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

PEER-REVIEWED

Cover Article

An update on attention deficit/hyperactivity disorder

Janet Ashley Gunter, PharmD, BCPS

98 Recent attention-deficit/hyperactivity disorder (ADHD) guideline changes from the American Academy of Pediatrics (AAP) recommend evaluating and diagnosing children aged 4 to 18 years. Stimulants continue to be recommended as first-line treatment for children aged 6 to 12, and 70% of children respond to therapy with any single stimulant chosen. Nonstimulants are now available and offer a treatment option for children who do not respond to stimulants. Adverse events such as growth suppression and cardiovascular risk are of concern, but recommendations for management have been made in the AAP guidelines and in the European guidelines on managing adverse effects of medications for ADHD. New formulations of stimulants and nonstimulants allow for individualization of therapy for patients to receive the maximum benefit while minimizing side effects.

PEER-REVIEWED

Feature Article

Researchers seek next class of anti-allergics

Paulo J. Gomes

110 Although there have been valuable improvements in antihistamine-based agents over the years (dual-action agents, once-daily therapies), researchers are still looking for the next class of anti-allergic agents that can address the needs of patients whose symptoms are unresponsive to available therapies.

Feature Article

Physician dispensing costs triple that of retail

Fred Gebhart

112 Key findings from the 2012 Survey of Prescription Drug Management from CompaPharma, LLC.

PEER-REVIEWED

Feature Article

Female sexual disorders: Treatment options in the pipeline

Michael L. Krychman, MD; Sheryl A. Kingsberg, PhD

113 Female sexual problems are best conceptualized from a biopsychosocial perspective that includes biological, psychological, sociocultural, and interpersonal factors. Treatment also follows a biopsychosocial model and options include psychotherapy, pharmacotherapy, physical therapy, and complementary approaches alone or in combination. Only 2 FDA-approved treatments currently exist for female sexual disorders, but a wide range of oral, topical, and SQ formulations are being investigated. This article focuses on promising treatments on the horizon for helping patients with female sexual disorders.

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Aspirin use linked to age-related macular degeneration

by Tracey Walker

Regular use of aspirin was associated with a 2-fold greater risk of developing the neovascular subtype of age-related macular degeneration (AMD) than in non-users, according to research reported online in *JAMA Internal Medicine*.

Australian researchers' finding of a longitudinal association—with temporal information in the association, ie, exposure to aspirin before the development of AMD—confirms an observation from a European cross-sectional survey (European Eye Study) that also reported a 2-fold higher prevalence of neovascular AMD among regular aspirin users compared with non-users (*Ophthalmology*. 2011;119:112–118).

"The reported association from the European Eye Study, however, lacked temporal information as the exposure and the disease outcome were measured simultaneously in the survey," Paul Mitchell, MD, PhD, principal investigator of the study, called the Blue Mountains Eye Study (BMES), told *Formulary*. "Nevertheless, this confirmation suggests a consistency of the evidence on this association in 2 different population-based samples. We felt that it would be important to see if there is a longitudinal association present between regular use of aspirin and subsequent development of AMD. As the BMES had such longitudinal data available, we acted on this project without delay."

Take away

Raise awareness of the potentially small, but increased, risk of incident neovascular AMD in patients on long-term aspirin therapy.

Evidence from observational studies can usually only generate and/or support a study hypothesis but cannot resolve completely the controversy of the study question or hypothesis, mainly due to the lack of a proven mechanism(s) for the associations from observational studies, said Dr Mitchell, who is also professor in ophthalmology and director of the Westmead Millennium Institute's Centre for Vision Research, Sydney, Australia.


Dr Mitchell

The research team conducted a population-based study of 2,389 older Australians aged 50+ years 2 decades ago (1992-1994). They followed this sample over 15 years with 5-year intervals between each examination, and collected a range of data including retinal photographs from study participants.

"We defined incident AMD using retinal photographic documentation with verification. We collected information on aspirin use via face-to-face interviews in multiple study visits. We used statistical models to assess the link between the 2 while adjusting for possible confounding factors that were also collected in our study, the Blue Mountains Eye Study," Dr Mitchell said.

While aspirin is among the most effective cardiovascular disease (CVD) preventive therapies to reduce recurrent CVD events (secondary prevention), regular use over the longer term has been associated with a number of well-documented adverse side effects such as increased gastrointestinal, intracerebral, and extracranial hemorrhage. "If our finding is further replicated by other studies, the possibility of a deleterious effect on vision via an increase in the risk of AMD needs to also be considered for patients who are at high risk of AMD [eg, existing neovascular AMD in the other eye], in addition to other known adverse effects," Dr Mitchell said.

"Given the widespread use of aspirin,

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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.

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MS specialty drug treatment costs climb to two-thirds of total MS treatment cost

from Staff Reports

Multiple sclerosis (MS) specialty drug costs now account for more than two-thirds of MS patients' total cost of care, according to a new study.

The study, by pharmacy benefit manager Prime Therapeutics, in collaboration with Blue Cross Blue Shield of Minnesota, found MS specialty drug costs, which are largely covered by the pharmacy benefit, have increased dramatically in the past several years and are not expected to plateau any time soon. In fact, Prime predicted that MS drug costs will exceed $50,000 per person per year in 2016.

Dr Gleason

While MS drugs have been shown to reduce relapses by approximately one-third, they have only minimally influenced progression of the disease and disability, according to a recent study published in the *New England Journal of Medicine*. Meanwhile, the costs continue to rise faster than traditional therapies. The price for MS self-injectable specialty drugs has increased 16.3% to 22.6% each year from 2008 to present. In addition, a 2009 study found the average annual total cost for treating MS among individuals utilizing a MS specialty drug was $37,592, of which 58.6% ($22,015) was the pharmacy cost. In 2010, the average total cost of care rose to $41,760; the MS specialty drug accounted for 67.4% ($28,152) of that total cost, almost all of which was covered by the pharmacy benefit.

"MS specialty drug costs are the fastest growing category within the total cost of MS care," said Pat Gleason, PharmD, FCCP, BCPS, director of health outcomes at Prime. "These drugs are quickly becoming one of the largest pharmacy expenses among commercially insured members."

> The annual double-digit price increases leveraged by MS specialty pharmaceutical manufacturers have now occurred for 5 consecutive years. If this trend continues, MS specialty drugs will soon be 75% of the total cost of MS care.

The cost of these drugs is growing at 6.4 times the rate of all other medical costs, Dr Gleason explained. In 2011, MS drugs alone accounted for 3.6% of all pharmacy benefit costs across 9 million of Prime Therapeutics' commercially insured members, amounting to an average per prescription cost of $3,135.

The annual double-digit price increases leveraged by MS specialty pharmaceutical manufacturers have now occurred for 5 consecutive years. If this trend continues, MS specialty drugs will soon be 75% of the total cost of MS care.

However, Dr Gleason noted that "the anticipated increases in the cost of care can be lessened through optimizing managed care tools such as formulary preferred products with utilization management, moving non-formulary specialty drugs to a fourth or fifth tier with a higher cost share, utilizing a specialty pharmacy network which provides better discounts and medication management services, and creating rebate contractual relationships that provide some level of price inflation protection.

"Pharmacy benefit managers and health plans also will continue to emphasize the importance of patient adherence to drugs, which not only will improve the quality of care but help eliminate the treatment relapses and lost productivity," he added. ■

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any increased risk of disabling conditions and morbidity would likely be important and may affect small subgroups of patients, in this case, patients who are at high risk of neovascular AMD," he said. "However, the magnitude of this potential risk is relatively small—9.3% after 15 years—and needs to be balanced with the significant morbidity and mortality of suboptimally treated CVD."

Currently there is insufficient evidence to recommend changing clinical practice, except perhaps in cases of patients with strong risk factors for neovascular AMD, in whom it could be appropriate to raise awareness among the patients and families of the potentially small, but increased, risk of incident neovascular AMD in patients on long-term aspirin therapy, according to Dr Mitchell.

"The increased risk of neovascular AMD was only detected after 10 or 15 years. This may suggest that cumulative dosage of aspirin may be important in pathogenesis," he said.

"Our findings also suggest the specificity of the association: only aspirin use (but not other pain killers) was associated with neovascular AMD—but not associated with the early stage of AMD or geographic atrophy, another subtype of late-stage AMD," Dr Mitchell concluded. ■

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Please see brief summary of Full Prescribing Information, including **Boxed WARNING**, on adjacent pages.

ELIQUIS is available in 2.5 mg and 5 mg tablets.

Bristol-Myers Squibb Pfizer

ELIQUIS (apixaban) tablets for oral use **℞ ONLY**

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered *[see Dosage and Administration and Warnings and Precautions].*

INDICATIONS AND USAGE

ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

DOSAGE AND ADMINISTRATION (Selected information)

Discontinuation for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled.

(For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (i.e., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Stroke with Discontinuation of ELIQUIS

Discontinuing ELIQUIS in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant *[see Dosage and Administration (2.3) in full Prescribing Information].*

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.2) in full Prescribing Information and Adverse Reactions].*

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitor, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions].*

Patients should be made aware of signs and symptoms of blood loss and instructed to report them immediately or go to an emergency room. ELIQUIS should be discontinued in patients with active pathological hemorrhage.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for about 24 hours after the last dose, i.e., for about two half-lives. A specific antidote for ELIQUIS is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information].* Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage].*

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS has not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

ADVERSE REACTIONS

The most serious adverse reactions reported with ELIQUIS were related to bleeding *[see Warnings and Precautions].*

Clinical Trials Experience

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

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information],* including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per year) in ARISTOTLE and AVERROES.

Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that was fatal. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE

	ELIQUIS N=9088 n (%/year)	Warfarin N=9052 n (%/year)	Hazard Ratio (95% CI*)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Gastrointestinal (GI)‡	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Intracranial	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Intraocular§	32 (0.21)	22 (0.14)	1.42 (0.83, 2.45)	-
Fatal¶	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
CRNM**	318 (2.08)	444 (3.00)	0.70 (0.60, 0.80)	<0.0001

* Confidence interval.
† International Society on Thrombosis and Hemostasis (ISTH) major bleed assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.
‡ GI bleed includes upper GI, lower GI, and rectal bleeding.
§ Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).
¶ Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke.
** CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, ELIQUIS (apixaban) dose, type of AF, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0%/year) than did subjects without diabetes (1.9%/year).

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

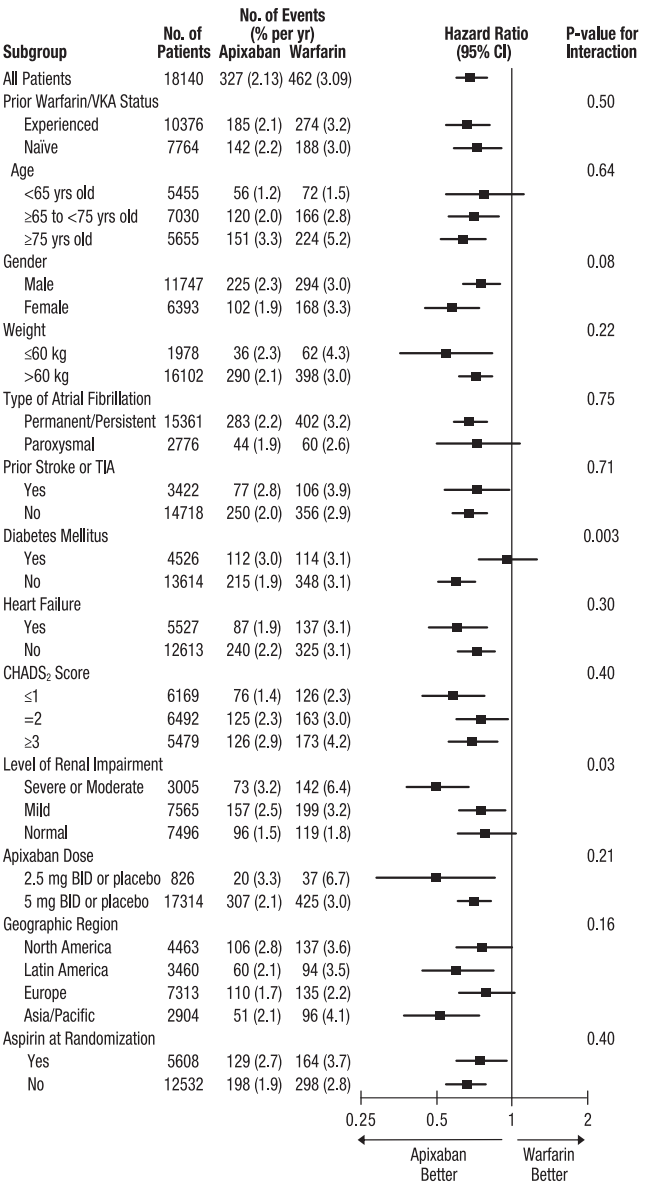

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke.

Strong Dual Inhibitors of CYP3A4 and P-gp

The dose of ELIQUIS should be decreased to 2.5 mg twice daily when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in full Prescribing Information].*

In patients already taking ELIQUIS (apixaban) at a dose of 2.5 mg daily, avoid coadministration with strong dual inhibitors of both CYP3A4 and P-gp *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.77%/year with apixaban versus 0.62%/year with placebo in patients receiving single antiplatelet therapy and was 5.91%/year with apixaban versus 2.50%/year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in clinical studies of apixaban, >69% were 65 and older, and >31% were 75 and older. The effects of ELIQUIS (apixaban) on the risk of stroke and major bleeding compared to warfarin were maintained in geriatric subjects.

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice-daily for 7 days or 50 mg once-daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Mean apparent half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban, indicating that charcoal blocked the continued absorption of apixaban from the gut *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion by leading to a more rapid fall in apixaban blood levels.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intends to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

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and

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High calcium intake could raise CV mortality in women

from Staff Reports

A high calcium intake, from diet or the combination of diet and supplements may raise the rate of mortality, especially cardiovascular (CV) mortality, said a study in the *British Medical Journal* (*BMJ*).

In an observational cohort study, Swedish researchers followed approximately 61,000 women, aged, on average, 53 years at baseline. Information about dietary and lifestyle habits were assessed by questionnaires. Based on the questionnaire information, calcium intake from diet and supplements was estimated. During follow-up (at about 20 years), 12,000 of the women died. Death rates by calcium intake levels were assessed.

