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The guidelines, written by Dr. Shawn Ralston (shown here) and colleagues, recommend preventive palivizumab for preemies.

Support, observation best for bronchiolitis

BY TARA HAELLE
Frontline Medical News

The main treatment for bronchiolitis in young children should be support and observation, according to new clinical practice guidelines for diagnosing, managing, and preventing bronchiolitis.

The guidelines apply to children aged 1-23 months and emphasize clinical diagnosis and no medications except nebulized hypertonic saline for infants hospitalized with bronchiolitis, wrote Dr. Shawn L. Ralston, Dr. Allan S. Lieberthal, and their associates (Pediatrics 2014 October 27 [doi:10.1542/peds.2014-2742]). These guidelines update and replace the ones issued by the American Academy of Pediatrics in 2006 (Pediatrics 2006 118:1774-93). The findings are based on a review of the evidence in the Cochrane Library, Medline, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) from 2004 through May 2014.

The most notable change to these updated guidelines, according to Dr. Lieberthal, is the preventive recommendation for palivizumab, which is now not indicated for children born at 29 weeks' gestation or older unless they have hemodynamically significant heart disease

See **Guidelines** • *page 12*

Vitamin D failed to improve ICU patients' outcomes

No differences in 6-month mortality.

BY AMY KARON
Frontline Medical News

High-dose vitamin D did not improve outcomes in critically ill, vitamin D–deficient patients, compared with placebo, researchers reported in JAMA and at the annual congress of the European Society of Intensive Care Medicine.

Although the study was adequately powered, length of stay did not differ between the vitamin D and placebo groups, said Dr. Karin Amrein of the Medical University of Graz (Austria), and her associates. "In the overall cohort, hospital and 6-month mortality rates were numerically lower in the vitamin D_3 group, but these differences were not significant," the researchers said.

A subgroup of patients with severe vitamin D deficiency did have significantly lower hospital mortality when treated with vitamin D, compared with placebo, but the effect "should be considered hypothesis generating and requires further study," the investigators concluded.

The randomized, double-blind, single-center trial enrolled 492 critically ill medical and surgical pa-

See **Vitamin D** • *page 13*

INSIDE

SLEEP STRATEGIES The how, why, and where of sleep telemedicine

BY DR. BARRY FIELDS

We practice in a medical world that physicians of a prior generation could never have envisioned. Not only do we have diagnostic modalities that can yield more rapid and definitive answers for a puzzling patient, but we can also treat and monitor patients who are dozens, if not hundreds, of miles away from our clinic. Sleep medicine is an area ripe for implementation of telemedicine, but building a successful sleep telemedicine program is a tricky endeavor, requiring resources, a clinical demand, and opportunities for such implementation. Despite these challenges, I have found practicing sleep in this

