although no cases of febrile neutropenia have been observed in Study 1. Monitor complete blood count prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first two cycles, and as clinically indicated.

Drug interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia [see Dosage and Administration].

Infections. Infections have been reported at a higher rate in patients treated with IBRANCE plus letrozole compared to patients treated with letrozole alone in Study 1. Median time to first infection of grade 3 or 4 infections occurred in 3% of patients treated with IBRANCE plus letrozole whereas no patients treated with letrozole alone experienced a Grade 3 or 4 infection. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Pulmonary Embolism. Pulmonary embolism has been reported at a higher rate in patients treated with IBRANCE plus letrozole (5%) compared with no cases in patients treated with letrozole alone in Study 1. Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate.

**Embryofetal Toxicity.** Based on findings in animals and mechanism of action, IBRANCE can cause fetal harm. IBRANCE caused embryofetal toxicities in rats and rabbits at maternal exposures that were greater than or equal to 4 times the human clinical exposure based on area under the curve (AUC). Advise females of reproductive potential to use effective contraception during therapy with IBRANCE and for at least two weeks after the last dose [see Use in Specific Populations and Clinical Pharmacology].
ADVERSE REACTIONS

Clinical Studies Experience. Because clinical trials are conducted under varying conditions, adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus letrozole alone was evaluated in Study 1. The data described below reflect exposure to IBRANCE in 83 out of 160 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of treatment in Study 1. The median duration of treatment for palbociclib was 13.8 months while the median duration of treatment for letrozole on the letrozole-alone arm was 24.7 months.

Dose reductions due to an adverse reaction of any grade occurred in 38.6% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole in Study 1.

Permanent discontinuation due to an adverse event occurred in 7 of 83 (8.5%) patients receiving IBRANCE plus letrozole, and in 2 of 77 (3%) patients receiving letrozole alone. Adverse reactions leading to discontinuation for those patients receiving IBRANCE plus letrozole included neutropenia (6%), asthenia (1%), and fatigue (1%).

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus letrozole arm were neutropenia, leucopenia, fatigue, anemia, upper respiratory tract infection, nausea, stomatitis, diarrhea, thoracopneumonia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and Epstein-Barr virus infection. The most frequently reported serious adverse reactions in patients receiving IBRANCE plus letrozole were pulmonary embolism (3 of 83; 3.6%) and diarrhea (2 of 83; 2.4%).

An increased incidence of infections events was observed in the palbociclib plus letrozole arm (55%) compared to the letrozole-alone arm (34%). Febrile neutropenia events have been reported in the IBRANCE clinical program, although no cases were observed in Study 1. Grade ≥3 neutropenia was managed by dose reductions and/or dose delay or temporary discontinuation consistent with a permanent discontinuation rate of 6% due to neutropenia [see Dosage and Administration].

The following table presents adverse drug reactions (≥10%) reported in patients who received IBRANCE plus letrozole or letrozole alone.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IBRANCE + Letrozole (N=83)</th>
<th>Letrozole Alone (N=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 events</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>URI*</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 events</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>URI*</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>General disorders</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Total Number of Patients</strong></td>
<td>83</td>
<td>77</td>
</tr>
</tbody>
</table>

• Adverse Reaction rates reported in the table include all reported events regardless of causality.
• Grading according to CTCAE Version 3.0.
• CTCAE=Common Terminology Criteria for Adverse Events; N=number of subjects; N/A=not applicable; URI=Upper respiratory infection.
• *URI includes: Influenza, Influenza like illness, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper respiratory tract infection.
• Peripheral neuropathy includes: Neuropathy peripheral, Peripheral sensory neuropathy.
• Stomatitis includes: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.
• Grade 1 events ≥1%; Grade 2 events ≥1%. No grade 3 events, Grade 4 events ≥1%.

Drug Interactions

Effect of CYPIA3 Inhibitors. Coadministration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. Avoid concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole). Avoid grapefruit or grapefruit juice during IBRANCE treatment. If coadministration of IBRANCE with a strong CYP3A inhibitor cannot be avoided, reduce the dose of IBRANCE [see Dosage and Administration and Clinical Pharmacology].

Effect of CYP3A Inducers. Coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85%. Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine and St John’s Wort) [see Clinical Pharmacology].

Coadministration of moderate CYP3A inducers may also decrease the plasma exposure of IBRANCE. Avoid concomitant use of moderate CYP3A inducers (e.g., bosentan, efavirenz, estramustine, fluoxetine, and nefazodone) [see Clinical Pharmacology].

Drugs That May Have Their Plasma Concentrations Altered by Palbociclib. Coadministration of midazolam with multiple doses of IBRANCE increased the midazolam plasma exposure by 61%, in healthy subjects, and decreased the administration of midazolam alone. The dose of the strong CYP3A substrate with a narrow therapeutic index (e.g., alfenatil, cyclosporine, diltiazem, erythromycin, everolimus, fentanyl, ketoconazole, quinidine, simvastatin and tacrolimus) may need to be reduced as IBRANCE may increase their exposure [see Clinical Pharmacology].

USE IN SPECIFIC POPULATIONS

Pregnancy. Based on findings in animals and mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology]. In animal studies, palbociclib was teratogenic and fetotoxic at maternal exposures that were ≥4 times the human clinical exposure based on AUC at the recommended dose level for IBRANCE. Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine and St John’s Wort) [see Clinical Pharmacology].

There are no data on the presence of palbociclib in human milk, the effects of IBRANCE on the breastfed infant, or the effects of IBRANCE on the breastfed infant due to the potential for serious adverse reactions in nursing infants from IBRANCE, advise a nursing woman to discontinue breastfeeding during treatment with IBRANCE.

Females and Males of Reproductive Potential. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least two weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with IBRANCE [see Use in Specific Populations].

Based on findings in animals, male fertility may be compromised by treatment with IBRANCE [see Carcinogenesis, Mutagenesis, Impairment of Fertility].

Pediatric Use. The safety and efficacy of IBRANCE in pediatric patients have not been studied.

Geriatric Use. Of 84 patients who received IBRANCE in Study 1, 37 patients (44%) were ≥65 years of age and 8 patients (10%) were ≥75 years of age. No overall differences in safety or effectiveness of IBRANCE were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment. Based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild hepatic impairment (total bilirubin ≤ULN and AST = ULN), or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology].

Renal Impairment. Based on a population pharmacokinetic analysis that included 183 patients, where 73 patients had mild renal impairment (60 mL/min ≤CrCl <90 mL/min), and 29 patients had the renal impairment (CrCl <60 mL/min), mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with severe renal impairment [see Clinical Pharmacology].

OVERDOSAGE

There is no known antidote for IBRANCE. The treatment of overdose of IBRANCE should consist of general supportive measures.

PARENTAL COUNSELING INFORMATION

• Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, diarrhea, shortness of breath, weakness or any increased tendency to bleed and/or to bruise [see Warnings and Precautions].

• Advise patients to immediately report any signs or symptoms of pulmonary embolism, such as shortness of breath, chest pain, tachypnea, and tachycardia [see Warnings and Precautions].

• Advise patients to take IBRANCE with food and swallow IBRANCE capsules whole. IBRANCE may interact with grapefruit. Patients should not consume grapefruit or grapefruit juice during IBRANCE therapy and for at least two weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with IBRANCE [see Use in Specific Populations].

• IBRANCE may interact with grapefruit. Patients should not consume grapefruit or grapefruit juice during IBRANCE therapy and for at least two weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with IBRANCE [see Warnings and Precautions and Use in Specific Populations].

Rx only

Issued: February 2015
ULN=upper limit of normal.

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Evolving Diagnostic and Therapeutic Strategies in the Management of Psoriasis

Gary M. Owens, MD

Summary
Psoriasis, particularly when moderate to severe, can cause significant morbidity and affect quality of life. Several biologic agents have been approved that target some of the underlying immune mechanisms of this disease. Managed care has implemented numerous strategies to manage access and cost of this medication category but will be increasingly challenged as more biologics reach the market.

Key Points
• Treatments need to be targeted to the degree of disease severity and tailored to patient needs.
• Guidelines for treatment exist, but they are relatively nonspecific.
• Targeted biologic treatments are effective for moderate to severe disease.
• Biologic treatments present challenges to payers who must manage both access and cost.
• Many additional agents are on the horizon which will further complicate payer management of this class.

Psoriasis is a immune-mediated inflammatory disease of the skin that can manifest at any age but most commonly occurs in those 20 to 30 and 50 to 60 years old. It affects about 2 percent of the overall population. Eighty-five to 90 percent of cases are plaque psoriasis. The majority of those affected have mild disease (65%), with 35 percent having moderate to severe disease. Severity is determined by the percentage of the body affected (Exhibit 1).²

Skin changes are the primary clinical feature of this disease. The typical clinical findings of erythema and scaling are the result of hyper-proliferation and abnormal differentiation of the epidermis, plus inflammatory cell infiltrates and vascular changes. Specifically, there are increased numbers of epidermal stem cells, increased numbers of cells undergoing DNA synthesis, a shortened cell cycle time for keratinocytes (36 hours compared with 311 hours in normal skin), and a decreased turnover time of the epidermis (four days from basal cell layer to stratum corneum compared with 27 days in normal skin).

Both genetics and environment play a role in the development of psoriasis. Psoriasis has long been known to occur in families. Approximately 40 percent of patients with psoriasis or psoriatic arthritis have a family history of these disorders in first-degree relatives. Family studies in psoriatic arthritis have demonstrated that the disease is 100 times more likely to occur among family members than among unrelated controls. Psoriasis tends to be concordant among monozygotic twins more commonly than among dizygotic twins. Environmental triggers in those genetically susceptible include infection, physical or psychological stress, and medications; however, they are not common to every patient. Smoking, vitamin D deficiency, and obesity are other environmental risk factors.

Moderate to severe psoriasis is associated with significant morbidity. Those with moderate to severe psoriasis are significantly more likely to have comorbidities, including psoriatic arthritis, cardiovascular disease, depression, diabetes, hypertension, and obesity compared with those with mild disease.²
Those with severe psoriasis are 58 percent more likely to have a major cardiac event and 43 percent more likely to have a stroke.\textsuperscript{2} Up to 30 percent of people with psoriasis also develop psoriatic arthritis.\textsuperscript{3} The systemic inflammatory effect of this disease likely contributes to the risk for many of these comorbidities.

Patients with psoriasis incur greater health care resource utilization and costs compared with the general population. Psoriasis severity also is positively associated with increased health care resource utilization and costs.\textsuperscript{4} Compared with control patients, patients with psoriasis had significantly greater total health care costs ($5,529 vs. $3,509), including greater medical costs ($3,925 vs. $2,687) and drug costs ($1,604 vs. $822; all p < 0.0001).

As more is learned about the inflammatory nature of this disease, therapy targeting various points in the disease process has been or is being developed. Some of the mediators of inflammation involved in psoriasis are tumor necrosis factor alpha (TNF-\(\alpha\)) and interleukins 12, 23, 22, and 17A (IL-12, IL-23, IL-22, IL-17A). In psoriasis, TNF-\(\alpha\) is believed to be broadly active at multiple points in the inflammatory cascade. Various cells produce TNF-\(\alpha\), including T cells, macrophages, mast cells, and keratinocytes, leading to cytokine production and immune cell recruitment. IL-12 is thought to be the primary driver of the differentiation and activation of the T helper one (Th1) cell subset. IL-23 is expressed at sites of inflammation in the skin by dendritic cells and possibly also by keratinocytes. IL-23 is believed to be essential for stabilizing the Th17 cell. IL-22 has both pro-inflammatory and tissue-protective properties. It modulates tissue responses during inflammation by inducing tissue proliferation, stimulating production of antimicrobial molecules, and can prevent damage and aid in tissue repair. IL-22 is highly expressed in several different chronic inflammatory conditions, including psoriasis, inflammatory bowel disease, and rheumatoid arthritis and is produced primarily by Th17 cells. In psoriasis, IL-22 contributes to keratinocyte hyperproliferation and expression of antimicrobial peptides and has synergistic effects with IL-17A. IL-17A is released from Th17 cells or innate immune cells and can act on keratinocytes to trigger hyperproliferation, release of antimicrobial peptides, which can stimulate innate immune responses, secretion of other proinflammatory; and release of chemokines that cause recruitment of neutrophils, T cells, and dendritic cells.

In addition, IL-17A can have synergistic inflammatory effects with other cytokines, such as TNF-\(\alpha\) and IL-22. Over the various cytokines that fuel chronic inflammation in psoriasis, TNF- \(\alpha\), IL-23, and IL-17A appear to play a central role in the disease and are thus logical targets of therapy.

The goals of psoriasis therapy are to gain initial rapid control of the disease; decrease the involvement of body surface area; decrease erythema, scaling and the thickness of lesions of individual plaques; maintain the patient in long-term remis-
sion and avoid relapse; avoid adverse effects as much as possible; and improve the patient’s quality of life. Treatment should be individually tailored to meet the needs of each patient, weighing risk/benefit profile, tolerance to therapy, presence of comorbid conditions, and emotional impact of the disease on the given patient.

Guidelines for treatment exist, but they are relatively nonspecific and have not been recently updated. Limited plaque psoriasis responds well to topical corticosteroids and emollients. Alternatives for mild to moderate disease include tar, topical retinoids (tazarotene), and vitamin D analogs, including calcipotriene and calcitriol. For facial or intertriginous areas, topical tacrolimus or pimecrolimus may be used as alternatives or as corticosteroid sparing agents, though improvement may not be as rapid. Localized phototherapy is another option for recalcitrant mild to moderate disease.

With proper adherence, considerable improvement with high-potency topical therapies may be seen in as little as one week, though several weeks may be required to demonstrate full benefits. Combinations of potent topical corticosteroids and either calcipotriene (Dovonex®), calcitriol, tazarotene (Tazorac®), or UVB phototherapy are commonly prescribed by dermatologists. Calcipotriene in combination with potent topical corticosteroids is highly effective for short-term control. Calcipotriene alone can then be used continuously and the combination with potent corticosteroids used intermittently (a few days a week) for maintenance.

Severe psoriasis requires phototherapy or systemic therapies such as retinoids, methotrexate, cyclosporine, or biologic immune modifying agents. Biologic agents used in the treatment of psoriasis include the anti-TNF agents [certolizumab pegol (Cimzia®), etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®) and golimumab (Simponi®)]; an anti-IL-12/23 antibody [ustekinumab (Stelara®)] and a phosphodiesterase 4 (PDE4) inhibitor [apremilast (Otezla®)]. The last agent is a recently approved oral agent making it the first oral biologic for psoriasis. Improvement usually occurs within weeks of starting a biologic.

Treatment of inflammatory conditions including psoriasis is the largest category of specialty spending. In 2013, inflammatory conditions were the most expensive specialty therapy class for the fifth year in a row. Per-member-per-year (PMPY) spend in this category was $63.31 in 2013, up 21.8 percent from 2012. There are numerous issues related to the increase in biologic use in the treatment of psoriasis and many other diseases affecting managed care payers (Exhibit 2).

Payers are trying numerous approaches to control biologic costs, but it is still about the right therapy for the right patient while being fiscally responsible. Management strategies include step therapy through topicals, phototherapy and nonbiological immunomodifiers before biologicals, prior authorization of biological agents, limited prescribing of biologicals.
to appropriate specialists, and managing site of service. Newer benefit designs are including multiple tiers of specialty benefit, specialty specific formularies, and alignment of patient incentives. Management of psoriasis therapy will become more complicated as more new agents are approved. Exhibit 3 lists a few of the agents under investigation for psoriasis and psoriatic arthritis.

**Conclusion**

Psoriasis is a moderately prevalent inflammatory condition with varying degrees of severity. Treatments need to be targeted to the degree of disease severity and tailored to the needs of patients. Guidelines for treatment exist, but they are relatively nonspecific. With an enhanced understanding of the underlying inflammatory mediators of psoriasis, targeted biologic treatments are now available. The cost of therapy for this class has grown significantly and presents challenges to payers who must manage both access and cost. There is a robust pipeline of agents that will further complicate payer management of this class.

Gary M. Owens, MD, is President of Gary Owens Associates.

