Formulary®

December 2013
VOL. 48, NO. 12
PAGES 378-403

A peer-reviewed drug management journal for managed care and hospital decision-makers

PEER-REVIEWED

Cover Article

Depression in the elderly: A pharmacist's perspective

Shana Castillo, PharmD, MBA Kimberley Begley, PharmD
Ann Ryan-Haddad, PharmD, Ellen Sorrentino, PharmD candidate
Kwasi Twum-Fening, PharmD candidate

388 Depression is a disease state that is commonly underdiagnosed and undertreated in patients over the age of 65 years. Elderly patients may differ from younger patients in the presentation of symptoms and in the prevalence of comorbidities. Risk factors for the development of depression are different for elderly patients. Treatment may also be dissimilar, including response and response time to treatment. Treatment should be tailored to the individual patient in the geriatric population to optimize therapeutic outcomes. Pharmacists can be vigilant of comorbidities and medications that potentially increase the risk of depression in the elderly. Pharmacists can play a significant role in advocating for the screening and treatment of this disease state. They are in a unique position to improve patient outcomes in late-life depression.

PEER-REVIEWED

Focus On

Focus on tapentadol: Role in the treatment of neuropathic pain

Kelly A. Macedo, PharmD
Michael D. Nailor, PharmD, BCPS AQ-ID

395 Neuropathic pain is a difficult-to-treat condition; pathologic changes in neuronal pathways may result in suboptimal analgesic control with opioid agents alone. Polypharmacy is employed often to simultaneously target multiple levels of the pain pathway, at the expense of escalated complexity of drug regimens and risk for drug–drug interactions and adverse effects. Tapentadol combines 2 mechanisms of action within a single molecule, allowing for mu-receptor activation and norepinephrine reuptake inhibition without the aforementioned drawbacks of multiple agent regimens. Recently approved in its extended-release formulation with favorable pharmacokinetics and improved gastrointestinal tolerance over pure opioids, tapentadol may prove cost effective when productivity and indirect costs are considered.

ADVANSTAR MEDICAL COMMUNICATIONS GROUP

Now Available from Teva...

A generic version of **Adenoscan®** (adenosine) Injection

- AP Rated
- Latex-Free & Preservative-Free
- Bar Coded

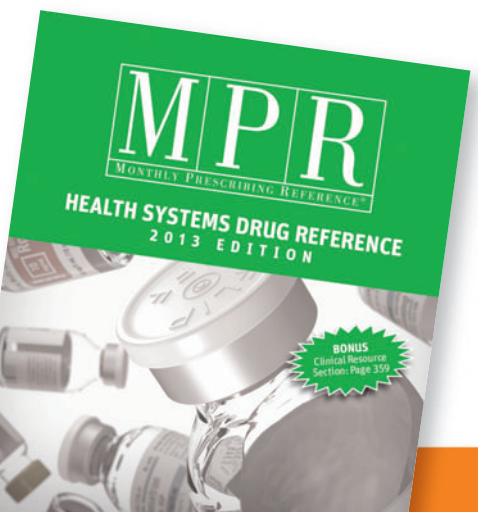
Teva's Adenosine Injection is proven to have the:

- ✓ **Same** active ingredient
- ✓ **Same** dosage strengths
- ✓ **Same** FDA standards of quality and performance

...as Adenoscan® Injection

Please see brief summary of Prescribing Information on adjacent page.

Learn more about Teva's quality generic medicines at **TevaGenerics.com**



Order your FREE copy of the Health Systems Drug Reference today at **TevaGenerics.com/SupportMaterials**

TEVA Pharmaceuticals

BRIEF SUMMARY

Adenosine Injection USP

FOR INTRAVENOUS INFUSION ONLY

℞ only

INDICATIONS AND USAGE

Intravenous adenosine is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately (see **WARNINGS**).

CONTRAINDICATIONS

Intravenous adenosine injection should not be administered to individuals with:

1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).
3. Known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma).
4. Known hypersensitivity to adenosine.

WARNINGS

Fatal Cardiac Arrest, Life Threatening Ventricular Arrhythmias, and Myocardial Infarction

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with adenosine infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

Sinoatrial and Atrioventricular Nodal Block

Adenosine injection exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia. Approximately 6.3% of patients develop AV block with adenosine, including first-degree (2.9%), second-degree (2.6%), and third-degree (0.8%) heart block. Adenosine can cause sinus bradycardia. Adenosine should be used with caution in patients with pre-existing first-degree AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). Adenosine should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. Sinus pause has been rarely observed with adenosine infusions.

Hypotension

Adenosine injection is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflex mechanism are able to maintain blood pressure and tissue perfusion in response to adenosine by increasing heart rate and cardiac output. However, adenosine should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia, due to the risk of hypotensive complications in these patients. Adenosine should be discontinued in any patient who develops persistent or symptomatic hypotension.

Hypertension

Increases in systolic and diastolic pressure have been observed (as great as 140 mm Hg systolic in one case) concomitant with adenosine infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction

Adenosine injection is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (Ve) and reduce arterial PCO_2 causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnea) or an urge to breathe deeply with adenosine. These respiratory complaints are transient and only rarely require intervention.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenosine has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenosine should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g., asthma). Adenosine should be discontinued in any patient who develops severe respiratory difficulties.

Atrial Fibrillation

Atrial fibrillation has been reported in patients (with and without a history of atrial fibrillation) undergoing myocardial perfusion imaging with adenosine infusion. In these cases, atrial fibrillation began 1.5 to 3 minutes after initiation of adenosine, lasted for 15 seconds to 6 hours, and spontaneously converted to normal sinus rhythm.

PRECAUTIONS

Drug Interactions

Intravenous adenosine injection has been given with other cardioactive drugs (such as beta adrenergic blocking agents, cardiac glycosides, and calcium channel blockers) without apparent adverse interactions, but its effectiveness with these agents has not been systematically evaluated. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, adenosine should be used with caution in the presence of these agents.

The vasoactive effects of adenosine are inhibited by adenosine receptor antagonists, such as methylxanthines (e.g., caffeine and theophylline). The safety and efficacy of adenosine in the presence of these agents has not been systematically evaluated.

The vasoactive effects of adenosine are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of adenosine in the presence of dipyridamole has not been systematically evaluated.

Whenever possible, drugs that might inhibit or augment the effects of adenosine should be withheld for at least five half-lives prior to the use of adenosine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential of adenosine injection. Adenosine was negative for genotoxic potential in the Salmonella (Ames Test) and Mammalian Microsome Assay.

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations.

Fertility studies in animals have not been conducted with adenosine.

Pregnancy

Teratogenic Effects

Pregnancy category C

Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. Because it is not known whether adenosine can cause fetal harm when administered to pregnant women, adenosine should be used during pregnancy only if clearly needed.

Pediatric Use

The safety and effectiveness of adenosine in patients less than 18 years of age have not been established.

Geriatric Use

Clinical studies of adenosine did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

ADVERSE REACTIONS

The following reactions with an incidence of at least 1% were reported with intravenous adenosine among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of adenosine but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of adenosine infusion.

Flushing	44%
Chest discomfort	40%
Dyspnea or urge to breathe deeply	28%
Headache	18%
Throat, neck or jaw discomfort	15%
Gastrointestinal discomfort	13%
Lightheadedness/dizziness	12%
Upper extremity discomfort	4%
ST segment depression	3%
First-degree AV block	3%
Second-degree AV block	3%
Paresthesia	2%
Hypotension	2%
Nervousness	2%
Arrhythmias	1%

Adverse experiences of any severity reported in less than 1% of patients include:

Body as a Whole

Back discomfort; lower extremity discomfort; weakness

Cardiovascular System

Nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause; sweating; T-wave changes; hypertension (systolic blood pressure > 200 mm Hg)

Central Nervous System

Drowsiness; emotional instability; tremors

Genital/Urinary System

Vaginal pressure; urgency

Respiratory System

Cough

Special Senses

Blurred vision; dry mouth; ear discomfort; metallic taste; nasal congestion; scotomas; tongue discomfort

Postmarketing Experience

(See **WARNINGS**.)

The following adverse events have been reported from marketing experience with adenosine. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, (3) strength of causal connection to the drug, or a combination of these factors.

Body as a Whole

Injection site reaction

Central Nervous System

Seizure activity, including tonic clonic (grand mal) seizures, and loss of consciousness

Digestive

Nausea and vomiting

Respiratory

Respiratory arrest, throat tightness

Teva Pharmaceuticals USA
Sellersville, PA 18960
TEVA
Rev. B 9/2012

Strep throat risk score brings together patient data and big data to potentially reduce unnecessary doctors' visits

by Tracey Walker

A new risk measure called a "home score" could potentially prevent 230,000 trips to US doctors' offices every year for suspected strep throat, according to a study online in *Annals of Internal Medicine*.

The score combines patients' symptoms and demographic information with data on local strep throat activity to estimate their strep risk, empowering them to seek care appropriately. The home score is said to represent the first healthcare tool to bring patient-contributed data and public health "big data" together to assess an individual's risk for a communicable disease.

"Integrating real-time strep throat biosurveillance with 2 patient-reported symptoms can accurately identify low-risk patients who are unlikely to even be tested for strep throat," said lead study author Andrew M. Fine, MD, MPH, pediatric emergency medicine, Boston Children's Hospital. "This approach could save hundreds of thousands of visits annually for patients with pharyngitis."

Currently, physicians use an office-based tool that takes into account symptoms and physical examination results to determine a person's risk for strep throat. If the risk is low, guidelines recommend against testing or treating the patient.

Take away

Integrating real-time strep throat biosurveillance with 2 patient-reported symptoms can accurately identify low-risk patients who are unlikely to even be tested for strep throat.

Dr Fine and colleagues used information collected between September 2006 and December 2008 from 71,776 people over aged 15 years who visited CVS MinuteClinics in 6 states for sore throats. They used patient's medical records and strep test results to test a tool that calculated a home score. Patients without medical training can assign themselves a score based on 2 symptoms—fever and cough. The tool also takes into account how common strep throat has been in the person's community during the past 2 weeks before calculating the home score.


Dr Fine

Based on the recent, local epidemiology of strep throat and 2 simple symptoms (fever, cough), the home score can be calculated to provide a patient's risk of strep, on a scale of 0-100. In this study, a patient with a home score of less than 10 was considered at low risk for strep throat. Researchers found that 90% of patients who scored below 10 on the at-home tool would have tested negative for strep throat. There would be 27 fewer doctors' visits for every 1 person with strep throat who was missed by the tool.

"Bringing local, recent epidemiology into the medical decision-making process is something that can be achieved on the local level," said Dr Fine. "Our study provides an early example of how to apply local epidemiology to individual patients. This study shows how valuable it can be to have quantitative information about the local incidence of disease. This is especially important for a communicable disease like strep throat.

"Once validated prospectively, any health system that tests patients for strep throat, could use the local epidemiology to help drive the decision about whether patients need to be seen right away, or whether they can wait to see if they get better on their own," he concluded. ■

News Capsules continued on page 380

Formulary
facebook.com/Formulary
twitter.com/Formulary_News
December 2013 | Vol. 48, No. 12
FormularyJournal.com

Editorial Mission

To provide timely, accurate, and practical drug-related information to assist our readers in their drug management responsibilities—evaluating drugs for the formulary and developing policies and procedures to guide the appropriate, rational, safe, and cost-effective use of drugs.

Formulary is abstracted or indexed in the following reference sources:

CINAHL
Current Contents
EMBASE/Excerpta Medica (online)
HEALTH (online)
Hospital Literature Index
Inpharma
International Pharmaceutical Abstracts
SCI-SEARCH (online)

FORMULARY ISSN 1082-801X(print), ISSN 1938-1166 (digital) is published monthly, by AdvanstarCommunications, Inc, 131 W. First St., Duluth, MN 55802-2065. Subscription rates: $67.00 for 1 year in the United States & Possessions ($12/year student rate); $96.00 for 1 year in Canada and Mexico; all other countries $132.00. $99.00 for 2 years in the United States & Possessions; $146.00 for 2 years in Canada and Mexico; all other countries $199.00. Single copies (prepaid only): $12.00 in the United States; $13.00 in Canada and Mexico; $21.00 all other countries. Back issues, if available, $20.00 in the U.S.; $25.00 in Canada and Mexico; $38.00 all other countries. Add $6.50 per order for shipping and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to FORMULARY, P.O. Box 6149, Duluth, MN 55806-6149. Canadian GST number: R-124213133RT001, Publications Mail Agreement Number 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA.