See **Sleep Strategies** • *page 34*

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CHANGE SERVICE REQUESTED

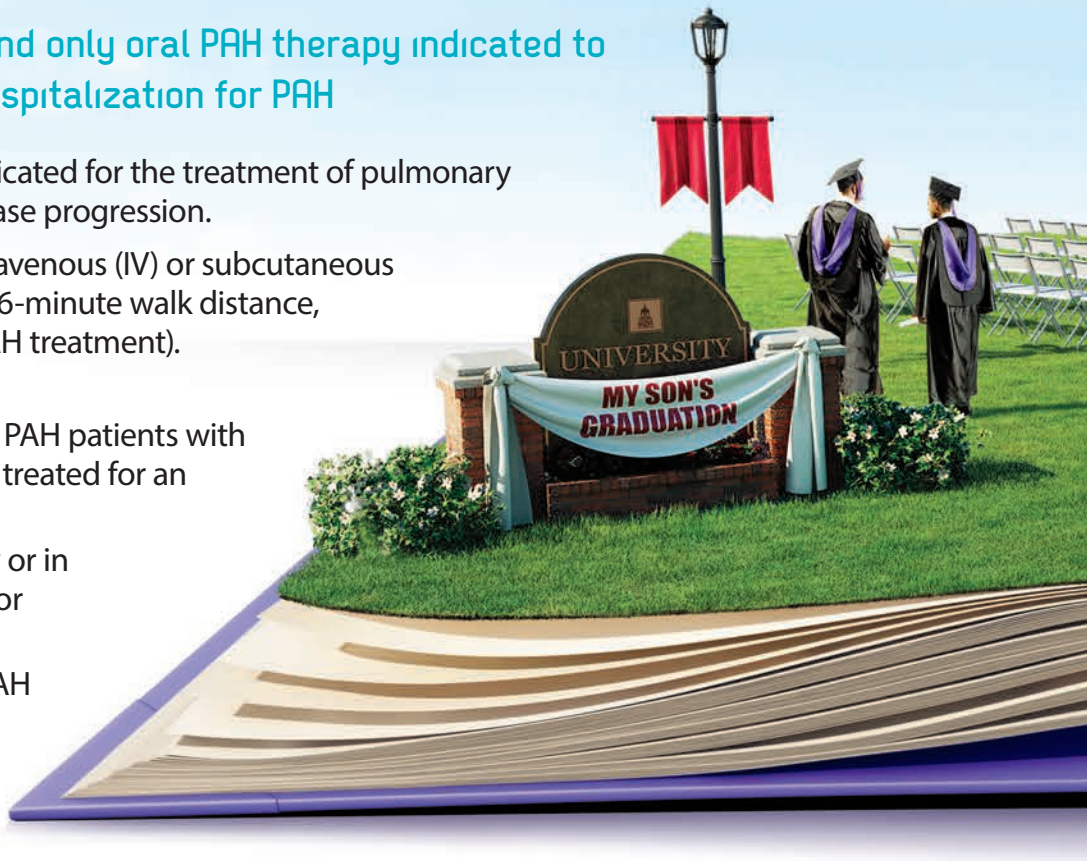
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

HELP HER WRITE FUTURE CHAPTERS

Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
  - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
  - Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).



IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS)**

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT

Patient dramatization

when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS

Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

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macitentan tablets 10 mg

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Opsumit®
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Rx only

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for OPSUMIT® (macitentan). Please review the full Prescribing Information prior to prescribing OPSUMIT.

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm *[see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), Use in Specific Populations (Pregnancy)]*.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Use in Special Populations (Females and Males of Reproductive Potential)]*.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (OPSUMIT REMS Program)]*.**

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

CONTRAINDICATIONS

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus [see *Warnings and Precautions (Embryo-fetal Toxicity)* and *Use in Specific Populations (Pregnancy)*].

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see *Dosage and Administration section 2.2 in full Prescribing Information* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see *Warnings and Precautions (OPSUMIT REMS Program)*].

OPSUMIT REMS Program

For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity [see *Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity),* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

Notable requirements of the OPSUMIT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (Females and Males of Reproductive Potential)*].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 × ULN	3.4%	4.5%
>8 × ULN	2.1%	0.4%

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see *Adverse Reactions (Clinical Trial Experience)*].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see *Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)*].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see *Warnings and Precautions (Embryo-fetal Toxicity)*]
- Hepatotoxicity [see *Warnings and Precautions (Hepatotoxicity)*]
- Decrease in Hemoglobin [see *Warnings and Precautions (Hemoglobin Decrease)*]

Clinical Trial Experience

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

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 2: Adverse Reactions

Adverse Reaction	OPSUMIT 10 mg (N=242)	Placebo (N=249)
Anemia	13%	3%
Nasopharyngitis/pharyngitis	20%	13%
Bronchitis	12%	6%
Headache	14%	9%
Influenza	6%	2%
Urinary tract infection	9%	6%

DRUG INTERACTIONS

Strong CYP3A4 Inducers

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see *Clinical Pharmacology (Pharmacokinetics)*].