**References**


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**Exhibit 3: Selected Investigational Agents for Psoriasis**

- **Briakinumab**: an injectable anti-inflammatory (IL-12/-23 blocker) for psoriasis.
- **Certolizumab pegol (Cimzia)**: an injectable anti-inflammatory (TNF blocker) for psoriatic arthritis. This drug is FDA approved for treatment of rheumatoid arthritis and Crohn’s disease.
- **CF101**: an oral anti-inflammatory (adenosine A3 receptor inhibitor) for psoriasis.
- **Tofacitinib (Xeljanz)**: an oral anti-inflammatory (JAK kinase inhibitor) for psoriasis and psoriatic arthritis already approved for RA.
- **Voclosporin**: an oral immune suppressant (calcineurin blocker) for psoriasis.
- **9-cis-beta-carotene**: an oral beta-carotene to be combined with UVB light therapy for psoriasis.
- **Brodalumab**: an injectable anti-inflammatory (IL-17 receptor blocker) for psoriasis.
OVERACTIVE BLADDER (OAB) IS NOT A disease but is a common symptom complex that has enormous impact on those affected. It is associated with urgency (a strong, sudden desire to void), frequency (more than 8 times per 24 hours), and a large amount of urinary leakage in patients who have episodes of incontinence. 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 U.S. adults over 40 years of age reported symptoms of OAB at least “sometimes.”

The most common risk factor for OAB is increasing age. Other common risk factors include obesity, Caucasian race, depression, and hormone replacement therapy. Neurogenic OAB may be secondary to multiple sclerosis, Parkinson’s disease, dementia, spinal cord injury, stroke, or diabetes.

OAB is more than the symptoms. Urinary tract infections, vulvovaginitis, skin infections, depression, falls, and fractures are common comorbidities. Additionally, OAB has a significant impact on quality of life (QOL). OAB symptoms compromise many aspects of patient QOL, including physical, occupational, sexual, psychological, domestic, and social aspects. OAB can affect physical QOL by restricting the amount of physical activity the patient will or can perform. OAB can lead to absence from work and, therefore, decreased productivity. OAB can reduce social interaction and limit travel, or at least hinder travel so it must be planned around accessibility to a toilet. Hygienically, specialized underwear (pads) and bedding may be required. OAB can also affect sexual QOL because it might lead to avoidance of sexual contact and intimacy. OAB can negatively affect the patient by causing guilt or depression; loss of self-esteem; and fear of being a burden, of lack of bladder control, or of an odor of urine.

The annual per capita cost of OAB has been estimated to be $1,925 of which 75 percent is direct medical costs, 22 percent lost productivity, and 4 percent direct nonmedical costs. This is $65.9 bil-
lion for the estimated 34 million people with OAB in the United States. The costs are projected to increase to $82.6 billion by 2020.\(^5\)

Although there can be overlap, a simple symptom assessment can differentiate between OAB, stress incontinence, and mixed incontinence (Exhibit 1).\(^6\) Screening for OAB can be done with simplified screening tools such as the OAB V-8. This validated in primary care settings tool comprises the first eight items of a larger screening tool.\(^7\) Patients rate how bothered they are by frequency, urgency, nocturia and urge urinary incontinence (UUI) on a scale of 0 to 5 (not at all; a very great deal). Reliability, validity and responsiveness have been demonstrated in clinical trials. OAB V-8 and other clinical research and patient management tools can be accessed for free at www.oabq.com. Screening can be further simplified by asking just two questions: (1) Is your bladder causing you any problems? (2) Do you have trouble controlling your urine?

Clinical practice guidelines for screening, diagnosis, and management of OAB recommend that the goal of the initial evaluation is to rule out other conditions which may cause or mimic OAB.\(^8\) The evaluation should include a focused history, a focused physical examination (abdominal, pelvic, and neurologic), an urinalysis, and the degree of bother. A bladder diary and post-void residual can supplement the evaluation. Urodynamics, cystoscopy, and ultrasound are not indicated in the initial evaluation of an uncomplicated patient. Post-void residual is not necessary for uncomplicated patients if the patient is being treated with first-line behavioral interventions. It is necessary for obstructive symptoms, history of incontinence or prostatic surgery, neurologic disease, and in men with symptoms before antimuscarinic therapy can be started. Certain patients should be referred to an urologist for further evaluation, including those with hematuria, significant pelvic organ prolapse, recurrent urinary tract infections, increased post-void residual, failure to improve with medical therapy, and prior pelvic surgery.

Management of OAB is multifaceted and includes education, behavioral modification, medications, and surgical procedures. Patients have to be educated regarding normal bladder function. They may have a goal of only voiding three times per day, but this may not be realistic. Getting to a more normal voiding pattern (less than 8 times daily) is the ultimate goal of treatment. Patients need to understand that OAB is not cured, it is managed. Patient goals are often task oriented instead of number oriented (i.e., be able to go out to dinner).

Behavioral modification is the first-line treatment. Useful strategies for behavioral modification include patient education, timed or delayed voiding, and positive reinforcement of any changes made. Pelvic floor exercises are useful for women, primarily those with concomitant stress urinary incontinence. Additionally, learning to tighten the correct muscles 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

<table>
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<th>Exhibit 1: Differential Diagnosis: AB and Stress Incontinence(^6)</th>
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<td>Frequency with urgency (&gt; 8 times per 24 hours)</td>
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<td>Leaking during physical activity; eg. Coughing, sneezing, lifting</td>
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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.

Pharmacologic therapy is the next step in managing OAB. For many years only antimuscarinic agents were available for treatment. In recent years, another class of medication, beta agonists, has been approved.

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. Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride are all antimuscarinic agents. All are effective for treating OAB symptoms, but there are differences in adverse effect profiles and thus tolerability. Now, there are also multiple different dosage forms, including extended-release oral, liquids, topical patch, topical gel, and bladder instillation. Finding an effective and tolerable antimuscarinic can require trying several different agents.

The guidelines suggest that clinicians should manage constipation and dry mouth before abandoning effective antimuscarinic therapy. Many patients will fluid restrict without realizing the impact on their bowel habits and the bladder irritant effect of concentrated urine. Exhibit 2 provides some tips for managing constipation and dry mouth.

Because of the anticholinergic effects, there are concerns regarding antimuscarinic use in elderly patients. Many commonly prescribed drugs have anticholinergic properties. Clinical manifestations of anticholinergic toxicity are likely to be nonspecific and reflect the effects of cumulative anticholinergic burden. Clinicians need to minimize the number of medications with anticholinergic effects in their elderly patients.

Mirabegron [Myrbetriq®] is a selective beta-3 adrenoceptor agonist. It activates beta-3 adrenoceptors on the detrusor muscle of bladder to facilitate filling of the bladder and improved storage. Essentially, this is a bladder relaxant that does not affect detrusor muscle contractility. 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.

Mirabegron is a CYP2D6 inhibitor so it may cause some drug interactions. Additionally, it can increase blood pressure which must be monitored. Unlike with the antimuscarinics, dry mouth or constipation is a major concern with this agent, so it would be a good choice for the person who already has these issues.

With medications, patients should see a response within one to two weeks of starting therapy. A significant reduction should be seen by the end of a month. Therefore, patients should give a medication at least one month to assess efficacy. Response can continue to increase out to three months.

For effective control of their symptoms, most patients will need both behavioral and pharmacologic therapy, which is more effective than either alone.9 If combination therapy fails, patients will need to move to third-line therapies. Third-line therapies include neuromodulation and onabotulinum toxin A injections. Neuromodulation can be with either sacral nerve stimulation or percutaneous tibial nerve stimulation.

Sacral nerve stimulation (SNS) is a minimally invasive surgical procedure that requires a two-step process with an initial test stimulation and, if good response occurs with the test, permanent stimulator implantation. Small doses of electric current are sent from the stimulator to the sacral nerve. A systematic review of four randomized, controlled trials found that 80 percent of patients achieved continence or greater than 50 percent improvement in main incontinence symptoms after SNS versus 3 percent of control subjects.10 The benefits persisted for three to five years after implantation. Patients may require reoperation for relocation of the generator due to pain or infection. The reoperation rate in implanted cases is 33 percent.11

Percutaneous tibial nerve stimulation (PTNS) is an external device treatment that is given in the office for 30 minutes once a week for 12 weeks. Patients who respond may require occasional medication to sustain response. In a trial of PTNS compared with antimuscarinic therapy, 79.5 percent of those in the PTNS arm reported significant improvement compared to 54.8 percent of subjects on tolterodine.12 It is an alternative to sacral nerve stimulation if the patient has failed other options and doesn’t want the implanted device.

Onabotulinum toxin A [Botox®] works at the parasympathetic nerve terminal to prevent the release of acetylcholine. In OAB, this agent reduces contractions of the detrusor muscle. The key issue with this toxin is the limited effective range of an injection. Thus, 20 to 30 injection sites one centimeter apart are required to treat the entire bladder. It takes about two weeks for efficacy onset. Patients are seen at two weeks to check for efficacy and urinary retention with a post-void residual.

Although the most common adverse effect is urinary tract infection, 5.4 percent of patients will develop urinary retention. Due to the risk of urinary retention, only people who are willing and able to initiate catheterization post-treatment, if required, should be considered for treatment. The need for self-catheterization can last for the duration of the drug efficacy, which is 12 weeks or more. The people who are at most risk for this adverse effect are the frail elderly.

In a Phase III randomized, placebo controlled trial, onabotulinum toxin A injections significantly decreased the frequency of UUI episodes per day versus placebo (-2.65 vs -0.87, p<0.001).13 Nine percent of the patients treated with the toxin had no incontinence versus 6.5 percent of those given a placebo injection.

There is a maximum total body dose of the toxin that can be given. This is primarily an issue if someone is getting injections somewhere else in the body for another indication. Onabotulinum toxin A injections do not cause a permanent change; repeat injections will be required. The median time between injections appears to stay about the same over time within an individual but will vary from person to person.

One last issue to discuss related to OAB is lower urinary tract symptoms (LUTS) in men. Male LUTS are highly prevalent among older men and have a negative impact on health-related quality of life. These men may have storage, voiding, and post-micturition symptoms (Exhibit 3). The question for each individual will be determining if the symptoms are from the prostate, bladder, or both.

Detrusor overactivity occurs in about 50 percent of men with prostate-related bladder outlet obstruction (BOO).14 Over time, BOO leads to cholinergic denervation of detrusor muscle fibers and supersensitivity of muscarinic receptors to acetylcholine.15 It also results in ischemia, increased detrusor collagen content, changes in electrical properties of detrusor smooth muscle and reorganization of spinal micturition reflex.16 BOO is not a prerequisite for OAB in men. OAB symptoms alone are highly prevalent in men. Prostatic pathology and coexisting OAB symptoms are not always causally related.

Pharmacotherapies that target the prostate (alphal-receptor antagonists and 5 alpha-reductase inhibitors) often fail to alleviate OAB symptoms, and may not be the most appropriate therapy for men.
with storage LUTS. Multiple studies have suggested that antimuscarinic therapy, alone or in combination with alpha1-receptor antagonists, improve OAB symptoms in men with and without bladder outlet obstruction. Men with mild obstruction, smaller prostates, low prostate specific antigen levels, and OAB symptoms are most likely to benefit from monotherapy with antimuscarinics.17,18 For those men with more prostate-related symptoms, starting with an alpha-blocker and then adding an antimuscarinic agent for continuing OAB symptoms is a reasonable approach.18

A few studies have been published evaluating mirabegron in men with LUTS. In men with OAB unresponsive to antimuscarinics or related to BPH, mirabegron was as effective as antimuscarinics for OAB.19 Mirabegron improved not only OAB symptoms related to BPH, but also voiding symptoms in men with a low and mild incidence of adverse effects. PVRs did not change significantly throughout this study. A study specifically evaluating urodynamic safety in males with LUTS and BOO found that mirabegron did not adversely affect urodynamic (maximum urinary flow and detrusor pressure at maximum urinary flow) compared with placebo after 12 weeks of treatment.20

Conclusion
OAB is a common condition that causes major impact on quality of life. It can be identified by a simplified evaluation and effectively managed with therapy. There are three tiers of therapy, with behavioral interventions first line. Second line is pharmacologic therapy with anticholinergic agents and beta3 agonists. Third line are onabotulinum toxin A intra detrusor injections and neuromodulation. Setting appropriate goals and treatment expectations and managing adverse effects are critical to a successful outcome. No single therapy is ideal for all patients.

Pamela Ellsworth, MD, is a Professor of Urology at UMassMemorial Medical Center at the University of Massachusetts Medical School.

References
Improving Patient Outcomes: Updated Treatment Strategies in the Management of Acute Coronary Syndrome

E. Magnus Ohman, MD, FRCPI, FESC, FACC
For a CME version of this, please go to www.namcp.org/cmeonline.htm which is supported by an educational grant from AstraZeneca.

Summary
After an episode of acute coronary syndrome (ACS), most patients will be started on dual antiplatelet therapy (DAPT). The regimen will include aspirin and one of the other antiplatelet agents. Evidence on which antiplatelet agent to combine with aspirin and duration of therapy for optimal outcome continues to evolve.

Key Points
- Ticagrelor is superior to clopidogrel, with a survival advantage in all ACS.
- Prasugrel is superior to clopidogrel in patients after percutaneous coronary intervention but has a higher bleeding risk.
- DAPT for one year is the current standard.
- Longer therapy may be better but more trials are needed.
- Switching antiplatelet agents after ACS may be problematic.

ACUTE CORONARY SYNDROMES (ACS) OCCUR when blood flow to the heart is disrupted. As shown in Exhibit 1, thrombin plays a central role among tissue injury, coagulation, and platelet response. When plaque ruptures, collagen and tissue factor exposure to blood in the vessel leads to thrombin activation and thrombus formation. Because the system is redundant, it takes more than one medication to block thrombus formation and reduce risk of future ACS episodes – dual antiplatelet therapy (DAPT).

Evidence-based therapy is informed by the ACS clinical management guidelines.1,2 Guideline adherence is important to achieve optimal patient outcomes. Based on work by Peterson and colleagues, for every 10 percent increase in guideline adherence in hospitals, there was a 10 percent decrease in mortality (Exhibit 2).3 Thus, the higher the guideline adherence, the lower the patient mortality.

One current challenge in ACS management with DAPT is the choice of the antiplatelet agent to add to aspirin. The three antiplatelet agents that are used in the outpatient setting are clopidogrel (Clopidogrel®, generic), ticagrelor (Brilinta®), and prasugrel (Effient®). Clopidogrel has been the standard of care, but newer data suggest the other two have advantages over clopidogrel.4

For clopidogrel, the major issue is determining the appropriate dose. The standard dose is 300 mg daily. Some trials have suggested that doubling the dose to 600 mg may improve outcomes, but the issue is not entirely straightforward.5 Double dosing does decrease the rate of cardiovascular events but does not lead to overall benefit.

Ticagrelor is a newer agent with a demonstrated survival advantage at one year post-ACS. Despite this evidence, less than 5 percent of patients receive this agent. Exhibit 3 shows how this agent lowers mortality by 20 percent compared to clopidogrel.6 Early in therapy (first 30 days), the mortality difference is not major, but the benefit of ticagrelor increases over time. Irrespective of age, mortality is lower with ticagrelor but the rate of bleeding is higher in those greater than 75, but not statistically significantly higher. This agent is given twice a day.
which is a disadvantage compared to clopidogrel.

Prasugrel is the newest potent antiplatelet therapy. Compared to clopidogrel in patients who underwent a percutaneous coronary intervention (PCI), one trial showed a 24 percent reduction in the rate of myocardial infarction with prasugrel. There was an increased rate of bleeding with prasugrel, and there were concerns that some patients, particularly the elderly, were being overdosed in this trial. Because of the safety concerns, prasugrel is probably not first choice for antiplatelet therapy after PCI. It has not been shown to be advantageous over clopidogrel in medically managed patients. Trials that have gone beyond one year do suggest a long-term benefit of prasugrel.