Your Editorial Board

Clinical Editor

Content
(800) 225-4569
24950 Country Club Blvd
Suite 200,
North Olmsted, OH 44070
formulary@advanstar.com
FormularyJournal.com

CONTENT CHANNEL DIRECTOR
Julie Miller
(440) 891-2723
julie.miller@advanstar.com

CONTENT CHANNEL MANAGER
Tracey L. Walker
(440) 891-2732
twalker@advanstar.com

CONTENT SPECIALIST
Julia Brown
(440) 891-2729
jbrown@advanstar.com

CONTENT COORDINATOR
Miranda Hester

GROUP ART DIRECTOR
Rob McGarr

Publishing & Sales
EXECUTIVE VICE PRESIDENT
Georgiann DeCenzo
(440) 891-2778
gdecenzo@advanstar.com

VP, GROUP PUBLISHER
Ken Sylvia
(732) 346-3017
ksylvia@advanstar.com

GROUP PUBLISHER
Mike Weiss
(732) 346-3071
mweiss@advanstar.com

NATIONAL ACCOUNT MANAGER
Sharon Ames
(732) 346-3033
sames@advanstar.com

NATIONAL ACCOUNT MANAGER
Phil Molinaro
(732) 346-3037
pmolinaro@advanstar.com

VICE PRESIDENT HEALTHCARE TECHNOLOGY SALES
Drew DeSarle
(440) 826-2848
ddesarle@advanstar.com

ACCOUNT MANAGER, CLASSIFIED/DISPLAY ADVERTISING
Darlene Balzano
(440) 891-2779
dbalzano@advanstar.com

ACCOUNT MANAGER, RECRUITMENT ADVERTISING
Joanna Shippoli
440-891-2615
jshippoli@advanstar.com

BUSINESS DIRECTOR, EMEDIA
Don Berman
(212) 951-6745
dberman@advanstar.com

DIRECTOR, SALES DATA
Gail Kaye
(732) 346-3042
gkaye@advanstar.com

SALES SUPPORT
Hannah Curis
(732) 346-3055
hcuris@advanstar.com

REPRINT SERVICES
877-652-5295, ext. 121/
bkolb@wrightsmedia.com
Outside US, UK, direct dial:
281-419-5725. Ext. 121

LIST ACCOUNT EXECUTIVE
Tamara Phillips
(440) 891-2773
tphillips@advanstar.com

PERMISSIONS
Maureen Cannon
(440) 891-2742
mcannon@advanstar.com

Production
SR. PRODUCTION MANAGER
Karen Lenzen
(218) 740-6371
klenzen@media.advanstar.com

Audience Development
CORPORATE DIRECTOR
Joy Puzzo
(440) 319-9570
jpuzzo@advanstar.com

DIRECTOR
Christine Shappell
cshappell@advanstar.com

MANAGER
Joe Martin
(218) 740-6375
jmartin@advanstar.com

ADVANSTAR

CHIEF EXECUTIVE OFFICER
Joe Loggia

CHIEF EXECUTIVE OFFICER FASHION GROUP, EXECUTIVE VICE-PRESIDENT
Tom Florio

EXECUTIVE VICE-PRESIDENT, CHIEF ADMINISTRATIVE OFFICER & CHIEF FINANCIAL OFFICER
Tom Ehardt

EXECUTIVE VICE-PRESIDENT
Georgiann DeCenzo

EXECUTIVE VICE-PRESIDENT
Chris DeMoulin

EXECUTIVE VICE-PRESIDENT
Ron Wall

EXECUTIVE VICE-PRESIDENT, BUSINESS SYSTEMS
Rebecca Evangelou

EXECUTIVE VICE-PRESIDENT, HUMAN RESOURCES
Julie Molleston

SR VICE-PRESIDENT
Tracy Harris

VICE-PRESIDENT, INFORMATION TECHNOLOGY
Joel Horner

VICE-PRESIDENT, LEGAL
Michael Bernstein

VICE-PRESIDENT, MEDIA OPERATIONS
Francis Heid

VICE-PRESIDENT, TREASURER & CONTROLLER
Adele Hartwick

News Capsules continued from page 378

Collaborative care to boost medication adherence may not improve outcomes significantly

by Julia Talsma

Collaborative care with pharmacists helped to boost medication adherence in patients with acute coronary syndrome (ACS) after hospital discharge. However, after 12- month follow-up, the proportion of patients who achieved blood pressure and LDL-cholesterol goals were not significantly different from patients treated under usual care, according to a recent study published online for *JAMA Internal Medicine*.

That was the result of a randomized clinical trial of more than 250 patients with ACS released from 1 of 4 Department of Veteran Affairs medical centers. Half of the patients in the intervention group had a pharmacist consultation—either in-person or telephonic—within 7 to 10 days following discharge for medication reconciliation and discussion of any medication adverse effects or problems. Within 1 month of discharge, the pharmacist called the patients to assess any new medications and any adverse effects. Also, an attempt was made by the pharmacist to synchronize the prescription refills. Pharmacists also educated patients about the importance of medication adherence. Patients also received medication reminder and refill calls from a voice messaging system for 6 months following discharge, and medication refill calls from 7 to 12 months following discharge.

"The pharmacists notified the patient's primary care clinician and/or cardiologist (if the patient had one) that the patient was enrolled in the adherence intervention by having them cosign the pharmacists' initial enrollment note in the computerized medical record," P. Michael Ho, MD, PhD, and colleagues wrote.

The enrollment note contained contact information for the physician to reach the pharmacists for any questions and concerns, Dr Ho noted.

RESULTS

The primary outcome of medication adherence, as measured by proportion of days covered (PDC), was greater in the intervention group (n=122) than in the control group (n=119) for the four classes of medications: statins, ACEI/ARB, clopidogrel, and beta-blockers. "The mean PDC for the 4 medications combined was greater for intervention patients (0.94 vs 0.87; $P<.001$)," the authors said.

The secondary outcomes of reaching BP or LDL-C level were not statistically significantly different between the 2 groups. The intervention group did trend toward greater BP control (58.6% vs 48.9%), but the LDL-cholesterol levels were not statistically significantly different (-13 vs -12 mg/dL).

"Additional studies are needed to understand the impact of the magnitude of adherence improvement shown in our study on clinical outcomes prior to broader dissemination of such an adherence program," the authors concluded. ■

Statins may lower prostate cancer-related mortality risk

from Staff Reports

Patients with prostate cancer who use statins may have a lower risk of death from their disease, according to a study published online ahead of print in the *Journal of Clinical Oncology*.

Using large population-based databases from the United Kingdom, Canadian researchers assembled a cohort of almost 12,000 men who had been newly-diagnosed with non-metastatic prostate cancer between 1998 and 2009. Within this group of men, the use of statins after prostate cancer diagnosis was associated with a 24% decreased risk in cancer-related mortality.

The men were tracked through 2012, for an average of more than 4 years after their diagnosis. During that time, nearly 3,500 died, and almost 1,800 of those deaths were attributed to prostate cancer.

"We observed duration- as well as dose-response relationships," study coauthor Laurent Azoulay, from Jewish General Hospital and McGill University in Montreal, told *Formulary*.

The researchers noted that they did not show a direct cause-and-effect relationship between statins taken by many to prevent heart disease and a lower death risk from prostate cancer.

PROMISING RESULTS

"The results of this study are promising, and if confirmed in other well-conducted observational studies and clinical trials, statins may be considered as a prostate cancer treatment," Dr Azoulay said. "However, for the time being, statins should be reserved for men who need to control their cholesterol levels and not for the sole purpose of improving prostate cancer prognosis. Additional studies are needed before adding prostate cancer as a new statin indication." ■

High-dose isotretinoin reduces risk of acne vulgaris relapse

by Julia Talsma

Higher doses of isotretinoin can effectively treat patients with acne vulgaris and reduce the relapse rate without significant increased adverse events, according to a recent report published in *JAMA Dermatology*.

Rachel C. Blasiak, MD, MPH, and her colleagues from the department of dermatology, School of Medicine, University of North Carolina at Chapel Hill, conducted a prospective observational study of 180 patients with severe nodular-cystic acne, to determine the effectiveness and safety of higher cumulative doses of isotretinoin (220 mg/kg or more). The higher dose of the drug was based on reviewing the medical records of patients at their institution and were associated with higher relapse and retrial rates.

Of the 180 patients, 116 (64%) completed the study and follow-up survey 12 months after the treatment. Approximately 52% were women, the mean age was 19.3 years, and the majority was white (74%). The mean cumulative dose of isotretinoin was 264.3 mg/kg with a mean treatment period of 6.3 months. In the lower-dose group, the mean cumulative dose was 170.8 mg/kg, and in the higher-dose group, the mean cumulative dose was 309.8 mg/kg. Treatments started from August 1, 2008 through August 31, 2009.

RESULTS

At the 12-month follow-up, patients in the high-dose group had a lower relapse rate (26.6%) compared with the patient in the low-dose group (43.8%) after adjustment for age, sex, race, treating physician, and treatment duration. Most patients (97%) reported in the survey that their condition had improved with the isotretinoin treatment, and more than 55% did not need to continue any acne medication treatments. Approximately 25% were treated with topical prescriptions at the 12-month follow-up, almost 15% used an over-the-counter medication, 1.7% were receiving an oral antibiotic, and 0.9% were being re-treated with isotretinoin.

"Of the patients in the lower-dose group, 42.3% were given a prescription for another acne medication after completing isotretinoin compared with 28.1% in the high-dose group," Dr Blasiak wrote. "In the lower-dose group, 12.8% of patients reported using over-the-counter acne treatment compared with 16.2% of patient in the high-dose group. This difference was not statistically significant (P=.23)."

> ■ Other adverse effects during treatment included cheilitis and xerosis, which was reported by most of the patients in both treatment groups.

ADVERSE EVENTS

In the study, 14% of patients had laboratory abnormalities, with most occurring in the higher-dose group. Elevated liver enzyme levels were seen in the higher-dose group, with 6.4% having elevated aspartate aminotransferase (AST) levels and 1.3% having elevated alanine aminotransferase (ALT) levels. In this higher-dose group, 1.3% also had elevated cholesterol levels and 11.5% had elevated triglycerides. In the lower-dose group, 5.3% had elevated triglycerides.

Other adverse effects during treatment included cheilitis and xerosis, which was reported by most of the patients in both treatment groups. Patients in the higher-dose group also reported retinoid dermatitis at higher rates (53.8%) than the patients in the lower-dose group (31.6%). Systemic effects included arthralgias, myalgias, and epistaxis.

After the 12-month follow-up, patients continued to report cheilitis, xerosis, and headaches, with both groups experiencing similar rates. "At the 12-month follow-up, the percentage of patients reporting rash decreased to less than 10%, with no statistically significant difference between the dosing groups, suggesting that isotretinoin has a transient, dose-dependent effect," Dr Blasiak wrote.

"At 1 year after completion of isotretinoin therapy, we found that patients in the high-dose group had a significantly decreased risk of relapse, which was defined as the need for prescription acne medication. Our overall rate or retrial or retreatment with a second course of isotretinoin was so low that we are unable to draw conclusions about the effect of dose on retrial rate," she concluded.

According to the American Academy of Dermatology, acne is the most common skin disorder in the United States, affecting 40 million to 50 million Americans. Nearly 85% of all people have acne at some point in their lives, most often on the face, chest, and back. ■

Analgesic overuse can exacerbate chronic post-traumatic headaches in adolescent concussion patients

from Staff Reports

Excessive analgesics use can contribute to the chronic headache associated with concussion in some adolescent patients and discontinuing these drugs can improve symptoms, according to researchers at the 42nd Annual Meeting of the Child Neurology Society, in Austin, Texas.

In a retrospective study, Geoffrey Heyer, MD, from Nationwide Children's Hospital in Columbus, Ohio, and colleagues, found that of the 104 patients referred to their clinic for persistent postconcussion symptoms over a 16-month period, 77 had post-traumatic headaches (headaches following concussion) of 3 to 12 months duration.

Fifty-four of the 77 (70.1%) met diagnostic criteria for probable medication-overuse headache. Only simple analgesics were overused. All patients received standard headache management, and those with overuse of analgesics were counseled to stop using the medicines. Thirty-seven (68.5%) stopped using analgesics and had resolution of headaches or improvement back to pre-concussion headache patterns; 7 (13%) stopped analgesics but denied headache improvements; and 10 (18.5%) did not discontinue medicine or were lost to follow up.

Under the International Classification of Headache Disorders (ICHD) criteria, medication overuse in headache may be diagnosed in patients with frequent at least 15 days per month that either developed or got worse while using over-the-counter or prescription analgesics, for example. The diagnosis is considered "probable" if either such medications have not yet been withdrawn or if the headaches continued for up to 2 months after medications were stopped, according to *MedPage Today*.

Daily headache (P=.006), female sex (P=.02), the presence of nausea (P<.001), throbbing headache versus steady or stabbing pain (P=.001), irritability following concussion (P=.03), and a relatively longer interval between the concussive event and neurological evaluation (P=.003) were factors significantly associated with probable medication overuse headache.

"Management of patients with chronic post-traumatic headache should include analgesic detoxification when medication overuse is suspected," Dr Heyer told *Formulary*. "While beyond the scope of this study, we recommend that the management of concussion and traumatic brain injury should be approached in a multidisciplinary manner." ■

Minimize risk of healthcare-associated infections in critical care environments with best practices

by Tracey Walker

Healthcare-associated infections (HAIs) are less likely to occur in favorable critical care work environments, said a study in the *American Journal of Critical Care*.

The study found nurses working in favorable critical care environments were about 40% less likely to report that HAIs, including urinary tract infections, ventilator-associated pneumonias, and central-line-associated blood stream infections, occurred frequently (more than once a month) compared to nurses working in poor critical care work environments.

"HAIs lead to the loss of tens of thousands of lives and cost the US healthcare system billions of dollars each year," said lead author Deena Kelly, RN, PhD, from the Center for Health Outcomes and Policy Research, University of Pennsylvania School of Nursing, Philadelphia.

The study employed a retrospective, cross-sectional design to examine the association between the critical care work environment and nurse-reported frequency of HAIs in 4 states during 2005 to 2008 using linked nurse and hospital survey data. The sample included adult, nonfederal, acute care hospitals that responded to the American Hospital Association Annual Survey in 2007 and also had at least 5 critical care nurse respondents from the University of Pennsylvania Multi-State Nursing Care and Patient Safety Study. The final sample totaled 3,217 ICU nurses from 320 hospitals.

Ms Kelly

"These findings substantiate efforts to focus on the quality of the work environment as a way to minimize the frequency of HAIs," Kelly said. "Critical care nurses . . . are well-positioned to influence the prevalence and prevention of HAIs in critically ill patients."

Efforts should be focused on addressing weaknesses in critical care work environments by using scores from the 31-item Practice Environment Scale of the Nursing Work Index as a guide. "Implementing a primary care staffing model, ensuring appropriate support staff and resources are available, and providing support for nurse managers are examples of interventions that might lower risk of HAIs," Kelly said. ■

Chemotherapy outpatients may benefit from blood-thinners to prevent VTE: Study

by Tracey Walker


Dr Lyman

Outpatients receiving chemotherapy are at high risk of developing venous thromboembolism (VTE) and of major bleeding complications, especially those with pancreas, stomach and lung cancer, according to a study published online in *The Oncologist*. Therefore thromboprophylaxis, or blood thinning treatments, should be considered for such patients, after carefully assessing the risks and benefits of treatment.

In a large population database of patients with newly diagnosed cancer, study author Gary H. Lyman, MD, at the Duke University School of Medicine and Duke Cancer Institute, in collaboration with scientists from Sanofi and King's College Hospital in London, UK, found that the rates of VTE in real-world unselected patients with cancer is substantially greater than that reported in highly selected patients placed on clinical trials.

"While the risk of thrombosis varies across cancer types, it is increased in all patients with cancer and increases cumulatively over the year following diagnosis," Dr Lyman told *Formulary*.

"The occurrence of thrombosis in unselected cancer patients in a more real-world setting appears to be substantially greater than reported in carefully controlled and selected clinical trials highlighting the importance of risk assessment and consideration of prophylactic anticoagulation in cancer patients including those hospitalized for various reasons as well as selected high-risk patients in the outpatient setting."