"We found a higher risk of mortality, especially CV mortality with a high calcium intake," Karl Michaëlsson, clinical professor, Department of Surgical Sciences and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, told *Formulary*.

"On the other hand, we also found a higher risk of mortality associated with a low calcium intake but this latter finding was not confirmed by us in our sensitivity analysis," he said. "The higher risk of death was seen with a higher dietary calcium intake. This risk increase was modest. If we did not consider the dietary component of calcium intake, we found on average no association with calcium supplement use and mortality."

However, women who consumed a high dietary calcium intake together with calcium supplements had a higher mortality rate, even though few had this combination in the cohort.

A research group from Auckland, New Zealand, previously published 3 re-analyses of randomized studies in *BMJ*. "They have shown a moderate higher risk of CV disease with calcium supplement use," Michaëlsson said. "In one of their analysis they also considered dietary calcium intake in addition to the calcium supplement."

They found that the higher risk of CV disease with calcium supplement use was only predominant in combination with a high dietary calcium intake. "However, other researchers have also re-examined their randomized trials and have not found a higher risk of CV disease," he said. "A complicating fact is that the methodologies of the re-examinations have differed. Cautious interpretation of all observational study results is always needed but our findings fit those from the New Zealand research group." ■

Patients who adhere to statin regimens are healthier, but higher drug spending makes overall care more costly

from Staff Reports

Individuals with high cholesterol who stay on their statin medications over a 2-year period are healthier than comparable nonadherent individuals, but the overall cost of their care is slightly higher, according to a new study.

While the new study, from pharmacy benefit manager Prime Therapeutics, aligns with earlier ones that also showed adherent individuals had improved health and lower medical costs, this study varies from others in concluding that the overall cost of care is higher. In the earlier studies, the overall cost of care was lower as decreased medical costs for their care more than offset the higher pharmacy costs. "It's important to emphasize that our study showed that adherence to statins was associated with lower medical costs and hospitalizations, leading to healthier outcomes for individuals," said lead author Pat Gleason, PharmD, FCCP, BCPS, director of health outcomes with Prime.

Done in collaboration with Blue Cross and Blue Shield of Minnesota, the study found individuals adherent to statin medications went to the hospital or emergency department 2.6% less often than nonadherent individuals, resulting in medical costs that were 7% lower (a difference of $767). The lower medical costs, however, were offset by pharmacy costs that were 45% higher (a difference of $1,606). Researchers compared medical and pharmacy costs among individuals with high cholesterol who were adherent to their statin medication to individuals who were not adherent ("adherence" was defined as "following the medication regime 80% of the time or more"). Of the 45,869 individuals included in the study, 21,693 (47.3%) were adherent and 24,176 (52.7%) nonadherent during the 2-year follow-up period.

Population differences, including the relatively young ages of the individuals in the new study, are a possible reason its findings differ from those of previous studies, Dr Gleason said. The earlier studies each had a specific population focus—individuals from a single employer, in 1 study, and retirees, in the other. As a result, the cost analyses from the earlier studies were limited in their generalizability.

"With the increasing availability of generic statins, especially the generic atorvastatin of the brand Lipitor, we may see lower pharmacy costs in future studies like this," Dr Gleason added. ■

Low-dose contraceptive patch comparable to combination oral contraceptive in safety, tolerability study

from Staff Reports

A low-dose contraceptive patch is comparable to combination oral contraceptive in a comparative study, according to phase 3 data presented at the American College of Obstetricians and Gynecologists' (ACOG) 60th Annual Clinical Meeting.

Dr Kaunitz

A once-weekly, low-dose combination contraceptive patch (AG200-15, Agile) containing ethinyl estradiol (EE) in combination with levonorgestrel (LNG) was evaluated in a diverse population of more than 1,500 women, including obese women, minorities, and new users of hormonal contraceptives. This comparative study demonstrated that AG200-15 has contraceptive efficacy comparable to that of an approved low-dose oral contraceptive comparator, as well as a similar safety and tolerability profile.

"Unlike many contraceptive clinical trials, this study was conducted in a population that reflects all US reproductive-age women," said Andrew Kaunitz, MD, associate chair and professor of the department of obstetrics and gynecology at the University of Florida. Dr Kaunitz is the principal investigator for the AG200-15 phase 3 trial.

Two additional studies also were presented at ACOG by David F. Archer, MD, professor of obstetrics and gynecology at Eastern Virginia Medical School. The first demonstrated that the investigational patch can be worn on any of the 3 administration sites (abdomen, buttock, or upper torso), without any clinically significant differences in blood levels of the active ingredients, EE and LNG. The second study showed that the patch can be worn under various conditions, including in the whirlpool and sauna, and during vigorous exercise, without any clinically significant difference in blood levels.

The phase 3 AG200-15 data also shows greater compliance than oral contraceptives with study participants having fewer missed days of contraception with the once-weekly patch than with oral contraceptives. Data were presented from 1,328 women, of whom 998 received the patch and 330 received an oral contraceptive. Over the first 6 cycles of the study, the percentage of cycles with perfect compliance was significantly higher in the patch group than in the pill group (90.5% vs 78.8%, $P<.001$). Additionally, compliance with the patch improved over the 6 cycles, while compliance with the pill worsened.

"Noncompliance among contraceptive users is an ongoing challenge, as the effectiveness of a contraceptive can decrease if it is not used correctly," Dr Kaunitz said. ■

Drug manufacturers seek payer feedback on new products

by Mari Edlin

Partnering in healthcare seems to be the prevailing wind while achieving access, cost effectiveness, and high quality remains the aim of the industry. It is evident in accountable care organizations, in hospitals buying up physician groups, and large pharmaceutical companies acquiring smaller ones.

Now a unique alliance is evolving between pharmaceutical companies and insurers, helping manufacturers guide drug development based on input and data from health plans.

US payers want more involvement in every stage of the drug development process, according to Quintiles, a biopharmaceutical services company in Research Triangle Park, N.C. Its New Health 2012 Report indicated more than 70% of survey respondents—US and UK payers and biopharma executives—believe that pre-competitive collaborations among biopharmaceutical companies would lead to more innovative and effective therapies. Only 31% of US payers, however, claim to participate in phase 3 testing.

"In the last 5 years, meeting the needs of health plans has become front and center as we focus on the unsustainability of healthcare, and see a shift from volume to value," said Jack Bailey, senior vice president, policy, payers, and vaccines for GlaxoSmithKline (GSK), also in Research Triangle Park, N.C. "We have to deliver products of value to customers who are paying for drugs in addition to developing drugs based on clinical and safety regulations. Pharma needs rewiring, a new process that allows payers to provide feedback early on that could ensure trials are designed with payers in mind, and help us achieve a 'reimbursable file.'"

Bailey outlined 3 payer priorities GSK factors into the development of its pipeline:

1. Develop a relevant comparison between drugs, when possible, not just against a placebo.

2. Create a meaningful clinical endpoint to assess a drug's performance. "That is the most compelling to payers in determining a drug's coverage on formulary," Bailey said.

3. Identify an appropriate target population for a drug to confirm its effectiveness.

It's not just a question of research and development but also commercialization of a drug product.

"There is a definite wall between the two, but integration of strategies is necessary. If we are unsure that we can provide sufficient clinical evidence and support reimbursement, we may have to redesign a drug," Bailey said.

He said GSK goes so far as to listen to payers to determine if developing a specific drug makes sense. For example, in 2009 GSK stopped its development of remogliflozin, an SGLT2 inhibitor for treating type 2 diabetes, when it was in phase 2 testing, based on feedback from payers and the company's assessment of the competitive environment.

Brian Solow, MD, chief medical officer, OptumRx, a pharmacy benefits manager (PBM) in Irvine, Calif., agreed that health plan involvement in drug development is a relatively new phenomenon. "As a PBM, we could only offer input after a drug was already developed and gone to market," he said, "but in the last 5 years, there has been a shift. Now pharma is coming to us to obtain input at phase 2 or phase 3."

He said communication is not based so much on needs—manufacturers typically know what payers want—but rather on what a manufacturer can do to make its drugs more attractive so that PBMs will recommend those drugs for plan formularies.

USING REAL-WORLD EVIDENCE

Edmund J. Pezalla, MD, national medical director, pharmacy policy and strategy for Aetna, sees a change in the way drug manufacturers are cooperating with payers. "Most marketing input occurs right before approval and is tied to reimbursement considerations," he said. "But now companies are backing up to phase 3 and asking us what we would like to know about a drug, while providing outcomes and end points, a drug's effect on quality of life, and results using a control rather than a placebo."

He said they are listening to Aetna's opinions about whether a drug should be covered under the pharmacy or medical side, how the drug could potentially perform in the marketplace, and where the drug might fall on formulary in conjunction with current therapies. Manufacturers are not, however, asking health plans whether they should develop a certain drug, he said.

Like his colleagues, Dr Pezalla said that real-world evidence and data are key to relationships between payers and pharma. Most of Aetna's available data, he said, is administrative and claims information rather than clinical. Nonetheless, he anticipated that the insurer will be able to provide additional information through the use of electronic medical records, enhanced relationships with providers and through participation in accountable care organizations.

Dr Pezalla pointed out that pharma faces 2 major hurdles—meeting regulation standards for FDA and getting a product to market. "You can't do the latter if no market exists," he said. "It no longer works to just be guided by science, but you also need to assess how drugs are used, their quality, cost, effectiveness, and safety."

TAKING THE RIGHT STEPS

John J. Doyle, senior vice president and managing director, global market access and commercialization for Quintiles, said pharmaceutical companies must engage payers to develop a value story, optimal price, and reimburseability.

Continued on page 94

Community-based intervention can help reduce mortality from opioid overdose

by Tracey Walker

In a study of communities in Massachusetts with high numbers of opioid overdose deaths, implementation of overdose education and naloxone distribution (OEND) were associated with a significant reduction in opioid overdose death rates.

The study was led by researchers at Boston Medical Center (BMC), Boston University Schools of Medicine (BUSM) and Public Health (BUSMPH) in collaboration with the Massachusetts Department of Public Health (MDPH) and published in the *British Medical Journal*.

In the United States, increases in fatal overdose since the mid-1990s have been fueled by the growth in prescriptions for opioid analgesics, according to the study. Drug overdose has surpassed motor vehicle crashes to be the leading cause of death by injury in the United States. Overdose is also a major cause of death in Canada, Europe, Asia, and Australia. Opioid-related emergency department visits and hospital admissions have increased over the same period. In Massachusetts, since 2005, annual opioid-related overdose deaths have exceeded motor vehicle deaths.

OEND is a community-based intervention that educates people at risk for overdose and potential bystanders on how to prevent, recognize and respond to an overdose. It also equips these individuals with a naloxone rescue kit. Naloxone, which may be administered by injection or by nasal spray, is a safe and effective antidote that reverses the life-threatening effects of an opioid overdose.

Between 2006 and 2009, Massachusetts OEND programs in 19 communities trained 2,912 potential bystanders who reported 327 rescues. Compared with no implementation, both low and high implementation of OEND were associated with lower rates of opioid related overdose deaths, when adjusted for demographics, addiction treatment utilization, and doctor shopping. Opioid overdose related visits to emergency departments and hospital admission rates did not differ significantly in communities with low versus high OEND implementation.

Study lead author Alexander Walley, MD, MSc, an attending physician in general internal medicine at BMC, and colleagues conducted an interrupted time series analysis of rates of opioid related deaths from overdose and acute care utilization from 2002 to 2009 that compared community-year strata with high and low rates of OEND implementation to those with no OEND implementation. Poisson regression models were adjusted for community-level demographics and substance use-related factors.

"OEND is an innovative, community-based program deployed in many settings that has not been examined in controlled studies," Dr Walley told *Formulary*. "This study provides observational evidence that OEND is an effective public health intervention to address increasing mortality from opioid overdose by training potential bystanders to prevent, recognize, and respond to opioid overdoses. OEND implementation seemed to have a dose-related impact where the higher the cumulative rate of OEND implementation, the greater the reduction in death rates."

This study provides strong support for the public health agency policy and community-based organization practice to implement and expand OEND programs as a key way to address the opioid overdose epidemic, according to Dr Walley. "Two features of the Massachusetts OEND programs that supported broad implementation include the use of an nasal naloxone delivery device and the use of a standing order issued by the health department, which allowed non-medical personnel to deliver OEND," he said. "These features may enable broader implementation with greater impact as more communities implement OEND."

"Opioid overdose death rates were reduced in communities where OEND was implemented," Dr Walley said. "This study provides observational evidence that by training potential bystanders to prevent, recognize, and respond to opioid overdoses, OEND is an effective intervention." ■

Continued from page 93

He believes that communication should start as early as phase 1 and 2 of clinical trials. "Payers want to know how decisions to develop a certain drug are made. To be successful, drug companies must look at the pharmaceutical landscape—what is already on the market and how they can fill gaps—consider reimbursement issues and determine how the drug can help patients," Doyle said.

The next steps are describing the drug profile (its clinical, safety, efficacy, and humanistic benefits), weighing potentially higher costs against value propositions (such as fewer side effects, a decrease in hospital and office visits, and fewer hospital readmissions), and testing new products against the competition and standards of care.

"Once the data set is available, manufacturers should determine the level of evidence payers require to move the needle toward a favorable decision," Doyle said. "Payers want to know how a drug performs beyond a randomized control trial; they need a drug to demonstrate its value in a population specific to their membership and provide real-world evidence that validates trial findings—more outcome metrics than FDA requires." ■

Vitamin D potency varies widely in dietary supplements

by Tracey Walker

The potency of vitamin D in compounded and over-the counter (OTC) supplements varied widely, according to a recent research letter published in the February 11 issue of *JAMA Internal Medicine*.

Researchers were conducting a randomized controlled trial of vitamin D in menopausal women. "We used compounded study pills so that vitamin D and placebo pills would look the same," Erin S. LeBlanc, MD, MPH, lead author and investigator with the Kaiser Permanente Center for Health Research in Portland, Ore., told *Formulary*. "As part of study quality assessment, we sent the compounded study pills to a lab for testing and found variability in the potency. This made me curious about the variability and accuracy of over-the-counter vitamin D supplements, so I tested them as well and found variability in potency."