Another challenge in DAPT is whether preloading antiplatelet therapy should be done. Standard practice today is to give these agents in the emergency room before a decision about invasive therapy such as PCI is made, but there is no evidence this practice leads to an overall benefit. When all the trials conducted with clopidogrel are combined, a benefit of preloading is not found. Preloading with prasugrel also did not show a benefit but did lead to more episodes of major bleeding. Another issue with preloading is a percentage of patients will need

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**Exhibit 1: Thrombus Formation**

**Exhibit 2: Linking Guideline Adherence and Mortality**

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to have coronary artery bypass grafts (CABG), and preloading leads to higher rates of bleeding during and after surgery. The guidelines recommend stopping either clopidogrel or ticagrelor five days before CABG and prasugrel seven days before CABG.\textsuperscript{1,2}

Cangrelor is a direct platelet P2Y12 receptor antagonist, which may revolutionize the use of antiplatelet agents during acute ACS. It has a very short half-life with an onset of four minutes and duration of antiplatelet effect of 60 minutes. The hope had been that this intravenous agent could be given at the presentation of ACS but then stopped and its effect quickly reversed if the patient needed a procedure. It has been studied in three large trials against clopidogrel before CABG and PCI.\textsuperscript{10-12} Minor bleeding does appear to be more common with cangrelor, but major bleeding is not. Despite fewer bleeding events during cardiac surgery, cangrelor carries the risk of autoimmune reactions manifesting as dyspnea. In February 2014, the FDA Cardiovascular and Renal Drugs Advisory Committee voted to recommend against approval of cangrelor for use in patients undergoing PCI or cardiac stent procedures or those that require bridging from oral antiplatelet therapy to surgery. With additional data, this agent may eventually be approved.

Another issue with DAPT is whether to switch antiplatelet agents at hospital discharge or later from the more expensive twice a day ticagrelor or once a day prasugrel to the generic once a day clopidogrel. Once a day clopidogrel may result in improved adherence and reduced incidence of bleeding or other adverse effects. On one side, a switch is reasonable as any DAPT is better than aspirin alone, and patients will not be compliant with therapy that causes adverse effects. On the other side, switching to generic clopidogrel may not save money because ischemic events are costly and occur more often with clopidogrel, compared to the other two agents. There is some evidence that switching to clopidogrel at discharge leads to a higher rate of events at 30 days post hospitalization compared to continuing a second generation agent.\textsuperscript{13} It is reasonable to switch to clopidogrel if the patient gets started on warfarin because the other agents have not been studied in combination with warfarin. Switching because of age alone is not reasonable.

Duration of DAPT after ACS is yet another challenge and is a balance of ischemia risk versus bleeding risk, medication costs, adherence, and adverse effects. After PCI for ACS, DAPT is essential to prevent stent thrombosis and other ischemic events for nine to 12 months. DAPT should be continued for longer in patients who have high-risk PCI (left main artery). It should be continued for the patient’s lifetime in the case of recurrent stent thrombosis. Use of clopidogrel out to three years has been studied, so patients should be switched to it when therapy is continued beyond one year.\textsuperscript{14}

Typically, one year of DAPT has been recom-
mended after placement of a drug-eluting stent, but there has not been an investigation to identify the best time to stop. DAPT has been shown to be especially important for patients to take at least 30 days after stent placement but continuing it beyond 30 days provides the most benefit.

The last challenge in preventing future ACS events is whether dual pathway (antiplatelet and antithrombin) therapy is a viable option to improve outcomes. Combining rivaroxaban 2.5 mg bid with aspirin and clopidogrel reduced death, myocardial infarction, and cardiovascular death rates after ACS at the cost of a modestly increased risk of bleeding. This triple combination has not yet been FDA approved and the 2.5 mg dosage form which was studied is not currently commercially available. Additional trials with this combination are underway.

**Conclusion**

Dual antiplatelet therapy is now a cornerstone of ACS management. Ticagrelor is superior to clopidogrel with a survival advantage in all ACS, whereas prasugrel is superior to clopidogrel in PCI patients. DAPT for at least one year is the current standard after an ACS episode. Patients who are started on ticagrelor or prasugrel should be continued on those rather than switched to clopidogrel. Therapy beyond one year may be better, but more trials are needed. If a decision is made to continue therapy beyond one year, a switch to clopidogrel is then appropriate.

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**References**


[www.namcp.org](http://www.namcp.org) | Vol. 18, No. 2 | Journal of Managed Care Medicine 31
IMPORTANT SAFETY INFORMATION FOR LATUDA

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. LATUDA is not approved for use in patients under the age of 18 years.

CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)
**MAKE LATUDA YOUR CHOICE FOR PATIENTS WITH BIPOLAR DEPRESSION**

- **Efficacy established** in both a monotherapy study and an adjunctive therapy study with lithium or valproate.
  - In these studies LATUDA was superior to placebo in reduction of Montgomery-Åsberg Depression Rating Scale (MADRS) scores at Week 6.
- **Safety and tolerability** evaluated in multiple bipolar depression studies for 6 weeks and 24 weeks.
- **Once-daily dosing**, taken with food (at least 350 calories).

Discover more at LATUDAhcp.com/info

**INDICATIONS AND USAGE**

LATUDA is indicated for treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate. The efficacy of LATUDA was established in a 6-week monotherapy study and a 6-week adjunctive therapy study with lithium or valproate in adult patients with bipolar depression. The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

**WARNINGS AND PRECAUTIONS**

**Cerebrovascular Adverse Reactions, Including Stroke:** In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

**Neuroleptic Malignant Syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Please see additional Important Safety Information, including Boxed Warning, and Brief Summary of Prescribing Information on adjacent pages.
Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

In the short-term, placebo-controlled monotherapy study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.1 ng/mL and was 1.5 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

In the short-term, placebo-controlled adjunctive therapy with lithium or valproate study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.2 ng/mL and was 2.4 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Patients with a preexisting low white blood cell count (WBC) or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, in patients with known cardiovascular disease or history of cerebrovascular disease and in patients who are antipsychotic-naïve.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer’s dementia).

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Suicide: The possibility of suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA were akathisia, extrapyramidal symptoms, and somnolence.

INDICATIONS

LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

Please see Brief Summary of Prescribing Information, including Boxed Warning, on adjacent pages.


Sunovion

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1 INDICATIONS AND USAGE

1.1 Schizophrenia

LATUDA is indicated for the treatment of patients with schizophrenia. The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia [see Clinical Studies (14.1)].

The effectiveness of LATUDA in longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2.2)].

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

4 CONTRAINDICATIONS

- Known hypersensitivity to laroxetine HCl or any components in the formulation. Laroxetine has been observed with laroxetine (see Adverse Reactions (6.1)).
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, midazolam, etc.) [see Drug Interactions (7.1)].
- Strong CYP3A4 inducers (e.g., rifampicin, avasimibe, St. John’s wort, phenytoin, carbamazepine, etc.) [see Drug Interactions (7.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (median duration of 10 weeks), largely in patients taking typical antipsychotic drugs, revealed a risk of death in drug-treated patients of 1.6- to 1.7-times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a clinically significant concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. 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 with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications (the highest incidence in MDD). The risk of differences (drug vs. placebo) however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>4</td>
</tr>
<tr>
<td>18-24</td>
<td>6</td>
</tr>
<tr>
<td>&gt;25</td>
<td>3</td>
</tr>
</tbody>
</table>

5.3 General Disorders During Antipsychotic Treatment

Symptoms of extrapyramidal syndrome (EPS) may occur during antipsychotic treatment, particularly during the period of dosage adjustment. Symptoms of EPS may be characterized by involuntary, sustained, repetitive movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are at risk.

5.4 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are at risk.

5.6 Nonspecific Laboratory Findings

Leukopenia, Neutropenia, and Agranulocytosis:

The proportion of male patients with leukopenia or neutropenia with other antipsychotic drugs is higher than that of placebo. These events were not thought to be drug-related.

5.7 Body Temperature Regulation

The possibility of suicide attempt is inherent in psychotic depression and certain other psychiatric disorders, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidal or symptomatic 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 being treated with antipsychotics for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidal thoughts and behaviors, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for LATUDA should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

5.8 Antidiabetic Agents

A small proportion of patients in placebo-controlled clinical trials of LATUDA had glucose monitoring data available. In the 6-week monotherapy study in adults with bipolar depression who were treated with LATUDA, the proportion of elevations in glucose levels that were ≥5x ULN was 1% for LATUDA-treated patients versus 11% for placebo. This ≤5% difference was not considered to be clinically significant.

6.7 Drug Interactions

The effectiveness of LATUDA in the treatment of mania associated with bipolar disorder has not been established.
patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketocidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 2.

Table 2: Change in Fasting Glucose in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo 20 mg/day</th>
<th>Placebo 40 mg/day</th>
<th>Placebo 80 mg/day</th>
<th>Placebo 120 mg/day</th>
<th>Placebo 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.6</td>
<td>+0.2</td>
<td>-0.4</td>
<td>+2.5</td>
<td></td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in fasting glucose of +1.7 mg/dL at week 24 (n=88).

5.8 Leukopenia, Neutropenia and Agranulocytosis

Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC), underlying disease and other conditions associated with bone marrow depression.

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Neither atypical antipsychotic products nor other antipsychotic products have undergone specific studies evaluating hematopoietic toxicity.

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n=356) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Bipolar Depression

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled bipolar depression studies are presented in Table 7.

Table 7: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo 20 mg/day</th>
<th>Placebo 40 mg/day</th>
<th>Placebo 80 mg/day</th>
<th>Placebo 120 mg/day</th>
<th>Placebo 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.6</td>
<td>+0.8</td>
<td>-0.2</td>
<td>-1.4</td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Table 8: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo 20 mg/day</th>
<th>Placebo 40 mg/day</th>
<th>Placebo 80 mg/day</th>
<th>Placebo 120 mg/day</th>
<th>Placebo 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.6</td>
<td>+0.8</td>
<td>-0.2</td>
<td>-1.4</td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Table 9: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo 20 mg/day</th>
<th>Placebo 40 mg/day</th>
<th>Placebo 80 mg/day</th>
<th>Placebo 120 mg/day</th>
<th>Placebo 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.6</td>
<td>+0.8</td>
<td>-0.2</td>
<td>-1.4</td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Table 10: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo 20 mg/day</th>
<th>Placebo 40 mg/day</th>
<th>Placebo 80 mg/day</th>
<th>Placebo 120 mg/day</th>
<th>Placebo 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.6</td>
<td>+0.8</td>
<td>-0.2</td>
<td>-1.4</td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Table 11: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo 20 mg/day</th>
<th>Placebo 40 mg/day</th>
<th>Placebo 80 mg/day</th>
<th>Placebo 120 mg/day</th>
<th>Placebo 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.6</td>
<td>+0.8</td>
<td>-0.2</td>
<td>-1.4</td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Table 12: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo 20 mg/day</th>
<th>Placebo 40 mg/day</th>
<th>Placebo 80 mg/day</th>
<th>Placebo 120 mg/day</th>
<th>Placebo 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.6</td>
<td>+0.8</td>
<td>-0.2</td>
<td>-1.4</td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Table 13: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo 20 mg/day</th>
<th>Placebo 40 mg/day</th>
<th>Placebo 80 mg/day</th>
<th>Placebo 120 mg/day</th>
<th>Placebo 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>-0.6</td>
<td>+0.8</td>
<td>-0.2</td>
<td>-1.4</td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).
In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA, as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of −0.9 (n=88) and 5.3 (n=88) mg/dL at week 24, respectively.

**Weight Gain**

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

**Schizophrenia**

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 8. The mean weight gain was +0.43 kg for LATUDA-treated patients compared to −0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 [see Clinical Studies (14.1)], respectively. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 4.6% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

**Table 8: Mean Change in Weight (kg) from Baseline in Schizophrenia Studies**

<table>
<thead>
<tr>
<th></th>
<th>LATUDA 20 mg/day (n=65)</th>
<th>LATUDA 40 mg/day (n=64)</th>
<th>LATUDA 80 mg/day (n=64)</th>
<th>LATUDA 120 mg/day (n=60)</th>
<th>LATUDA 160 mg/day (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>−0.3</td>
<td>+0.2</td>
<td>+0.4</td>
<td>+0.6</td>
<td>+0.9</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of −0.63 kg at week 24 (n=755), −0.59 kg at week 36 (n=443) and −0.73 kg at week 52 (n=377).

**Bipolar Depression**

**Monotherapy**

Data from the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in Table 9. The mean weight gain was +0.29 kg for LATUDA-treated patients compared to −0.04 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 2.4% for LATUDA-treated patients versus 0.7% for placebo-treated patients.

**Table 9: Mean Change in Weight (kg) from Baseline in the Monotherapy Bipolar Depression Study**

<table>
<thead>
<tr>
<th></th>
<th>LATUDA 20 mg/day (n=41)</th>
<th>LATUDA 40 mg/day (n=42)</th>
<th>LATUDA 80 mg/day (n=42)</th>
<th>LATUDA 120 mg/day (n=38)</th>
<th>LATUDA 160 mg/day (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>−0.04</td>
<td>+0.04</td>
<td>+0.02</td>
<td>+0.11</td>
<td>+0.09</td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in weight of −0.02 kg at week 24 (n=130).

**Adjuvant Therapy with Lithium or Valproate**

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 10. The mean weight gain was +0.11 kg for LATUDA-treated patients compared to −0.16 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients versus 0.3% for placebo-treated patients.

**Table 10: Mean Change in Weight (kg) from Baseline in the Adjuvant Therapy Bipolar Depression Studies**

<table>
<thead>
<tr>
<th></th>
<th>LATUDA 20 mg/day (n=15)</th>
<th>LATUDA 40 mg/day (n=14)</th>
<th>LATUDA 80 mg/day (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>−0.06</td>
<td>+0.06</td>
<td>+0.09</td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate in the short-term and continued in the longer-term study, had a mean change in weight of +1.28 kg at week 24 (n=86).

**5.7 Hypoprolanemia**

As with other drugs that antagonize dopamine D₂ receptors, LATUDA elevates prolactin levels. LATUDA, as adjunctive therapy with either lithium or valproate in the short-term and continued in the longer-term study, had a mean change in weight of +1.28 kg at week 24 (n=86).

**Table 11: Median Change in Prolactin (ng/mL) from Baseline in Schizophrenia Studies**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
<th>LATUDA 120 mg/day</th>
<th>LATUDA 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>−1.9</td>
<td>−1.1</td>
<td>−1.4</td>
<td>−0.2</td>
<td>+3.3</td>
<td>+3.1</td>
</tr>
<tr>
<td>Females</td>
<td>−0.1</td>
<td>−0.7</td>
<td>−0.9</td>
<td>−0.2</td>
<td>+6.7</td>
<td>+7.1</td>
</tr>
<tr>
<td>Males</td>
<td>−0.7</td>
<td>+2.4</td>
<td>−2.1</td>
<td>+2.1</td>
<td>+7.1</td>
<td>+7.1</td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 2.8% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5× ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5× ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of −0.9 ng/mL at week 24 (n=357), −3.9 ng/mL at week 36 (n=319) and −2.2 ng/mL at week 52 (n=307).

**Bipolar Depression**

**Monotherapy**

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 12.

**Table 12: Median Change in Prolactin (ng/mL) from Baseline in the Monotherapy Bipolar Depression Study**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.3</td>
<td>+1.7</td>
<td>+3.5</td>
</tr>
<tr>
<td>Females</td>
<td>+0.0</td>
<td>+1.8</td>
<td>+5.3</td>
</tr>
<tr>
<td>Males</td>
<td>+0.4</td>
<td>+7.0</td>
<td>+8.8</td>
</tr>
</tbody>
</table>

Patients were randomly assigned LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo.

In the uncontrolled, open-label, longer-term bipolar depression study, LATUDA was associated with a mean change in prolactin of +1.15 mg/mL at week 24 (n=130).

**Adjuvant Therapy with Lithium or Valproate**

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.9 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dose range are shown in Table 13.

**Table 13: Median Change in Prolactin (ng/mL) from Baseline in the Adjunctive Therapy Bipolar Depression Studies**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>0.0</td>
<td>+2.6</td>
</tr>
<tr>
<td>Females</td>
<td>+0.4</td>
<td>+3.2</td>
</tr>
<tr>
<td>Males</td>
<td>−0.1</td>
<td>+2.4</td>
</tr>
</tbody>
</table>

Patients were randomly assigned LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 0.4% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5× ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5× ULN was 0% versus 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA as monotherapy in the short-term and continued in the longer-term study, had a median change in prolactin of +1.15 mg/mL at week 24 (n=130).