Dr Lyman and colleagues hypothesized that there is a definable high-risk cohort of patients who would benefit from thromboprophylactic treatment for VTE and that the scope of this risk warrants consideration for the use of prophylaxes such as low- and ultra-low-molecular-weight heparins, which recent studies have found to be safe and effective for use in the prevention of VTE in chemotherapy patients.

The study involved a random sample of approximately 27,500 patients with high-VTE-risk cancer types (ie, lung, pancreas, stomach, colon/rectum, bladder, or ovary) who had undergone chemotherapy. The group retrospectively evaluated the patients' VTE risk as well as their risk of bleeding and the economic burden borne by the patient as a result of the disease.

The risk of VTE increased over time, with a greater percentage of patients developing the complication at 12 months after initiation of chemotherapy than at 3 months; this held true across 3 definitions of VTE considered. According to definition A, the least conservative of the 3, VTE was most frequently observed in cancers of the pancreas, lung, and stomach, and the overall incidence of the complication was 13.5% at a year, with no indication of plateau or tapering at that time point. Patients with VTE showed a higher risk of major bleeding events in the year following chemotherapy initiation. According to definition A, that risk was 19.8%, compared with 9.6% in patients without VTE. These rates are higher than has been reported with anticoagulation use in clinical trials, again likely reflecting how clinical claims data can be more representative of actual practice than clinical trial data. Moreover, while the baseline healthcare costs of patients who would develop VTE were comparable to those of patients who would not, the costs of the VTE patients soared over the year following chemotherapy initiation. On average, patients with VTE had $110,719 in expenses compared with $76,804 for patients without VTE, a difference primarily accounted for by VTE-related inpatient, outpatient, and emergency room expenses.

> Patients with VTE had $110,719 in expenses compared with $76,804 for patients without VTE, a difference mostly accounted for by VTE-related inpatient, outpatient, and ER expenses.

"VTE is a serious and life-threatening complication of cancer and cancer treatment that requires constant awareness, prompt diagnosis, and urgent treatment to previous serious complications including death," Dr Lyman said.

Recently updated guidelines from the American Society of Clinical Oncology recommend routine prophylactic anticoagulation in hospitalized medical and surgical patients, and consideration of prophylaxis in high-risk ambulatory cancer patients receiving systemic chemotherapy, according to Dr Lyman.

"The importance of risk assessment and assessment of the balance of risk and benefit from anticoagulation are emphasized," he said. ■

Alzheimer's research: Now is the time for advocates to unite

by Kathyrn Foxhall

A dozen promising trials of Alzheimer's disease could be launched today, if funds were available, said Paul Aisen, MD, director of the Alzheimer's Disease Cooperative Study at the University of California, San Diego. "We know how to pick the drugs. We even know what designs we would use for the trials. But these are expensive and we don't have the money."

With a tsunami of future Alzheimer's cases facing the nation and a number of recent drug trials proving unsuccessful, an October meeting in Washington, D.C., sponsored by the Pharmaceutical Research and Manufacturers of America (PhRMA) and others, focused on how to better fund and accelerate research.

The clinical trials he referred to, said Dr Aisen, would focus on presymptomatic patients and emphasize "anti-amyloid drugs in combinations, but extending to unrelated therapeutic approaches." The nation would be able to fund all that with $2 billion, he said.

According to the Alzheimer's Association, spending on Alzheimer's disease by the National Institutes of Health totaled about $484 million in fiscal year 2013, the equivalent of $100 "for every $29,000 Medicare and Medicaid spends, caring for individuals with Alzheimer's."

Data from the Kaiser Family Foundation indicate that as of 2011, long-term care, much of it related to patients with Alzheimer's disease, already accounted for approximately 30% of Medicaid expenditures.

The Alzheimer's Association estimates that costs associated with the disease for Medicare and Medicaid beneficiaries will climb from $122 billion in 2010 to $344 billion in 2030.

CHALLENGES

At present, according to PhRMA, only three new medicines for Alzheimer's disease have been approved since 1998, resulting in a 34-to-1 ratio of "failures" to successes, although researchers stress that failures teach researchers a great deal.

Dr Aisen also told meeting attendees that although the members of the Alzheimer's disease research community have developed good communications with each other, there still is no "czar" or other infrastructure for coordinating the effort. This is another example, he said, of recommendations from the 2012 National Plan to Address Alzheimer's Disease that have not been addressed.

Reed Tuckson, MD, consultant and former chief of medical affairs for UnitedHealth Group, warned that, days into the October government shutdown, the nation was already facing the next battleground for federal dollars. In a budget-cutting process that will be hard, fast, and ugly, he said, Alzheimer's disease research advocates need to be united behind a strategically designed set of a few investigations, in spite of the fact that there is so much research to be done.

FOCUS

A key component for research success would be finding a connection between a clinical biomarker and a clinical outcome, said Nicholas Kozauer, MD, clinical team leader in the FDA division of neurology products. He emphasized that FDA is not in a position to approve a drug solely on the basis of a biomarker such as amyloid as a surrogate.

"If anything, we have evidence, at least from the dementia stage of the disease, that affecting amyloid doesn't necessarily correlate with clinical outcomes," he said.

But once there is reassurance a biomarker is clinically meaningful, "that is going to accelerate phase 2 development significantly," he said.

In Alzheimer's disease, he said, where researchers look for small changes caused by treatment over time, being able to screen drugs more quickly will open up many avenues. FDA released an Alzheimer's disease draft guidance for developing drugs for early stage Alzheimer's in February.

LIFESTYLE

Neill Graff-Radford, MD, neurologist at the Mayo Clinic, urged that research into the effects of lifestyle factors should not be forgotten. There is powerful evidence, for example, that aerobic exercise and other factors may be helpful for the brain, actually increasing the hippocampus volume. What researchers don't know is whether aerobic exercise will work in the setting of Alzheimer's pathology, he said.

But a critical factor about Alzheimer's disease, he said, is the fact that people are afraid of the disease, even more than they are of cancer. "If we knew that exercise could prevent Alzheimer's disease, genuinely," he said, maybe people at risk would actually do the exercise.

Robert Egge, the Alzheimer's Association's vice president for policy, said that advocacy for the disease now has a movement and a path forward. Positive indicators include President Obama's mention of Alzheimer's disease in the State of the Union address, the Department of Health and Human Services' emphasis on Alzheimer's in talking points about its proposed budget, and the resources NIH has directed to it from its discretionary funds.

Egge also noted there have been indications in Congressional budget statements that Alzheimer's disease research has bipartisan support, a rare commodity these days, and there has been increased grassroots lobbying for it on Capitol Hill. ■

This article originally appeared in *Drug Topics,* December 2013.

Studies: Lurasidone effective for treating depression associated with bipolar disorder

by Tracey Walker

Lurasidone HCl (Latuda) reduces depressive symptoms in adult patients with bipolar depression when used as monotherapy and adjunctive therapy to lithium or valproate. This flexibility is important given the multiple unmet needs of patients with bipolar depression, according to two phase 3 studies published recently in *The American Journal of Psychiatry*.

In the first study, adult patients with bipolar depression in the double-blind, randomized, placebo-controlled, 6-week monotherapy clinical trial were randomly assigned to receive 6 weeks of treatment with lurasidone flexibly dosed within 2 dose ranges, 20 mg/day to 60 mg/day (N=166) and lurasidone 80 mg/day to 120 mg/day (N=169), or placebo (N=170).

In this monotherapy study, adverse events reported with an incidence ≥5% (and greater than placebo) in at least one of the lurasidone 20 mg/day to 60 mg/day, lurasidone 80 mg/day to 120 mg/day and placebo groups were nausea, headache, akathisia, somnolence, sedation, dry mouth, and vomiting.

In the second study, adult patients with bipolar depression in the double-blind, randomized, placebo-controlled, 6-week adjunctive clinical trial were randomized to receive 6 weeks of adjunctive treatment with lurasidone (N=183) or placebo (N=165) (added to background treatment with lithium or valproate).

In this adjunctive therapy study, adverse events reported with an incidence ≥5% (and greater than placebo) in patients receiving lurasidone versus placebo were nausea, somnolence, tremor, akathisia, and insomnia.

The primary end point in both studies was change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 6. The key secondary end point was change from baseline at week 6 in the Clinical Global Impression, Bipolar Severity of Depression (CGI-BP-S) score, which assessed global severity of depressive symptoms.

Other secondary end points included responder rates; rates of remission; Hamilton Anxiety Rating Scale (HAM-A); Sheehan Disability Scale (SDS); Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR16); and Quality of Life, Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF).

These studies demonstrated that [lurasidone] significantly reduced depressive symptoms in adult patients with bipolar depression, both as monotherapy and as adjunctive therapy with lithium or valproate," said Antony Loebel, MD, executive vice president and chief medical officer at Sunovion, the manufacturer of Latuda.

■ Bipolar disorder is a serious mental illness characterized by severe and debilitating mood swings that affects approximately 10.4 million adults in the United States.

IMPACT OF BIPOLAR DISORDER

Bipolar disorder is a serious mental illness characterized by severe and debilitating mood swings that affects approximately 10.4 million adults in the United States. Bipolar depression refers to the depressive phase of bipolar disorder. When symptomatic, most people with bipolar disorder spend most time in the depressive phase.

Major depressive episodes associated with bipolar disorder have been shown to result in significant impairment in work, family, and social function. Bipolar depressive episodes are also associated with increased direct and indirect healthcare costs, as well as an increased risk of suicide.

"Many of the most commonly used mood stabilizers, antidepressants and antipsychotic agents actually have little data to support their efficacy in treating bipolar depression," said Dr Loebel.

"The dearth of data means that healthcare providers must often exercise a 'trial-and-error' approach to managing their patients' symptoms," he continued. "This can be frustrating, time-consuming, and costly for patients and the healthcare system. Very few medications have been approved as monotherapy treatment and no medications to date have been approved as adjunctive treatment of bipolar depression, despite the fact that mood stabilizers [such as lithium or valproate] are a mainstay treatment for people with bipolar disorder."

According to Dr Loebel, the last FDA approval of any drug for bipolar depression occurred in 2006. "There is a pressing need for additional effective and safe treatment options for this severely disabling and difficult to treat condition," he said.

Latuda was approved by FDA in June 2013 for the treatment of bipolar depression. ■

Pipeline preview

Complete response

■ Cariprazine (Forest Laboratories and Gedeon Richter Plc) an atypical antipsychotic for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. In the complete response letter, FDA acknowledged that cariprazine clearly demonstrated effectiveness in the treatment of schizophrenia and mania associated with bipolar disorder. However, the Agency indicated more information, including additional clinical trial data, would be needed.

Priority review

■ Oritavancin (The Medicines Company) was designated as a Qualified Infectious Disease Product (QIDP) for the treatment of acute bacterial skin and skin structure infections (ABSSSI). The QIDP designation provides oritavancin priority review by FDA, eligibility for FDA's fast-track status, and an additional 5 years of exclusivity upon approval of the product for ABSSSI.

Fast-track designation

■ Patisiran, ALN-TTR02 (Alnylam Pharmaceuticals) for the treatment of transthyretin (TTR)-familial amyloid polyneuropathy (FAP).

Orphan drug designations

■ KB001-A (KaloBios Pharmaceuticals) anti-PcrV monoclonal antibody fragment for the treatment of cystic fibrosis patients with Psuedomonas aeruginosa.

■ NNZ-2566 (Neuren Pharmaceuticals) for treatment of Fragile X Syndrome.

Continued on page 387

New molecular entity

Tivicay

Dolutegravir

GLAXOSMITHKLINE

An integrase strand transfer inhibitor for treatment of HIV 1 infection in adults and pediatric patients aged 12 years and older and weighing at least 40 kilograms, as part of combination antiretroviral therapy.

FDA approved dolutegravir (Tivicay, GlaxoSmithKline) in August 2013, for treatment of HIV 1 infection in adults and pediatric patients 12 years of age and older and weighing at least 40 kilograms, as part of combination antiretroviral therapy. Dolutegravir is an integrase strand transfer inhibitor (INSTI), which prohibits HIV-1 virus multiplication by interfering with HIV integrase, an enzyme required for viral replication. Dolutegravir is indicated for treatment of both INSTI-naïve and INSTI-experienced adults, but is indicated for pediatric patients only if they are INSTI-naive. A new once-daily option, dolutegravir may allow improved personalization of a patient's medication regimen.

■ Dolutegravir has not been studied in INSTI treatment-experienced pediatric patients and is not indicated for this patient population.

Efficacy. FDA based its approval of dolutegravir for adults on 4 phase 3 trials. In the studies, patients received dolutegravir or raltegravir plus additional appropriate antiretroviral therapy.

Two trials, SPRING-2 (n=822) and SINGLE (n=833) evaluated once-daily dolutegravir in INSTI treatment-naïve patients. By 48 weeks, dolutegravir demonstrated statistically equal or superior virological suppression, achieving <50 copies/mL of HIV-1 RNA in participants, versus raltegravir comparison regimens.

Use of dolutegravir in treatment-experienced patients was investigated in 2 studies, SAILING (n=719) and VIKING-3 (n=183). In both studies, the addition of dolutegravir to patients' background therapy improved virologic suppression at 24 weeks. VIKING-3 investigated the use of twice-daily dolutegravir in patients with multidrug-resistant infection, including resistance to other approved integrase inhibitors (raltegravir, elvitegravir). Subjects with INSTI resistance Q148 and 2 or more additional INSTI resistance substitutions demonstrated poor virologic response with the addition of twice-daily dolutegravir treatment to their background regimen.

FDA approved use of dolutegravir as part of combination antiretroviral therapy in pediatric patients ≥12 years of age and weighing a minimum of 40 kilograms based on a 24-week open-label trial of INSTI-naïve participants. Findings were similar to those for adults: At week 24, 70% of participants taking dolutegravir demonstrated viral suppression by achieving a viral load of <50 copies/mL, with improved CD4+ cell count compared to baseline levels. Dolutegravir therapy has not been studied in INSTI treatment-experienced pediatric patients and is not indicated for this patient population.