The researchers tested 55 bottles of OTC vitamin D pills made by 12 different manufacturers, and compounded pills made on three different occasions over 4 months. Potency variability ranged from 9% to 146% of the amount listed on the label.

"The vitamin D with only 9% potency was an outlier and we retested another pill in the bottle to be sure," Dr LeBlanc said. "The second pill was just as low. But we think this low value shows it is possible for vitamin D pills to contain very little of the actual active ingredient. The pill with the next lowest potency was 52%.

Dr LeBlanc

"The amount listed on the label did not necessarily match the amount contained in the bottle," Dr LeBlanc continued. "It takes a lot of vitamin D to result in toxic effects so the main safety issue is really for consumers with low vitamin D levels. In these people, taking pills that are less potent than they expect could pose health risks. About one-third of the pills we analyzed had less vitamin D than was listed on the label."

The amount of vitamin D in supplements is not necessarily the amount listed on the label, the researchers concluded.

"Consumers and patients may be getting more or less than they expect," Dr LeBlanc said. "The USP verification stamp is probably the best way to get some reassurance that the amount listed on the label is close to what's in the bottle. In our study, the verification stamp wasn't a guarantee that every pill in the bottle contained the amount of vitamin D listed on the label, but when averaged together, the 5 pills from the USP verified bottle generally contained at least 100% of what was listed on the bottle."

Dr LeBlanc reminds clinicians to caution patients when buying OTC vitamin D supplements.

"Vitamin D insufficiency can be harmful to health, hence supplementation is commonly prescribed. However, vitamin D supplements are not regulated by the FDA, meaning that potency might not be evaluated," said Dr LeBlanc. "We were surprised by the variation in potency among these vitamin D pills." ■

New strategies needed to reduce mortality associated with cardiometabolic risk factors in young people

by Tracey Walker

Among US adolescents and young adults, hig h HbA_{1c} levels, central obesity, and smoking were associated with an increased risk of dying before 55 years of age, according a study published recently in *Pediatrics*.

"We looked at risk factors for dying before the age of 55 years among adolescents and young adults in the United States," lead author Sharon Saydah, PhD, CDR USPHS, Centers for Disease Control and Prevention, Division of Diabetes Translation, told *Formulary*.

"We found that after adjusting for age, sex, race/ethnicity; smoking status, measure of obesity, and glucose levels were associated with increased risk of early deaths. We found no association with cholesterol measures and early deaths," Saydah said.

The researchers used data from CDC's National Health and Nutrition Examination Survey (NHANES), 1988-1994, of participants aged 12 to 39 years with follow-up data on mortality status through 2006.

"We looked at the association of a number of risk factors included three measures of adiposity, glycated hemoglobin [HbA_{1c} level, cholesterol levels, blood pressure, self-reported smoking status and cotinine level with death prior to age 55," she said.

While previous studies have found risk factors such as obesity, cholesterol, glucose, smoking to increase the risk of disease among the younger adult population, few had looked at the association with early mortality, according to Saydah.

"These associations indicate a need for more effective community and clinical strategies for reducing the prevalence of these risk factors among US residents in these age groups," she said. "The CDC has a number of resources and programs to address reducing these risk factors in the population including smoking cessation, type 2 diabetes prevention, and obesity reduction." ■

Pipeline preview

Complete response

■ Rintatolimod (**Ampligen**, Hemispherx Biopharma) for chronic fatigue syndrome (CFS). FDA said Hemispherx should conduct at least 1 additional clinical trial, complete various nonclinical studies, and perform a number of data analyses. In the complete response letter (CRL), FDA set forth the reasons for this action and provided recommendations to address certain outstanding issues. FDA stated that the submitted data do not provide substantial evidence of efficacy of Ampligen for the treatment of CFS and that the data do not provide sufficient information to determine whether the product is safe for use in CFS due to the limited size of the safety database and multiple discrepancies within the submitted data. Hemispherx plans to request an end-of-review conference with FDA as a precursor to submitting a formal appeal to the Office of New Drugs in FDA's Center for Drug Evaluation and Research regarding the Agency's decision.

■ Insulin degludec (**Tresiba**, Novo Nordisk) and insulin degludec/insulin aspart (**Ryzodeg**, Novo Nordisk) for the treatment of diabetes. In the CRL, FDA requested additional cardiovascular data from a dedicated cardiovascular outcomes trial before the review of the New Drug Applications can be completed. Novo Nordisk is evaluating the content of the CRL and will work closely with FDA to provide the requested data. Novo Nordisk does not expect to be able to provide the requested data during 2013. In the letter, FDA also states that approvals for Tresiba and Ryzodeg cannot be granted until the violations cited in the previously announced warning letter, dated December 12, 2012, have been resolved.

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New molecular entity

Sirturo

Bedaquiline

JANSSEN THERAPEUTICS

A diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multidrug-resistant TB.

Late last year FDA approved bedaquiline (Sirturo, Janssen Therapeutics) tablets for the treatment of pulmonary multidrug-resistant tuberculosis (MDR-TB) as part of combination therapy in adults. The accelerated approval was based on the end point of time to sputum culture conversion compared with placebo. Bedaquiline, a diarylquinolone antimycobacterial drug, is recommended when other alternative treatments cannot be provided. It is not indicated for the treatment of latent, extra-pulmonary, or drug-sensitive TB.

■ Bedaquiline is the first drug approved specifically for MDR-TB and is used in combination with other antimycobacterial agents.

In 2011 TB affected more than 10,000 patients in the United States and almost 9 million worldwide, according to the Centers for Disease Control and Prevention. TB is caused by *Mycobacterium tuberculosis* and commonly infects one's lungs, but also may infect the brain, kidneys, and spine. MDR-TB is TB resistant to isoniazid and rifampin. Although only 98 cases occurred in 2011 in the United States, the World Health Organization estimates that MDR-TB will affect 2 million people from 2011 to 2015.

Bedaquiline is the first drug approved specifically for MDR-TB and is used in combination with other antimycobacterial agents. Bedaquiline carries a boxed warning about the risk of QT prolongation and an increased risk of death as seen in 1 placebo-controlled trial. It should only be used when an effective drug regimen is not available or cannot be provided.

Efficacy. FDA's approval of bedaquiline was based on data from TMC207-C208 studies 1 and 2, with the primary end point being the time to sputum culture conversion. In study 1, a placebo-controlled, double-blind, randomized trial of newly diagnosed patients with MDR-TB, 79 patients received bedaquiline in combination with other drugs to treat MDR-TB and 81 received placebo and the combination of other drugs for MDR-TB, which included ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone or an available alternative. Bedaquiline was given at a dose of 400 mg once daily for the first 2 weeks of treatment and at a dose of 200 mg 3 times per week for another 22 weeks. After the 24-week treatment with bedaquiline, patients were continued on their other MDR-TB drugs for 18 to 24 months, or another 12 months following the first confirmed negative culture. At 24 weeks, culture conversion success was demonstrated in 77.6% of patients who received bedaquiline combination treatment versus 57.6% of patients in the placebo group (P=.014). At 72 weeks, culture conversion success was seen in 70.1% of the bedaquiline treatment group versus 56.1% of the placebo treatment group (P=.092). The median time to conversion was 83 days in the bedaquiline group compared with 125 days in the placebo group.

In study 2, a smaller placebo-controlled study, bedaquiline was administered for only 8 weeks instead of 24 weeks. The patients treated with bedaquiline (n=23) had greater success than the placebo group (n=24) in terms of decreased time to culture conversion and improved rates of culture conversion at week 8.

Safety. The most common adverse reactions that occurred in patients treated with bedaquiline during the clinical trials were nausea (38%), arthralgia (32.9%), headache (27.8%), hemoptysis (17.7%), and chest pain (11.4%). Bedaquiline exposure may be reduced if coadministered with CYP3A4 inducers or increased if coadministered with CYP3A4 inhibitors. The manufacturer recommends strong CYP3A4 inhibitors not be used for more than 14 consecutive days

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Priority review

- Dolutegravir (GlaxoSmithKline and ViiV) for the treatment of HIV/AIDS.
- Radium-223 dichloride (radium-223, Bayer HealthCare) for the treatment of castration-resistant prostate cancer patients with bone metastases.

Orphan drug designations

- APG101 (**Apocept**, Apogenix GmbH), a first-in-class, fully human fusion protein combining the extracellular domain of the CD95 receptor and the Fc portion of IgG, for the treatment of myelodysplastic syndromes.
- LG631-CD34 (Lentigen) for bone marrow protection in the treatment of glioblastoma multiforme.
- PLacental eXpanded (PLX) cells (Pluristem Therapeutics) for the treatment of aplastic anemia.

First-time generic approvals

Buprenorphine hydrochloride (HCl) and naloxone HCl dihydrate sublingual tablets in 2-mg/0.5-mg and 8-mg/2-mg strengths (equiv to Suboxone)
AMNEAL PHARMACEUTICALS

Doxorubicin hydrochloride liposome injection (equiv to Doxil)
SUN PHARMA GLOBAL

Clindamycin in 5% dextrose (equiv to Cleocin Phosphate in Dextrose 5%)
SANDOZ

Mixed salts of a single-entity amphetamine in 5-mg, 15-mg, 20-mg, 25-mg, and 30-mg capsules (equiv to Adderall)
TEVA

while on bedaquiline unless benefit outweighs the risks.

Bedaquiline carries a boxed warning of increased risk of death, observed during 1 of the clinical trials in comparison to the placebo arm (11.4% vs 2.5%). Therefore, the drug should only be used when other effective treatments are not provided. The warning also includes the risk of QT prolongation when administering bedaquiline and additional risk when used with drugs that prolong the QT interval. A baseline electrocardiogram should be obtained and repeated at 2, 12, and 24 weeks after therapy initiation.

> Bedaquiline carries a boxed warning of increased risk of death, observed during 1 of the clinical trails in comparison to the placebo arm.

Dosing. The recommended dosage of bedaquiline is 400 mg once daily with food for the first 2 weeks of treatment. Then from weeks 3 to 24, the dosage should be 200 mg 3 times per week with food with 48 hours between doses. If a patient misses a dose during the first 2 weeks of treatment, the dose should not be made up but the patient should continue the dosing schedule. At weeks 3 to 24, the missed doses should be taken as soon as possible and then the patient can resume the 3 times per week treatment regimen. Nonadherence to the treatment regimen could result in treatment failure or resistance. Therefore bedaquiline should be administered under direct observation. It should be administered in combination with at least 3 drugs that are active against the patient's TB isolate. ■

FDA actions *in brief*

Ado-trastuzumab emtansine (**Kadcyla**, Genentech, a member of the Roche Group) was approved for patients with HER2-positive, metastatic breast cancer.

Everolimus (**Zortress**, Novartis) was approved to prevent organ rejection in adult liver transplant patients.

Adapalene 0.1%/benzoyl peroxide 2.5% (**Epiduo**, Galderma) was approved to treat acne in children aged 9 and older.

Pomalidomide (**Pomalyst**, Celgene) was approved to treat patients who have received at least 2 prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Alogliptin (**Nesina**, Takeda Pharmaceuticals), alogliptin and metformin hydrochloride (**Kazano**, Takeda Pharmaceuticals), and alogliptin and pioglitazone (**Oseni**, Takeda Pharmaceuticals) were approved for use with diet and exercise to improve blood sugar control in adults with type 2 diabetes.

Imatinib (**Gleevec**, Novartis) was approved for the treatment of children newly diagnosed with Philadelphia chromosome positive acute lymphoblastic leukemia.

Mesalamine (**Delzicol**, Warner Chilcott) 400-mg delayed-release capsules were approved for the treatment of ulcerative colitis.

Mipomersen sodium (**Kynamro**, Genzyme and Isis Pharmaceuticals) once-a-week injection as an addition to lipid-lowering medications and diet was approved to treat patients with homozygous familial hypercholesterolemia.

Over-the-counter Oxytrol for Women (Merck) was appoved for treatment of overactive bladder in women aged 18 years and older.

Glycerol phenylbutyrate (**Ravicti**, Hyperion Therapeutics) was approved for the chronic management of some urea cycle disorders in patients aged 2 years and older.

Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein] (**Prevnar 13**, Pfizer) was approved for use in older children and adolescents aged 6 years through 17 years for active immunization for the prevention of invasive disease caused by the 13 *Streptococcus pneumoniae* serotypes contained in the vaccine. For this age group, Prevnar 13 is administered as a 1-time dose to patients who have never received Prevnar 13.

PEER-REVIEWED

An update on attention deficit/hyperactivity disorder

Janet Ashley Gunter, PharmD, BCPS

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children. Recent guideline changes from the American Academy of Pediatrics (AAP) recommend evaluating and diagnosing children ages 4 to 18 years. Medication therapy for ADHD has been shown to decrease impulsivity and hyperactivity and to increase attention in children. Stimulants continue to be recommended as first-line treatment for children ages 6 to 12, and 70% of children respond to therapy with any single stimulant chosen. Nonstimulants are now available and offer a treatment option for children who do not respond to stimulants. Adverse events such as growth suppression and cardiovascular risk are of concern to patients and caregivers, but recommendations for management have been made in the AAP guidelines and in the European guidelines on managing adverse effects of medications for ADHD. New formulations of stimulants and nonstimulants allow for individualization of therapy for patients to receive the maximum benefit while minimizing side effects. (*Formulary.* 2013;48:98–109.)