**5.8 Leukopenia, Neutropenia and Agranulocytosis**

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.
Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1,000/m^3) should discontinue LATUDA and have their WBC followed until recovery.

5.9 Orthostatic Hypotension and Syncope
LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and syncope. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydrating, hypovolemic, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antihypertensive-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing position.

Schizophrenia
The incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was [LATUDA incidence, placebo incidence]: orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)].

In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.3% with LATUDA 160 mg compared to 0.7% with placebo.

Bipolar Depression
Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.6% with LATUDA 80 to 120 mg compared to 0% with placebo.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy studies, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

5.10 Seizures
As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer’s dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.11 Potential for Cognitive and Motor Impairment
LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Caution patients about operating hazardous machinery, including motor vehicles, until they are known to be able to perform safely.

In clinical studies with LATUDA, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

In short-term, placebo-controlled schizophrenia studies, somnolence was reported with 17.0% (256/1508) of patients treated with LATUDA compared to 15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day compared to 7.1% (50/708) of placebo patients.

Bipolar Depression
Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, somnolence was reported with 7.3% (12/164) and 13.8% (23/167) with LATUDA 20 to 60 mg and 0.3% with LATUDA 160 mg compared to 0.7% with placebo.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, somnolence was reported with 11.4% (81/708) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

5.12 Body Temperature Dysregulation
Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration [see Patient Counseling Information (7.9)].

5.13 Suicide
The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Schizophrenia
In short-term, placebo-controlled schizophrenia studies, the incidence of treatment-emergent suicidal ideation was 0.4% (6/1508) for LATUDA-treated patients compared to 0.8% (8/708) on placebo. No suicide attempts or completed suicides were reported in these studies.

Bipolar Depression
Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the incidence of treatment-emergent suicidal ideation was 0.0% (0/331) with LATUDA-treated patients compared to 0.0% (0/168) with placebo-treated patients. No suicide attempts or completed suicides were reported in this study.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, the incidence of treatment-emergent suicidal ideation was 1.1% (4/360) for LATUDA-treated patients compared to 0.3% (1/334) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.14 Activation of Mania/Hypomania
Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

5.15 Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of mortality and morbidity in elderly patients, in particular those with Alzheimer’s dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.16 Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies
Patients with Parkinson’s Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Boxed Warning and Warnings and Precautions (5.1)]
- Suicidal Thoughts and Behaviors [see Boxed Warning and Warnings and Precautions (5.2)]
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis [see Warnings and Precautions (5.23)]
- Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.4)]
- Tardive Dyskinesia [see Warnings and Precautions (5.5)]
- Metabolic Changes [Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain] [see Warnings and Precautions (5.6)]
- Hyperprolactinemia [see Warnings and Precautions (5.7)]
- Leukopenia, Neutropenia, and Agranulocytosis [see Warnings and Precautions (5.8)]
- Orthostatic Hypotension and Syncope [see Warnings and Precautions (5.9)]
- Seizures [see Warnings and Precautions (5.10)]
- Potential for Cognitive and Motor Impairment [see Warnings and Precautions (5.11)]
- Body Temperature Dysregulation [see Warnings and Precautions (5.12)]
- Suicide [see Warnings and Precautions (5.13)]
- Activation of Mania/Hypomania [see Warnings and Precautions (5.14)]
- Dysphagia [see Warnings and Precautions (5.15)]
- Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies [see Warnings and Precautions (5.16)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The information below is derived from an integrated clinical study database for LATUDA consisting of 3799 patients exposed to one or more doses of LATUDA for the treatment of schizophrenia and bipolar depression in placebo-controlled studies. This experience corresponds to a total experience of 1250.9 patient-years. A total of 1106 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in categorized using MedDRA terminology.

Schizophrenia
The following findings are based on the short-term, placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Common Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5%) and at least twice the rate of placebo in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to
adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

**Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:** Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 14.

<table>
<thead>
<tr>
<th>Commonly Observed Adverse Reactions:</th>
<th>Placebo (N=360) (%)</th>
<th>LATUDA 20-60 mg/day (N=164) (%)</th>
<th>LATUDA 80-120 mg/day (N=167) (%)</th>
<th>All LATUDA (N=331) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>11</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Salivary Hyposalivation</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence*</td>
<td>7</td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Extrapyramidal Syndrome**</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Psychiatric Disorders</td>
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<td>Insomnia</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>11</td>
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<tr>
<td>Agitation</td>
<td>4</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer.

<table>
<thead>
<tr>
<th>Commonly Observed Adverse Reactions:</th>
<th>Placebo (N=360) (%)</th>
<th>LATUDA 20-60 mg/day (N=164) (%)</th>
<th>LATUDA 80-120 mg/day (N=167) (%)</th>
<th>All LATUDA (N=331) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>11</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Salivary Hyposalivation</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Musculoskeletal and Connective Tissue Disorders:**

<table>
<thead>
<tr>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body System or Organ Class</td>
</tr>
<tr>
<td>Dictionary-derived Term</td>
</tr>
<tr>
<td>Placebo (N=708) (%)</td>
</tr>
<tr>
<td>LATUDA</td>
</tr>
<tr>
<td>20 mg/day (N=381) (%)</td>
</tr>
<tr>
<td>40 mg/day (N=387) (%)</td>
</tr>
<tr>
<td>80 mg/day (N=380) (%)</td>
</tr>
<tr>
<td>120 mg/day (N=297) (%)</td>
</tr>
<tr>
<td>160 mg/day (N=230) (%)</td>
</tr>
<tr>
<td>All LATUDA (N=1500) (%)</td>
</tr>
</tbody>
</table>

**Adverse Reactions in the Schizophrenia Studies:**

Akathisia and extrapyramidal symptoms were dose-related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

**Bipolar Depression (Monotherapy):**

The following findings are based on the short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

<table>
<thead>
<tr>
<th>Commonly Observed Adverse Reactions:</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=396) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer.

<table>
<thead>
<tr>
<th>Commonly Observed Adverse Reactions:</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=396) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>
Extrapyramidal Symptoms

Schizophrenia

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.9% versus 8.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 8.7% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 17.

Table 17: Incidence of EPS Compared to Placebo in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=708) (%)</th>
<th>LATUDA 20 mg/day (N=487) (%)</th>
<th>LATUDA 40 mg/day (N=487) (%)</th>
<th>LATUDA 80 mg/day (N=536) (%)</th>
<th>LATUDA 120 mg/day (N=291) (%)</th>
<th>LATUDA 160 mg/day (N=121) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>8</td>
<td>18</td>
<td>27</td>
<td>23</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Dystonia</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, eclampsic crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Bipolar Depression

Monotherapy

In the short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness, was 6.9% versus 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% versus 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 18.

Table 18: Incidence of EPS Compared to Placebo in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=169) (%)</th>
<th>LATUDA 20 to 60 mg/day (N=164) (%)</th>
<th>LATUDA 80 to 120 mg/day (N=167) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>3</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>2</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, eclampsic crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adjunctive Therapy with Lithium or Valproate

In the short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 13.9% versus 8.6% for placebo. The incidence of akathisia for LATUDA-treated patients was 10.8% versus 4.8% for placebo-treated patients. Incidence of EPS is provided in Table 19.

Table 19: Incidence of EPS Compared to Placebo in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=360) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Dystonia</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, eclampsic crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (BAS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinasias.

Schizophrenia

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%); the SAS (LATUDA, 5.0%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

Bipolar Depression

Monotherapy

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.4%; placebo, 5.5%); the SAS (LATUDA, 7.9%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adjunctive Therapy with Lithium or Valproate

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%); the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Schizophrenia

In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.7% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily within the premarketing database of 2905 patients with schizophrenia. The reactions listed are those that could conceivably be drug-related, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 14 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent), only those not already listed in the tabulated results from placebo-controlled studies appear in this listing; those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

- Blood and Lymphatic System Disorders: Infrequent: anemia
- Cardiovascular Disorders: Frequent: tachycardia; Infrequent: AV block 1st degree, angina pectoris, bradycardia
- Ear and Labyrinth Disorders: Infrequent: vertigo
- Eye Disorders: Frequent: blurred vision
- Gastrointestinal Disorders: Frequent: abdominal pain, diarrhea; Infrequent: gastroparesis
- General Disorders and Administrative Site Conditions: Rare: sudden death
- Investigations: Frequent: CPK increased
- Metabolism and Nutritional System Disorders: Frequent: decreased appetite
- Musculoskeletal and Connective Tissue Disorders: Rare: rhabdomyolysis
- Nervous System Disorders: Infrequent: cerebrovascular accident, dysarthria
- Psychiatric Disorders: Infrequent: abnormal dreams, panic attack, sleep disorder
- Renal and Urinary Disorders: Infrequent: dysuria; Rare: renal failure
- Reproductive System and Breast Disorders: Infrequent: amenorrhea, dysmenorrhea; Rare: breast enlargement, breast pain, galactorrhea, erectile dysfunction
- Skin and Subcutaneous Tissue Disorders: Frequent: rash, pruritus; Rare: angioedema
- Vascular Disorders: Frequent: hypertension
- Clinical Laboratory Changes
- Schizophrenia

Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-
treated patients and 1.6% (11/881) on placebo. The threshold for high creatinine value varied from >0.79 to >1.3 mg/dL based on the centralized laboratory definition for each study (Table 20). Table 20: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=508)</th>
<th>LATUDA 20 mg/day (N=971)</th>
<th>LATUDA 40 mg/day (N=587)</th>
<th>LATUDA 80 mg/day (N=330)</th>
<th>LATUDA 120 mg/day (N=932)</th>
<th>LATUDA 160 mg/day (N=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Bipolar Depression

Monotherapy

Serum Creatinine: In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for LATUDA-treated patients compared to -0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.9% (95/222) of LATUDA-treated patients and 0.6% (11/162) on placebo (Table 21).

Table 21: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in a Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=334)</th>
<th>LATUDA 20 to 60 mg/day (N=106)</th>
<th>LATUDA 80 to 120 mg/day (N=291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>&lt;1%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

7.2 Potential for LATUDA to Affect Other Drugs

No adjustment is needed for lithium, substrates of P-gp, CYP3A4 (Figure 2) or valproate when coadministered with LATUDA. Figure 2: Impact of LATUDA on Other Drugs

Table 22: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=334)</th>
<th>LATUDA 20 to 60 mg/day (N=106)</th>
<th>LATUDA 80 to 120 mg/day (N=291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well controlled studies of LATUDA use in pregnant women. Neighbors exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Animal Data

No adverse developmental effects were observed in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day, which is approximately half of the maximum recommended human dose (MRHD) of 160 mg/day, based on mg/m² body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-times, in rats and rabbits, respectively, the MRHD of 160 mg/day based on mg/m² body surface area.

8.3 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk of drug discontinuation to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].
### Other Patient Factors

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

**Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics**

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Cmax</th>
<th>AUC</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td>adjustment not required</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td>Starting dose = 20 mg</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td>Maximum dose = 80 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic Impairment</th>
<th>Cmax</th>
<th>AUC</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td>adjustment not required</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td>Starting dose = 20 mg</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td>Maximum dose = 40 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population Description</th>
<th>Cmax</th>
<th>AUC</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>adjustment not required</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Compare to Caucasian

### OVERDOSAGE

#### 10.1 Human Experience

In premarketing clinical studies, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

#### 10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consider the possibility of multiple-drug overdose.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.
Summary

Many people with asthma have inadequately controlled disease. Patients being adherent with asthma medication, particularly inhaled corticosteroids, have improved outcomes. Providers can help those with asthma be more adherent and achieve disease control by prescribing based on the asthma management guidelines and by providing education and ongoing support.

Key Points

- Uncontrolled asthma is expensive.
- Many patients are not well controlled.
- Therapy should be selected and adjusted using the asthma management guidelines.
- When asthma is not controlled, providers should confirm proper diagnosis, proper treatment, adherence, inhaled medication technique, environmental control, and search for other reasons for lack of control such as reflux.
- Medication nonadherence is an issue in asthma but can be overcome with patient education and support.

As shown in Exhibit 1, asthma remains a major health issue in the United States.1 There are 25 million asthmatics in the America. Annually, it causes two million emergency room visits, 500,000 hospitalizations, 3,800 deaths per year, and costs of $56 billion. Uncontrolled asthmatics cost three times as much as those who are controlled.

The goals of asthma therapy are:

- Control of daily and nocturnal symptoms
- Minimize need for rescue inhaler (<2 days a week)
- Maintain (near) “normal” pulmonary function
- Maintain normal activity levels (including exercise and attendance at work or school)
- Prevent recurrent exacerbations
- Minimize emergency department visits and hospitalizations
- Prevent progressive loss of lung function
- Provide optimal therapy with minimal adverse effects

The asthma management guidelines recommend starting treatment based on severity and risk (Exhibit 2). Therapy is started at the highest step where the patient has an issue (symptoms, nighttime awakened, beta-agonist use, interference with normal activity, lung function, and history of exacerbations). For example, patients not on a controller medication are classified as having mild persistent asthma if they have any one of the following: albuterol use >2 days/week but not daily, asthma symptoms >2 days/week but not daily, nighttime awakenings 3 to 4x/month (>2x/month), minor limitation of normal activity, and forced expiratory volume in one minute (FEV1) >80% of predicted.

After initiation of treatment, patients should be followed up in two to six weeks for evaluation of control. Therapy adjustment is done based on level of control (Exhibit 3).2 Validated survey tools such as The Asthma Control Test (ACT) can be used to assess control. Once the patient is well controlled for three months, treatment can be stepped down one level. It is important to note that asthma con-
control varies over time, so therapy has to be frequently adjusted.

Patient education is important for asthma control. It is essential for optimal management and requires a partnership with the patient and their family. Education can come from many different avenues, including physicians, nurses, respiratory therapists, or pharmacists. The components of an educational program include basic facts about asthma, goals of asthma management, medication adverse effects, inhaler technique, and environmental control measures. Additional components include teaching the need for adherence with medications and environmental control, risks of suboptimal treatment, early recognition and management of worsening symptoms, action plans, when
and where to seek care, and the need for regular follow-up. It is especially important for patients to understand that even when they feel better or have no symptoms the disease is still there. It is chronic and does not go away with control.

Although there are published clinical management guidelines, many patients are not well controlled and experience frequent symptoms and exacerbations. Thirty percent of asthmatics report nocturnal awakenings at least once per week. Thirty-two percent of children required ER visits annually and 41 percent of patients had unscheduled visits. In one study, 41 percent of patients with asthma were “not well controlled” by ACT. Of those uncontrolled, 25 percent were using only a short-acting beta2-agonist and 85 percent considered their asthma somewhat or completely controlled.

There are many reasons that patients are not well controlled. Clinicians can frequently underestimate the severity of the disease and overestimate control and, therefore, do not step up therapy adequately. Patients can also lack access to quality care. Underestimation of severity and overestimation of control on part of the patient is associated with decreased adherence to environmental controls and medication. Untreated reflux, allergic rhinitis, or sinusitis can be a factor in uncontrolled asthma. Additionally, stress, family disruption, anxiety, depression, and cultural issues can also be factors. All these potential reasons for lack of disease control need to be identified and managed. A small subset of patients remain poorly controlled despite optimal therapy and should be cared for by an asthma specialist.

Use of a short-acting beta agonist (SABA) more than two days a week for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment. Daily albuterol use is a marker of poorly controlled asthma. Using four canisters per year could equal daily albuterol use.