Safety. In trials, dolutegravir was well tolerated. The most common adverse reactions occurring with moderate-to-severe intensity and a frequency of at least 2% were headache and insomnia. Rare but serious adverse effects demonstrated with this therapy include redistribution or accumulation of body fat, immune reconstitution syndrome, and hypersensitivity reactions. Patients who have experienced a serious hypersensitivity reaction should discontinue the medication and avoid rechallenge with the drug to prevent progression to a life-threatening reaction. Patients with hepatitis B and/or C co-infection may be at increased risk for worsening liver enzyme elevations. Baseline laboratory tests should be performed before therapy is initiated and should be monitored periodically throughout treatment. Dolutegravir should be used with

Pipeline from page 386

First-time generic approvals

Rabeprazole sodium delayed-release tablets
(EQUIV TO ACIPHEX)

Dr. Reddy's Laboratories, Kremers Urban Pharmaceuticals, **LUPIN, MYLAN PHARMACEUTICALS, TEVA, TORRENT**

caution in geriatric patients, as this group was not represented in trials sufficiently to permit identification of differences in response to the medication. Patients taking dofetilide should not take dolutegravir. This combination is contraindicated due to the increase in dofetilide levels and the potential for serious adverse effects. Dolutegravir is classified pregnancy category B.

Dosage. In adult patients without INSTI resistance, the daily dose of dolutegravir is 50 mg orally. Dolutegravir 50 mg twice daily is recommended for patients with INSTI resistance. The recommended dosage for pediatric patients is 50 mg daily. There are no dosing adjustments necessary for patients with renal or hepatic impairment. There are several clinically significant drug interactions requiring dosing adjustments or avoidance of coadministration. Strong inducers of CYP3A4 and UGT1A1 may reduce plasma concentrations of dolutegravir and necessitate a dose adjustment. The full prescribing information provides a chart of interactions with clinical comments and recommendations. Dolutegravir may be taken with or without food but should be administered 2 hours before or 6 hours after administration of polyvalent medications. Dolutegravir is highly plasma protein-bound (98.9%). ■

> ■ Strong inducers of CYP3A4 and UGT1A1 may reduce plasma concentrations of dolutegravir and necessitate a dose adjustment.

This column is researched and compiled by **Kathryn Wheeler PharmD, BCPS,** *assistant clinical professor of pharmacy practice, University of Connecticut School of Pharmacy, Storrs, Conn.*

FDA actions *in brief*

Luliconazole (**Luzu Cream, 1%**, Valeant Pharmaceuticals) was approved for the 1-week, once-daily treatment of interdigital tinea pedis, tinea cruris, and tinea corporis, caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients aged 18 years and older.

Ibrutinib (**Imbruvica**, Pharmacyclics and Janssen) was approved to treat patients with mantle cell lymphoma, a rare and aggressive type of blood cancer. It is the second drug with breakthrough therapy designation to receive FDA approval.

Eslicarbazepine acetate (**Aptiom**, Sunovion Pharmaceuticals) was approved for use as adjunctive treatment of partial onset seizures, the most common type of seizure seen in people with epilepsy.

Morphine sulfate injection, USP (BD Rx) was approved for the management of pain not responsive to non-narcotic analgesics.

Vigabatrin (**Sabril**, Lundbeck) was approved as an add-on therapy for the treatment of refractory complex partial seizures in children aged 10 years and older who have adequately responded to several other treatments and if the possible benefit outweighs the risk of vision loss.

Follitropin alfa injection (**Gonal-F RFF Rediject**, EMD Serono) disposable pre-filled injector pen for subcutaneous injection was approved for induction of ovulation and pregnancy in oligo-anovulatory women in whom the cause of infertility is functional and not due to primary ovarian failure, development of multiple follicles in ovulatory women as part of an Assisted Reproductive Technology cycle.

Obinutuzumab (**Gazyva**, Genentech, a member of the Roche Group), also known as GA101, in combination with chlorambucil chemotherapy was approved for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). Obinutuzumab is the first drug approved with FDA's breakthrough therapy designation.

PEER-REVIEWED

Depression in the elderly: A pharmacist's perspective

Shana Castillo, PharmD, MBA; Kimberley Begley, PharmD; Ann Ryan-Haddad, PharmD; Ellen Sorrentino, PharmD candidate; Kwasi Twum-Fening, PharmD candidate

Abstract

Depression is a disease state that is commonly underdiagnosed and undertreated in patients over the age of 65 years. Elderly patients may differ from younger patients in the presentation of symptoms and in the prevalence of comorbidities. Risk factors for the development of depression are different for elderly patients. Treatment may also be dissimilar, including response and response time to treatment. Treatment should be tailored to the individual patient in the geriatric population to optimize therapeutic outcomes. Pharmacists can be vigilant of comorbidities and medications that potentially increase the risk of depression in the elderly. Pharmacists can play a significant role in advocating for the screening and treatment of this disease state. They are in a unique position to improve patient outcomes in late-life depression. (*Formulary*. 2013;48:388–394).

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) defines late-life depression as depressive symptoms in adults older than 65 years of age. This includes elderly patients who have experienced a mood disorder for the first time in later life and those whose symptoms initially presented earlier in life and are now recurring. The diagnosis of depression in older patients utilizes the same criteria as young adults. The diagnosis may be more difficult in the elderly due to coexisting chronic medical conditions and medication use, disability, or cognitive decline.[1] Depression in the elderly population is widespread and is often underdiagnosed and inadequately treated. Healthcare personnel who oversee care of the elderly may not be equipped to recognize or treat patients with depression. This is likely due to the presentation of depression in the elderly, which is often atypical—insomnia, anorexia, and fatigue—as opposed to the typical depressed mood reported by the younger depressed patient. Rather than reporting feeling sad or depressed, elderly more often have somatic complaints such as chronic pain, weight loss, headache, or gastrointestinal symptoms.[2] The elderly often dismiss their less-severe depressive symptoms as an acceptable response to life stress or a normal part of aging; however, depression is not a normal consequence of aging. Late-life depression, when untreated, has a significant impact on a patient's quality of life, healthcare resources, functional status, morbidity, and mortality.[3,4] Late-life depression should be treated with antidepressants that are safe in geriatrics and carefully chosen to meet each patient's needs.

EPIDEMIOLOGY

There are over 39 million adults age 65 years and older in the United States and an estimated 7 million of these are affected by depression.[5] About 5% of community-dwelling older adults meet the criteria for a major depression diagnosis. In institutional settings, the incidence of depression in the elderly population ranges from 12% to 30% and increases up to 50% among long-term care residents.[6] By 2020, the World Health Organization predicts that in developed countries, depression will be the second leading cause of disability and untimely death, after heart disease.[2]

RISK FACTORS FOR GERIATRIC DEPRESSION

Risk factors for depression in elderly persons include a family history of depression; chronic medical illness; use of certain medications; female gender; single, widowed, or divorced marital status; those with social isolation; lower socioeconomic status; and, stressful life events. Significant life events have been identified that increase an older adult's risk for depression. These include death of a spouse or loved one, disease or injury, disability and functional impairment, and loneliness.[7]

In a meta-analysis, 5 major risk factors for depression in older adults were reported. These risk factors included grief, sleep problems, disability, previous episodes of depression, and female gender. Of these, sleep issues, grief, and disability may be potentially modified.[8]

Dr Castillo is assistant professor of pharmacy practice, Creighton University School of Pharmacy and Health Professions, Omaha, Nebraska. **Dr Begley** is assistant professor of pharmacy practice, Creighton University School of Pharmacy and Health Professions. **Dr Ryan-Haddad** is associate professor of pharmacy practice, Creighton University School of Pharmacy and Health Professions. **Ms Sorrentino** is a PharmD candidate, Creighton University School of Pharmacy and Health Professions. **Mr Twum-Fening** is a PharmD candidate, Creighton University School of Pharmacy and Health Professions.

Disclosure information: The authors report no financial disclosures as related to products discussed in this article.

COMORBIDITIES

Rates of depression are higher for elderly patients with coexisting medical conditions. Older adults with possible depression should have a complete physical examination, medication history, and necessary laboratory assessment to rule out medical conditions such as hypothyroidism, alcohol use, or prescription drug abuse that may contribute to depression.

Untreated depression may result in patients developing chronic medical illnesses such as cardiovascular disease, and worsening others such as diabetes mellitus and Alzheimer's disease.[9-11] Depressed patients with comorbid diabetes are at greater risk for decreased adherence to medications, poor diet, decreased physical activity, higher functional impairment, and increased healthcare costs compared to their nondepressed peers.[12,13]

A number of medical illnesses have been reported to have the highest rates linked to late-life depression. Nearly 25% to 50% of all stroke patients develop depression post stroke.[14-16] Major depression also may affect 20% to 25% of patients with Alzheimer's disease.[17] Other medical illnesses include cancer (18%–39%), Parkinson's disease (10%–37%), rheumatoid arthritis (13%), diabetes (5%–11%), and myocardial infarction (MI) (15%–19%).[18]

The American College of Cardiology and the American Heart Association recommend screening for and treating depression for secondary prevention in patients with ST-segment elevation MI. Evaluation is recommended while hospitalized, 1 month after hospital discharge, and yearly.[19]

Researchers have reported that depression in the hospital after an MI is a significant predictor of 1-year cardiac mortality for both men and women. Depressed patients were significantly more likely to die of cardiac causes and to have an arrhythmic episode than patients without depression.[20]

Common psychiatric comorbidities of depression have been reported in a cohort study of 378 older depressed patients. Rates of anxiety-related disorders included any anxiety (41%), social phobia (19.6%), agoraphobia (10.8%), generalized anxiety disorder (10.6%), and panic disorder (7.7%).[21]

MEDICATIONS THAT CAUSE DEPRESSION

A number of medications are believed to be capable of causing depression. Although these medications may be associated with depression, there have been no studies assessing the risk they pose above and beyond that normally present in geriatric patients with comorbid disease states. Case reports, post-marketing surveillance, and retrospective studies have linked the following medications with depression: antipsychotics, digoxin, hydralazine, efavirenz, antineoplastic agents, beta blockers, corticosteroids, benzodiazepines, anti-Parkinson's agents, hormone-altering drugs, stimulants, triptan antimigraine medications, anticonvulsants, proton-pump inhibitors and H_2 blockers, statins and other lipid-lowering drugs, and anticholinergic drugs.[22] Table 1 lists some medications associated with depression, their reported incidence, and proposed mechanism of action.[22]

> Untreated depression may result in patients developing chronic medical illnesses such as cardiovascular disease, and worsening others such as diabetes mellitus and Alzheimer's disease.

PHARMACOTHERAPY

When treating elderly patients with depression, it is important to remember that although they may respond to therapy as well as younger patients, the time to full response may require up to 8 to 12 weeks. For a first-time depressive episode, treatment for up to 2 years may be required. In patients with 3 or more episodes, lifelong maintenance treatment may be considered. Dosage reduction may lead to relapse; thus dosages to which patients respond should be maintained.[2] Currently available antidepressants are listed in Table 2.[23,24]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective serotonin reuptake inhibitors (SSRIs) work by enhancing the action of serotonin by blocking its reuptake at the presynaptic terminals.[23] First-line treatment of depression in an elderly patient is generally an SSRI, because of the drug's fewer side effects, ease of use, and safety (especially in overdose). Time to full patient benefit with an SSRI in the elderly population may be longer than the usual 4 to 6 weeks.[25] Despite the more favorable tolerability of SSRIs, some side effects such as Parkinsonism, akathisia, anorexia, sinus bradycardia, and hyponatremia may warrant caution in the elderly population.[25] A rare but potentially lethal side effect, serotonin syndrome, may be seen if the patient is taking other drugs that enhance the availability of serotonin.[24] One study reported a 2-fold increase in the risk of clinical fragility fracture in patients older than 50 years on a daily SSRI. An increased risk of falling and lower bone mineral density at the hip was also reported in the same group.[26] Suicide risk should be monitored in the elderly patient, especially during the first month of

VIDEO

Watch **Ann Ryan-Haddad of Creighton University School of Pharmacy and Health Professions,** talk about depression in the elderly.

Visit www.formularyjournal.com/elderlydepression

Table 1

Medications that cause depression

Medication	Reported incidence	Proposed mechanism
Cardiovascular agents		
■ Clonidine	1.5%	Reduces NE output via alpha-adrenergic receptor agonism
■ Guanethidine	1.5%	Depletes neuronal NE
■ Methyldopa	3.6%	Partial agonism of NE receptor
■ Reserpine	7%	Depletes neuronal NE, serotonin, and dopamine
Retinoic acid derivatives		
■ Isotretinoin	1.5%-5%	Alters dopaminergic, serotonin, and possibly NE systems
Anticonvulsants		
■ Phenobarbital	40%	Reduces plasma unbound tryptophan, which influences plasma serotonin concentrations
■ Topiramate	5%-10%	Increases the amount of GABA available
■ Vigabatrin	12.1%	Increases the amount of GABA available
Hormonal agents		
■ Corticosteroids	1.3%-18%	Elevates plasma cortisol concentrations
■ GnRH agonists	26%-54%	Reduces both estrogen and androgen production
■ Tamoxifen	1%-20%	Reduces estrogen function via antagonizing estrogen receptors
Immunologic agents		
■ Interferon-alpha	13%–33%	Increases interleukin-6 production
■ Interferon-beta	0%–33%	

Abbreviations: GABA, gamma-aminobutyric acid; GnRh, gonadotropin-releasing hormone; NE, norepinephrine

Formulary/Source: Ref 22

treatment. One study found the suicide risk in men older than 66 years of age in their first month of antidepressant therapy to be 5-fold higher with SSRIs than with other antidepressants. No difference in risk, however, was observed in the second month or subsequent months of treatment.[27] There is no evidence to show that one SSRI antidepressant is more effective than another and no evidence to show that SSRIs are more effective than older antidepressants.[25,28] One SSRI that requires dosage adjustment in the elderly population is citalopram. Due to the risk of QT prolongation with citalopram, the maximum recommended dosage in patients older than 60 years of age is 20 mg daily.[29] Citalopram, escitalopram, and sertraline may be preferred due to fewer drug interactions and cognitive effects.[30]

SEROTONIN–NOREPINEPHRINE REUPTAKE INHIBITORS

Serotonin–norepinephrine reuptake inhibitors (SNRIs) work similarly to the SSRI class, while additionally blocking the reuptake of norepinephrine.[23] Adverse effects are similar to the SSRIs but also include sweating, tachycardia, and urinary retention.[31] SNRIs should be avoided in patients with uncontrolled hypertension because these agents can cause dose-dependent increases in diastolic blood pressure.[32] Similar to SSRIs, SNRIs can cause serotonin syndrome, usually resulting from interactions with monoamine oxidase inhibitors (MAOIs). Examples of drugs with MAOI properties include linezolid, dextromethorphan, sumatriptan, tramadol, and St. John's Wort.[31] Both SSRI and SNRI agents are less lethal in overdose as compared to tricyclic antidepressants.[24] Even though the SSRIs and SNRIs are not addictive, it is important to educate