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent neurobehavioral disorder in children.[1] ADHD is a chronic, debilitating condition that affects approximately 5.4 million children aged 4 to 17 in the United States. Prevalence estimates have varied from 3% to 7% in school-aged children, and recent parent surveys reveal that 9.4% of children aged 4 to 17 in the United States have been diagnosed with ADHD. Boys are diagnosed with ADHD 4 times as often as girls. This difference could be due to both a selection bias, since boys are more active, as well as to a true gender difference.[2] The annual cost of ADHD for each child is estimated to be between $12,005 and $17,458 in the United States.[3] The 2005 annual societal costs are estimated to be between $36 billion and $52 billion.[4] ADHD was previously thought to be a childhood disorder with adults outgrowing symptoms, but ADHD has been shown to continue into adulthood in up to 60% of patients.[5]

The most common symptoms of ADHD are impulsivity, hyperactivity, and inattention. ADHD can affect all aspects of a child's life, including schoolwork and relationships with family and friends.[5] Parents can be stressed due to difficulties with children at home or on outings. Siblings of children with ADHD report feelings of victimization, responsibility for caretaking, and sorrow in relation to the child with ADHD.[5] Inability to succeed in the classroom can lead to low self-esteem in children with ADHD and place them at risk for substance abuse and injury from high-risk behavior.[5]

The criteria for diagnosis of ADHD are defined within the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV–TR), listed in Table 1 (page 99), although there are proposed changes for DSM V.[6] DSM V will continue to have the exact wording of each of the 18 symptoms as in DSM-IV, but examples such as "overlooks or misses details, work is inaccurate" and "starts tasks but quickly loses focus and is easily side-tracked; fails to finish schoolwork, household chores, or tasks in the workplace" have been proposed for some symptoms to make ADHD more easily diagnosed across the lifespan.[7] Another significant proposed change for DSM V is to change the requirement for symptoms to be present by 7 years of age to symptoms are present by 12 years of age. Both of these changes would be expected to increase the prevalence of ADHD.[7] ADHD diagnosis relies heavily on reports from parents and teachers to determine if patients meet the criteria. It is anticipated DSM V will place a greater emphasis on providers receiving information from 2 different informants.

Many times ADHD may be diagnosed by primary care providers rather than psychologists and psychiatrists. It has been reported that DSM criteria were used by only 38% of primary care providers to diagnose a child with ADHD, and psychiatrists have reported using intuition to reach clinical decisions.[2,3] Reasons why providers do not use the guidelines are presumed to be lack of awareness of the key recom-

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Dr Gunter is the clinical pharmacy coordinator at Fort Belvoir Community Hospital, Fort Belvoir, Va.

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Table 1

Diagnostic criteria (DSM-IV–TR)

1. The patient must have at LEAST 6 of the symptoms of **inattention.**	**Inattention**
	Often fails to pay attention to details or makes careless errors in schoolwork or other activities
	Often has difficulty maintaining attention in tasks or play activities
	Often does not seem to listen when spoken to directly
	Often does not follow through on instructions and fails to compete schoolwork, chores or duties in the workplace
	Often has difficulty with organization in regards to tasks and activities
	Often avoids, dislikes or is reluctant to engage in activities that require sustained concentration
	Often loses things necessary for tasks or activities (toys, school assignments, pencils, books)
	Often easily distracted by external stimuli
	Often forgetful in daily activities
2. The patient must have at LEAST 6 of the symptoms of **hyperactivity** or **impulsivity.**	**Hyperactivity**
	Often fidgets with hands or squirms in seat
	Often leaves seat in classroom or other situations where seating is expected
	Often runs about or climbs excessively when it is inappropriate
	Often has difficulty playing or engaging in leisure activities quietly
	Often "on the go" or acts as if "driven by a motor"
	Often talks excessively
	Impulsivity
	Often blurts out answers prior to questions being completed
	Often has difficulty awaiting turn
	Often interrupts or intrudes on others
3. Symptoms have been occurring at LEAST 6 months. Evaluations for learning disabilities should be ruled out.	
4. There are 3 subtypes based on predominant symptoms.	ADHD, combined type: if the criterion is met for (1) and (2) above.
	ADHD, predominantly inattentive: if criterion is only met for (1) above.
	ADHD, predominantly hyperactive impulsive: if criterion is only met for (2) above.
5. Symptoms must have been present before the age of 7.	
6. Symptoms cause clinically significant impairment and should be present in more than 1 setting.	
7. Symptoms are not caused by another psychiatric or medical condition.	

Formulary/Source: Ref 6

Table 2

FDA-approved medications for ADHD

Medication	Time to initial effect	Duration, hours	Maximum dose	Delivery system	Usual starting dose
Stimulants					
Mixed amphetamine salts	20–60 min	6	40 mg	Immediate-release tablets	3–5 years old: 2.5 mg once or twice daily; > 6 years old: 5 mg twice daily
Mixed amphetamine salts XR	20–60 min	10	40 mg	Bead-filled capsules; 50% of dose delivered immediately, remaining 50% delayed-release; simulates twice daily dosing	10 mg every AM
Dextroamphetamine	20–60 min	4–6	40 mg	Immediate-release tablets	3–5 years old: 2.5 mg once or twice daily; >6 years old: 5 mg twice daily
Dextroamphetamine spansules	≥60 min	≥6	40 mg	Capsule with 50:50 mix of short and delayed-release medication	5-, 10-, or 15-mg capsule
Dextroamphetamine liquid		4–5	40 mg	Oral solution	2.5 mg 2 or 3 times daily
Lisdexamfetamine	60 min	10–12	70 mg	Capsule containing 1-lysine and dextroamphetamine; active drug is cleaved off in the GI tract	6–12 years old: 30 mg every AM; 13 years and older: 50 mg every AM
MPH–OROS	20–60 min	12	54 mg (<13 y); 72 mg (≥13 y)	Osmotic release system simulates 3-times-a-day dosing	27 mg every AM
MPH–ER	20–60 min	8	60 mg	Wax-based matrix, slowly dissolves over time	20 mg every AM; may need second dose in PM
MPH (Ritalin)	20–60 min	3–5	60 mg	Immediate-release tablets	5 mg, 2 or 3 times a day
MPH (Methylin)	20–60 min	3–5	60 mg	Immediate-release chewable tablets and oral solution	5 mg, 2 or 3 times a day
Transdermal MPH	60 min	11–12	30 mg	Transdermal daily patch	10-mg patch applied in the AM and removed in the PM
MPH–LA	20–60 min	6–8	60 mg	Bead-filled capsules; 50% of dose is delivered immediately and the remaining 50% is delayed-release; simulates twice daily dosing	20 mg every AM
MPH–SR	1–3 h	2–6	60 mg	Wax-based matrix, slowly dissolves over time	20 mg every AM; may need second dose in PM
MPH–CD	20–60 min	6–8	60 mg	Bead-filled capsules; 30% of dose is delivered immediately and the remaining 70% is delayed-release; simulates twice-daily dosing	20 mg every AM
Dexmethylphenidate (Focalin)	20–60 min	3–5	20 mg	Immediate-release tablets	2.5 mg twice daily
Dexmethylphenidate (Focalin XR)	20–60 min	8–12	30 mg	Bead-filled capsules; 50% of dose delivered immediately and the remaining 50% is delayed-release; simulates twice daily dosing	5 mg every AM
Nonstimulants					
Atomoxetine	1–2 wk	At least 10–12 h	1.4 mg/kg	Capsule	400 mg every AM (may be given in divided doses)
Extended-release guanfacine	1–2 wk	At least 10–12 h	4 mg/d	Extended-release tablet	1 mg daily
Extended-release clonidine	1–2 wk	At least 10–12 h	0.4 mg/d	Extended-release tablet	0.1 mg at bedtime

Abbreviations: MPH, methyphenidate; ER, extended release; SR, sustained release, CD, controlled delivery; LA, long acting; XR, extended release; OROS, osmotic-controlled release oral delivery system

Formulary/Source: Ref 12

Continued from page 98

mendations of the guidelines, lack of agreement with the guidelines, and patient-related factors.[3] The etiology of ADHD suggests that there are neurochemical, neurophysiological, genetic, and psychosocial components for the disorder. There is a heredity link for ADHD that has been determined through family history and twin studies.[2]

The most recent clinical practice guideline from the American Academy of Pediatrics (AAP) expanded the age range for evaluation and diagnosis of ADHD from 6 to 12 years to 4 to 18 years.[8] The guideline places emphasis on the use of DSM-IV–TR recommendations criteria and on gathering information from multiple sources. The guideline states that ADHD is a chronic disease and children with ADHD should be followed in the manner recommended by the chronic care model and the medical home.

The guideline includes recommendations for treatment of ADHD; these vary by the patient's age and the literature.[8] The goal of treatment in ADHD is to minimize hyperactivity and improve attention. Treatment of ADHD is often approached through multiple modalities including medications and behavioral therapy.[1] Review of the literature by the Agency for Healthcare Research and Quality concluded that medication management is effective for school-age children and should be recommended first line.[9] In preschoolers who do not respond to behavioral therapy, methylphenidate (MPH) is recommended first line. This is in accordance with the AAP guideline.

For preschool-age children (4 to 5 years), AAP recommends behavioral therapy be tried first.[8] If behavioral therapy does not provide significant improvement, treatment with medication can be considered. Dextroamphetamine has an indication for pediatric use, but this indication was given when FDA requirements were less stringent.[8] The strongest study to support use of MPH in small children is the Preschool ADHD Treatment Study (PATS).[10] It is important to note that PATS was limited to preschool-aged children who had moderate to severe dysfunction. Based on these data, AAP recommends that only preschool-aged children with moderate to severe dysfunction who meet PATS inclusion criteria be considered for drug treatment.[8] PATS included preschoolers aged 3 to 5.5 years with moderate to severe dysfunction who had symptoms that had persisted at least 9 months, with dysfunction present at home and other places (preschool or daycare), and whose dysfunction did not improve with behavioral therapy.[10] PATS demonstrated that preschoolers' ADHD symptoms significantly decreased with MPH treatment. PATS concluded that MPH was tolerated well by preschoolers; however, adverse reactions of emotional lability and dysphoria presented more commonly than in school-age children.[10] Preschoolers did respond at lower doses than used in the school-age studies, which correlates with pharmacokinetic data for slower clearance in children 4 to 5 years of age.[11] For treatment of preschoolers, it is recommended to start with a low dosage and titrate slowly. It is important to note that treatment with MPH for preschool-aged children is an off-label use.

■ It is important to note that treatment with methylphenidate (MPH) for preschool-aged children is an off-label use.

For school-age children, stimulants continue to be recommended as the first-line agent, followed by nonstimulants atomoxetine, extended-release guanfacine, and then extended-release clonidine.[8] FDA-approved medications for the treatment of ADHD are listed in Table 2 (page 100). These medications have all been shown to reduce the core symptoms of ADHD, but substantially more literature exists for stimulants.[8] Stimulants were first reported more than 70 years ago for treatment of behavioral disorders in children.[12] Stimulants have the most evidence of efficacy and safety for ADHD in the school-age population and have been shown to improve attention and to decrease hyperactivity and impulsivity. Children may respond to one stimulant but not another; therefore, failure of one class does not mean that stimulants will not be useful.[1] Stimulants are available as either MPH or amphetamines.

The landmark study by the MTA Cooperative Group demonstrated that in school-age children with ADHD (7 to 9.9 years), medication management with stimulants (alone or with behavioral therapy) is superior to behavioral treatment and treatment in the community.[13] The study, which was conducted for 14 months, concluded that stimulants were tolerated well, even with a third dose in the afternoon. It was postulated that the patients receiving medication management had better symptom control than community treatment patients who were also on MPH medications due to better dose optimization.[13] The medication management group had closer follow-up and had higher doses of MPH. Based on these data, the AAP recommends that primary care clinicians should titrate doses of ADHD medications to achieve maximum benefit with minimum side effects.[8] Stimulant medications can be titrated every 3 to 7 days.[8] Expected effects from stimulants are seen immediately, so

multiple trials can be done in a short timeframe. Stimulants are generally well-tolerated, but common adverse effects include insomnia, anorexia, headaches, nausea, abdominal pain, sadness, and irritability.

Most of the recent developments for stimulant treatments for ADHD have been formulation changes to extend duration of action. The longer-acting formulations allow for simplification of dosing, increased adherence, and the potential for once-daily dosing.[11]

Dexmethylphenidate XR has a quick onset, within 30 minutes, and lasts up to 10 hours at the recommended dose. If patients are transitioning to dexmethylphenidate XR from MPH, then half the daily dose is the recommended starting dose; however, if patients are switching from dexmethylphenidate to the extended-release product, an equivalent starting dose is recommended.[14] Even though it is an extended-release product, the capsules can be opened and the beads can be sprinkled on food for patients who are unable to swallow capsules.[14]

The MPH transdermal patch is worn up to 9 hours per day, but has an onset of up to 2 hours, so parents should be advised to apply the patch or have the child apply the patch upon awakening.[14] It has been approved for wear at durations of 4 and 6 hours for children who may sleep longer. The patch should be applied to the hip area and was shown to have a 31% decrease in bioavailability if applied to the scapular area.[14]

Lisdexamfetamine is the first prodrug approved for the treatment of ADHD. It is activated when lysine is cleaved from the drug during metabolism. It is hypothesized that this medication will have limited abuse potential compared to other stimulants. It lasts up to 12 hours after administration but has a longer onset due to requiring metabolism for activation.[14] One advantage of this medication may be its ease of administration for younger children who have difficulty swallowing capsules. The capsule can be dissolved in water for administration due to its unique metabolism unlike the beaded extended-release formulations that can only be sprinkled on food.[15] Multiple formulations of stimulants for ADHD allow patient-centered medication regimens to be developed.

It has been approximated that up to 30% of children do not respond to stimulants.[16] Currently, there are 3 FDA approved nonstimulants for treatment of ADHD. Atomoxetine was the first nonstimulant to be approved and works by selective inhibition of the presypnaptic norepinephrine reuptake transporter.[16] It inhibits the reuptake of norepinephrine; however, it has no effect on dopamine in the striatum or nucleus accumbens. This decreased effect on dopamine makes it less likely to be abused than stimulants.[16] Atomoxetine has weight-based dosing in school-age children (aged 6 to 12) up to 1.4 mg/kg/day, and the benefit is typically seen in 2 to 8 weeks after initiation. Studies have found no greater efficacy at a higher dosage.[16] Long-term studies have shown that treatment with atomoxetine remains effective at 12 and 18 months of therapy.[9] The most common side effects of atomoxetine are gastrointestinal upset and somnolence.[8] These side effects can be minimized with a slow dose titration. Atomoxetine has warnings for hepatotoxicity and suicidality risk. Patients initiated on atomoxetine should be monitored closely for mood and behavioral changes.[14]

Two of the nonstimulant medications for ADHD are α_2-adrenergic agonists, extended-release guanfacine and extended-release clonidine. These medications have indications for treatment alone or as adjunctive treatment with stimulant medications for ADHD. Other medications utilized for adjunctive therapy have only anecdotal evidence and are used off-label.[8] The α_2-adrenergic agonists require dose tapering prior to discontinuation to avoid rebound hypertension and cannot be abruptly stopped like the stimulants and atomoxetine. The most common adverse effects of the α_2-adrenergic agonists are somnolence and dry mouth.