Strong CYP3A4 Inhibitors

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see *Clinical Pharmacology (Pharmacokinetics)*]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see *Clinical Pharmacology (Pharmacokinetics)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see *Contraindications (Pregnancy)*].

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Nursing Mothers

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

Pediatric use

The safety and efficacy of OPSUMIT in children have not been established.

Geriatric use

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Females and Males of Reproductive Potential

Females

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see *Boxed Warning* and *Dosage and Administration section 2.2 in full Prescribing Information*].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

Males

Testicular effects: Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see *Warnings and Precautions (Decreased Sperm Counts)* and *Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility*].

OVERDOSAGE

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

Renal impairment: Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

OPSUMIT® (macitentan)

Drug Interactions

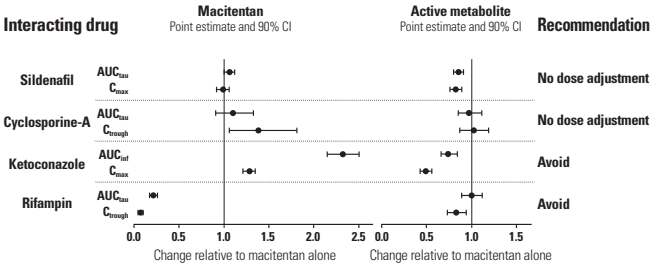
In vitro studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

Effect of other drugs on macitentan: The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

Figure 1



Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see *Drug Interactions (Strong CYP3A4 Inhibitors)*].

Effect of macitentan on other drugs

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies of 2 years' duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

Mutagenesis: Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an *in vivo* micronucleus test in rats.

Impairment of Fertility: Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

Animal Toxicology

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

Manufactured for:
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
ACT20131018

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. October 2013.

Nintedanib, pirfenidone OK'd for pulmonary fibrosis

BY M. ALEXANDER OTTO
Frontline Medical News

The Food and Drug Administration approved two new oral medications for idiopathic pulmonary fibrosis, Boehringer Ingelheim's nintedanib (Ofev) and Roche's pirfenidone (Esbriet).

The drugs significantly slowed the decline of forced vital capacity (FVC), compared with placebo, in phase III testing. They did not significantly reduce mortality. The FDA granted both agents fast track, priority review, orphan product, and breakthrough designations. Both were also approved ahead of schedule, according to the agency.

Each of the drugs should be available for patients within the next 2 weeks, according to their manufacturers.

FDA NEWS

For pirfenidone, already on the market in Europe and Canada, Roche said it plans "a comprehensive patient support program designed to help with access, financial support, and ongoing education."

For nintedanib, Boehringer Ingelheim plans "a comprehensive patient support program that will provide a broad range of financial and nursing support services," called "Open Doors."

In testing, the most frequent serious adverse reactions with nintedanib, versus placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). Pneumonia (0.7% vs. 0.6%), lung cancer (0.3% vs. 0%), and MI (0.3% vs. 0.2%) were the most common fatal adverse events.

The most common side effects of nintedanib were diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight loss, and high blood pressure. Nintedanib is not recommended for patients who have moderate to severe liver problems or are pregnancy class D. Women of childbearing potential should use contraception for at least 3 months after stopping the drug, according to the FDA.

For pirfenidone, the most serious adverse events vs. placebo were liver enzyme elevations (3.7% vs. 0.8%), sensitivity to light or rash (9.0% vs. 1.0%), and gastrointestinal side effects that caused 2.2 % of patients to discontinue treatment, compared with 1.0% of those who received placebo.

The most common side effects of pirfenidone were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, loss of appetite, gastroesophageal reflux, sinusitis, insomnia, decreased weight, and arthralgia.

The FDA warned about use of pirfenidone in patients with severe liver problems or end-stage kidney disease, or in those who require dialysis. Patients taking pirfenidone also must monitor and guard against sun exposure.

Clinical trials of pirfenidone included 1,247 idiopathic pulmonary fibrosis patients. In one with 555 patients, 17% of pirfenidone patients had decline in forced vital capacity of at least 10% after a year, compared with 32% who received placebo, Roche said.