The first steps in managing uncontrolled asthma is to confirm the proper diagnosis, treatment, and environmental control and confirm adherence and inhaler techniques. Once the confirmations are made, the patient should be assessed for undiagnosed allergies. Finally, consideration should be given to unsuspected asthma triggers, such as other medications (including eye drops), pets, mold, occult reflux, and occult sinus disease. Lastly, IgE levels should be checked to screen for allergic bronchopulmonary aspergillosis (ABPA), which is found in only 1 percent of U.S. asthmatics. IgE levels over

---

Exhibit 3: Assessing Asthma Control and Adjusting Therapy in Patients > 12 Years of Age

<table>
<thead>
<tr>
<th>• Components of Control</th>
<th>• Classification of Asthma Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>• Well Controlled</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 days/week</td>
</tr>
<tr>
<td></td>
<td>• Not Well Controlled</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 days/week</td>
</tr>
<tr>
<td></td>
<td>• Very Poorly Controlled</td>
</tr>
<tr>
<td></td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime Awakenings</td>
<td>• Well Controlled</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 times/month</td>
</tr>
<tr>
<td></td>
<td>• Not Well Controlled</td>
</tr>
<tr>
<td></td>
<td>1 - 3 times/week</td>
</tr>
<tr>
<td></td>
<td>• Very Poorly Controlled</td>
</tr>
<tr>
<td></td>
<td>≥ 4 times/week</td>
</tr>
<tr>
<td>Interference with Normal Activity</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Well Controlled</td>
</tr>
<tr>
<td></td>
<td>Some limitation</td>
</tr>
<tr>
<td></td>
<td>• Very Poorly Controlled</td>
</tr>
<tr>
<td></td>
<td>Extremely limited</td>
</tr>
<tr>
<td>SABA Use</td>
<td>• Well Controlled</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 days/week</td>
</tr>
<tr>
<td></td>
<td>• Not Well Controlled</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 days/week</td>
</tr>
<tr>
<td></td>
<td>• Very Poorly Controlled</td>
</tr>
<tr>
<td></td>
<td>Several times/day</td>
</tr>
<tr>
<td>FEV1 or Peak Flow</td>
<td>• Well Controlled</td>
</tr>
<tr>
<td></td>
<td>&gt; 80% predicted/ personal best</td>
</tr>
<tr>
<td></td>
<td>• Not Well Controlled</td>
</tr>
<tr>
<td></td>
<td>60 - 80% predicted/ personal best</td>
</tr>
<tr>
<td></td>
<td>• Very Poorly Controlled</td>
</tr>
<tr>
<td></td>
<td>≤ 60% predicted/ personal best</td>
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<tr>
<td>ATAQ</td>
<td>0</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤ 0.75</td>
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<tr>
<td>ACT</td>
<td>≥ 20</td>
</tr>
<tr>
<td></td>
<td>1 - 2</td>
</tr>
<tr>
<td></td>
<td>≥ 1.5</td>
</tr>
<tr>
<td></td>
<td>16 - 19</td>
</tr>
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<td></td>
<td>3 - 4</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>≤ 15</td>
</tr>
</tbody>
</table>

• Risk

| • Exacerbations requiring OSC | 0 - 1 per year |
| • Consider severity and interval since last exacerbation |

| • Progressive loss of lung function | • Evaluation requires long-term follow-up care |

| • Treatment-related AEs | • Medication side effects vary intensity |

SABA = short acting beta agonist; OSC = oral systemic corticosteroid; ACT = asthma control test; ATAQ = asthma therapy assessment questionnaire; ACQ = asthma control questionnaire
1,000 may indicate ABPA.

On average, a patient started on an inhaled corticosteroid (ICS) will fill it four times a year, rather than monthly. ICS nonadherence significantly increases a patient’s risk of death (Exhibit 4). Many of these deaths could be prevented by getting people to actually use their ICS. SABA overuse, a marker for not taking the proper anti-inflammatory agent, also increases risk of death. Adherence to prescribed therapy is the single most important issue in improving management of asthma. Reasons for nonadherence can vary but can include the cost of therapy, inadequate education, fear of adverse effects (steroid phobia), fear of medication dependency, cultural and family issues, or depression.

Adherence to prescribed therapy is the single most important issue in improving management of asthma. Reasons for nonadherence can vary but can include the cost of therapy, inadequate education, fear of adverse effects (steroid phobia), fear of medication dependency, cultural and family issues, or depression.

No single strategy has been found to be effective to improve adherence. Comprehensive interventions combining multiple strategies may be effective. Clinicians need to tailor educational goals and messages to individual patients. The optimal frequency of encouraging adherence is unknown, but repetition is important. Many patients will need an asthma “partner” to help them manage their disease. For children, this will typically be a parent; however, some adult patients need one also to help them manage their medications and environment.

Asthma action plans need to be simple to follow and minimize the number and frequency of medications. Dosing needs to fit the patient’s routine. Once a day dosing is ideal. Clinicians need to consider affordability by being aware of the cost of various medications and insurance coverage issues.

Health literacy is a major issue in providing effective education and disease management. Twenty-five percent of people cannot read and understand basic written material. All written material should
be at a 5th grade level or below. Tailored education can overcome health illiteracy.

Language barriers also have to be considered. Education and written materials need to be delivered in an individual’s native/preferred language. For example, even if a patient speaks some English, if Spanish is the preferred language, the patient is 40 percent more likely to be nonadherent if education is not delivered in Spanish.

Ethno-cultural factors also have to be considered. Minorities often accept suboptimal control of asthma. Over 50 percent of low income/high risk, predominantly minority asthma patients or caregivers believe “no symptoms equals no asthma.” Adherence is a third less in this group compared to higher income, non-minority groups. Adequate education may alter this belief.

Sometimes, Latinos classify diseases as “hot” or “cold”. Asthma is “cold” and is thus believed amenable to “hot” treatment. Recommending taking oral medications with hot tea or water improves adherence. Some Hispanics believe medication is overused in the United States and may prefer a folk remedy prescribed by a traditional healer.

Awareness of the ethno-cultural issues found in a clinician’s patient population can be beneficial in improving asthma outcomes. One way to determine a patient’s beliefs is to ask “In your community, what does having asthma mean?” Try to incorporate harmless or potentially beneficial remedies.

Exhibit 5 gives information on a female patient. Based on her information, she has moderate persistent asthma and should be on Step 3 therapy. The options are a medium-dose inhaled corticosteroid (ICS) or combination of low-dose inhaled corticosteroid and a long-acting beta agonist inhaler (LABA). Most clinicians would opt for dual therapy, which is available in combination inhalers. Albuterol as needed and pre-exercise to improve her exercise tolerance should be instituted. Education and environmental control strategies are also important for her. These should include dust mite and cat dander avoidance strategies.

At her three-month follow-up visit, she still has daily dyspnea, nocturnal symptoms every night and is using albuterol two to three times a day. She is having trouble walking from the level parking lot at work and is unable to exercise despite pre-exercise albuterol. Upon questioning, she appears adherent with her medication regimen and has an acceptable inhaler technique. She is using dust covers on her mattress and pillow, and the cat is no longer allowed in her bedroom and is being washed weekly. She does not use a HEPA-filter vacuum. Additionally, she has new onset acid reflux symptoms. Her FEV1 is 65 percent, Asthma Control Test score = 14, and her IgE = 320. According to Exhibit 3, her asthma is very poorly controlled. To try to improve control, her therapy should be stepped up to Step 5 with high-dose combination therapy. Additionally, intensification of dust mite and cat dander avoidance and treatment of reflux should improve her control.

**Conclusion**

Despite well-disseminated asthma treatment guidelines, many patients still are not well controlled. Two major reasons are underprescribing and medication nonadherence. Adherence and thus disease control can be improved with patient and family education and ongoing provider support.

Robert Sussman, MD, is a Pulmonologist with the Atlantic Health System Overlook Medical Center.

**References**


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Inflammatory Bowel Disease: Update on Diagnosis and Management

David H. Kerman, MD

Summary
The understanding of the underlying immunology and genetics of inflammatory bowel disease (IBD) continues to evolve. This is leading to more personalized approaches in developing and choosing medications. The introduction of immune system-altering biologics has altered the goals of therapy from just symptom control to intestinal mucosal healing.

Key Points
- IBD therapy is moving to personalized medicine.
- Genetic, serologic, and immune markers can be used to identify the type of disease, predict prognosis, and, likely in the future, predict response to therapy.
- Biologics, initiated early in the disease and in combination with immunosuppressants, are very effective in controlling IBD by inducing long-term steroid-free mucosal healing and remission.

INFLAMMATORY BOWEL DISEASE (IBD) IS A fairly common condition that has traditionally been divided into Crohn’s disease (CD) and ulcerative colitis (UC). It is estimated that more than one million people in the United States have IBD. It occurs most commonly in the “industrialized world,” predominantly North America and Europe and, to a lesser extent, in Australia and Japan. Why IBD is more common in the industrialized world is unknown. Factors suggested as responsible include the relative cleanliness of the industrialized world, dietary differences, the use of antibiotics, smoking and stress.

There is a bimodal distribution of age at disease onset. The peak incidence occurs between 10 and 30 years of age, although very young children (2% of cases) do occasionally develop IBD. Another peak occurs between the sixth and seventh decade. The earlier in life the disease presents, the more aggressive the course typically. Women appear just slightly more likely to develop CD than men; some studies suggest men develop UC at slightly higher rates than women.

Although there are many theories on the cause of IBD, it is thought to be an interaction between genetic predisposition, environmental triggers, and issues with the gastrointestinal mucosal adaptive and innate immune system (Exhibit 1). Exhibit 2 shows the distribution of genetic loci that have been identified for IBD. While much progress has been made in identifying genetic factors in IBD, there is still a long way to go; only 20 percent of the heritability of CD has been identified.

Environmental triggers that combine with the genetic predisposition to provoke the development of IBD are being increasingly clarified, though much remains unclear. In some individuals, infections appear to play a role in initiating the disease. Clostridium difficile colitis is a risk factor for development of disease and worsening disease in those already affected. Smoking is a negative risk factor for UC development but results in a decreased response rate.
to therapy in CD.

Environmental triggers such as infections, antibiotic use, and cleanliness all impact the intestinal microbiome, which in turn affects the gastrointestinal mucosal adaptive and innate immune function. The intestinal microbiome is also affected by diet. Overuse of antibiotics alters the intestinal microbiome which may trigger alterations in GI immune response.

The recognition of the variety of immunologic mechanisms involved in IBD has prompted a new view of the disorder. In the classic differentiation of IBD, patients are grouped into separate categories of UC or CD. Traditionally, serologic markers and immune responses have been used to validate these categories and separate patients into groups. With the recognition of the diverse clinical manifestations of disease, it has been suggested that IBD is a spectrum of disease rather than just two disorders, UC and CD. This emerging model of IBD distinguishes subgroups of patients by differences in genetics (IBD1, IBD2, NOD2/CARD15), serologic markers [perinuclear antineutrophil cytoplasmic (pANCA), anti-Saccharomyces cerevisiae antibodies (ASCA), anti-flagellin antibody (anti-CBir1a), anti-outer membrane protein C antibody (anti-OmpC), and immune responses [T helper cell one (Th1), not Th1]. For example, individuals with NOD2 allelic variants more frequently have fibrostenosing disease, rather than perforating disease. These genetic, serologic, and immune markers can be used to identify the type of disease, predict prognosis (i.e.,
risk for complications or surgery), and, likely in the future, predict response to therapy.

IBD is a costly disease to manage. In the United States, IBD patients account for 700,000 physician visits per year and 100,000 hospitalizations per year. Most of the hospitalizations for IBD involve surgery. Only 20 percent of UC patients in the United States undergo surgery while 50 to 80 percent of CD patients will eventually require surgery to repair some complication, such as obstruction, hemorrhage, fistulization or refractory disease.

IBD is a chronic, lifelong disease with discrete flares with periods of quiescence and is not curable. In as much as IBD cannot be cured, it is best managed with a maintenance strategy to minimize symptoms, prevent complications and avoid premature mortality. With good care, most patients live a normal existence and life span.

Management of IBD in 2015 includes early aggressive therapy in those most likely to have a severe course to achieve mucosal healing, avoidance of corticosteroids as much as possible, and preventative health maintenance care. Starting therapy in the early phases of the disease is important because this is when the most inflammation is present and the least long-term damage has been done (Exhibit 3). The desired endpoints of therapy are clinical and endoscopic remission. It has been shown that achievement of mucosal healing on endoscopy leads to significantly lower colectomy rate at one year. Those who achieve mucosal healing also have higher rates of steroid-free remission at one year. Lastly, remission can lead to lower rates of cancer.

Preventive measures in IBD include bone loss assessment (in those on chronic corticosteroids), an annual influenza vaccination, a pneumococcal vaccination, a herpes zoster vaccination, testing for latent tuberculosis (TB) prior to initiation of anti-tumor necrosis factor (TNF) therapy, testing for hepatitis B (HBV) prior to initiation of anti-TNF therapy, and tobacco cessation screening.

Older therapies used in IBD include mesalamine, corticosteroids, and immunomodulators (azathioprine, mercaptopurine). Because of the long term adverse effects of corticosteroids, it is best to minimize use of them chronically and to use steroid-sparing immunomodulators. Patients with limited disease may be managed with mesalamine or immunomodulator therapies alone. More extensive disease will usually require combination therapy. Thiopurines can be used as monotherapy but are primarily used in combination with the biologics in moderate to severe disease.

Personalized management of the disease can be done by selecting therapies and doses that are likely to be effective. One way to personalize therapy is to use tests such as thiopurine methyltransferase (TPMT) enzyme activity to predict response and possible adverse effects with azathioprine therapy. Those patients with low TPMT activity are at risk...
of adverse effects. Those who are high metabolizers respond best to therapy. Intermediate metabolizers need dose adjustments to maximize benefits before abandoning therapy. The metabolites of thiopurines can also be measured to personalize therapy.

Biologic medications that target areas of the immune system known to be involved in IBS have revolutionized therapy. Three anti-tumor necrosis factor (TNF) biologics are approved for IBD – infliximab (Remicade®), adalimumab (Humira®), and certolizumab (Cimzia®). These agents are very effective in controlling IBD by inducing long-term steroid-free mucosal healing and remission.

There are some downsides to the biologics. All of the anti-TNF biologics can lead to immunogenicity (i.e., antibodies against the medication). Biologics can stop working after a period of time because of immunogenicity. Human anti-biologic antibodies are associated with shorter duration of response, higher rate of infusion reaction, and worse clinical outcomes. Giving biologics with concomitant immunomodulators will lower antibody titers, result in higher trough levels, reduce reactions, and provide for long-term efficacy. Combining biologics with immunomodulators from the beginning of biologic therapy has been shown to provide better mucosal healing and higher remission rates than adding the immunomodulator once antibodies have already developed.

Anti-TNF therapy does increase risk for reactivation of TB or HBV and infection with intracellular pathogens (pneumocystis, atypical mycobacteria, listeriosis, legionella, coccidiomycosis, histoplasmosis, and aspergillus). There is also a modest increased risk of lymphoma. Other risks include demyelinating disorders, drug-induced lupus, arthralgias, and heart failure. When considering the possible adverse outcomes, the risk of no treatment also has to be considered.

Avoiding surgery in IBD is a goal, but sometimes it is the best therapy and is often a very viable option. Surgical options differ between UC and CD. Removing just the part of the colon that is most severe or diseased is not performed in UC, because the risk of recurrence in the remaining colon is so high. In UC, a colectomy is the standard treatment for refractory disease or high-grade dysplasia. After this surgery, although there can occasionally be other issues, the UC is considered cured. Surgery does not cure CD. The disease typically recurs after resection in another part of the bowel. Resection of inflamed segments to treat complications (stricture, abscess, fistula) or refractory disease is done.

Other therapies for IBD on the horizon include local and systemic stem cell treatments for CD, other biologics, parasite therapy, and microbial transplants. Parasitic worms are natural immunomodulators and are being studied for UC. People in parts of the world routinely exposed to parasites do not develop UC. Fecal microbial transplants have been studied for treating C. diff infections and are being evaluated for IBD. Eventually, this could evolve into determining which bacteria are the most benefit in IBD and giving these in a probiotic pill form.

**Conclusion**

With a greater understanding of the underlying mechanisms of disease and how to best treat it, IBD therapy is moving to personalized medicine. Genetic, serologic, and immune markers can be used to identify the type of disease, predict prognosis, and, likely in the future, predict the response to therapy. Biologics, initiated early in the disease and in combination with immunosuppressants, are very effective in achieving the goals of long-term steroid-free mucosal healing and remission.