The AAP guideline has special considerations for treatment of adolescent patients (12 to 18 years) that include screening the patient for substance abuse and diversion of medications.[8] AAP recommends that clinicians monitor symptoms and refill history to be alert for signs of misuse or diversions. The guideline further recommends considering use of a medication without abuse potential such as atomoxetine, extended-release guanfacine, or extended-release clonidine, or with less abuse potential such as lisdexamfetamine, transdermal MPH, or MPH OROS.[8] Both transdermal MPH and MPH OROS make extraction of the MPH more difficult, reducing medication abuse potential, and lisdexamfetamine has lessened medication abuse potential since it must be ingested before activation. Finally, AAP recommends longer-acting formulations or late afternoon short-acting medications to ensure symptom coverage for periods when teenagers may be driving.[8]

There are 2 adverse effects of medications for ADHD that may cause practitioners and families concern. Guidelines from the European ADHD Guidelines Group were recently released to assist practitioners with managing adverse effects.[17] The stimulant medications and atomoxetine have been shown to decrease appetite and cause growth delay. It is thought that reduced caloric intake and lack of proper nutrition due to the decreased appetite may enhance the growth delay seen in children treated with medications for ADHD.[17] Loss of appetite with both MPH and atomoxetine can be long

term and may not attenuate over time. Providers should monitor the patient's height and weight and body mass index at least every 6 months.[17] In order to decrease appetite suppression, the medication can be given after meals, and the use of high-caloric snacks should be encouraged. Height reduction is dose-dependent and reversible after treatment is discontinued. If patients fall below 2 percentile lines, consider dose reduction, drug holiday, medication change, or a referral to a pediatric endocrinologist or growth specialist.[11,17]

In recent years, reports of serious and fatal cardiovascular events in children taking stimulants have been well-publicized and have brought up the concern of the cardiovascular risk associated with stimulants.[18] It has been known that stimulants raise blood pressure and heart rate in children, and recent studies have shown that tolerance to these effects does not develop with time. FDA has reviewed reports and issued warnings about the use of stimulants in patients with cardiovascular disease.[18] Most of the data regarding cardiovascular risk in children taking stimulants are from trials conducted to test efficacy and may not be powered to assess cardiovascular risk. Cooper et al conducted a retrospective cohort study to determine if children and young adults given ADHD medications were at an increased relative risk for cardiac events compared with nonusers.[19] In the study, medical records of 1.2 million children and young adults (ages 2 to 24) were reviewed, and it was determined that ADHD medication users were not at increased risk for cardiovascular events (adjusted HR, 0.75; 95% CI, 0.29–1.72). The AAP guideline recommends expanding the history of patients with ADHD to include cardiac symptoms, Wolf-Parkinson White syndrome, sudden death in the family, long QT syndrome, and hypertrophic cardiomyopathy.[8] The European ADHD Guidelines Group also recommends measuring baseline heart rate and blood pressure, repeating every 3 to 6 months, and performing auscultation to identify any murmurs.[17] While ADHD was once thought of as a childhood disorder, it is now known to have a longitudinal course in some patients. AAP guideline have extended the age range for ADHD evaluation and diagnosis to 4 to 18 years, and proposed DSM V criteria require an onset of symptoms by age 12. The American Academy of Child and Adolescent Psychiatry recommends that treatment be individualized for patients.[11] ADHD treatment offers symptomatic reduction of inattention and hyperactivity, which allows patients to better perform in home, school, and work environments. Stimulants remain first-line therapy for ADHD; multiple formulations allow a patient's medication regimen to be optimized to their individual needs. Nonstimulants such as atomoxetine, extended-release guanfacine, and extended-release clonidine offer new treatment options for patients who may not respond to stimulants. Duration of the treatment should last as long as impairing symptoms persist, but the need for therapy should be reevaluated periodically since some children with ADHD may have reduced symptoms over time.[11] ■

REFERENCES

1. Spencer R, Curtis J, Sherr D. Psychiatric disorders in children and adolescents. In: Koda-Kimble MA, Young LY, eds. Applied Therapeutics: The Clinical Use of Drugs. Philadelphia: Lippincott Williams & Wilkins, 2004: 81-2–81-9.
2. Rowland A, Lesesne C,Abramowitz A. The epidemiology of attention-deficit/hyperactivity disorder (ADHD): a public health view. *MRDD Res Rev* 2002;8:162–170.
3. Kovshoff H, Williams S, Vrijens M, et al. The decisions regarding ADHD management (DRAMa) study: uncertainties and complexities in assessment, diagnosis and treatment, from the clinician's point of view. *Eur Child Adolesc Psychiatry* 2012;21:87–99.
4. Attention Deficit Hyperactivity Disorder Data/Statistics. Available at: http://www.cdc.gov/ncbddd/adhd/data.html. Accessed January 23, 2013.
5. Harpin VA. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. *Arch Dis Child* 2005; 90(Suppl 1):i2–i7.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Rev. Washington, DC: 2000.
7. Dalsgaard S. Attention-deficit/hyperactivity disorder (ADHD). *Eur Child Adolesc Psychiatry* 2012. Published online ahead of print, December 1, 2012. DOI 10.1007/S00787-012-0360-z.
8. American Academy of Pediatrics, Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2011;128:1007–1022.
9. Charach A, Dashti B, Carson P, et al. Attention deficit hyperactivity disorder: effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Comparative Effectiveness Review No. 44. (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02-0020.) AHRQ Publication No. 12-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.
10. Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry* 2006;45:1284–1293.
11. Vaughan B, Kratochvil C. Pharmacotherapy of pediatric attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatric Clin N Am* 2012;21:941–955.
12. Findling RL. Evolution of the treatment of attention-deficithyperactivity disorder in children: a review. *Clin Ther* 2008;30:942–957.
13. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;56:1073–1086.
14. May D, Kratochvil C. Attention-deficit hyperactivity disorder: recent advances in paediatric pharmacotherapy. *Drugs* 2010;70:15–40.
15. Wigal SB, Raja P, Shukla A. An update on lisdexamfetamine dimesylate for the treatment of attention deficit hyperactivity disorder. *Expert Opin Pharmacother* 2013;14:137–145.
16. Christman AK, Fermo JD, Markowitz JS. Atomoxetine, a novel treatment for attention-deficit—hyperactivity disorder. *Pharmacotherapy* 2004;24:1020–1036.
17. Cortese S, Holtmann M, Banaschewski T, et al, on behalf of the European ADHD Guidelines Group. Practitioner teview: vurrent best practice in the management of AEs during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry* 2013. Published online ahead of print. January 23, 2013. Doi:10.1111/jcpp.12036.
18. Hammerness PG, Perrin JM, Shelley-Abrahamson R, Wilens TE. Cardiovascular risk of stimulant treatment in pediatric attention-deficit/hyperactivity disorder: update and clinical recommendations. *J Am Acad Child Adolesc Pschiatry* 2011;50:978–990.
19. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med* 2011;365:1896–1904.

Researchers seek next class of anti-allergics

Paulo J. Gomes

Spring is on the horizon, and with it comes the renewal of seasonal allergies. Lately, though, it seems that while allergy seasons come and go, allergy therapies remain the same. For more than 3 decades, antihistamine-based agents have been the standard of care. Although there have been valuable improvements over the years (dual-action agents, once-daily therapies), researchers are still looking for the next class of anti-allergic agents that can address the needs of patients whose symptoms are unresponsive to available therapies.

This unmet need includes those with severe allergy, many of those with perennial allergies, and those with allergy combined with additional ocular surface disease, such as dry eye. Add these patients to individuals whose symptoms are unresponsive to antihistamines, and it may be that as many as 20% to 30% of all allergy sufferers constitute those without an effective treatment option. Here, we consider possible remedies for these patients, as well as new approaches to identifying novel therapeutic alternatives.

Current alternatives to antihistamine therapy include steroids, non-steroidal anti-inflammatory drugs (NSAIDs), and other immunosuppressive agents. Steroids such as loteprednol etabonate are effective choices for patients with severe or chronic allergy, but their use must be carefully monitored. As with all steroids, ocular use (especially prolonged use) increases the risks of ocular infection (bacterial, fungal, or viral), cataracts, and ocular hypertension.

To address these issues, partial selective glucocorticoid receptor agonists are being evaluated.[1] These compounds retain the anti-inflammatory effects of corticosteroid agonists but have a reduced spectrum of adverse effects. A number of these compounds are in clinical trials for treatment of inflammation, and one or more of these partial steroids may ultimately be used for ocular allergy in the future.

Like corticosteroids, there is evidence that NSAIDS can be effective alternative treatments for symptoms associated with ocular allergies, particularly the itching that is the hallmark symptom of the disease. One NSAID, ketorolac 0.4%, is FDA-approved for relief of itching associated with allergic conjunctivitis. Despite this, head-to-head studies have shown NSAIDs to be substantially less efficacious than dual-action agents, antihistamine agents, or even mast cell stabilizers.[2,3]

In addition, NSAIDs often cause a stinging or burning upon instillation that can lead to eye rubbing and eventual exacerbation of allergic symptomatology. Although there is good reason to believe that inflammation is a worthwhile therapeutic target, NSAIDs leave much room for improvement in this disease.

The immunosuppressant cyclosporine has been used for therapy of vernal and atopic keratoconjunctivitis (VKC and AKC) for years, but there are few placebo-controlled studies examining its efficacy in these conditions or other, less severe allergic diseases of the eye. Despite this, there is little question that the drug is an efficacious treatment for the most serious forms of allergic keratitis. A 2009 prospective study confirmed this in a large cohort (n=594) of patients with either VKC or AKC.[4]

There are issues remaining with the use of this drug for less severe allergies, however. Formulation has been a huge hurdle, and, as with steroids, a balance between reductions in inflammation without excessive immune-suppression is key to overall therapeutic efficacy.

In addition to improvements to existing drug classes, a handful of new targets for allergy therapy is on the horizon, including protein kinase inhibitors, cytokine antagonists, and immunomodulators. As with any drug development process, establishing reliable end points will be a critical issue for these new allergy therapies.

To focus on treatments that can minimize the persistent aspects of the disease, we have recently tested a new clinical paradigm that combines the traditional allergen challenge model with exposure to adverse environmental conditions of temperature and humidity.[5] Our goal is to establish the techniques that can provide a platform for developing therapies capable of filling the gaps in current treatment options.

Mr Gomes is vice president, allergy, for Ora Inc., in Andover, Mass.

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CONFOCAL VIDEO MICROSCOPY

In this study we also tracked inflammatory responses in real time, using confocal video microscopy of the conjunctiva. This technique provides a continuous picture detailing the immune status of the ocular surface, from initial allergen exposure to recruitment of immune cells, and then finally to clearing of the immune response.

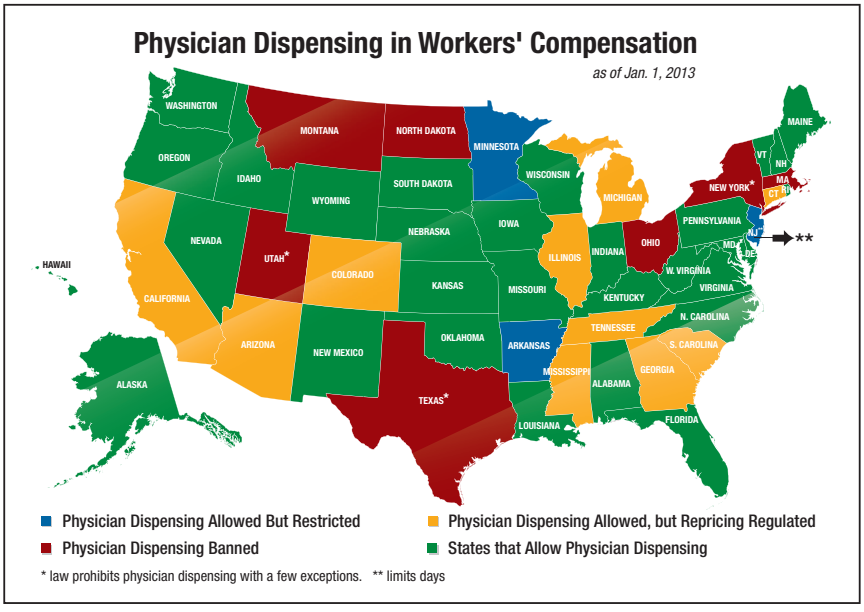
Clearly visible conjunctival vessels are progressively populated with increasing numbers of opaque cells (leukocytes, basophils, eosinophils); these cells eventually adhere to points along the vascular surface, and then enter the surrounding tissue through a process of transient disruption of the vessel integrity or extravasation. At later time points the white cells become less visible as they migrate deeper into surrounding tissues. Quantitative data can be extracted from these video records using standardized, descriptive scales. It is hoped that techniques such as video microscopy will provide the diagnostic guidance needed to find the next generation of ocular anti-allergic agents. ■

REFERENCES

1. Schäcke H, Berger M, Rehwinkel H, Asadullah K. Selective glucocorticoid receptor agonists (SEGRAs): Novel ligands with an improved therapeutic index. *Mol Cell Endocrinol.* 2007;275:109–117.
2. Shulman DG, Amdahl L, Washington C, Graves A.A combined analysis of two studies assessing the ocular comfort of antiallergy ophthalmic agents. *Clin Ther.* 2003;25:1096–1106.
3. Bielory L, Lien KW, Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs.* 2005;65:215–228.
4. Ebihara N, Ohashi Y, Uchio E, et al. A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. J Ocul Pharmacol Ther. 2009;25:365-372.
5. Gomes PJ, Ousler GW, Welch DL, Smith LM, Coderre J, Abelson MB. Exacerbation of signs and symptoms of allergic conjunctivitis by a controlled adverse environment challenge in subjects with a history of dry eye and ocular allergy. Clin Ophthalmol. 2013;7:157–165.

Physician dispensing costs triple that of retail

Fred Gebhart, Contributor



Formulary/Source CompPharma, LLC

Physician dispensing is more expensive than pharmacy dispensing. Sometimes 10 to 20 times more expensive.