Table 2

Currently available antidepressants

Selective serotonin reuptake inhibitors (SSRIs)
Citalopram
Escitalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Serotonin–norepinephrine reuptake inhibitors (SNRIs)
Desvenlafaxine
Duloxetine
Venlafaxine
Tricyclic antidepressants (TCAs)
Amitriptyline
Clomipramine
Desipramine
Doxepin
Imipramine
Nortriptyline
Protriptyline
Trimipramine
Monoamine oxidase inhibitors (MAOIs)
Isocarboxazid
Phenelzine
Selegiline
Tranylcypromine
Other
Amoxapine
Bupropion
Maprotiline
Mirtazapine
Nefazodone
Trazodone
Vilazodone
Atypical antipsychotics*
Aripiprazole
Quetiapine
Atypical antipsychotic/SSRI combination**
Olanzapine/fluoxetine

*FDA approved for adjunctive treatment of depression
**FDA approved for treatment-resistant depression

Formulary/Source: Refs 23,24

patients to avoid abrupt discontinuation of therapy with both classes due to the potential for antidepressant discontinuation syndrome.[24] After abrupt cessation, symptoms associated with antidepressant discontinuation usually appear within 2 to 3 days. The medications associated with the highest risk of producing these symptoms are paroxetine and venlafaxine. Sertraline, citalopram, and escitalopram have a lower risk, but the risk with fluoxetine is the lowest.[33] An SSRI is usually the drug of choice for patients with late-life depression, but an SNRI is also appropriate first-line treatment.[31]

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants (TCAs) work by decreasing reuptake of norepinephrine and serotonin.[23] TCAs work well as antidepressants; however, their actions at the additional adrenergic, cholinergic, and histaminic receptors produce adverse effects that detract from their overall tolerability in all patients, especially the elderly. These adverse effects include orthostasis, dry mouth, sexual dysfunction, constipation, urinary retention, blurred vision, confusion, and weight gain. Patients often discontinue the medication or are unable to titrate to the highest effective dose of the medication due to the intolerability of the TCAs.[24] These agents should be used with caution in patients who have urinary retention, benign prostatic hyperplasia, arrhythmias, cardiac conduction abnormalities, or narrow-angle glaucoma.[25] This class of antidepressants is not recommended for first- or second-line treatment in any age group.[25] The TCAs still remain an option for patients who do not respond to or cannot tolerate an SSRI or SNRI.[31] TCAs, however, are rarely the antidepressant of choice for elderly patients. They should generally be avoided in the elderly population.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors (MAOIs) work by inhibiting monoamine oxidase

enzyme, which increases the availability of monoamines causing increased concentration of neurotransmitters such as epinephrine, norepinephrine, and dopamine.[23] Adverse effects of this class (sleep disturbance, orthostatic hypotension, sexual dysfunction, weight gain) detract from their use as an antidepressant in the elderly population. Not only are MAOIs associated with a poor adverse-effect profile, they also can cause a potentially fatal interaction with SSRIs, sympathomimetics, and tyramine-rich foods that can result in delirium or hypertensive crisis.[24,34] MAOIs are not recommended as a first-line agent for treating late-life depression. Generally, this class is only used when a patient is treatment resistant to other antidepressant agents. Some studies have shown efficacy superior to other antidepressant agents in the treatment of atypical depression, mixed anxiety-depressive states, and panic disorder; however, few studies have included an elderly population of patients.[25] Selegiline is available as a transdermal patch, which may provide a convenient dosage form for some elderly patients. An additional benefit with this patch is that when used at its lowest recommended dose (6 mg/24 hr), there appear to be no significant interactions with tyramine-containing foods, as well as fewer sexual dysfunction, weight gain, or hypotensive adverse effects. The absence of these interactions and adverse effects, however, is not seen with higher dosages.[31]

Not only are MAOIs associated with a poor adverse-effect profile, they also can cause a potentially fatal interaction with SSRIs, sympathomimetics, and tyramine-rich foods that can result in delirium or hypertensive crisis.

OTHER AGENTS

BUPROPION

The actions of bupropion with regard to antidepressant activity are not fully understood. It does inhibit the neuronal reuptake of dopamine.[23] It may be as effective as the SSRI and TCA classes when treating major depression.[35] Patients who suffer with lethargy, fatigue, or daytime sedation may benefit from treatment with bupropion because it is generally an activating medication. It should not be used in patients who have seizure disorders, past or current diagnosis of bulimia nervosa, or are undergoing alcohol detoxification.[25] Patients with hypertension should have their blood pressure checked regularly due to the potential for elevation.[23] The combination of an SSRI plus bupropion is commonly used.[33]

MIRTAZAPINE

The chemical structure of mirtazapine is not related to any other antidepressants.[23] It has both serotonergic and noradrenergic properties.[25] Mirtazapine has an anxiolytic effect and might be beneficial in patients with insomnia, agitation, or restlessness due to its sedating nature. Its sedating effects do tend to diminish with further treatment that includes titration to higher doses.[23,25] Its appetite-stimulating effect may prove useful in an anorexic depressed patient.[31] Mirtazapine is generally considered a second-line agent.[25] Elderly patients should be initiated at lower dosages and titrated more slowly. They are also more susceptible to hyponatremia, a rare side effect of mirtazapine.[23] Abrupt withdrawal of mirtazapine should be avoided.

NEFAZODONE

Nefazodone's antidepressant activity is due to actions on the serotonergic and noradrenergic systems.[23] It is rarely prescribed due to its association with rare, hepatic failure requiring transplantation. Nefazodone has been removed from the market in Canada and Europe because of this serious adverse effect.[31] It might be a choice for patients who have insomnia, anxiety, or agitation. It should be used with caution because it is a potent inhibitor of the CYP-50-3A4 isoenzyme, which can lead to significant drug–drug interactions.[25] In elderly patients, nefazodone should be initiated at half the normal adult dose.[23]

TRAZODONE

Trazodone and nefazodone have similar structures.[35] Trazodone is rarely prescribed as a sole antidepressant agent but is commonly prescribed as an adjunct to an SSRI in patients with insomnia due to its sedating properties.[25,31] Elderly patients usually require a lower dose and may be at increased risk for adverse reactions. If a patient cannot tolerate an SSRI or SNRI, however, trazodone may be preferred over a TCA because it has fewer cardiac effects.[23]

ATYPICAL ANTIPSYCHOTICS

FDA has approved both aripiprazole and quetiapine for the adjunctive treatment of depression. A combination of olanzapine and fluoxetine has been approved for treatment-resistant depression.[31] Atypical antipsychotics used as adjunctive treatment for depression in the geriatric population have not been systematically studied. Of concern is the association between atypical antipsychotics and increased mortality in geriatric patients with dementia; however, it is not clear if the low doses used in adjunctive treatment of depression will produce the same association.[36]

NONPHARMACOLOGIC TREATMENT

Nonpharmacologic therapy continues to have an important role in treating depression. Consensus guidelines for first-line treatment of both mild and severe depression in the elderly population include not only an anti-

Continued on page 393

Continued from page 392

depressant but also psychotherapy.[36] Psychotherapy may include cognitive-behavioral therapy, supportive psychotherapy, problem-solving therapy, or interpersonal therapy.[35] Increased exercise and exposure to bright light have also shown benefit in the depressed elderly population.[25] Electroconvulsive therapy (ECT) can be effective for severe depression. If two trials of antidepressants have failed, ECT may be an option. ECT is also effective for patients with depression that exhibits psychotic features, who have not responded to antipsychotics and antidepressants.[35]

OUTCOMES

The best therapeutic outcome of antidepressant therapy is remission. Nevertheless remission rates for geriatric patients are only approximately 30%. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, only 30% of study participants attained remission status.[37] Similarly, other researchers noted that 71% of the 792 geriatric patients with major depression did not achieve remission. Factors increasing nonremission included comorbid anxiety, female sex, general medical comorbidity, and increased baseline depressive symptom severity.[38]

Depression may affect older patients' use of medical services such as physician visits and hospital admission rates. In the KORA-Age study, participants with depressed mood had significantly more physician visits than those without depressed mood.[39] In the Health in Men Study 44.8% of patients with depressive symptoms had at least one emergency hospital admission for nonpsychiatric conditions compared to 22.9% of male patients without depression. In addition, those with depression had longer hospital stays and worse hospital outcomes.[40] Depressed patients' nonadherence to treatment plans are a possible reason for the increased hospital admission rates. Because of their nonadherence, patients may be admitted to the hospital in a more serious or advanced stage of their condition, which can significantly impact hospital stay durations and health outcomes.

The frequency of antidepressant use in US nursing home residents has increased from 21.9% to 47.5% (1996–2006).[41] Investigators have also evaluated antidepressant use for older patients admitted to Veterans Affairs (VA) Community Living Centers during an 18-month period. They identified that 25% of patients potentially underused antidepressants (patients had depression diagnosis but were not receiving an antidepressant), 42% potentially overused antidepressants (patients without depression were taking an antidepressant), and nearly 60% of patients with depression receiving antidepressant therapy had 1 or more prescribing problems (eg, drug–drug and drug–disease interactions). Patients with moderate-to-severe pain and those taking anxiolytic/hypnotic medications were at significantly increased risk for inappropriate use of antidepressants. Patients with mild/moderate cognitive impairment, polypharmacy (>5 medications), cerebrovascular accidents, other anxiety, or taking an antipsychotic without diagnosis of schizophrenia were at greater risk for overuse of antidepressants. The only associated risk factor for antidepressant underuse was activities of daily living (ADL) dependencies.[42]

ROLE OF PHARMACISTS

Pharmacists can provide several important services to their older patients with depression. Providing educational information about depression and antidepressant medication could enhance medication adherence. Additionally, monitoring patients for medication effectiveness, side effects, and adherence could improve treatment outcomes. For patients who are not aware of or have not sought medical care for depression, the pharmacist may encourage them to make an appointment with their primary care provider for assessment.[43] Researchers have evaluated pharmacists' perceived barriers to providing depression care and found deficiency in psychiatric education, minimal time for personalized care for patients, limited patient information related to treatment, lack of private spaces in the pharmacy to talk to patients about mental health issues, and concerns about effectively communicating with depressed patients were the most commonly noted barriers.[44]

In a study evaluating the impact of pharmacist intervention on outcomes of depressed primary care patients, investigators reported significant improvement in antidepressant use rates for intervention patients (57.5% vs 46.2%) and for patients not on antidepressants at enrollment (32.3% vs 10.9%) as compared to non-intervention patients. Pharmacist consultation was either conducted in person or by telephone.[45]

As the most accessible healthcare provider, pharmacists are in a unique position to inform patients and assist in recognition of depression, offer screening, provide education, and offer support to their elderly patients who may be suffering from depression. Pharmacists can monitor for patients' somatic complaints that might indicate undiagnosed depression. Pharmacists should be cognizant and able to recognize comorbidities and medications that may contribute to depression in the elderly patient. They can also advocate for their patients to discuss their symptoms with their primary care providers. For those patients receiving medication therapy for depression, pharmacists should be mindful of potential drug–drug and drug–disease interactions as well as side effects, monitor refills to ensure medication adherence, and counsel patients about the possible need for continued maintenance therapy.

Pharmacists may also consider innovative practice or outreach opportunities, such as community presentations on the signs and symptoms of depression, developing a call intervention system for elderly patients taking antidepressants, offering medication reviews to determine potential medication causes of depression, offering educational brochures in the pharmacy, or collaborating with primary care providers in the community to provide free screenings.

Because so many elderly are affected by depression and studies have shown depressed elderly have a higher morbidity and mortality with increased use of healthcare resources and costs, pharmacists have a professional duty to ensure they receive optimal pharmacy care in their treatment of depression. ■