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**References**

Hepatitis C Virus, a single-stranded RNA virus, is the only member of genus Hepacivirus in the Flaviviridae family and humans are the only known natural host. Unlike the DNA viruses human immunodeficiency virus (HIV) and hepatitis B virus (HBV), HCV infection can be cured. This is possible because the virus resides in the cytoplasm of the cell rather than the nucleus or incorporated into DNA like HBV and HIV, respectively.

HCV infection is underdiagnosed and undertreated. Three and a half million Americans are known to be infected with HCV (anti-HCV positive), but the true prevalence is probably over five million. Of those known to be infected, 2.7 million have chronic disease (HCV RNA positive). Chronic HCV cases not included in this estimate include those who are homeless, incarcerated, veterans, active military, health care workers, nursing home residents, chronic hemodialysis, or hemophiliacs. Of those who get diagnosed, only 41 percent of them get treated.

In the United States, males and African Americans have the highest rates of HCV infection (Exhibit 1). Baby boomers (>51) are the most common age group to be affected. Of the six different HCV genotypes, the most commonly seen in the U.S. are 1, 2, and 3. The majority of those infected in the U.S. have genotype 1.

The major reason to diagnose and treat HCV infection is to prevent the consequences of long-term infection (Exhibit 2). The majority of people who get infected with HCV acutely will develop chronic HCV. About 20 percent of those will develop cirrhosis. Some will develop hepatocellular carcinoma and decompensated cirrhosis. HCV infection is the reason for 60 percent of all cases of hepatocellular...
There are several factors associated with progression from chronic HCV infection to cirrhosis including alcohol consumption (>30 g/day in males, >20 g/day in females), disease acquisition at greater than 40 years, male gender, HIV or HBV co-infection, concomitant hepatic steatosis, and daily cannabis use. Patients who are initially exposed to HCV when they are older than 40 years of age generally have a higher degree of fibrosis regardless of how long they have had the disease, compared with individuals who are infected at a younger age. Because of high obesity rates, hepatic steatosis is relatively common in the U.S. Other factors have been shown to not affect progression. These include transaminase level (ALT), viral load, mode of transmission, and genotype.

The primary care provider (PCP) has a unique window of opportunity to make a diagnosis of HCV and refer for treatment prior to the development of cirrhosis and its complications. Early diagnosis and treatment can improve survival, improve quality of life, and will reduce the economic burden of HCV and result in cost savings. HCV screening is the first step to a cure.

Although screening is the first step to a cure, there are both patient and provider barriers to screening. Persons infected with HCV are usually asymptomatic in the U.S.
atic, unaware of their infection, and are unaware of the risk factors for HCV (Exhibit 3). Fifty-six percent of infected people are asymptomatic. For those that are symptomatic, the most common symptom is nonspecific fatigue. In general, PCPs do not include routine HCV risk factor assessment in their practice. Elevated LFTs, not risk factors, are the typical reason for PCPs to screen patients.

The CDC and the U.S. Preventive Services Task Force (USPSTF) recommends a one-time screening for all persons born between 1945 and 1965 because of their high prevalence of HCV. Under new health care regulations, all screening tests recommended by the USPSTF are covered for those with insurance. Cost is no longer a patient factor for not being screened. Thus, PCPs should screen all baby boomers, all patients with risk factors regardless of age, and all patients with elevated liver function tests.

The primary goal of HCV treatment is permanent eradication of virus from serum. This is defined as a sustained viral response (SVR), which is an undetectable HCV RNA six months after completion of treatment. Undetectable HCV RNA three months after treatment with the newer combinations in the future may be the deciding point for an SVR. An SVR is synonymous with “cure”. Cure rates have significantly improved since the early 1990s from 5 percent of patients to greater than 90 percent with improved regimens utilizing direct-acting antivirals (DAAs). SVR leads to improved outcomes of reduced morbidity and mortality including decreased rates of HCC, decompensated cirrhosis, and improved liver histology.

Interferon and ribavirin were the first two therapies approved for HCV management. Because it is injectable, has multiple contraindications and causes adverse effects, interferon is difficult to adhere with. Because of the multiple issues with interferon and newer more effective therapies, guidelines for treatment-naïve patients no longer recommend interferon as first-line therapy. Ribavirin is still a part of some of the recommended regimens.

The unsatisfactory response rate in genotype 1 (54 to 56%) to interferon and ribavirin led to the development of the DAAs that directly inhibit viral replication. The first approved DAAs were two protease inhibitors, telaprevir and boceprevir. Because of significant adverse effects, drug interactions, multiple daily dosing, and lower efficacy, the first-generation DAAs are no longer recommended for use. Two second-generation protease inhibitors [Simeprevir (Olysio®) and sofosbuvir (Sovaldi®)] were approved in late 2013. These agents are improvements over the first-generation agents in terms of pill burden, drug interactions, and adverse effects. A third second-generation agent, ledipasvir, was approved in a combination product with sofosbuvir (Harvoni®) in October 2014. It is the first approved regimen that does not require administration with interferon or ribavirin. In December of 2014, another evolution in therapy was approved - Viekira Pak®. This product contains ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets to treat chronic HCV genotype 1 infection, including those with cirrhosis.

Simeprevir, a NS3/4A protease inhibitor given once a day, is effective in genotypes 1, 2, 4, 5, 6 but is FDA approved for use in genotype 1 only. Patients will not benefit from this agent if they are Q80K positive; NS3 Q80K is a naturally occurring polymorphism that occurs in 48 percent of U.S. genotype 1a infections. This agent has numerous drug-drug interactions. The most common adverse effects are photosensitivity, rash, pruritus, nausea, myalgia, dyspnea, and mild-moderate bilirubin elevations.

Sofosbuvir is a NS5B polymerase nucleoside inhibitor with potent antiviral activity against genotypes 1 through 6 with a high barrier to resistance. Treatment is for 12 weeks. Drugs that are potent

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**Exhibit 3: Risk Factors for HCV**

<table>
<thead>
<tr>
<th>Common</th>
<th>Less Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal cocaine with shared implements</td>
<td>Sharing of household items that could carry infected blood</td>
</tr>
<tr>
<td>Body piercing with contaminated needles</td>
<td>Traumatic contact with blood</td>
</tr>
<tr>
<td>Tattooing with contaminated needles or ink</td>
<td>Perinatal transmission</td>
</tr>
<tr>
<td>Incarceration</td>
<td>High-risk sexual behavior (multiple sex partners, prostitutes, man to man sex)</td>
</tr>
</tbody>
</table>
P-gp inducers in the intestine (e.g., rifampin, St. John’s wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect. It is generally safe and well-tolerated in clinical studies to date. SVR rates with this agent vary from 80 to 100 percent.

A once-daily fixed-dose combination of the NS5A inhibitor ledipasvir and sofosbuvir for the treatment of chronic hepatitis C genotype 1 infection in adults was approved for the treatment of HCV genotype 1 infection in treatment-naïve patients. SVRs at 12 weeks were 97 to 99 percent across all arms, with no differences based on length of treatment, addition of ribavirin, or HCV genotype 1 subtype.

The other combination product is different tablets packaged together. Two tablets contain ombitasvir, paritaprevir, and ritonavir and are both taken once daily (in the morning). The other tablet contains dasabuvir, which is taken twice daily (morning and evening) with a meal. Ombitasvir is a NS5A inhibitor, paritaprevir is an inhibitor of the NS3/4A serine protease, and dasabuvir is a nonnucleoside NS5B polymerase inhibitor. Ritonavir is a potent inhibitor of CYP3A4 enzymes and is used as a pharmacologic booster for paritaprevir—it significantly increases peak and trough paritaprevir plasma concentrations. This product is dispensed in a monthly carton (28 days of therapy) containing four weekly cartons. Each weekly carton contains seven daily dose packs. The daily dose packs indicate which tablets need to be taken in the morning and evening.

The standard of care for HCV infection in treatment-naïve patients as of January 2015 is the use of sofosbuvir in combination with ledipasvir or simeprevir or the new combination product (Viekira Pak®), depending on genotype and presence of cirrhosis.7 Ribavirin is recommended to be added in some instances. The current duration of therapy is 12 to 24 weeks, again depending on which therapy is selected, genotype, and presence of cirrhosis. Because therapy for HCV is changing rapidly, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) has developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management. These up-to-date guidelines can be found at hcvguidelines.org. Because the recommendations change rapidly, a table of recommended regimens is not published here.

Although the oral only regimens are expensive in terms of acquisition costs, they are cost effective. Treatment is short term and curative in almost all patients. Although DAAs can cost $84,000 for 12 weeks of therapy, the cost is similar to previous 12 week protease inhibitor regimes, which have a lower SVR (telaprevir $68,000, interferon $12,340).12 Additionally, there are not as many costs associated with interferon-free treatment compared to interferon treatment.

The cost of not treating patients is higher than $84,000. Patients with compensated cirrhosis may live for over a decade, accruing over $270,000 in expenses prior to developing end-stage liver disease. Curing HCV markedly reduces the national cost of treating cirrhosis and hepatocellular carcinoma ($30,000 to $70,000 annual cost x 5 to 10 years/patient) and markedly reduces the need for liver transplantation ($350,000/transplant + $145,000 year maintenance).13

The higher SVR rates with the oral regimens provide significant benefits. An SVR in noncirrhotic HCV patients prevents the development of cirrhosis and its complications. An SVR in compensated cirrhosis lowers the rate of complications, liver cancer, and transplants. SVR improves all-cause mortality in all patients, quality of life in all patients, and increases life expectancy.

Conclusion

With the recently approved oral regimens for HCV infection, therapy is moving closer to the ideal—low pill burden, oral only, highly effective for multiple genotypes, short regimens, and minimal adverse effects. Because recommended regimens are constantly being updated, clinicians are urged to consult online updated guidelines.

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References


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Novel Therapeutic Strategies in Lipid Management: Lowering LDL-C to Improve Patient Outcomes

Rajat Deo, MD, MTR

For a CME version of this, please go to www.namcp.org/cmeonline.htm which is supported by educational grants from Amgen and Merck & Co.

Summary
The updated lipid management guidelines significantly changed how the risk of atherosclerotic disease is assessed and when treatment is recommended. Other changes in lipid management are on the horizon with new novel agents close to market. These novel agents will bring about another paradigm shift to selecting therapy based on genetic factors.

Key Points
• Statins have reduced the risk of atherosclerotic disease, but the reduction is not yet optimal.
• Revised guidelines recommend a wider population for statin treatment.
• Novel therapies targeting genetic mutations that lead to elevated lipids will likely be approved in the near future.

IT IS WELL KNOWN THAT ELEVATED LOW-density lipoprotein cholesterol (LDL-C) levels increase the risk of coronary heart disease and that risk increases as LDL-C levels increase.¹ The LDL-C level that carries the lowest risk of disease is in the 40 to 70 mg/dl range.

There are many different pharmacologic and dietary strategies that can safely lower LDL-cholesterol; however, much has been learned over the past decade which has influenced the current lipid management guidelines. These guidelines underwent a significant revision and were published in 2013.

Exhibit 1 provides an overview of the major changes to the lipid management guidelines.² The guidelines now recommend the use of pooled cohort equations for atherosclerotic cardiovascular disease (ASCVD) risk assessment.³ The equations estimate the 10-year risk of stroke and MI compared with the former guidelines that focused only on MI risk. The addition of stroke highlights the large burden of disability from nonfatal ASCVD events. There are separate equations for nonwhite populations which account for the importance of race/ethnicity in risk of ASCVD. LDL-C or high-density lipoprotein cholesterol (HDL-C) treatment targets are no longer specified in the guidelines.

Statin therapy is now recommended in four specific groups (Exhibit 1).² In the United States, statin therapy has produced a relative risk reduction in cardiovascular deaths, but optimal targets in CV risk reduction have not been achieved, which was one of the factors that led to the guideline revisions. The recommendation that adults with a 7.5 percent or greater estimated 10-year risk of ASCVD be treated with statins greatly expanded the pool of statin candidates. This was lowered from a former threshold of 20 percent risk of MI over 10 years, or greater than 10 percent risk with multiple risk factors.

The expansion of statin use generated significant controversy, but the 7.5 percent risk cut-off was based on valid national data. Fifty percent of all African American men, 30 percent of white men in their 50s and almost all men in their 70s meet the threshold of 7.5 percent risk. In women, 70 percent
of African Americans and 60 percent of white women in their 60s meet the cut point.

Statin therapy is recommended for primary and secondary prevention of ASCVD. Based on RCTs, statins reduce morbidity and mortality associated with ASCVD. Statin therapy is cost-effective, especially now that many statins are generic. Appropriate intensity of statin therapy is recommended to reduce the risk of ASCVD by lowering LDL-C and non-HDL-C. “Treat to target” and “lower is best” strategies are no longer advocated, but more clinical trials are needed to better define the most appropriate goals of therapy.2

Lifestyle modifications are also critical to primary prevention efforts and should be implemented in all individuals. These include a DASH-like diet (high in fruits, vegetables, fish, and low in sweets, red meat, and sodium), regular moderate to vigorous physical activity, weight management, and smoking cessation.

High-risk of ASCVD is defined as one or more of the following: clinically established coronary heart disease, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, chronic kidney disease, or 10-year predicted ASCVD risk ≥7.5% by a Pooled Cohort Equation. Exhibit 2 lists the treatment recommendations for those with high-risk.2,4-6

Intermediate-risk is defined as 5 to 7.5 percent 10-year ASCVD risk by a pooled cohort equation. Optional additional risk measurement tools, including family history of premature ASCVD, high-sensitivity C-reactive protein (CRP), coronary artery calcium, and ankle brachial indices, can be used to refine predicted risk in intermediate individuals.2 It is still debatable how to use these additional metrics to select therapy. Patients with intermediate risk, especially those with family history of premature heart disease, may benefit from the same treatments listed in Exhibit 3. Clinicians should reassess patients every five years or sooner if he/she have a change in risk factors.

The search continues for additional therapies to lower LDL-C. Greater than 1,000 mutations in the LDL receptor have been identified in familial hyperlipidemia patients and different mutations lead to variations in phenotype (LDL-C levels and risk of ASCVD). One mutation that leads to increased LDL-C is in the proprotein convertase subtilisin/ kexin type 9 (PCSK9) gene. PCSK9 is a protein that targets LDL receptors for degradation and thereby reduces the liver’s ability to remove LDL-C from the blood. PCSK9 mutations increase degradation of LDL receptors which limits binding and endocy-

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Exhibit 1: Highlights of 2013 Guidelines2

- **New Pooled Cohort Equations** for atherosclerotic cardiovascular disease (ASCVD) risk assessment
- **Statin Therapy** recommended in 4 groups:
  1. Adults with clinical ASCVD, without Class II-IV heart failure or receiving hemodialysis
  2. Adults with LDL-C >190 mg/dL
  3. Adults 40 to 75 years of age with diabetes and LDL-C 70-189 mg/dL
  4. Adults with ≥7.5% estimated 10-year risk of ASCVD and LDL-C 70-189 mg/dL
- **No** LDL-C or non-HDL-C treatment targets

Exhibit 2: High-Risk of ASCVD2,4-6

Implement treatment recommendations:

- A - Aspirin / Antiplatelet therapy
- B - Blood pressure control
- C - Cholesterol control / Cigarette smoking cessation
- D - Diet and weight management / Diabetes and blood sugar control
- E - Exercise
tosis of LDL particles into hepatocytes.

Evolocumab is an investigational fully human monoclonal antibody that inhibits PCSK9. In trials, evolocumab reduced LDL–C by up to 65 percent and was well tolerated in four randomized, placebo-controlled, Phase II clinical trials of 12 weeks duration in over 1,300 hypercholesterolemic patients.\textsuperscript{7-10} An open label extension study of patients from Phase II trials with evolocumab reported one-year safety and efficacy data.\textsuperscript{11} The effect of evolocumab was evaluated in a 52-week randomized, double-blind, placebo-controlled multicenter study to provide longer-term data on efficacy and safety.\textsuperscript{12} It included patients with a wide range of cardiovascular risk who were 18 to 75 and excluded those with LDL–C of 99 mg/dL or lower and not receiving a statin. Evolocumab was added to four different lipid-lowering regimens (diet alone, atorvastatin 10 mg, atorvastatin 80 mg, or atorvastatin 80 mg plus ezetimibe) and compared to placebo. More patients were able to reach LDL–C levels of less than 70 mg/dL (Exhibit 3) with the addition of evolocumab to other lipid-lowering therapy. Reductions in apoB, lipoprotein a [Lp(a)], and triglycerides and modest increases in (HDL–C) are also seen with this agent. Increases in liver function tests and myopathy are the two main adverse effects seen with evolocumab in combination with statins.