That's a key finding from the 2012 Survey of Prescription Drug Management from CompPharma, LLC, a consortium of workers' compensation pharmacy benefit managers (PBMs). Physician dispensing and opioid use are the top 2 cost-drivers of workers' comp spending. Physician dispensing alone accounted for more than 35% of workers' comp drug costs in 2011, up from 28% in 2009.

Physician-dispensed prescriptions typically cost 3 to 4 times what the same prescriptions cost in a retail pharmacy, said Joseph Paduda, president of CompPharma.

"The taxpayer ends up footing the increased profits and bills, because workers' comp is typically first-dollar coverage with no tiers, no copays, and no utilization management," Paduda said.

Florida, which has no restrictions on physician dispensing, paid an average of $565 per workers' comp drug claim in 2010, 38% more than the median for states surveyed.

After Massachusetts banned physician dispensing, the average payment per claim for workers' comp scripts dropped by $289, about 30% less than the median for states in the survey. California saw a significant decrease in prescription drug costs after it tied workers' comp drug reimbursement to the state Medicaid fee schedule.

Most physicians dispense repackaged products, noted Anne Burns, American Pharmacists Association vice president for professional affairs. Repackaging gives drug distributors an opportunity to create a new NDC number. The new NDC number lets physicians sidestep state laws that link workers' comp drug reimbursement to average wholesale price (AWP) by creating new, often inflated, AWPs.

DRIVING UP COST OF CARE

Michael R. Cohen, RPh, MS, president of the Institute for Safe Medication Practices (ISMP), calls physician dispensing a practice that begins with good intentions but has uncertain outcomes. Proponents cite improved patient access to prescription products, convenience, enhanced adherence, and higher rates of generic substitution. ISMP cites safety issues in opposing physician dispensing.

"There is no oversight at all," Cohen said. "The safety aspect should outweigh convenience in most places. These scripts may or may not go through drug use review. Whoever is giving out these meds may or may not check on other drugs and potential interactions. And there could easily be a conflict of interest that puts patients at risk by giving them drugs they don't really need."

Physicians Total Care, which markets dispensing technology to physicians, claims dispensing can produce $20,000 to $100,000 in additional profits per physician per year. Another physician dispensing firm, Automated HealthCare Solutions, spent more than $3.3 million in political contributions in Florida to beat back legislative attempts to curb physician dispensing.

"Those who make policy in our state are aware of the spread between actual acquisition cost and what the same drug costs through a physician who dispenses," said Michael A. Jackson, BPharm, CPh, executive vice president and CEO of the Florida Pharmacists Association. "It is a political debate, not a care debate. It comes down to who has more friends in the state capital." ■

Mr Gebhart is a medical writer based in San Francisco.

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PEER-REVIEWED

Female sexual disorders: Treatment options in the pipeline

Michael L. Krychman, MD
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Abstract

Female sexual problems are best conceptualized from a biopsychosocial perspective that includes biological, psychological, sociocultural, and interpersonal factors. Treatment also follows a biopsychosocial model and options include psychotherapy, pharmacotherapy, physical therapy, and complementary approaches alone or in combination. Only 2 FDA-approved treatments currently exist for female sexual disorders, but a wide range of oral, topical, and SQ formulations are being investigated. This article focuses on promising treatments on the horizon for helping patients with female sexual disorders. (*Formulary*. 2013; 48:113–115.)

Female sexual problems are best conceptualized from a biopsychosocial perspective that includes biological, psychological, sociocultural, and interpersonal factors. Treatment also follows a biopsychosocial model and options include psychotherapy, pharmacotherapy, physical therapy, and complementary approaches alone or in combination.

This article focuses on emerging treatment options for female sexual disorders. Currently, only 2 treatment options for female sexual complaints are approved by FDA: 1) The Eros clitoral stimulator, approved in 2000 for female sexual arousal disorder (FSAD); and 2) conjugated equine estrogen, approved in 2008 for treatment of moderate to severe dyspareunia.

Most of the research and development currently under way in this area is focused on pharmacologic options for treatment of hypoactive sexual desire disorder (HSDD)—the most prevalent female sexual disorder. Treatments primarily involve both steroid hormone and neurohormone mediators. The table provides a glossary of terminology related to female sexual disorders discussed in this article.

Central brain studies have shown that serotonin, norepinephrine, and dopamine are implicated in sexual function. Dopamine agonists and central melanocyte-stimulating hormone (MSH) analogs also are currently being investigated as possible mediators of female sexual function. In addition, estrogen therapy (ET) and testosterone replacement continue to be common treatments in female sexual medicine for vulvovaginal health and HSDD in postmenopausal women, respectively.

Clinicians and patients, however, are still somewhat hesitant to use ET, even locally, because of concerns about systemic risks of local ET. Off-label use of systemic testosterone for HSDD is associated with similar concerns. The following is an overview of investigational treatments of female sexual disorders, including drugs currently in phase 2 or 3 clinical trials and a thermal therapy.

FLIBANSERIN

Flibanserin is a 5-HT(1A) agonist/5-HT2 antagonist for treatment of HSDD. Phase 3 pivotal trials have shown it to be effective, with mild adverse effects including nausea, dizziness, fatigue, and sleeplessness.

In a recent phase 3 trial in premenopausal women with HSDD, Katz and colleagues found that flibanserin 100 mg at bedtime was associated with clinically meaningful and significant improvement in the number of satisfying sexual events (SSE) and the sexual desire domain of the female sexual function index (FSFI).[1] Significant differences also were demonstrated between treatment and placebo on the secondary end points of the Female Sexual Distress Scale-Revised total (FSDS-R total) and distress associated with low desire (FSDS-R item 13). In a trial of postmenopausal women with HSDD, flibanserin 100 mg at bedtime also was associated with clinically meaningful and significant improvement. The coprimary end points were SSE and sexual desire (FSFI-desire domain). Secondary end points for distress (FSDS-R total) and distress associated with low sexual desire (FSDS-R item 13) improved compared with placebo.[2–4] To date, flibanserin has been studied in trials involving approximately 11,000 women.

LYBRIDO AND LYBRIDOS

Lybrido and Lybridos are novel combination drugs that are in development for treatment of HSDD. Lybrido combines testosterone with a phosphodiesterase inhibitor (PDE5 inhibitor) and Lybridos

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combines testosterone with a 5HT(1A) agonist (buspirone). Lybrido is designed for women with HSDD and low motivation, theorized to be a result of a relatively insensitive system for sexual cues. Testosterone is believed to improve desire, whereas the PDE5 inhibitor works to increase genital sensitivity. Because Lybrido is administered sublingually, the time of peak concentration of the PDE5 inhibitor coincides with the 4-hour delay in behavioral effect of testosterone.

Lybridos is designed for women with HSDD who also have sexual inhibition. Testosterone increases sexual motivation, and buspirone counters the sexual inhibition mechanism in the prefrontal area of the brain. As with Lybrido, administration of Lybridos is sublingual. The time frame for the pharmacologic effects of the buspirone coincide with the behavioral window for testosterone administration.[5,6]

Table 1

Glossary of terminology associated with female sexual disorders

Abbreviation	Definition
DHEA	Dehydroepiandrosterone
FSAD	Female sexual arousal disorder
FSDS	Female Sexual Distress Scale
FSDS-R total	Female Sexual Distress Scale-Revised total
FSFI-desire	Female Sexual Function Index-desire domain
GAQ	Global Assessment Questionnaire
HSDD	Hypoactive sexual desire disorder
MCR4 agonist	Melanocortin receptor 4 agonist
PDE5 inhibitor	Phosphodiesterase inhibitor
RF	Radiofrequency
SSE	Satisfying sexual events

Formulary/Source: Michael L. Krychman, MD

LIBIGEL

LibiGel is a low-dose (300 µg) gel formulation of topical testosterone in development for treatment of HSDD in postmenopausal women. In recent phase 3 clinical trials, it did not demonstrate efficacy in primary end points, and the sponsor has announced plans to repeat this pivotal research.[7]

Coprimary end points of the efficacy trials were the change in the total number of days with a satisfying sexual event from baseline and the change in mean sexual desire from baseline. The Data Safety and Monitoring Board also made 9 "unblinded" reviews of all the data in the safety study and allowed the research to continue without changes. No specific safety signal has been observed with respect to cardiovascular disease or breast cancer.[8]

TBS-2: TEFINA

TBS-2 is an intranasal low-dose nasal gel formulation of testosterone. It is being developed to offer women with female orgasmic disorder (inability to achieve orgasm despite adequate sexual stimulation) an on-demand treatment option.

Tefina is expected to have an attractive safety profile, with virtually no androgen-related adverse effects such as acne, growth of facial and body hair, or deepening of the voice that may be associated with other chronic regimens. Moreover, there is no expected risk of skin-to-skin transfer of testosterone to family members with the unit-dose nasal applicator currently under development. A phase 2 trial of Tefina is under way in the United States, Canada, and Australia.[9,10]

ALPROSTADIL: FEMPROX

Alprostadil (prostaglandin E1-PGE1) is a naturally occurring, potent vasodilator that has an important role in regulating blood flow to the female reproductive tract. Alprostadil also potentiates the activity of sensory afferent nerves. Femprox is an alprostadil-based cream intended for treatment of FSAD. Nine clinical studies of Femprox have been completed to date, including a 98-patient, phase 2 US study and a 400-patient, phase 3 study in China. In a randomized clinical phase 3 trial of topical alprostadil 0.4% cream with a skin penetration enhancer, an ester of N,N-dimethylalanine and dodecanol (DDAIP), a 900-µg dose showed significant and clinically relevant improvements in primary arousal success and secondary efficacy outcomes (FSFI) and Global Assessment Questionnaire (GAQ) and FSDS.[11]

APOMORPHINE

Apomorphine is a dopamine agonist that has been used as a subcutaneous (SQ) injection for treatment of Parkinson disease and researched in oral form for treatment of arousal disorder. Research findings have been inconclusive, and apomorphine can be associated with emesis. In a small study of subjective or objective arousal in women with arousal complaints, changes in peak velocity of clitoral hemodynamics were significantly higher in patients given 3 mg apomorphine than in controls.[12] This translated into changes in arousal and lubrication that were also significantly improved in the apomorphine group. The researchers concluded that the medication was beneficial in women with orgasmic prob-

lems or difficulties in the domains of subjective and objective complaints. Incidence of adverse events, which were mostly mild and transient, was low.

MSH ANALOG: BREMELANOTIDE

Bremelanotide is a melanocortin receptor 4 agonist (MCR4 agonist) for treatment of HSDD and FSAD. It is a synthetic analog of a MSH and an agonist that activates the melanocortin receptors MC3-R and MC4-R in the central nervous system. Bremelanotide was initially delivered as a nasal spray. Phase 2 results with that formulation were promising, but development was stopped because of adverse effects on blood pressure.[13] The drug has recently been reformulated in a lower dose for SQ injection and a phase 2b study is under way in premenopausal women with HSDD and FSAD.

INTRAVAGINAL DHEA SUPPOSITORIES

Intravaginal dehydroepiandrosterone (DHEA) is currently under investigation for treatment of vulvovaginal atrophic changes. Preliminary data are encouraging and suggest that this drug can reverse atrophic effects without increasing systemic estradiol levels. Intravaginal DHEA suppositories also may have an effect on HSDD. Phase 3 clinical trials of DHEA are under way, and more data are forthcoming.[14]

OSPEMIFENE

Ospemifene is a novel estrogen agonist and antagonist that has been studied as an oral agent for treatment of vulvovaginal atrophy (VVA) and, therefore, would be effective for VVA-related sexual pain. In phase 3 clinical trials, 826 women were randomized to 30 mg or 60 mg of this unique compound or to placebo for 12 weeks. The 60-mg dose was shown to be effective, well tolerated, and efficacious for vaginal dryness and dyspareunia.[15] No proliferative effects on endometrium were seen, and adverse effects were minimal. The most commonly reported complaint was an increase in hot flashes.[15]

THE VIVEVE PROCEDURE

Viveve (Sunnyvale, Calif.) has developed a monopolar radiofrequency (RF) thermal therapy to improve laxity of the vaginal introitus and sexual satisfaction in women after vaginal deliveries. To assess sexual satisfaction, sexual function, and distress associated with sexual activity, the FSFI and the FSDS-R scales were used in the clinical design. In addition, to discern effectiveness, patient-reported outcome questionnaires (Vaginal Laxity Questionnaire and Sexual Satisfaction Questionnaire) were used. In a pilot study in 24 women aged 25 to 44 years, reverse-gradient RF (energy range, 60 joules [n=3], 75 joules [n=3], and 90 joules [n=18]) was delivered through the vaginal mucosa. No adverse events were reported, and no topical anesthetics were required. Self-reported vaginal tightness improved in 67% of patients at 1 month posttreatment and in 87% at 6 months ($P<0.001$). Mean sexual function scores improved, and FSDS-R score before treatment was 13.6 ± 8.7, declining to 4.3 ± 5.0 at month 6 posttreatment ($P<0.001$). The office-based procedure is well tolerated and has shown excellent preliminary results.[16]

SUMMARY

Only 2 FDA-approved treatments currently exist for female sexual disorders, but a wide range of oral, topical, and SQ formulations are being investigated. The etiologies of female sexual disorders are multifactorial, and a variety of treatment options are necessary to individualize treatment. Development of effective therapies is 1 important step for improving the sexual health of women. ■