REFERENCES

1. Alexopoulos GS, Buckwalter K, Olin J, et al. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. *Biol Psychiatry.* 2002;52:543–558.
2. Rojas-Fernandez C, Mikhail M. Contemporary concepts in the pharmacotherapy of depression in older people. *Can Pharm J (Ott).* 2012;145:128,135.e2.
3. Frederick JT, Steinman LE, Prohaska T, et al. Community-based treatment of late life depression: an expert panel-informed literature review. *Am J Prev Med.* 2007;33:222–249.
4. Snowden M, Steinman L, Frederick J. Treating depression in older adults: challenges to implementing the recommendations of an expert panel. *Prev Chronic Dis.* 2008;5:A26.
5. CDC promotes public health approach to address depression among older adults. http://www.cdc.gov/aging/pdf/CIB_mental_health.pdf. Accessed August 20, 2013.
6. Park M, Unutzer J. Geriatric depression in primary care. *Psychiatr Clin North Am.* 2011;34:469,487, ix-x.
7. Bruce ML. Psychosocial risk factors for depressive disorders in late life. *Biol Psychiatry.* 2002;52:175–184.
8. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: A systematic review and meta-analysis. *Am J Psychiatry.* 2003;160:1147–1156.
9. Lustman PJ, Anderson RJ, Freedland KE, et al. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care.* 2000;23:934–942.
10. Jiang W, Krishnan RR, O'Connor CM. Depression and heart disease: evidence of a link, and its therapeutic implications. *CNS Drugs.* 2002;16:111–127.
11. Alexopoulos GS, Meyers BS, Young RC, et al. The course of geriatric depression with "reversible dementia": a controlled study. *Am J Psychiatry.* 1993;150:1693–1699.
12. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med.* 2000;160:3278–3285.
13. Lin EH, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care.* 2004;27:2154–2160.
14. Robinson RG, Kubos KL, Starr LB, et al. Mood disorders in stroke patients. Importance of location of lesion. *Brain.* 1984;107(Pt 1):81–93.
15. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. *Stroke.* 1993;24:976–982.
16. Wade DT, Legh-Smith J, Hewer RA. Depressed mood after stroke. A community study of its frequency. *Br J Psychiatry.* 1987;151:200–205.
17. Lyketsos CG, Olin J. Depression in Alzheimer's disease: overview and treatment. *Biol Psychiatry.* 2002;52:243–252.
18. Sable JA, Dunn LB, Zisook S. Late-life depression. How to identify its symptoms and provide effective treatment. *Geriatrics.* 2002;57:18–26.
19. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol.* 2004;44:671–719.
20. Frasure-Smith N, Lesperance F, Juneau M, et al. Gender, depression, and one-year prognosis after myocardial infarction. *Psychosom Med.* 1999;61:26–37.
21. Comijs HC, van Marwijk HW, van der Mast RC, et al. The Netherlands Study of Depression in Older Persons (NESDO); a prospective cohort study. *BMC Res Notes.* 2011;4:524,0500-4-524.
22. Botts S, Ryan M. Depression. In: Tisdale J, Miller D, eds. *Drug-Induced Diseases: Prevention, Detection, and Management.* 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2010:317–332.
23. Clinical pharmacology. Updated 2013. http://clinicalpharmacology-ip.com/default.aspx. Accessed July 2, 2013.
24. Finley PR, Lee KC. Providing pharmaceutical care to patients with depression. *Pharmacy Today: Topics in Patient Care.* 2006:S1.
25. Diagnosis and management of late-life depression. Updated 2013. http://www.uptodate.com/contents/diagnosis-and-management-of-late-life-depression#H1. Accessed August 8, 2013.
26. Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med.* 2007;167:188–194.
27. Juurlink DN, Mamdani MM, Kopp A, Redelmeier DA. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. *Am J Psychiatry.* 2006;163:813–821.
28. Gartlehner G, Gaynes BN, Hansen RA, et al. Comparative benefits and harms of second-generation antidepressants: Background paper for the American College of Physicians. *Ann Intern Med.* 2008;149:734–750.
29. FDA drug safety communication: Revised recommendations for celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. Updated 2012. http://www.fda.gov/drugs/drugsafety/ucm297391.htm. Accessed August 12, 2013.
30. Pollock B, Semla T, Forsyth C. Psychoactive drug therapy. In: Halter JB, ed. *Hazzard's Geriatric Medicine and Gerontology.* 6th ed. New York, NY: McGraw-Hill Professional; 2009:767–778.
31. Drugs for depression and bipolar disorder. *Treat Guidel Med Lett.* 2010;8:35–42.
32. Wernicke J, Pangallo B, Wang F, et al. Hepatic effects of duloxetine-I: Non-clinical and clinical trial data. *Curr Drug Saf.* 2008;3:132–142.
33. Finley PR, Rens HR, Pont JT, et al. Impact of a collaborative care model on depression in a primary care setting: A randomized controlled trial. *Pharmacotherapy.* 2003 Sep;23(9):1175-85.
34. Transdermal selegiline (Emsam). *Med Lett Drugs Ther.* 2006;48:41–42.
35. Birrer RB, Vemuri SP. Depression in later life: a diagnostic and therapeutic challenge. *Am Fam Physician.* 2004;69:2375–2382.
36. Alexopoulos GS. Pharmacotherapy for late-life depression. *J Clin Psychiatry.* 2011;72:e04.
37. Zisook S, Ganadjian K, Moutier C, et al. Sequenced treatment alternatives to relieve depression (STAR*D): lessons learned. *J Clin Psychiatry.* 2008;69:1184–1185.
38. Azar AR, Chopra MP, Cho LY, et al. Remission in major depression: results from a geriatric primary care population. *Int J Geriatr Psychiatry.* 2011;26:48–55.
39. Lacruz ME, Emeny RT, Haefner S, et al. Relation between depressed mood, somatic comorbidities and health service utilisation in older adults: results from the KORA-age study. *Age Ageing.* 2012;41:183–190.
40. Prina AM, Huisman M, Yeap BB, et al. Association between depression and hospital outcomes among older men. *CMAJ.* 2013;185:117–123.
41. Hanlon JT, Handler SM, Castle NG. Antidepressant prescribing in US nursing homes between 1996 and 2006 and its relationship to staffing patterns and use of other psychotropic medications. *J Am Med Dir Assoc.* 2010;11:320–324.
42. Hanlon JT, Wang X, Castle NG, et al. Potential underuse, overuse, and inappropriate use of antidepressants in older veteran nursing home residents. *J Am Geriatr Soc.* 2011;59:1412–1420.
43. Wells BG. Underrecognition and undertreatment of depression: what is the pharmacist's culpability? *Pharmacotherapy.* 1999;19:1237–1239.
44. Scheerder G, De Coster I, Van Audenhove C. Pharmacists' role in depression care: a survey of attitudes, current practices, and barriers. *Psychiatr Serv.* 2008;59:1155–1160.
45. Adler DA, Bungay KM, Wilson IB, et al. The impact of a pharmacist intervention on 6-month outcomes in depressed primary care patients. *Gen Hosp Psychiatry.* 2004. May-Jun;26(3):199–209.

PEER-REVIEWED

Focus on tapentadol: Role in the treatment of neuropathic pain

Kelly A. Macedo, PharmD
Michael D. Nailor, PharmD, BCPS AQ-ID

Abstract

Neuropathic pain is a difficult-to-treat condition; pathologic changes in neuronal pathways may result in suboptimal analgesic control with opioid agents alone. Polypharmacy is employed often to simultaneously target multiple levels of the pain pathway, at the expense of escalated complexity of drug regimens and risk for drug–drug interactions and adverse effects. Tapentadol combines 2 mechanisms of action within a single molecule, allowing for mu-receptor activation and norepinephrine reuptake inhibition without the aforementioned drawbacks of multiple agent regimens. Recently approved in its extended-release formulation with favorable pharmacokinetics and improved gastrointestinal tolerance over pure opioids, tapentadol may prove cost effective when productivity and indirect costs are considered. (*Formulary*. 2013;48:395-402.)

Neuropathic pain is a complex condition that affects up to 3% to 9% of the global population, with significant implications for quality of life and healthcare utilization.[1,2] Characterized by a burning, shooting, stabbing quality, neuropathic pain is mechanistically unique from nociceptive pain and poses significant treatment challenges. In the neuropathic pain state, mu-opioid receptors are downregulated in the spinal dorsal horn and dorsal root ganglion neurons, resulting in diminished efficacy of mu agonists.[3,4] For this reason, opioid analgesics used in chronic nociceptive pain often provide suboptimal relief for neuropathic symptoms, necessitating high doses often with intolerable adverse effects. Adjunctive and alternative agents are thus often employed in this patient population. Current therapeutic options in neuropathic pain include anticonvulsants, tricyclic antidepressants (TCAs), antiepileptics, topical anesthetics, and opioid analgesics.[5,6] Many of these agents are used off-label, but some carry FDA indications specific to neuropathic pain (Table 1, page 396).[7-10] Although studies demonstrate the effectiveness of these agents, pain score reductions are often modest and thus regimens using multiple agents may be initiated. Use of multiple drugs in a single regimen, however, increases the risk for drug–drug interactions, side effects, and patient nonadherence.[11]

Tapentadol, a novel multimodal analgesic, is an agent with potential for reducing polypharmacy in patients with neuropathic pain. The immediate-release (IR) formulation of tapentadol (Nucynta) was approved by FDA in 2008 for moderate-to-severe acute pain and the extended-release (ER) preparation was approved in 2011 for moderate-to-severe chronic pain, both limited to the adult population. In August 2012, FDA widened the indications for tapentadol ER to include neuropathic pain associated with diabetic peripheral neuropathy.[12,13] Tapentadol's approval is the first entrant for diabetic peripheral neuropathy utilizing the following 2 mechanisms of action: An agonist at the mu receptor and a norepinephrine reuptake inhibitor. It joins 2 other agents approved for diabetic peripheral neuropathy; the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine and the anticonvulsant pregabalin. With 10% to 20% of patients with diabetes experiencing some form of neuropathy, tapentadol's unique mechanism of action may provide relief to a large number of patients.[14] The drawback remaining, however, is that clinical trials directly comparing tapentadol to commonly utilized neuropathic pain agents are lacking. Although current data suggest tapentadol may have a role in the treatment of neuropathic pain, its safety and efficacy as compared to its predecessors has not been studied to date.

CHEMISTRY AND PHARMACOLOGY

Neuropathic pain is characterized by sensitization of affected areas of

Dr Macedo is a PGY-1 pharmacy practice resident at Veterans Affairs Boston Healthcare System, Boston, MA. At the time of writing, she was a student at The University of Connecticut School of Pharmacy, Storrs, Conn. **Dr Nailor** is an associate clinical professor of pharmacy practice, University of Connecticut School of Pharmacy, Storrs, Conn., and a clinical specialist in infectious diseases, Hartford Hospital, Hartford, Conn.

Disclosure information: The authors report no financial disclosures as related to products discussed in this article.

In each issue, the "Focus on" feature reviews a newly approved or investigational drug of interest to pharmacy and therapeutics committee members.

EDITORS' NOTE: The clinical information provided in "Focus on" articles is as current as possible. Due to regularly emerging data on developmental or newly approved drug therapies, articles include information published or presented and available to the author up until the time of the manuscript submission.

Table 1

Medications indicated for use in neuropathic pain states

Name	Class	Indication	Usual maintenance dose	Approximate cost (30-day supply)	Controlled substance schedule
Tapentadol ER (Nucynta ER)	Mu-opioid agonist/ norepinephrine reuptake inhibitor	Diabetic neuropathy	100 mg–250 mg twice daily	$340–$560	C-II
Duloxetine (Cymbalta)	SNRI	Diabetic neuropathy	60 mg daily	$240	N/A
Pregabalin (Lyrica)	Anticonvulsant, miscellaneous	Diabetic neuropathy; spinal cord associated neuropathy; postherpetic neuralgia	150 mg–300 mg daily in 3 divided doses; 150 mg–600 mg daily in 2 divided doses; 150 mg–300 mg daily in 2–3 divided doses	$360	C-V
Capsaicin 8% (Qutenza)	TRPV1 agonist	Postherpetic neuralgia	Apply patch to most painful area for 60 min, up to 4 patches may be applied at once; do not apply more frequently than every 3 mo	$810 (1 patch)	N/A
Lidocaine patch (Lidoderm patch 5%)	Local anesthetic	Postherpetic neuralgia	Apply patch to most painful area for up to 12 hr in 24-hr period, up to 3 patches may be applied at once	$280 (30 patches)	N/A
Gabapentin (Neurontin)	GABA analog anticonvulsant	Postherpetic neuralgia	1,800 mg–3,600 mg in divided doses	$230–$450	N/A
Gabapentin ER (Gralise)	GABA analog anticonvulsant	Postherpetic neuralgia	1,800 mg once daily	$270	N/A
Gabapentin enacarbil (Horizant)	GABA analog anticonvulsant	Postherpetic neuralgia	600 mg twice daily	$270	N/A

Abbrevations: GABA, gamma-aminobutyric acid; SNRI, serotonin norepinephrine reuptake inhibitor; TRPV1, transient receptor potential vanilloid 1

Formulary/Source: Refs 7-10

the spinal cord, expansion of nerve pathways, and increased pain sensation after both painful and nonpainful stimuli.[5] Tapentadol [(3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride)] consists of a single enantiomer that exerts its analgesic effect at the spinal cord via a dual mechanism of action. As both a mu-opioid receptor agonist and norepinephrine reuptake inhibitor, tapentadol acts at multiple levels within the pain pathways of the central nervous system (CNS).[4,13] Activation of the mu receptor inhibits gamma-aminobutyric acid (GABA) release, with predictable downstream effects on dopaminergic signaling.[5] Meanwhile, inhibition of presynaptic norepinephrine reuptake at both interneurons and descending inhibitory fibers results in increased levels of this neurotransmitter in the synaptic cleft. Elevated norepinephrine levels are believed to activate alpha-adrenergic receptors and cause a decrease in the conduction of painful impulses.[4] In a departure from previous agents with norepinephrine reuptake inhibition, tapentadol does not exhibit significant

effects on serotonin reuptake.[13] This distinction differentiates tapentadol from the multimodal agent tramadol, which combines both serotonin and norepinephrine reuptake with secondary mu-opioid activation from its primary active metabolite. Preclinical and clinical studies of TCAs, selective serotonin reuptake inhibitors (SSRIs), and SNRIs suggest that norepinephrine reuptake inhibition may have a greater impact on analgesia than serotonin reuptake inhibiton.[15,16] Experimental support for this theory has been demonstrated in preclinical trials of milnacipran on spinal nerve ligation in mice, with denervation of the adrenergic system, but not denervation of the serotonergic system, resulting in loss of milnacipran-induced analgesia.[17] The continuing uncertainty over serotonin's analgesic utility may be explained by a distinction between serotonergic pathways utilized in acute versus chronic pain. Inhibitory pathways that terminate on serotonin $(5HT)_7$ receptors appear to dominate in acute pain, resulting in an overall analgesic effect. In chronic pain, however, there appears to be a shift to excitatory $5HT_3$ spinal receptors, which serve to augment rather than reduce painful stimuli. The time course since injury induced therefore may predict the analgesic efficacy of serotonergic agents.[18] Tapentadol's minimal effect on the serotonergic system may demonstrate a reduced risk for undesirable serotonergic effects without necessarily compromising analgesic efficacy.[11]

Although the dual mechanisms of tapentadol would be predictably expected to compound the analgesic effect, the degree of analgesia observed in neuropathic pain models suggests that the actions are synergistic rather than merely additive. Two studies using modified isobolographic analysis demonstrated supra-additive effects for mu-receptor agonism and norepinephrine reuptake inhibition when selective mechanistic inhibition was employed with the opioid antagonist naloxone and the $alpha_2$-adrenergic agonist yohimbine, respectively.[19] Anatomically, this synergism may be explained by the finding that opioid agonists disinhibit supraspinal GABAergic interneurons in addition to their traditional role in activating presynaptic and postsynaptic mu receptors in the spinal cord. This GABAergic effect of opioids disinhibits descending inhibitory projections and ultimately increases the release of norepinephrine at the spinal cord, thereby augmenting norepinephrine reuptake inhibition.[3] However, the clinical relevance of the synergy between tapentadol's dual mechanisms of action may be difficult to quantify. Tapentadol's predominant mechanism of action differs between neuropathic and nonneuropathic pain states, with norepinephrine reuptake inhibition taking precedence in the former and mu-receptor agonism in the latter. This distinction is supported by preclinical studies in which the $alpha_2$-adrenoreceptor antagonist atipamezole was more effective at reversing tapentadol's analgesia in nerve-injured rats, while naloxone, a mu-receptor antagonist, was more effective in rats without a neuropathic state.[18] Furthermore, tapentadol has been shown to be up to 10 times more potent in treating hyperalgesia in mice with induced diabetic polyneuropathy than in providing antinociception in control animals. Lower doses of the agent appear to be effective only in the neuropathic state, with dose escalation required to induce analgesia in healthy controls.[20] One possible explanation for this phenomenon is that neuropathic pain models show a decrease in spinal expression of mu-opioid receptors and an increase in noradrenergic spinal innervation. With diminished returns from its opioid effects, tapentadol's efficacy in neuropathic pain may be retained due to its norepinephrine reuptake inhibition.[3,18,21]

In terms of comparison to pure opioid agonists, tapentadol's affinity for the mu receptor is approximately 50-fold lower than seen with morphine.