Conclusion

New lipid management guidelines have resulted in a larger patient population eligible for treatment of lipids. Statin therapy alone has been successful but still undertreats cardiovascular risk. Novel therapies are under investigations for LDL-C reductions to hopefully further reduce risk.

Rajat Deo, MD, MTR, is an Assistant Professor of Medicine in the Division of Cardiology at the University of Pennsylvania.

References


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National Association of Managed Care Physicians Institutes

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For more information on the Institutes, visit www.namcp.org.
There are four types of chemotherapy-induced nausea and vomiting (CINV). Acute CINV is nausea and vomiting that occurs within the first 24 hours after administration of chemotherapy. It occurs in 70 to 80 percent of patients given emetogenic chemotherapy without preventive medications. Delayed CINV starts more than 24 hours after administration of chemotherapy and typically lasts three to four days. Without prophylaxis, delayed CINV can occur in up to 80 percent of patients. Anticipatory CINV is a conditioned response that happens after a negative past experience with chemotherapy and has been reported in 33 percent of patients. Breakthrough CINV is that which occurs despite prophylaxis and requires rescue medications.

Chemotherapy can cause nausea and vomiting by two major ways—peripheral or central mechanisms. In response to chemotherapy, enterochromaffin cells in the gastrointestinal tract release serotonin, which starts the syndrome of chemotherapy-induced nausea and vomiting (Exhibit 1). Serotonin stimulates vagal afferent nerves which communicate with the brain. Through the dorsal vagal complex, the brain communicates back to the stomach causing reverse peristalsis, which results in nausea and vomiting. Centrally, stimulation of the neurokinin 1 (NK1) receptors by substance P in the brainstem can also lead to CINV. Although many other neurotransmitters are involved, serotonin and substance P are the primary neurotransmitters targeted with medications.

Acute CINV is predominately mediated by serotonin-dependent mechanisms, whereas delayed is predominately substance P mediated, but there is some overlap. The overlap of differential involvement of neurotransmitters supports combination therapy to enhance prevention of emesis. Both acute and delayed mechanisms need to be covered from the first day chemotherapy is given.
There are patient or chemotherapy-related risk factors for CINV. Patient factors which predispose to the development of CINV include low alcohol consumption (< 10 drinks/week), younger age (< 50), female gender, history of motion sickness, and poor control with prior chemotherapy. The most important factor for determining whether CINV will occur is the emetogenic potential of the chemotherapy being given. Chemotherapy agents can be classified as having high, moderate, low, or minimal potential for inducing emesis. Examples of highly emetogenic agents are cisplatin and doxorubicin. Because combinations of chemotherapy agents are commonly given, the emetogenic potential of all the agents used have to be considered in choosing prophylactic therapy. Additionally, there are now many oral chemotherapy agents which can also cause CINV. The National Comprehensive Cancer Network (NCCN) guidelines provide guidance on the emetogenic category for each chemotherapy agent.2

Three sets of treatment guidelines for preventing CINV are available to assist clinicians.2-4 The guidelines are similar with some subtle differences.

The major agents used for CINV prevention when highly emetogenic chemotherapy is given are serotonin antagonists, corticosteroids, and neurokinin 1 (NK1) antagonists. The recommended regimens include all three; omission of the steroid is the most common mistake that clinicians make when prescribing these regimens.

The serotonin antagonists include dolasetron (Anzemet®), granisetron (Kytril®), ondansetron (Zofran®, generic), and palonosetron (Aloxi®). These are given on the same day as highly emetogenic chemotherapy to prevent acute CINV and are available in a variety of dosing forms – intravenous, oral, and transdermal patch – which varies by agent. In the NCCN guidelines, palonosetron intravenous is listed as the preferred agent for highly emetogenic chemotherapy.2 Palonosetron does have a longer half-life (40 hours versus 4 to 8 hours for others) and higher receptor binding affinity, but it has not been shown to be significantly more effective than the other serotonin antagonists for acute CINV related to highly emetogenic chemotherapy.5,6 Because of purchasing contracts, some institutions use ondansetron as the preferred agent for most patients. Transdermal ondansetron can be especially useful in patients who are having difficulty keeping oral agents down.

The response rate to serotonin antagonists is greatly improved when these agents are combined with dexamethasone, which is the standard of care (Exhibit 2).7 Dexamethasone is given on the day of highly emetogenic chemotherapy administration and for three to four days afterwards to prevent both acute and delayed CINV. A meta-analysis of 32 randomized, controlled trials with 5,613 patients suggested superiority of dexamethasone over a serotonin antagonist for preventing delayed em-
Olanzapine must be used with caution in elderly patients. It carries a black box warning about increased mortality in elderly patients with dementia-related psychosis. The American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer (MASCC) guidelines do not currently address olanzapine.3,4

For moderately emetogenic chemotherapy, the recommended regimens are slightly different from the regimen for highly emetogenic. On the day of moderately emetogenic chemotherapy administration, both a serotonin antagonist and dexamethasone are recommended. Any serotonin antagonist is an option, but at least one study found improved complete response rates with palonosetron compared with ondansetron for moderately emetogenic chemotherapy, and palonosetron is listed as preferred by the NCCN.11 The addition of aprepitant is only recommended by the NCCN if certain chemotherapy is given (carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate).2 Olanzapine is recommended as an alternative to aprepitant.2 The ASCO and the MASCC recommend palonosetron for day one, but state that other agents can be substituted.3,4

For moderately emetogenic chemotherapy, there are three options for therapy beyond day one. If palonosetron was used on day one as the serotonin antagonist, no further therapy needs to be given. The NCCN guidelines recommend either steroid monotherapy or a serotonin antagonist (other than

---

**Exhibit 2: The Effect of Adding Dexamethasone to 5-HT₃ Antagonists for Acute Emesis**

<table>
<thead>
<tr>
<th>Author</th>
<th>0 5-HT₃ + DEX better</th>
<th>1 5-HT₃ better</th>
<th>2 5-HT₃ better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesketh</td>
<td></td>
<td></td>
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<tr>
<td>Smith</td>
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<td></td>
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<td>Roila</td>
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<tr>
<td>Joss</td>
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<td>Smyth</td>
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<td>Heron</td>
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<tr>
<td>Latreille</td>
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<tr>
<td>Italian Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carmichael</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adams</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment effect p<0.00001
palonosetron) be used for subsequent days of therapy.\(^2\) The ASCO and MASC also recommend dexamethasone monotherapy for one to three days.\(^2,3\)

For chemotherapy regimens with low emetic risk, the NCCN guidelines recommend dexamethasone, a serotonin antagonist, metoclopramide, or prochlorperazine started before chemotherapy and given daily during therapy.\(^2\) The ASCO guidelines recommend dexamethasone.\(^3\) For minimal emetogenic potential chemotherapy, all the guidelines agree that no prophylaxis needs to be given.\(^2-4\)

Oral chemotherapy is becoming more common and can cause significant CINV. Prophylactic regimens are recommended for moderate or highly emetogenic oral chemotherapy. Because oral chemotherapy is given for a longer duration, only oral agents are recommended. Serotonin antagonists with or without lorazepam are typically the first choice. If the regimen has low or minimal emetogenic potential, metoclopramide, a serotonin antagonist, prochlorperazine, or haloperidol can be prescribed for as needed use.

Prevention of CINV with optimal antiemetics is the best way to reduce the incidence of anticipatory CINV. If patients develop anticipatory CINV, they can be taught behavioral techniques, such as relaxation techniques or guided imagery to manage symptoms. Antianxiety agents such as alprazolam or lorazepam can be started the night before treatment to lessen this type of CINV.

Breakthrough CINV is treated with a class of agent not previously used. There are many different choices to add to the regimen, including benzodiazepines, cannabinoids, metoclopramide, haloperidol, phenothiazines, olanzapine, scopolamine, or gabapentin. Gabapentin has been found to be an effective low-cost strategy to improve complete control of CINV, especially delayed CINV control.\(^12,13\) When a patient is having breakthrough CINV, it is important that clinicians check that the correct regimens were originally prescribed and that the patient was adherent.

In late 2014, a combination product containing serotonin and NK1 receptor antagonists in a single capsule was approved. Akynzeo\(^6\) contains netupitant, a highly selective NK1 antagonist, in combination with palonosetron. The combination’s effectiveness was established in two clinical trials of 1,720 participants.\(^14,15\) The clinical trials demonstrated that the combination (300 mg of netupitant plus 0.5 mg of palonosetron) significantly improved the prevention of CINV compared to the use of palonosetron alone in patients receiving either highly or moderately emetogenic chemotherapy. One netupitant- and-palonosetron capsule is taken about one hour before the start of chemotherapy. The package labeling also recommends for highly emetogenic chemotherapy the addition of 12 mg of dexamethasone orally 30 minutes before a course of chemotherapy starts and then 4 mg of dexamethasone orally once daily on days two, three, and four. Recipients of anthracycline- or cyclophosphamide-based che-

---

**Exhibit 3: Impact of CINV on Health-Related Quality of Life: Functional Living Index-Emesis (FLIE)\(^6\)**

![Chart showing the impact of CINV on FLIE scores.](chart)

\*P = 0.001  CIE = chemotherapy induced emesis
motherapy or chemotherapy not considered highly emetogenic need to take dexamethasone only once per course: 12 mg orally before the start on day one.

Other antiemetics are under development. Ro-

lapitant is another NK1 receptor antagonist, which will likely reach the market in the next year. It has a very long half-life, which might provide up to five days of coverage.

CIJV has a significant effect on quality of life (Ex-
hibit 3).

The dread of future chemotherapy can lead to anticipatory nausea, which requires significant health care provider time to manage. Chemotherapy may have to be stopped or delayed because of un-

trolled CIJV. This can have an impact on the ultimate treatment outcome. It can also lead to loss of work days.

The major financial costs of uncontrolled CIJV include nursing time, physician time, antiemetic rescue medication, additional office visits, trips to the emergency room, intravenous hydration, and hospital admission. In a retrospective cohort study, 13.8 percent of patients had a CIJV-associated hospital visit.

The majority of these visits were because of delayed CIJV and the mean costs were $5,299 per patient. In another study, 25 percent of patients who received highly or moderately emeto-
gen chemotherapy required medical care for un-

controlled CIJV. This can have an impact on the ultimate treatment outcome. It can also lead to loss of work days.

Conclusion
Because of the substantial costs of uncontrolled CIJV, prevention of CIJV is the goal. To achieve this goal, the antiemesis guidelines should be followed. Optimal control for highly or moderately emetogenic chemotherapy will require combination therapy to prevent both acute and delayed CIJV.

Susan Urba, MD, is Professor of Medicine in the Division of Hematology and Oncology at the University of Michigan Comprehensive Cancer Center.

References
Iron Deficiency Anemia: Prevalence and Treatment in Oncology

Lawrence Tim Goodnough, MD

Anemia can have many causes, including cancer and its treatment. Many times this anemia is the result of iron restricted-erythropoiesis. Clinicians need to determine what type of iron issue is leading to the anemia. Correction of the iron issues will usually require intravenous iron and may also require combination with erythropoiesis-stimulating agents.

Key Points
- Iron-restricted erythropoiesis is a common cause of anemia.
- Three forms of anemia are absolute iron deficiency, iron sequestration in anemia of inflammation, and functional iron deficiency.
- Patients with cancer can have a combination of these forms.
- Intravenous iron is preferred over oral iron supplementation to manage iron-restricted erythropoiesis.
dietary groups are pediatrics because of high growth and development requirements for iron and the elderly when they do not eat properly. In women, iron requirements are higher during pregnancy and breast feeding. Menstrual blood losses can also lead to iron deficiency. Chronic blood loss related iron deficiency can be caused by blood donation, non-steroidal anti-inflammatory drugs (NSAIDs), gastrointestinal neoplasms and gastrointestinal parasites (in developing countries). Celiac disease, *Helicobacter pylori* infection, autoimmune atrophic gastritis, and hereditary iron refractory iron deficiency anemia.

---

### Exhibit 1: Anemia of Chronic Disease: Underlying Causes

<table>
<thead>
<tr>
<th>Associated Diseases</th>
<th>Estimated Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections (acute and chronic)</td>
<td>18% - 95%</td>
</tr>
<tr>
<td>Viral infections, including human immunodeficiency virus infection</td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
</tr>
<tr>
<td>Parasitic</td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>30% - 77%</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td>8% - 71%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus and connective-tissue diseases</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Chronic rejection after solid-organ transplantation</td>
<td>8% - 70%</td>
</tr>
<tr>
<td>Chronic kidney disease and inflammation</td>
<td>23% - 50%</td>
</tr>
</tbody>
</table>

---

### Exhibit 2: Anemia of Chronic Disease: Biology and Iron

![Diagram of Anemia of Chronic Disease: Biology and Iron](image-url)

- **Inflammation (e.g., Cancer)**
- **IL-6**
- **Liver**
- **Hepcidin**
  - **Decreased Red Cell Survival**
  - **Decreased Iron Absorption**
  - **Increased Iron Sequestration**
  - **Decreased Erythropoietin Response to Anemia**
  - **Bone Marrow Suppression**
(IRIDA) are all conditions with decreased iron absorption.

Iron sequestration in anemia of inflammation occurs when iron is trapped in the reticuloendothelial system and is unable for erythropoiesis. Interleukin-6 (IL-6) induces production of hepcidin, an inflammatory protein made in the liver. Hepcidin excess causes endocytosis and proteolysis of the sole known cellular iron exporter, ferroportin, trapping iron in macrophages and iron-absorbing enterocytes. The supply of iron to hemoglobin synthesis becomes limited, eventually resulting in anemia. Exhibit 2 illustrates how inflammation from cancer or other causes can lead to anemia of chronic disease. Conditions associated with iron sequestration include inflammatory disease (inflammatory bowel disease, rheumatoid arthritis), infection, malignancy, heart failure, diabetes mellitus, chronic kidney disease, and aging. Thus, patients with anemia of cancer may have different forms of iron-deficient erythropoiesis.

Management of anemia of cancer may include iron, erythropoiesis stimulation agents (ESA), or transfusions. Transfusions have been recommended in the past, but there is a move away from transfusions because they may not actually be beneficial and may be harmful.

Transfusions are one of the top five overused/misused interventions in all of medicine. The Joint Commission and American Medical Association will be releasing guidance on the evidence for appropriate transfusions and, at least at first, will recognize hospitals that are demonstrating best practices in terms of their frequency of transfusions. In future years, payers may include transfusion overuse as a quality indicator linked to payment. One of the most common reasons for a blood transfusion in the hospital (on a medicine service) is iron-deficiency anemia.
Although things have improved significantly over the years, there are still definite risks with any transfusion. In the past, there were significant risks of infections, but most of these are now fairly low risk. Beyond potential risk of infection, other risks of transfusion include transfusion reactions (alloimmunization, febrile, and allergic), medical errors (wrong blood to patient due to mislabeled specimen or patient misidentification), transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), iron overload, immunomodulation, and storage lesions. Storage lesions include issues with oxygen transfer from hemoglobin and loss of red cell malleability and occur because of the age of stored blood. In one trial, the longer blood has been stored (>14 days), the higher the complication rate post cardiac surgery.\(^3\) Another trial found that red cell storage age (<10 days vs >21 days) was not associated with a significant difference in multiple-organ dysfunction score or mortality in transfused cardiac surgery patients.\(^4\)

An algorithm for evaluating anemia is shown in Exhibit 3.\(^5\) For patients with chronic inflammatory illnesses, including cancer, the traditional non-red blood cell iron parameters (serum iron, ferritin, serum transferrin) may be unreliable. Ferritin is an acute phase reactant which is elevated in inflammatory states. For patients who fall in the category on the algorithm of serum ferritin of 30 to 100 or iron saturation of < 20 percent, a diagnostic trial of intravenous iron can be used to determine if iron deficiency is present. A response means the patient had absolute or functional iron deficiency.