REFERENCES

1. Katz M, DeRogatis L, Ackerman R, et al. Efficacy of flibanserin as a potential treatment for hypoactive sexual desire disorder in North American premenopausal women: results of the Begonia Trial. J Sex Med. 2011; 3(suppl 1):153.
2. Simon J, DeRogatis L, Dennerstein L, et al. Efficacy of flibanserin as a potential treatment for hypoactive sexual desire disorder in North American post-menopausal women. *J Sex Med*. 2012;9(suppl 1):23.
3. Goldfischer ER, et al. Continued efficacy and safety of flibanerin in premenopausal women with hypoactive sexual desire disorder (HSDD): results from a randomized withdrawal trial. *J Sex Med*. 2011;8(11):3160-3172.
4. Derogatis L, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET STUDY. *J Sex Med*. 2012;9(4):1074-1085.
5. van der Made F, Bloemers J, van Ham D, et al. Childhood sexual abuse, selective attention for sexual cues and the effects of testosterone with or without vardenfil on physiological sexual arousal in women with sexual dysfunction: a pilot study. *J Sex Med*. 2009;6(2):429-439.
6. van der Made F, Bloemers J, Yassem WE, et al. The influence of testosterone combined with a PDE5-inhibitor on cognitive, affective, and physiological sexual functioning in women suffering from sexual dysfunction. *J Sex Med*. 2009;6(3):777-790.
7. BioSante rises after ending LibiGel safety study. Businessweek.com Web site. www.businessweek.com/ap/2012-09-04/biosante-rises-after-ending-libigel-safety-study. Published September 4, 2012. Accessed October 3, 2012.
8. BioSante Pharmaceuticals announces positive LibiGel phase III safety data review and decision to conclude the safety study [press release]. Lincolnshire, IL: BioSante Pharmaceuticals; September 4, 2012.
9. van Gorsel H, Laan E, Tkachenko N, Dickstein J, Kreppner W. Pharmacokinetics and pharmacodynamic efficacy of testosterone intranasal gel in women with hypoactive sexual desire disorder and anorgasmia. Poster presented at: International Society for the Study of Women's Sexual Health Annual Meeting (ISSWSH); February 19-22, 2012; Jerusalem, Israel.
10. Efficacy and safety of TBS-2 testosterone gel in premenopausal women with acquired female orgasmic disorder. Clinical Trials Identifier: NCT01607658. www.clinicaltrials.gov/ct2/show/NCT01607658.
11. Goldstein I, Bassam D, Frank D, Hachicha M, Fernando Y, Schupp J. Results of a phase 3 clinical trial for female sexual arousal disorder (FSAD) with Femprox, A topical alprostadil 0.4% cream with a novel transdermal delivery technology. *J Sex Med*. 2012;9(suppl 1):22.
12. Bechara A, Bertolino MV, Casabé A, Fredotovich N. A double blind randomized placebo control study comparing the objective and subjective changes in female sexual response using sublingual apomorphine. *J Sex Med*. 2004;1(2):209-214.
13. Levine SB, Brown C, Palace E, Fischkoff S, Schnorrbusch C. Bremelanotide study in pre- and post-menopausal women with female sexual arousal disorder. Poster presented at: ACOG 56th Annual Clinical Meeting; May 3-7, 2008; New Orleans, LA.
14. Labrie F, Archer D, Bouchard C, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause. 2009;16(5);923-931.
15. Bachmann GA, Komi JO. Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause. 2010;17(3):480-486.
16. Millheiser LS, Pauls RN, Herbst SJ, Chen BH. Radiofrequency treatment of vaginal laxity after vaginal delivery: nonsurgical vaginal tightening. *J Sex Med*. 2010; Sep;7(9):3088-3095.

FROM THE LITERATURE

What to do about multidrug-resistant gonorrhea

from Staff Reports

Gonorrhea, caused by the bacterium, *Neisseria gonorrhoeae*, continues to be a major US public health problem in terms of its prevalence as well as the lack of effective treatments available.

Multidrug-resistant gonorrhea is a growing problem that the Centers for Disease Control and Prevention (CDC) has based on the evidence that cephalosporin resistance may be emerging in the United States, according to the February 15, 2013, *Morbidity and Mortality Weekly Report* (*MMWR*).

"Gonorrhea is the second most commonly reported notifiable infection in the United States; >300,000 cases were reported in 2011," according the CDC Grand Rounds. "In the United States, health inequities persist; the incidence of reported gonorrhea among blacks is 17 times the rate among whites, likely because of structural socioeconomic factors."

Ongoing surveillance of gonococcal antimicrobial resistance has been undertaken by the CDC since 1986, with the introduction of the Gonococcal Isolate Surveillance Project (GISP). This system monitors gonococcal antimicrobial susceptibility from urethal *N gonorrhoeae* isolates that have been collected from men at STD clinics. These results help to form gonorrhea treatment recommendations before a major public health problem develops, according to the *MMWR* article.

"Cefiximine minimum inhibitory concentrations (MICs) recently increased, suggesting that the effectiveness of cefixime might be threatened," the authors said. "The percentage of isolates with elevated cefixime MICs (≥0.25 µg/mL) increased from 0.1% in 2006 to 1.4% in 2011."

The populations with higher increases in isolates were seen from men in the western United States and from men who have sex with men, which is the place where the fluoroquinolone-resistant *N gonorrhoeae* was first seen.

In 2011, approximately 12% of the isolates could no longer be treated with penicillin, about 23% could not be treated with tetracycline, and 13% were resistant to fluoroquinolones. With the development of cephalosporin resistance to the bacterium, treatment of gonorrhea has become much more complicated.

CDC currently recommends treatment of gonorrhea at any anatomic site with a single dose of 250 mg intramuscular ceftriaxone, which should then be followed with either one single dose of 1 g of azithromycin or 100 mg of doxycycline orally twice daily for 7 days. CDC also offers 2 alternative treatments for urogenital and rectal gonorrhea:

1) cefixime 400 mg as single oral dose and either azithromycin 1 g as a single oral dose or the doxycycline regimen above.

2) If the patient is allergic to cephalosporins, a single oral dose of azithromycin 2 g can be taken. Patients must return in a week to be tested for a cure, the authors noted.

At the moment, only 1 new antimicrobial is being tested in a clinical study for the treatment of gonorrhea. The National Institutes of Health has provided funding for more than 130 research grants on gonorrhea, including research to identify other targets for antimicrobial development. Unfortunately, a vaccine has not yet been developed, but research on this is in the works. ■

IOM report focuses on impact of counterfeit, substandard drugs

by Tracey Walker

A new Institute of Medicine (IOM) report addresses growing concerns in the global community surrounding the public safety matters of fake and substandard drugs.

"The integrity of the pharmaceutical supply chain continues to be a primary concern in the United States especially in the wake of high-profile problems with the contaminated blood thinner sourced from China, and the ongoing challenges with counterfeit Avastin," said Gary J. Kerr, MBA, PharmD, chief pharmacy officer, president, Mass. Society of Health Systems Pharmacists, in Springfield.

The key recommendations of the IOM report include:

■ The secondary wholesale market in the United States represents a weak point in the distribution system.

"Only wholesalers with accreditation from the National Association of Boards of Pharmacy [NABP] should be licensed to distribute medicines," said IOM Committee Member Pat-

rick Lukulay, PhD, vice president, Global Health Impact Programs. "There is currently no database for states to share information about disreputable wholesalers or pharmacies. FDA and state boards are asked to develop such a database."

■ National medicine registration systems need strengthening to make medicine registration a more efficient process to prevent rogue actors from taking advantage of medicine shortages and putting falsified or substandard medicines in the supply chain.

"In this regard, drug dossiers should adopt a common Technical Document format and regulators should share inspection reports to avoid replication of inspections," said Lukulay, who also serves as director, Promoting the Quality of Medicines Program, a USP/USAID partnership that was established to help ensure the quality, safety, and efficacy of medicines essential to USAID priority diseases.

■ Procurement organizations should follow World Health Organization Quality Management Systems for procurement of pharmaceuticals. "Procurement done properly provides a good layer of protection against falsified and substandard medicines after registration systems fail," Lukulay said.

■ Internet pharmacies pose a challenge to public safety and require stronger accreditation processes.

"Internet pharmacies also are identified as a weak line, presenting challenges to public safety and requiring stronger accreditation processes," Dr Kerr said.

In a press release, FDA Commissioner Margaret A. Hamburg, MD, praised the IOM's efforts and said that "actions and efforts [are] already underway at the FDA, including advancing technology, strengthening global regulatory capacity, strengthening surveillance, developing science-based standards and engaging in global dialogue."

Dr Hamburg also pointed out several related international activities already underway, all aimed at battling substandard, mislabeled, and counterfeit products worldwide.

"For pharmacists, this progress on the international level addressing substandard drugs in the supply chain bears some resemblance to the ongoing work between the states, and the FDA on the subject of sterile compounding," Dr Kerr said. ■

CPOE systems can reduce drug errors by almost half

from Staff Reports

Processing a prescription through an electronic ordering system decreases the likelihood of error on that order by 48%, and averts more than 17 million such incidents in US hospitals in 1 year alone, according to research published online in the *Journal of the American Medical Informatics Association*.

"Medication errors in hospitals are common, expensive, and sometimes harmful to patients," one of the study's authors Lauren Olsho, PhD, senior associate, Abt Associates, told *Formulary*.

"This study is the first to derive a rigorous estimate of medication error reduction in hospitals attributable to electronic prescribing through computerized provider order entry [CPOE] systems using existing evidence from the peer-reviewed literature applied to nationally representative data."

EFFECT OF CPOE ON DRUG ERRORS

Researchers conducted a systematic literature review and applied random-effects meta-analytic techniques to derive a summary estimate of the effect of CPOE on medication errors.

This pooled estimate was combined with data from the 2006 American Society of Health-System Pharmacists Annual Survey, the 2007 American Hospital Association Annual Survey, and the latter's 2008 Electronic Health Record Adoption Database supplement to estimate the percentage and absolute reduction in medication errors attributable to CPOE.

"Our findings suggest that CPOE can substantially reduce the frequency of medication errors in inpatient acute-care settings even at relatively modest levels of adoption and implementation; however, there is still plenty of room for growth. Current HITECH Act incentives to increase health IT adoption and use will likely prevent millions of additional medication errors each year—over 50 million if all orders were processed via CPOE," Olsho said. "More evidence is also needed on the extent to which lower error rates result in reduced harm to patients."

The study was funded by the Agency for Healthcare Research & Quality and carried out by researchers at Abt Associates. ■

FROM THE AMERICAN COLLEGE OF GASTROENTEROLOGY ANNUAL SCIENTIFIC MEETING

Know your options for cost-effective management of HE

by Guy Neff, MD, MBA

Chronic liver disease affects more than 8 million people in the United States. The etiology of chronic liver disease ranges from infections, medications, inheritable disorders, and metabolic- and alcohol-related disease mechanisms. There are numerous liver-related problems as a consequence of chronic liver disease that can culminate into extensive damage, known as cirrhosis. Presently 800,000 to 1 million patients currently suffer from cirrhosis in the United States resulting in more than 30,000 deaths annually.

Of the numerous comorbid complications associated with cirrhosis, overt hepatic encephalopathy (HE), carries an ominous long-term survival, less than 50% at 12 months. HE is reflective of various levels of cognitive impairment and is commonly found in patients with cirrhosis and can lead to an overt event that requires hospitalization to recover.

The economic implications of HE are numerous and marked altered as based upon direct and indirect costs, worsening of patient's and patient's family members quality of life, employment status, and autonomy. One of the most expensive components when measuring cirrhosis economics is HE-related hospital admission and readmissions—up by 70% over the past 8 years. Additionally the cost has increased 80% to $37,598 over the same timeframe, yet the length of stays has stabilized at 6 days.[1]

Hepatologists struggle with the ongoing disease process of cirrhosis while patients await the possibility of liver transplant, the only cure, or likely death. The patients and their families are affected with the day-to-day management of a loved one suffering from alternating stages of cognizance, until transplantation or death.

There are a number of therapeutic medication options to abate HE and the associated memory changes. FDA has approved 3 therapies; neomycin, lactulose, and the most recent, rifaximin. Lactulose has been an effective HE therapy for the past 30 plus years for HE. Recognition of lactulose-related side effects can affect quality of life and compliance, often resulting in poor disease control due to the daily drug dosage adjustments.[2,3] Rifaximin (Xifaxan, Salix) 550 mg is another option that offers patients effective therapy with few, if any, side effects. As a result most patients prefer rifaximin and tend to remain more compliant on therapy, thus requiring less hospitalizations.[4,5]

> Length of hospital stay and hospital readmissions are quickly becoming important economic parameters, including CMS milestones.

Of importance is the combined economic downturn and increased number of patients with cirrhosis forcing physicians to evaluate economic-minded treatment algorithms. The medical community has historically been mindful of drug price and not cognizant of the economics of the entire disease spectrum; direct and indirect costs. Understanding not only drug costs but rather the overall disease process and economic impact has gained much needed attention. Additionally, traditional treatment protocols in all diseases continue to progress toward early disease recognition and intervention. However in patients diagnosed with cirrhosis and suffering from HE, physicians often allow for disease development culminating in a non-surprising poor 1-year survival rate of less than 50%.[6] Thus therapeutic paradigm advances, disease frequency, hospitalizations costs, and disease awareness and prevention, are necessary components to consider when managing any disease process.

Length of hospital stay (LOS) and hospital readmissions are quickly becoming important economic parameters, including CMS milestones. In fact, CMS penalties are in place for readmission and likely forthcoming for patients with cirrhosis. Bundled reimbursements are forthcoming and will force the medical community to become mindful of shortened LOS and reductions in readmissions. During the recent American College of Gastroenterologists (ACG) meeting, numerous retrospective reports demonstrated improvements in various pharmacoeconomic patterns when comparing rifaximin, and lactulose.

Several reports, based upon research work done at Tampa General Hospital, were presented at the ACG 2012, and show the economic importance of preventing readmission and shortening

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FROM THE GASTROINTESTINAL CANCERS SYMPOSIUM

Statins use may reduce mortality in hepatocellular cancer by 30%

by Tracey Walker

Use of statins in hepatocellular carcinoma (HCC) patients may be associated with prolonged overall survival, according to a poster session presented at the recent Gastrointestinal Cancers Symposium, in San Francisco.

Young Kwang Chae, MD, of the University of Texas MD Anderson Cancer Center in Houston, and colleagues researched the association between statin use and the outcome of patients with HCC.

"There has been observational studies that statins may reduce the risk of hepatocellular carcinoma," Dr Chae told *Formulary*. "Also, there is consistent preclinical studies showing anti-tumor effect of statins across different types of cancers."

In a retrospective survival analysis using single institution data, Dr Chae and colleagues followed 644 patients diagnosed with pathologically confirmed HCC from 2000 to 2011. Survival analysis was done using Cox regression model.

DROP IN MORTALITY

In the HCC cohort of patients, those who took statins in addition to local and systemic therapy or surgical resection had a 30% reduction in mortality versus non-statin users (HR=0.7, 95% CI, 0.5-0.9; *P*=.03).