Whether tapentadol's efficacy can be fully retained with a single mechanism remains unclear. In one report, complete blockade of either mechanism with antagonism of the $alpha_2$-adrenoreceptor or mu receptor resulted in total or near total reversal of tapentadol's effects. This suggests that although preference for either mechanism may predominate in various pain states, there is some degree of mutual dependence between these actions.[18] On the other hand, studies conducted in mu-opioid receptor knockout mice found that tapentadol was successful in producing a reduced but significant degree of analgesia, despite its opioid action being eliminated.[20] Further research is needed to elucidate the true degree of reliance between tapentadol's dual mechanisms.

Due to its novel pharmacology, tapentadol may be beneficial as combination therapy with nonopioid neuropathic pain agents. In a study of spinal nerve ligation in rats, combination therapy with tapentadol and the anticonvulsant pregabalin demonstrated synergistic effects, whereas addition of pure opioids to pregabalin therapy was merely additive and resulted in significantly more side effects. Combination tapentadol and pregabalin therapy addresses pain from multiple angles, targeting mu-opioid receptors, norepinephrine reuptake inhibition, and $alpha_2$delta subunit calcium-channel blockade.[21]

In terms of comparison to pure opioid agonists, tapentadol's affinity for the mu receptor is approximately 50-fold lower than that seen with morphine. Despite this, tapentadol only exhibits 2 to 3 times less anal-

Table 2

Pharmacokinetic profile of tapentadol

Absorption	Rapid, complete
F	32%
T_{max}	1.25 hr (IR) 3–6 hr (ER)
V_d	442–638 L
Protein binding	20%
$T_{1/2}$	4 hr (IR) 5–6 hr (ER)
Metabolism	Primary: phase 2 glucuronidation Minimal: phase 1 oxidation Minimal: CYP 2C9, 2C19, 2D6
Elimination	99% excreted in urine

Abbreviations: F, bioavailability fraction; ER, extended release; IR, immediate release; T_{max}, time to maximum plasma concentration; T½, half-life; Vd, volume of distribution

Formulary/Source: Ref 7

gesic potency than morphine in nociceptive pain states and has actually been shown to have greater efficacy in reducing heat hyperalgesia than morphine, supporting the hypothesis that it may be uniquely suited for use in neuropathic pain. Differences between pure opioid agonists and tapentadol are also seen with regard to development of tolerance. In animal models, tolerance develops more slowly with tapentadol than with pure opioid analgesics.[5] Compared to morphine, tapentadol exhibited longer time to development of tolerance in rat models. Development of tolerance was documented at 23 days with tapentadol versus 10 days with morphine in one trial.[11] A second model cited complete tolerance as occurring at 51 and 21 days, respectively.[4,22] The implications of this in clinical practice are not yet known, and it remains uncertain whether delayed tolerance will have any effect on need for dose escalation in the chronic pain population.

PHARMACOKINETICS

The first-pass effect on tapentadol is significant, with a reported bioavailability of 32%. Approximately 20% is bound to plasma proteins, minimizing the likelihood of drug–drug displacement interactions. Available as both IR and ER formulations, tapentadol demonstrates distinct pharmacokinetics with respect to time to maximum concentration and elimination rate between the products (Table 2).[7] It is estimated that tapentadol's maximum concentration is reached at 1.25 to 1.5 hours with the IR formulation and 3 to 6 hours with the ER formulation. The elimination half-life of tapentadol IR is 4 hours; the half-life of the ER product is extended to 5 to 6 hours.[4,7]

Tapentadol is administered in its active form, and therefore requires no metabolism to exert its analgesic effect and retains predictable analgesic effects regardless of patient-specific CYP polymorphisms. Glucuronidation via UGT1A9 and UGT2B7 enzymes accounts for up to 70% of tapentadol's metabolism and yields tapentadol-O-glucuronide as the major metabolite.[19] The remainder of metabolism is achieved via the CYP2C9, 2C19, and 2D6 enzyme systems. These processes yield N-desmethyl tapentadol and hydroxytapentadol, from the 2C19/2C9 and 2D6 enzyme systems, respectively. All of tapentadol's metabolites lack analgesic activity, and tapentadol has not demonstrated clinically significant induction or inhibition of CYP enzyme systems.[5]

Renal elimination accounts for up to 99% of clearance of tapentadol and related metabolites, with the remainder being excreted in the feces. Due to its dependence on the hepatic and renal systems for metabolism and excretion, tapentadol is not recommended in patients with severe liver or kidney dysfunction, and has not been studied in these patient populations. Dose modification is suggested in moderate hepatic dysfunction, with reduction of the starting dose to 50 mg and extension of the interval to every 8 hours recommended. Moderate renal dysfunction and mild renal and hepatic dysfunction require no modifications.[4,5]

CLINICAL TRIALS

Approval for tapentadol ER for diabetic neuropathic pain was granted on the basis of 2 placebo-controlled trials in patients with moderate-to-severe painful diabetic neuropathy (Table 3, page 397).[14,23] In a recent trial, 588 patients reporting a minimum of 3 months of opioid and/or nonopioid analgesic use, an average pain score of at least 5 on an 11-point numerical rating scale (NRS), and dissatisfaction with their current treatment were entered into a 3-week open-label phase with tapentadol ER. Of these patients, 395 reported at least a 1-point improvement in pain intensity score at the conclusion of the open-label period and were randomly assigned 1:1 to continue tapentadol ER or placebo for a 12-week assessment period. The assessment period was blinded to both

Table 3

Summary of major clinical trials for tapentadol in neuropathic pain

Study	Design	Study duration	n (randomized)	Mean pain intensity (NRS) at start of open-label period	Mean pain intensity (NRS) at end of open -label period	Δ in pain intensity (NRS) DB tapentadol ER	Δ in pain intensity (NRS) DB placebo	Least-squares mean difference between groups (*P* value)
Schwartz, et al	Randomized withdrawal	3-week OL, 12-week DB, PC	588 (395)	7.3	3.5	0.0	1.4	-1.3 (<.001)
Vinik, et al	Randomized withdrawal	3-week OL, 12-week DB, PC	459 (320)	7.3	3.6	0.28	1.3	-0.95 (<.001)

Abbrevations: DB, double blind; ER, extended release; NRS, 11-point numerical rating scale; OL, open label; PC, placebo controlled

Formulary/Source: Refs 14,23

patients and investigators with the primary endpoint set as the change in pain intensity post randomization, as evaluated on an NRS. The maintenance dose range for the active treatment arm of the study was 100-mg to 250-mg tapentadol ER taken orally twice daily. The control arm was given tapentadol ER 100 mg orally twice daily for the first 3 days of double-blind treatment, and received placebo thereafter. Both groups were allowed a once-daily dose of tapentadol ER 25 mg for supplemental pain relief.[14]

By the end of the open-label titration period, 60.5% of all patients achieved at least a 30% improvement in pain intensity score and 34.9% of patients reported improvements of greater than 50%.[14]

In patients maintained on tapentadol ER during the randomization phase, the improvement in pain intensity seen during the open-label phase was maintained; as indicated by a least-squares mean change in average pain intensity of 0.0. In comparison, the placebo group's least-squares mean change in average pain intensity was 1.4, indicating a worsening of pain control over the duration of the active study period.[14] This resulted in a least-squares mean difference between tapentadol ER and placebo of -1.3, indicating a statistically significant difference in favor of tapentadol ER (P<.001).[14]

Within the active treatment arm, no differences in efficacy were seen when evaluated for differences in gender, age, and prior opioid use. Approximately 60% of patients who achieved at least a 30% improvement in pain control during the open-label period maintained this improvement at the end of the 12-week active maintenance phase; 59% of patients maintained improvements of greater than 50%. In contrast, 49% and 36% of patients in the placebo arm maintained their pre-randomization improvements in pain intensity of at least 30% and at least 50%, respectively.[14]

Treatment-emergent adverse effects were reported at an incidence of 71% in the open-label titration phase; rates of adverse events during the double-blind period were 71% in the active treatment arm and 52% in the placebo arm. The most common adverse events reported with tapentadol ER included nausea, dizziness, somnolence, constipation, vomiting, headache, fatigue, pruritus, anxiety, and diarrhea. No significant differences were observed in frequency of adverse events when assessed for gender, age, and prior opioid use. Discontinuation due to adverse events occurred in 20% of patients in the open-label phase, 11% of patients in the double-blind active arm, and 6% of patients in the double-blind placebo arm.[14]

A subsequent trial utilized a nearly identical randomized-withdrawal, placebo-controlled design, again consisting of both a 3-week open-label titration phase and a 12-week double-blind maintenance phase. A total of 459 patients entered the tapentadol ER open-label titration phase, and 320 met criteria of 1 point or more improvement on NRS and acceptable tolerability to enter the randomization phase.[23]

In the open-label phase, the mean pain intensity score for all enrolled patients decreased from 7.3 at time of titration onset to 3.6 at its conclusion. After randomization, however, both groups showed a worsening in pain intensity over the duration of the 12-week maintenance period. In the tapentadol ER arm, mean pain intensity scores increased from 3.7 to 4.01, whereas in the placebo arm a larger increase was seen from 3.53 to 4.83 over the 12-week period. This represents a mean worsening of pain intensity over the maintenance period of 0.28 and 1.30 for the active and control groups, respectively. Tapentadol ER was favored significantly in this study as represented by a least-squares mean difference between groups of -0.95 ($P<.001$). An overall greater than 30% improvement in pain intensity was seen in significantly more patients in the tapentadol ER arm than in the placebo arm (55.4% vs 45.4%, $P=.032$); the same was true of those achieving greater than 50% improvement (40.4% vs 28.9%, $P=.015$). Incidence of treatment-emergent adverse effects was similar to the previous trial, with nausea, dizziness, constipation, and somnolence again being the primary complaints.[23]

In both studies the use of neuroleptics, monoamine oxidase inhibitors (MAOIs), SNRIs, TCAs, anticonvulsants, and antiparkinsonian drugs was not allowed within 14 days prior to screening or during the study duration. SSRIs taken at stable doses for at least 30 days prior to screening could be continued. Approximately 65% of patients in the trial by Schwartz, et al reported prior opioid use, versus approximately 30% of those patients in that by Vinik, et al.[14,23]

Although these studies demonstrated acceptable safety and superior efficacy compared to placebo, there are considerable limitations in their design. The model of randomized withdrawal could potentially lead to unblinding in patients accustomed to the effects of the active agent, although this likelihood was partially reduced by the administration of active drug to the placebo group for the first 3 days of double-blind therapy. Furthermore, an enriched enrollment design has the potential to positively skew results by limiting randomization to patients in whom tapentadol demonstrated significant improvements in pain intensity scores. Finally, the studies were limited to patients who had failed or were dissatisfied with at least a 3-month treatment trial of opioid or nonopioid analgesics. This inclusion criteria suggests the study findings are most supportive of tapentadol's use as a second-line or adjunctive agent. Furthermore, because both studies were placebo rather than active controlled the tolerability and efficacy of tapentadol as compared to previously approved agents for neuropathic pain remains to be seen. Head-to-head and combination trials are needed before further comment can be made on tapentadol's potential place in the neuropathic pain algorithm.[14,23]

> Due to tapentadol's minimal protein binding and lack of effect of CYP enzyme systems, pharmacokinetic drug–drug interactions do not pose a significant concern.

ADVERSE EVENTS

Tapentadol has potential for causing treatment-emergent adverse effects, the most common of which include nausea, dizziness, somnolence, constipation, vomiting, headache, fatigue, and pruritus.[7,14] Nevertheless, the adverse-effect profile of tapentadol is superior to that of comparative opioid analgesic agents such as oxycodone, with respect to gastrointestinal (GI) effects. By having a dual mechanism of action, tapentadol relies less on mu-receptor activation.[4] Due to this partial opioid sparing, tapentadol has exhibited significantly less constipation, nausea, and vomiting in clinical trials with subsequently reduced patient attrition citing intolerable side effects. In a phase 3 trial, tapentadol IR 50 to 75 mg resulted in 3 to 5 times less nausea and vomiting than oxycodone IR 10 mg. The difference was even more pronounced for constipation, with constipation 8 times less likely in the tapentadol IR 50-mg group and 5 times less likely in the tapentadol IR 75-mg group versus those taking oxycodone IR 10 mg.[19] This benefit is maintained with the ER formulation, with the odds of experiencing constipation with tapentadol ER 60% less than that seen with oxycodone.[13] Tapentadol's beneficial adverse-event profile, however, does not extend to its CNS effects. Significant differences have not been detected in the rates of dizziness or somnolence between tapentadol and comparative opioids. Although it has been suggested that respiratory depression from tapentadol may potentially be less than that of a pure opioid analgesic, this hypothesis has not been proven in randomized studies and tapentadol should continue to be regarded as a CNS depressant.[4]

Tapentadol is classified as a schedule II substance by FDA, as it may cause physical and psychological dependence. Safeguards against diversion of the ER dosage form have been made by formulating a tamper-resistant tablet to chewing and crushing. With abrupt discontinuation after prolonged use, mild-to-moderate withdrawal symptoms may occur. Tapering on discontinuation of tapentadol is recommended in patients on chronic therapy.[4]

DRUG INTERACTIONS

Due to tapentadol's minimal protein binding and lack of effect on CYP enzyme systems, pharmacokinetic drug–drug interactions do not

pose a significant concern with this agent. Tapentadol has been coadministered safely in drug interaction studies with acetaminophen, naproxen, aspirin, omeprazole, metoclopramide, and probenecid, with no alternations in tapentadol serum concentration noted.[19] Tapentadol's effect may be diminished by concurrent use of ammonium chloride, $5HT_3$-antagonists, mixed agonist/antagonist opioids, and peginterferon alfa-2b; tapentadol's effect may be augmented by amphetamines, phenothiazines, antipsychotics, hydroxyzine, magnesium sulfate, perampanel, and succinylcholine.[7] The documented interactions with peramperal, phenothiazines, and mixed agonist/antagonist opioids are considered to be of major significance, and coadministration with these agents is not advised. The others mentioned previously are considered to be of moderate or minor significance and can be coadministered if the risks are outweighed by the potential benefit with careful monitoring of the patient.[7]