Treatment with ESA therapy is an effective means of treating anemia of cancer. Importantly, without concomitant iron supplements, a functional iron deficiency can occur secondary to ESA-induced erythropoiesis. Although oral iron in combination with ESA does improve hemoglobin, the most effective way to increase hemoglobin is with intravenous iron.\(^6\) It also results in a higher response rate than oral therapy. Bolus dosing of iron and total dose infusion (entire estimated iron deficit is corrected in one infusion) appear to be equally effective.\(^7\) Using intravenous iron is also used to reduce the dose of ESA necessary to maintain hemoglobin in those with chronic kidney disease.\(^8\)

In the National Comprehensive Cancer Network guidelines, intravenous iron is the recommended therapy over oral iron in those with iron-restricted erythropoiesis.\(^9\) Exhibit 4 compares the currently available intravenous iron products.\(^10\) Intravenous iron infusions do cause more adverse effects than oral iron therapy. All intravenous iron preparation carry a small risk of causing adverse reactions that can be life-threatening if not treated promptly. The benefits of intravenous iron outweigh the risk in the treatment of iron deficiency when the oral route is insufficient or poorly tolerated, which occurs in a significant number of patients. Giving intravenous iron can be used to determine if iron deficiency is present. A response means the patient had absolute or functional iron deficiency.

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Iron products does require a trained staff and resuscitation facilities for certain products.

**Conclusion**

Iron-restricted erythropoiesis is a common cause of anemia. It occurs because of absolute iron deficiency, iron sequestration in anemia of inflammation, and functional iron deficiency. Innovative alternatives to oral iron supplementation are needed to manage iron-restricted erythropoiesis.

**Lawrence Tim Goodnough, MD,** is a Professor of Pathology and Medicine at Stanford University School of Medicine and Director of Transfusion Services at Stanford University Medical Center in Stanford, CA.

**References**


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Personalizing Treatment Strategies in the Management of Metastatic Breast Cancer

Vandana G. Abramson, MD

Summary
With greater understanding of tumor histology and genetics, the treatment of breast cancer continues to move toward truly personalized medicine. Although considered incurable, there are many treatment options for metastatic breast cancer. The areas where advances are needed the most are overcoming treatment resistance and management of triple negative breast cancer.

Key Points
- Underlying tumor histology and genetics dictate the choice of therapy.
- Hormone responsive disease is treated primarily with antiestrogen therapies.
- HER-2 positive disease is treated with targeted therapies in addition to chemotherapy.
- Triple negative disease is treated with chemotherapy.

At least 40,000 patients die due to metastatic breast cancer (MBC) each year in the United States. The vast majority are patients relapsing after having received adjuvant treatment for early stage disease. Most relapses occur in the first five years, but can occur at any time, with up to 20 percent occurring after 10 years. One to 5 percent of women with breast cancer have metastatic disease at presentation.

Once metastatic, breast cancer is treatable, but not curable. The median survival for MBC is two to three years, with 5 to 10 percent of patients surviving over five years. Two to 5 percent may survive over 10 years.

The treatment of breast cancer has changed dramatically over the years with greater understanding of physiology and tumor biology. The first breast cancer cases documented were in the Edwin Smith Papyrus in approximately 3000 to 2500 BC. Breast cancer was also described by the Greeks (Hippocrates and Galen) in 500 to 100 BC. At that time, the etiology was explained by the humoral theory (excess of black bile in the blood led to liver and spleen dysfunction which led to cancer). Treatment was purging, bleeding, diet, and topical solutions. During the Renaissance, autopsies led to an understanding of the lymphatic system and circulation and many theories on the origin of breast cancer were put forward. In 1878, because the breast was “held in control” by the ovaries, Beatson decided to test removal of the ovaries in advanced breast cancer. He found that oophorectomy often resulted in improvement for breast cancer patients and in the process discovered the stimulating effect of estrogen on breast cancer, even before the hormone itself was discovered. His work provided a foundation for the modern use of hormone therapy, such as tamoxifen, to treat or prevent breast cancer.

Tamoxifen was first synthesized in 1966 as a morning-after oral contraceptive and was found to have estrogen antagonist properties. In 1969, it was first tested in 46 women with MBC; 27 had visible responses (not estrogen receptor selected). In 1974, it was found that tamoxifen responders express the
estrogen receptor, thus it became the first targeted therapy for cancer with its FDA approval in 1977 for Stage IV disease. Women taking tamoxifen for five years have an average reduction in recurrences by 50 percent at 15 years. Assuming one million women took tamoxifen for five years, an estimated 90,000 lives would be saved worldwide over 15 years.

It is now known that different cell types within the breast give rise to cancer. Thus, breast cancers have different molecular signatures, depending on where they arise, that dictate tumor biology and predict outcome. Treatment is now selected based on tumor biology. Sixty to 70 percent of breast cancer tumors will express hormone receptors (either estrogen or progesterone), 20 to 25 percent will express human epidermal growth factor receptor 2 (HER2), and 15 percent will be triple negative (no hormone receptors or HER2).

Once the tumor biology is known, therapy can be selected based on risk of recurrence, which is determined by the type of cancer, grade, and size. Adjuvant Online can be used to illustrate for patients the risk of recurrence with various treatment options (Exhibit 1).

Estrogen or progesterone positive (ER+ or PR+) disease is generally biologically less aggressive than other types, but it can recur at any point. By gene expression profiling, these tumors are usually luminal A or B. The mainstay of treatment is anti-endocrine therapy including a selective estrogen receptor modulator (SERM, tamoxifen), an estrogen receptor antagonist [fulvestrant (Faslodex®)], aromatase inhibitors [AI, anastrozole (Arimidex®), letrozole (Femara®), exemestane (Aromasin®)] and ovarian ablation using surgical removal, medication, or radiation.

Resistance to hormonal therapy, either de novo or acquired, is currently a major limitation in the therapy of patients with HR+ breast cancer. Many patients with ER/PR+ disease will develop resistance to therapy over time and require a therapy switch because the disease will begin to regrow. Strong evidence links hormone resistance to cross-talk between signal transduction pathways and ER signaling. An emerging mechanism of endocrine resistance is aberrant signaling via the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) intracellular signaling pathway. mTOR is a key central regulator of cell growth and proliferation in response to nutrient availability as well as to stimulatory signals from growth factors via the RAS and PI3K pathways. Growing evidence supports a close interaction of the mTOR pathway with ER signaling, thus targeting mTOR with medications is rational.

Everolimus is an oral and potent inhibitor of
mTOR. It is approved for renal cell carcinoma (multiple countries), astrocytoma (U.S.), and MBC. It is approved for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole. In the trial that led to FDA approval, everolimus treatment resulted in a 2.6-fold prolongation in median progression-free survival (PFS), 10.58 months versus 4.14 months, resulting in a 64 percent risk reduction of progression or death.1 Adverse events are consistent with previous experience with everolimus including stomatitis, fatigue, non-infectious pneumonitis and hyperglycemia. Everolimus is the first agent to enhance the clinical benefit of hormonal therapy in refractory ER+ patients. These results represent a paradigm shift in the management of patients with hormone receptor-positive breast cancer.

Another approach to hormone resistance would be to combine two hormonal agents with different mechanisms of action. The combination of anastrozole and fulvestrant has been studied and appears to be better than either alone in the setting of resistance.2 Thus, when a patient progresses on one hormonal agent, a second agent may be added.

Twenty to 25 percent of breast cancers overexpress HER2. Tumors that overexpress HER2 are typically poorly differentiated tumors, have markers of high proliferation, and result in worse disease free survival (DFS) and overall survival (OS). The median survival with HER2 overexpression is three years versus six to seven years with normal HER2 expression.3 The most developments in the last few years have been with this type of breast cancer.

Trastuzumab (Herceptin®) was the first targeted therapy approved for this type of breast cancer. It is a monoclonal antibody to the HER2 protein on the tumor cell surface that prolongs survival of patients with MBC by 5 to 7 months.4 Resistance to trastuzumab occurs in a significant percentage of patients with HER2+ disease recur or progress on trastuzumab treatment. Current treatment options beyond trastuzumab include lapatinib, pertuzumab, and TDM-1. Other avenues of overcoming resistance are under study.

Lapatinib (Tykerb®) is a small molecule tyrosine kinase inhibitor that binds to both intracellular ATP binding site of epidermal growth factor receptor (EGFR) and HER2 on the cell surface preventing phosphorylation and activation. It blocks down-stream signaling through homodimers and heterodimers of EGFR and HER2. Dual blockade of signaling may be more effective than the single-target inhibition provided by trastuzumab. Lapatinib in combination with capecitabine increased the median time to progression compared with placebo/capecitabine (8.4 vs 4.4 months).5 Lapatinib has also been studied in combination with trastuzumab in heavily pretreated patients, resulting in an improvement in median OS over trastuzumab alone (9.75 vs 12.9 months).6 Using this combination that targets both the inside and outside of the cancer cell is a way for patients to avoid chemotherapy.

Pertuzumab (Perjeta®) is a HER dimerization inhibitor that prevents HER2 from partnering with HER3. In combination with trastuzumab and docetaxel as first-line therapy in HER2+ disease, the addition of pertuzumab improved PFS (18.7 vs 12.4 months) and preliminary OS.7 Triple combi-

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**Exhibit 2: Frequency of Mutations in the PIK3CA and PTEN Genes in 1,261 Human Breast Cancers**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>PIK3CA</th>
<th>AKT1</th>
<th>PTEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER (n = 305)</td>
<td>35%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>HER2 (n = 98)</td>
<td>25%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Basal/TN (n = 262)</td>
<td>8%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Claudin low (n = 14)</td>
<td>0</td>
<td>0</td>
<td>nd</td>
</tr>
<tr>
<td>Metaplastic (n = 19)</td>
<td>47%</td>
<td>0</td>
<td>5%</td>
</tr>
</tbody>
</table>

PIK3CA = phosphatidylinositol 3-kinase
AKT1 = protein kinase B
PTEN = phosphatase and tensin homolog deleted on chromosome ten
nation therapy of pertuzumab, trastuzumab, and taxane chemotherapy is the recommended first-line therapy for HER2+ metastatic disease.8

T-DM1 (Kadcyla®) is a combination of trastuzumab and emtansine (DM1) which is a derivative of maytansine, a very effective but highly toxic chemotherapy. Combined with trastuzumab, the emtansine enters HER2 expressing cells. T-DM1 treatment, when compared with capecitabine/lapatinib, resulted in improvement of PFS (9.6 vs 6.4 months) and OS (30.9 vs 25.1 months).9 T-DM1 has also been compared with trastuzumab plus docetaxel in the first-line setting. There is an improvement of PFS but no difference in OS. The combo of trastuzumab/docetaxel is no longer the standard of care. There is an ongoing trial of T-DM1 versus T-DM1/ pertuzumab versus paclitaxel/trastuzumab.

One mechanism of trastuzumab resistance may be through mutations of other cell growth pathways beyond HER2 such as phosphatidylinositol 3-kinases (PI3K). PI3K are a family of lipid kinases involved in many cellular processes, including cell growth, proliferation, differentiation, motility, and survival.10 The PI3K pathway leads to downstream signaling proteins, such as AKT. Mutant PI3K (PI3KCA) has been implicated in the pathogenesis of several cancers, including colon cancer, gliomas, gastric cancer, breast cancer, endometrial cancer, and lung cancer. Numerous PIK3CA inhibitors are under development. Exhibit 2 shows the rate of various PIK3CA and other mutations in different types of breast cancer. As more mutations are identified and targeted with therapy, breast cancers will likely be further sub-classified. For example, a tumor might be classified as HER2+/PIK3CA+.

Fifteen percent of new cases of breast cancer will be triple negative (ER/PR/HER2 negative, TNBC), which are typically more aggressive than other types. TNBC has higher proliferative rates, higher histologic grades, larger tumors on presentation, higher recurrence rates, and lower survival (stage for stage than ER+). It is more common in younger, Hispanic, and African American women. Recurrences tend to occur more often in visceral organs (compared to ER/PR+ BC) with a higher rate of brain, lung, distal nodal, and liver metastases.

Not all TNBC tumors are the same. Although TNBC is defined based on immunohistochemistry (i.e., lack of expression of ER/PR/HER2), gene expression profiling (GEP) shows there are several types of TNBC. Most TNBC tumors are basal-like, which carries a worse prognosis than the overall breast cancer population. GEP of basal-like tumors shares characteristics with basal epithelial cells. On gene expression profiling, 25 percent of TNBC do not have basal-like patterns. Non-basal TNBC is usually claudin-low and express epithelial-mesenchymal transition genes and stem cell-like patterns. Poor prognosis associated with TNBC is likely driven by the majority with basal-like biology.

No validated targets have been identified for TNBC, thus chemotherapy is the standard of care. A tremendous amount of clinical research is being done to identify personalized medicine targets for TNBC.

Inhibitors of poly (ADP-ribose polymerase) (PARP) are being studied as targeted therapy for breast cancer gene mutation one (BRCA-1) and TNBC, which share clinical and pathologic features.11 Base excision repair through PARP1 is one of the two major mechanisms for repairing cellular DNA damage caused by environmental causes and carcinogens. Homologous recombination through BRCA is the other major mechanism of DNA repair. When a patient is treated with chemotherapy, DNA damage is the desired outcome of therapy but PARP or BRCA can “fix” the effects of chemotherapy.

Because BRCA is nonfunctional in BRCA mutation disease, these tumors rely on PARP1 to repair DNA damage. PARP inhibitors that circumvent DNA repair after chemotherapy have shown activity in BRCA+ disease. Single-agent oral olaparib (Lynparza®) 400 mg BID has substantial activity in heavily pretreated BRCA1/2 carriers with advanced breast or ovarian cancer but is still investigational for breast cancer. It was approved in December of 2014 by the FDA for germline BRCA-mutated advanced ovarian cancer treated with three or more prior lines of chemotherapy. Veliparib is another PARP inhibitor under study.

PARP is upregulated in most TNBC, thus blockade may enhance the efficacy of chemotherapy. Although the studies with PARP inhibitors in TNBC have not been highly successful, selecting patient populations for trials may be the issue.

Because TNBC is composed of a number of subtypes, the challenge in effective treatment is recognizing which subtypes are targetable. Clinical trials are underway to target TNBC by gene expression profiles, but it is important to select patients rationally, not just “TNBC” patients. TNBC needs to be subdivided so only those with the same gene expression profiles are studied together.

Personalized medicine in MBC can be achieved to a limited extent by gene profiling testing. Vanderbilt University provides a website, mycancergenome.org that anyone can use to learn about individual mutations and ongoing clinical trials targeting those mutations. At Vanderbilt, each patient with breast
cancer has gene profiling done and can then educate themselves on their particular mutations to help them find appropriate treatment.

**Conclusion**
The future of treating metastatic breast cancer continues to improve with better understanding of underlying immunohistology and genetics. The underlying biology of a given tumor determines not only the prognosis but also the response to treatment. Although great strides have been made in treating some subsets of breast cancer, triple negative disease is the area where improvement is needed.

Vandana G. Abramson, MD, is an Assistant Professor of Medicine in the Division of Hematology/Oncology at Vanderbilt University.

**References**
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- 50% fewer infections with Grafix vs control (18% vs 36%, \( p=0.044 \))


Actual sizes shown

- 5 cm x 5 cm
- 4 cm x 4 cm
- 3 cm x 4 cm
- 2 cm x 3 cm
- 1.5 cm x 2 cm
- 14 mm

Grafix demonstrated significantly higher wound closure compared to control (62% vs 21%, \( p=0.0001 \))

Median time to closure: 42 days with Grafix vs 70 days with control (\( p=0.019 \))

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<th>Clinical Significance</th>
<th>Panorama™</th>
<th>All Other NIPTs</th>
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<tbody>
<tr>
<td>Triploidy</td>
<td>Miscarriage or severe birth defects in fetus; risk of severe complications for the mother</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Maternal contribution¹ ²</td>
<td>May lead to false positive or false negative results when not detected</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Vanishing twin</td>
<td>Common cause of false positive results when not detected ³ ⁴</td>
<td>✓</td>
<td>X</td>
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References:
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