The mean age of the HCC cohort was aged 63.1 years; 73.4% were men, and 65.5% were Caucasians. Approximately 70% were diagnosed at TNM stage 3 and 4, and 52.6% had no evidence of hepatitis B or C virus infection. More than 80% had local and systemic therapy, while 18.3% underwent surgical resection. The median overall survival of HCC patients was higher among statin users than non-users at 25.4 months versus 18.5 months (*P*=.04).

> Even after controlling for various clinical variables, including age, sex, race, staging, HCV, HBV, liver cirrhosis, treatment, alcohol use, and diabetes, statin use was still associated with favorable overall survival in HCC patients.

"Even after controlling for various clinical variables including age, sex, race, staging, HCV, HBV, liver cirrhosis, treatment, alcohol use and diabetes, statin use was still associated with favorable overall survival in HCC patients," the researchers wrote.

"We found that among patients without underlying liver cirrhosis the favorable effect of statins on survival was significant," Dr Chae said.

"Statin use may have beneficial role in patients with hepatocellular carcinoma. However, this finding has to be validated with a prospective study," Dr Chae concluded. ■

LOS. Patients treated with rifaximin 550 mg twice per day were shown in monotherapy or combination therapy (rifaximin and lactulose) to have shortened LOS and reduced readmission frequency. Numerous issues account for the elevated readmission rates related to HE including noncompliance due to therapy intolerance, patient abstinence, in addition to disease progression, resulting in more frequent readmissions to the hospital.

Major cost benefits were found in the group with decreased LOS, shortened time to full diet, and reduced frequency of readmission (*P*=.038). Additionally this group treated with rifaximin benefitted despite having higher MELD (liver transplant score) scores. All in all, the results demonstrate the importance of evaluating economics of the disease spectrum, not limiting the focus to the drug costs but rather to the entire equation that includes all direct and indirect costs. As the healthcare system transforms into a payer system that will include primarily bundle reimbursements, lowering hospitalization frequency, the LOS will result in cost benefits to the hospital and clinical benefits to patients. ■

REFERENCES

1. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. Available at www.hcup-us.ahrq.gov. Accessed February 15, 2013.
2. Bajaj JS, Wade JB, Gibson DP, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *Am J Gastroenterol*. 2011;106(9):1646–1653. Epub 2011 May 10.
3. Sanyal A, Younossi ZM, Bass NM, et al. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Aliment Pharmacol Ther*. 2011;34(8):853–861. Epub 2011 Aug 17.
4. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362(12):1071–1081.
5. Neff G. Pharmacoeconomics of hepatic encephalopathy. *Pharmacotherapy*. 2010;30(5 Pt 2):28S–32S.
6. Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol*. 1999;30(5):890–895.

FROM THE AMERICAN ACADEMY OF OPHTHALMOLOGY ANNUAL MEETING

Pediatric treatments for allergic ocular diseases improve

By Lynda Charters

Recent advances in treatments of allergic ocular diseases are available to help relieve the signs and symptoms in pediatric patients. Stephen C. Pflugfelder, MD, described those treatments in a symposium during the recent annual meeting of the American Academy of Ophthalmology, in Chicago

Dr Pflugfelder

The prevalent allergic conditions in pediatric patients are seasonal and perennial allergic conjunctivitis (SAC/PAC); conditions that are less prevalent in these patients are vernal and atopic keratoconjunctivitis (VKC/AKC).

Dr Pflugfelder explained that in SAC the most recent findings in the early disease of the stage indicate that allergen binds to IgE or conjunctival mast cells and causes degranulation and release of histamine, kinins, prostaglandins, and leukotrienes. In the disease's late phase, mast-cell derived cytokines and chemokines promote leukocyte recruitment and retention, and chronic inflammation.

ALLERGEN-MEDIATED COMPONENT

In VKC, like SAC, there is an allergen-mediated component in which pollens bind to mast cells; there is also an adaptive immune component in which allergens bind to dendritic cells in the conjunctiva that activate type 2 helper lymphocytes. These in turn produce cytokines, such as interleukin (IL)-3, IL-5, and IL-13, that mediate other events. In AKC, thymic stromal lymphopoetin is produced by epithelial and dendritic cells that become inflamed and activate type 2 helper T cells, resulting in production of IL-4, IL-5, and IL-13. The mechanisms of these diseases dictate that inhibition of the T cells is key for therapy.

"A number of therapeutic advances have been achieved, said Dr. Pflugfelder, who is professor, James and Margaret Elkins Chair, Department of Ophthalmology, Baylor College of Medicine, Houston. "We now have an array of antihistamine and mast cell stabilizer drugs, including alcaftadine (Lastacaft, Allergan), azelastine (Optivar, Meda Pharmaceuticals), bepostatine (Bepreve, Bausch + Lomb), epinastine (Elestat, Allergan), ketotifen (Zaditor, Novartis Pharmaceuticals), and olopatadine (Pataday, Alcon Laboratories). These drugs block histamine receptors and stabilize the mast cells, and they have been approved to relieve itching associated with SAC."

In addition, some patients with severe disease require topical steroids that inhibit a variety of mediators that promote chronic allergic disease. The esterified corticosteroid loteprednol etabonate (Lotemax, Bausch + Lomb) has been approved to treat SAC and has an excellent safety profile with prolonged use. Subtarsal triamcinolone 20-mg injections are safe and effective for treating AKC and VKC that are unresponsive to topical therapy.

> "A number of therapeutic advances have been achieved. We now have an array of antihistamine and mast cell stabilizer drugs."

Montelukast (Singulair, Merck & Co.) is an oral leukotriene receptor antagonist that improves the signs and symptoms of VKC in patients with asthma at a dose of 5 mg/day. Burning, tearing, photophobia, and ocular redness improved in 15 days from the start of treatment.

Regarding the key factor of inhibition of T cells, calcineurin inhibitors inhibit activation and cytokine production by CD4+ T cells and significantly improve the conjunctival and corneal disease associated with AKC and VKC. Dr. Pflugfelder noted that cyclosporine C administered topically or systemically is effective for AKC and VKC.

Another treatment approach, prosthetic replacement of the ocular surface ecosystem (PROSE, Boston Foundation for Sight), is a specially designed, fluid-filled contact lens that can protect the cornea from damage resulting from irregular lids and the superior tarsal conjunctiva in patients with vision-threatening VKC and AKC.

"This device shields the cornea from the irregularity of the eye lids and can help patients who have severe corneal epithelial disease," he said.

Tacrolimus, oral cyclosporine, administered as a 0.1% suspension on the ocular surface or in a 0.03% ointment applied to the lid margins or in the conjunctival sac also can effectively treat AKC and VKC.

"We now have an improved understanding of immunopathologic mechanisms in these allergic conditions," Dr Pflugfelder concluded. "Seasonal and perennial allergic conjunctivitis involve an innate mast cell response to allergens; the disorders respond to histamine blockers and corticosteroids. AKC and VKC have adaptive T cell components that require calcineurin inhibitors to treat sight-threatening ocular surface disease." ■

Ms Charters is a freelance medical writer based in Framingham, Mass.

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FROM THE AMERICAN ACADEMY OF OPHTHALMOLOGY ANNUAL MEETING

Anti-VEGF drugs: Not just for retinal pathologies alone

By Lynda Charters

Use of anti-vascular endothelial growth factor (VEGF) drugs may be beneficial in patients with neovascular glaucoma and to control complications after filtration surgeries.

Many questions remain about their applicability during trabeculectomy, however.

Dr Mattox

The anti-VEGF drugs, ranibizumab (Lucentis) and bevacizumab (Avastin), both from Genentech, can be used in patients with neovascular glaucoma to prevent vascularity and to prevent aggressive wound healing and fibrosis after filtering surgeries.

Patients with neovascular glaucoma have an abundance of VEGF in the vitreous and aqueous that stimulates angiogenesis and fibroblast proliferation. Injection of anti-VEGF drugs results in a rapid clinical improvement within days to weeks in iris and angle neovascularization, explained Cynthia G. Mattox, MD, during Glaucoma Subspecialty Day at the recent annual meeting of the American Academy of Ophthalmology, in Chicago.

Important factors to consider, according to Dr Mattox, when using anti-VEGF agents in this patient population is that the drugs have a short half-life, which necessitates additional application of panretinal photocoagulation (PRP) to sustain the treatment effect.

"The 2 primary scenarios in which anti-VEGF [drugs] would be useful are in eyes with mild iris or angle neovascularization and in eyes with severe synechial angle closure resulting from neovascularization," said Dr Mattox, associate professor of ophthalmology, Tufts University School of Medicine, and director, Glaucoma and Cataract Service, New England Eye Center, Boston.

In the former, anti-VEGF drugs can prevent the development of uncontrolled intraocular pressure and in the latter they can "dramatically reduce" surgical complications, such as bleeding, hyphema, and postoperative inflammation.

In addition, anti-VEGF drugs can markedly improve the pain control in these eyes, Dr Mattox noted. Another area in which anti-VEGF drugs may be useful is postoperative filtration surgery complications.

"The main cause of filtration failure is subconjunctival fibrosis," she said. "In these eyes, VEGF stimulates angiogenesis and Tenon's fibroblast proliferation, creates scar formation, and releases more inflammatory cytokines. Anti-VEGF drugs may not cause widespread death of fibroblasts compared with mitomycin C (MMC). The anti-VEGF drugs have a number of theoretical advantages as a tool to modulate postoperative wound healing after filtration surgery."

Unfortunately, few studies have been conducted on the use of anti-VEGF drugs during glaucoma surgery. While anecdotal evidence points to a beneficial effect of anti-VEGF drugs in trabeculectomy, the early studies have not indicated that ranibizumab or bevacizumab is superior to MMC or 5-fluorouracil during trabeculectomy to control IOP or bleb morphology.

Dr Mattox discussed 1 study of Ahmed valve implantation in pediatric patients (60 eyes). The eyes were divided into 3 treatment groups of 20 eyes each: intraoperative subconjunctival bevacizumab (1.25 mg), intraoperative MMC applied to the sclera beneath the plate, and the Ahmed valve alone.

"Compared with Ahmed valve implantation alone in these eyes, there was a significant improvement in the success rate of the blebs 6 months postoperatively," Dr Mattox sad. "The bevacizumab group had a 70% complete success rate. The patients in the MMC group had 8 serious complications of scleral or tube erosions. The Ahmed valve alone group had a 60% complete success rate."

> When using anti-VEGF agents in this patient population, consider that the drugs have a short half-life, which necessitates additional application of panretinal photocoagulation to sustain the treatment effect.

Many questions remain to be answered about the use of anti-VEGF drugs in filtration surgery, such as their superiority over MMC in the long and short term postoperatively. Other problems to be addressed are the study design of such a comparison, the proper delivery method of the anti-VEGF drug being studied, the optimal dose, the time(s) of administration, the frequency and duration of administration, and the potential for combination therapy, Dr Mattox concluded. ■

Ms Charters is a freelance medical writer based in Framingham, Mass.

Disclosure Information: Dr Mattox reports no financial disclosures as related to products discussed in this article.

Diabetes

Selected literature

■ **Degludec.** Mathieu C, Hollander P, Miranda-Palma B, et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): A 26-week randomized, treat-to-target trial with a 26-week extension. ***J Clin Endocrinol Metab.*** **2013 Feb 7 [Epub ahead of print]**.

■ **Degludec.** Meneghini L, Atkin SL, Gough SC, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: A 26-week, randomized, open-label, parallel-group, treat-to-target trial in people with type 2 diabetes. ***Diabetes Care.*** **2013 Jan 22 [Epub ahead of print]**.

■ **Dulaglutide.** Grunberger G, Chang A, Garcia Soria G, et al. Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with type 2 diabetes: dose-dependent effects of glycaemic control in a randomized, double-blind, placebo-controlled study. ***Diabet Med.*** **2012 Oct;29(10):1260–1267. doi: 10.111/j. 1464-5491.2012.03745.x.**

■ **Empagliflozin.** Heise T, Seewaldt-Becker E, Macha S, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. ***Diabetes Obes Metal.*** **2013 Jan 28. doi: 10.1111/dom.12073 [Epub ahead of print]**.

Selected websites

http://www.diabetes.org
American Diabetes Association

http://www.cdc.gov/diabetes
Centers for Disease Control and Prevention Diabetes Public Health Resource

New drugs	Product type/proposed indication	FDA status/notes
empagliflozin Boehringer Ingelheim/Eli Lilly	an oral, sodium-glucose co-transporter-2 (SGLT-2) inhibitor/for the reduction of blood glucose in patients with type 2 diabetes	phase 3
insulin degludec Novo Nordisk	a subcutaneous, ultra-long-acting basal insulin/for the treatment of both type 1 and type 2 diabetes	phase 3 (FDA recently denied the approval requesting additional cardiovascular safety data)
insulin degludec/insulin aspart Novo Nordisk	a subcutaneous, co-formulation of the ultra-long-acting insulin degludec with the rapid-acting insulin aspart/for the treatment of both type 1 and type 2 diabetes	phase 3 (FDA recently denied the approval requesting additional cardiovascular safety data)
insulin degludec/liraglutide Novo Nordisk	a subcutaneous, co-formulation of insulin degludec and the glucagon-like peptide (GLP)-1 receptor agonist liraglutide/for the treatment of type 2 diabetes	phase 3
semaglutide Novo Nordisk	a subcutaneous, GLP-1 receptor agonist/for the treatment of type 2 diabetes	phase 3
albiglutide GlaxoSmithKline	a subcutaneous, GLP-1 receptor agonist/for the treatment of type 2 diabetes	phase 3
dulaglutide Eli Lilly	a subcutaneous, GLP-1 receptor agonist/for the treatment of type 2 diabetes	phase 3
ITCA 650 Intarcia Therapeutics	a miniature osmotic subcutaneous pump that provides continuous delivery of the GLP-1 receptor agonist exenetide/for the treatment of type 2 diabetes	phase 3

The purpose of Drug Watch is to keep drug decision-makers informed about pharmaceuticals in late-stage development. In each column, 1 or more disease areas or drug classes are presented. The column is researched and compiled by **Diana M. Sobieraj, PharmD,** assistant professor, University of Connecticut School of Pharmacy, in Hartford, Conn.

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