Due to tapentadol's potential to cause respiratory depression, use of other depressant agents should be discouraged in these patients to avoid additive effects. Use of MAOIs with tapentadol is contraindicated due to the overlap of their effects on norepinephrine levels and subsequent risk for cardiovascular events. For this reason, MAOIs should be discontinued 14 days prior to initiation of tapentadol therapy.[4,19] Theoretically, serotonin syndrome may result from coadministration of tapentadol with serotonergic agents, due to the minor extent by which tapentadol affects serotonin reuptake blockade. Although this outcome is unlikely, caution should be exercised when tapentadol is used concurrently with SSRIs, SNRIs, TCAs, and triptans.[19]

Of special consideration with tapentadol ER are agents that alter drug release, as accelerated release from this formulation may result in accidental overdose. Alcohol in particular has been found to cause excessive release from tapentadol ER and should be avoided for this reason, as well as for its CNS depressant effects.[13]

DOSING AND ADMINISTRATION

With regard to opioid analgesics, tapentadol is generally considered to be 2 to 3 times less potent than morphine, but 3 to 4 and a half times more potent than tramadol.[4,5] Oxycodone 10 mg to 15 mg is the accepted equianalgesic dose for 50-mg to 75-mg tapentadol IR; however, adequate data are not available for direct conversion of total daily doses of ER preparations between tapentadol and other opioids. In general, a direct mg to mg conversion can be made between the tapentadol IR and ER products based on total daily dose. When converting, product labeling recommends initiating tapentadol ER at a dose 50% of the expected daily tapentadol requirement, with titration and supplemental IR doses as required.[5,7,19]

> Cost-effectiveness analyses suggest that tapentadol may prove financially beneficial due to its decreased burden in drug interactions, adverse effects, and failed treatment trials.

Tapentadol ER should be initiated in opioid-naïve patients at 50 mg orally every 12 hours, and titrated in 50-mg increments at a minimum of 3-day intervals. Therapeutic doses range from 100 mg to 250 mg orally every 12 hours, with a maximum daily dose of 500 mg. Breakthrough pain medication in the form of tapentadol IR is recommended at half the estimated daily tapentadol requirement, administered every 4 to 6 hours as needed. If used without an ER component, tapentadol IR can be dosed to a maximum of 700 mg per day on initial day of therapy, and 600 mg per day on subsequent days. Tapentadol ER is commercially available as tablets of 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg; tapentadol IR is available as tablets of 50 mg, 75 mg, and 100 mg.[5,7]

Unlike pure opioid agonists, tapentadol has a published maximum dose due to the possibility of excessive norepinephrine reuptake inhibition. Although maximum dosages of 600 mg and 500 mg have been assigned to maintenance therapy with ER and IR products, respectively, these cut-offs reflect maximum doses tested in clinical trials rather than absolute evidence of risk above these values.[5,7]

Given tapentadol's propensity for somnolence and confusion, patients taking tapentadol should be counseled to avoid tasks requiring mental alertness and coordination until extent of effect is determined. Withdrawal symptoms may result from abrupt discontinuation of tapentadol maintenance therapy; tapering is recommended in all patients chronically using tapentadol.[7]

FORMULARY CONSIDERATIONS

Tapentadol is currently only available as brand names Nucynta and Nucynta ER; therefore it has predictably higher direct drug acquisition costs in comparison to generically available opioid analgesics. Published pricing for tapentadol IR 75 mg is approximately $310 per 100 count, whereas oxycodone 10 mg is approximately $60 and morphine 15 mg is approximately $20 for the same quantity.[8] With regard to ER preparations, the corresponding pricing is reported at approximately $435, $300, and $100 for 30-day supplies of tapentadol ER, oxycodone ER, and morphine ER, respectively.[8]

Cost-effectiveness analyses nevertheless suggest that tapentadol may prove financially beneficial due to its decreased burden in drug interactions, adverse effects, and failed treatment trials. With respect to the treatment of

acute surgical and nonsurgical pain, tapentadol IR was found to be cost effective as compared to the use of oxycodone IR in both a 3-day acute postsurgical pain model and a 10-day acute nonsurgical pain model. Despite higher costs for the pain medication itself in the tapentadol group, total cost was lower due to less switching or discontinuation of opioids, less need for treatment of adverse effects, and less associated medical costs.[24]

In 2 cost-effectiveness analyses in severe, chronic, nonmalignant pain, tapentadol was also found to be cost effective versus oxycodone as both a first-line and second-line therapy after morphine.[25,26] A reduced need for physician visits and treatment of adverse effects factored considerably into the cost analysis, with tapentadol producing superior quality-of-life outcomes to oxycodone.[25,26]

Given that tolerance does not develop to opioid-induced constipation, tapentadol's reduced risk for this side effect marks a significant advantage for patient tolerability and adherence. The correlation between tapentadol's improved GI side-effect profile and reduced work absenteeism was assessed via means of multiparameter evidence synthesis, combining data from randomized, controlled trials of tapentadol versus oxycodone, incidence of opioid-induced constipation, and a survey of opioid-induced constipation's influence on productivity. Study conclusions indicated that tapentadol resulted in less work absenteeism and productivity lost versus oxycodone. Specifically, a 1.92% increase in productivity was seen with tapentadol ER versus oxycodone ER. This value is comparable to 0.8 hours of gained productivity per week, or approximately 1 week per year.[27]

Despite these promising indications, tapentadol ER's use in neuropathic pain has not been specifically evaluated for cost effectiveness. Given that neuropathic pain sufferers often seek polypharmacy to achieve adequate pain control, the elimination of multiple medications with successful tapentadol therapy should be studied for possible economic benefit.[26]

CONCLUSION

Although a promising alternative for neuropathic pain, there remains a need for evaluation of tapentadol versus first-line neuropathic options, such as pregabalin and duloxetine. Current publications compare tapentadol to opioid analgesics, which are not ideal for use in neuropathic pain states. As a result, the appropriate place for tapentadol in the neuropathic pain treatment ladder remains to be seen. Future studies of head-to-head comparisons and combination therapy in this patient population would greatly supplement the evidence base for use of this novel agent. ■

REFERENCES

1. Haanpää M, Treede R-D. Diagnosis and classification of neuropathic pain. *Pain: Clinical Updates.* 2010;18:1–6.
2. Yawn BP, Wollan PC, Weingarten TN, et al. The prevalence of neuropathic pain: clinical evaluation compared with screening tools in a community population. *Pain Med.* 2009; 10:586–593.
3. Christoph T, De Vry J, Schiene K, et al. Synergistic antihypersensitive effects of pregabalin and tapentadol in a rat model of neuropathic pain. *Eur J Pharmacol.* 2011;666(1-3):72–79.
4. Vadivelu N, Timchenko A, Huang Y, Sinatra R. Tapentadol extended-release for treatment of chronic pain: a review. *J Pain Res.* 2011;4:211–218.
5. Pierce DM, Shipstone E. Pharmacology update: tapentadol for neuropathic pain. *Am J Hosp Palliat Care*. 2012;29:663–666.
6. Namaka M, Gramlich CR, Ruhlen D, et al. A treatment algorithm for neuropathic pain. *Clin Ther.* 2004;26:951–979.
7. Lexi-Comp. (Lexi-Drugs). Lexi-Comp; July 1, 2013.
8. Medi-Span Pricing Database, Hudson, OH: Lexi-Comp; July 28, 2013.
9. University of Massachusetts Medical School. Therapeutic class overview: neuropathic pain agents. MedMetrics Health Partners. http://www.medicaid.nv.gov/Downloads/provider/Neuropathic%20Pain%20Agents.pdf. Updated June 21, 2012. Accessed July 28, 2013.
10. U.S. Department of Justice: Drug Enforcement Administration. Controlled Substance Schedules. Office of Diversion Control. http://www.deadiversion.usdoj.gov/schedules/. Accessed October 12, 2013.
11. Pergolizzi J, Alon E, Baron R, et al. Tapentadol in the management of chronic low back pain: a novel approach to a complex condition? *J Pain Res.* 2011;4:203–210.
12. Nucynta ER (tapentadol) [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2012.
13. Hartrick CT, Rodríquez Hernandez JR. Tapentadol for pain: a treatment evaluation. *Expert Opin Pharmacother.* 2012;13:283–286.
14. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin.* 2011;27:151–162.
15. Tzschentke TM, Christoph T, Kögel B, et al. (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther.* 2007;323:265–276.
16. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med.* 1992;326:1250–1256.
17. Suzuki T, Ueta K, Tamagaki S, Mashimo T. Antiallodynic and antihyperalgesic effect of milnacipran in mice with spinal nerve ligation. *Anesth Analg.* 2008;106:1309–1315.
18. Bee LA, Bannister K, Rahman W, Dickenson AH. Mu-opioid and noradrenergic α2-adrenoreceptor contributions to the effects of tapentadol on spinal electrophysiological measures of nociception in nerve-injured rats. *Pain.* 2011;152:131–139.
19. Hartrick CT, Rozek RJ. Tapentadol in pain management: a μ-opioid receptor agonist and noradrenaline reuptake inhibitor. *CNS Drugs.* 2011;25:359–370.
20. Kogel B, De Vry J, Tzschentke T, Christoph T. The antinociceptive and antihyperalgesic effect of tapentadol is partially retained in OPRM1 (μ-opioid receptor) knockout mice. *Neurosci Lett.* 2011;491:104–107.
21. Christoph T, De Vry J, Tzschentke TM. Tapentadol, but not morphine, selectively inhibits disease-related thermal hyperalgesia in a mouse model of diabetic neuropathic pain. *Neurosci Lett.* 2010;470:91–94.
22. Riemsma R, Forbes C, Harker J, et al. Systematic review of tapentadol in chronic severe pain. *Curr Med Res Opin.* 2011;27:1907–1930.
23. Vinik A, Shapiro DY, Rauschkolb C, et al. Efficacy and tolerability of tapentadol extended release in patients with chronic, painful diabetic peripheral neuropathy: results of a phase 3, randomized-withdrawal, placebo-controlled study. Poster session presented at: 31st Annual Scientific Meeting of the American Pain Society (APS); 2012 May 16–19; Honolulu, HI.
24. Kwong WJ, Ozer-Stillman I, Miller JD, et al. Cost-effectiveness analysis of tapentadol immediate release for the treatment of acute pain. *Clin Ther.* 2010;32:1768–1781.
25. Ikenberg R, Hertel N, Moore RA, et al. Cost-effectiveness of tapentadol prolonged release compared with oxycodone controlled release in the UK in patients with severe non-malignant chronic pain who failed 1st line treatment with morphine. *J Med Econ.* 2012;15:724–736.
26. Obradovic M, Ikenberg R, Hertel N, et al. Cost-effectiveness of tapentadol in severe chronic pain in Spain: a cost analysis of data from RCTs. *Clin Ther.* 2012;34:926–943.
27. Cepeda MS, Sutton A, Weinstein R, Kim M. Effect of tapentadol extended release on productivity: results from an analysis combining evidence from multiple sources. *Clin J Pain.* 2012;28:8–13.

FROM THE LITERATURE

Warnings on kids' cold products slashed ER visits

from Staff Reports

After manufacturers began printing new warnings on medicine bottles, a smaller percentage of emergency room (ER) visits resulted from children taking cold and cough products, according to a study in *Pediatrics*.

Drug-makers voluntarily recalled over-the-counter cough and cold medicines for children in 2007, following reports of emergency room visits and deaths related to the products.

Eventually, the medicines were rereleased with warnings that children younger than aged 4 years should not take them. Since the new warnings, the percentage of ER visits related to children taking cough and cold medicines has dropped significantly, according to a report from the US Centers for Disease Control and Prevention (CDC).

"Progress has been made, but there is still a lot of work to do to reduce adverse events from cough and cold medications," said Lee Hampton, a CDC medical officer who was the study's lead author.

CDC officials said there were 61,168 ER visits between 2004 and 2011 among children younger than aged 12 years related to adverse events from cough and cold medicines.

■ Drug-makers voluntarily recalled OTC cough and cold medicines for children in 2007, after reports of ER visits and deaths related to the products.

Prior to 2007, when the children's products were pulled from shelves, children under aged 2 who had a reaction to cough and cold medicines accounted for about 4% of all ER visits. After the medicines were reintroduced with the stronger warnings, that number fell to about 2%.

Before the products were removed and relabeled, reactions to cough and cold medicines among 2 and 3 year-olds represented 10% of all ER visits. That percentage dipped to 7% after warnings were added to labels.

While happy with the label-change results, CDC officials and others believe the bottles containing such medicines need to be made safer. CDC officials said 64% of the children under aged 2 years who ended up in the ER after taking the medicines had swallowed it while unsupervised. ■

Long-term oral contraceptive users at risk for glaucoma

by Julia Talsma

Women using oral contraceptives for 3 years or more may be at risk for developing glaucoma and should be screened for the eye disease if they have additional risk factors, according to researchers at the American Academy of Ophthalmology annual meeting in New Orleans.

Shan C. Lin, MD, the lead researcher from the University of California San Francisco (UCSF), and his colleagues presented a poster about their findings using 2005-2008 data from the National Health and Nutrition Examination Survey, administered by the Centers for Disease Control and Prevention. More than 3,400 women aged 40 and older answered the survey's vision and reproductive survey and underwent eye examinations.

"It found that females who had used oral contraceptives, no matter which kind, for longer than three years are 2.05 times more likely to also report that they have the diagnosis of glaucoma," according to the press statement.

These data indicate that long-term use of oral contraceptives may be a risk factor for glaucoma. Other factors include African-American ethnicity, family history of glaucoma, history of increased intraocular pressure, and existing visual field defects.

"This study should be an impetus for future research to prove the cause and effect of oral contraceptives and glaucoma," said Dr Lin, professor of clinical ophthalmology, UCSF.

He suggested that women with long-term oral contraceptive use and other risk factors be screened for glaucoma and followed closely by an ophthalmologist. ■