Trials of nintedanib included 1,231 patients. One trial with 513 patients showed a relative reduction in annual forced vital capacity of 52% (–115 vs. –240 mL for placebo) at 1 year, Boehringer Ingelheim noted.

aotto@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: The approval of these two agents for IPF was long awaited and is an encouraging step toward treating this progressive, fatal disease. While the therapeutic results from these medicines are far from a cure or even a complete arrest of progression, they represent the first beneficial options in a disease marred by disappointing treatment attempts in the past. We can be hopeful that this marks the beginning of advancing research and the additional availability of treatments in the future, and that the reported cost of nearly $100,000 a year for one of these agents doesn't complicate and limit treatment of IPF further.

IN THIS ISSUE

Dr. Vera A. De Palo, M.D., MBA, FCCP, is Medical Editor in Chief of *CHEST* Physician.

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Vaccine cut resistant IPD in kids

BY SHARON WORCESTER
Frontline Medical News

PHILADELPHIA – The 13-valent pneumococcal conjugate vaccine introduced in 2010 has led to a substantial reduction in cases of antibiotic-resistant invasive pneumococcal disease, IPD, in children under the age of 5 years, resulting in early achievement of a Healthy People 2020 goal, according to Dr. Sara Tomczyk.

Between 2010 and 2013, 378 cases of antibiotic-resistant invasive pneumococcal disease – or 3.5 per 100,000 children – were identified from 10 Active Bacterial Core (ABC) sites, marking a 62% decrease from the 745 cases (9.3 per 100,000 children) identified between 2005 and 2009, Dr. Tomczyk of the Centers for Disease Control and Prevention reported.

Similarly, cases of antibiotic resistant and multidrug-resistant invasive pneumococcal disease and cases from PCV5-type invasive pneumococcal disease covered by the 13-valent vaccine but not by the previously available 7-valent vaccine decreased by 93% and 86%, respectively. Nonvaccine-type antibiotic-resistant cases increased in incidence from 2.5 to 3.1 per 100,000.

The cases reviewed were from the CDC's ABC surveillance sites, which include about 29 million patients, or 10% of the U.S. population. Isolates were serotyped, and antimicrobial susceptibility testing was performed at a reference laboratory. Bacterial isolates were considered antibiotic resistant if they exhibited intermediate or resistant patterns to at least 1 antimicrobial class, and were considered multidrug resistant if they were resistant to at least 3 antimicrobial classes.

The findings demonstrate that the Healthy People 2020 goal to reduce cases of antibiotic-resistant IPD among children under 5 from 9.3 to 6.0 cases per 100,000 was achieved in 2011 – 9 years early, and they underscore the importance of appropriate antimicrobial use and a sustained high rate of PCV13 vaccination, Dr. Tomczyk said at the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

About 85% of U.S. children have received the recommended four doses.

Dr. Tomczyk had no disclosures.

How ICUs, health providers can prepare for Ebola

ARTICLES BY WHITNEY McKNIGHT
Frontline Medical News

AUSTIN, TEX. – Why would travel restrictions make the Ebola epidemic worse in West Africa and expand its spread to U.S. shores? What can American intensive care units do to prepare, even if they aren't designated Ebola centers? And are there lessons medical professionals and policymakers can apply from the successes and failures of the AIDS epidemic 30 years ago?

In a video interview at CHEST 2014, the annual meeting of the American College of Chest Physicians, Dr. Lewis Rubinson offered answers to those questions and perspectives on the current American response to the Ebola outbreak. Dr. Rubinson recently returned from treating more than 300 Ebola patients in Sierra Leone as a consulting physician for the World Health Organization.

"Honestly, I think if we don't get it under control in the next few months in West Africa, there will be sporadic cases coming back [to the United States] for as long as we can think of," cautioned Dr. Rubinson, director of the R. Adams Cowley Shock Trauma Center at the University of Maryland, Baltimore.

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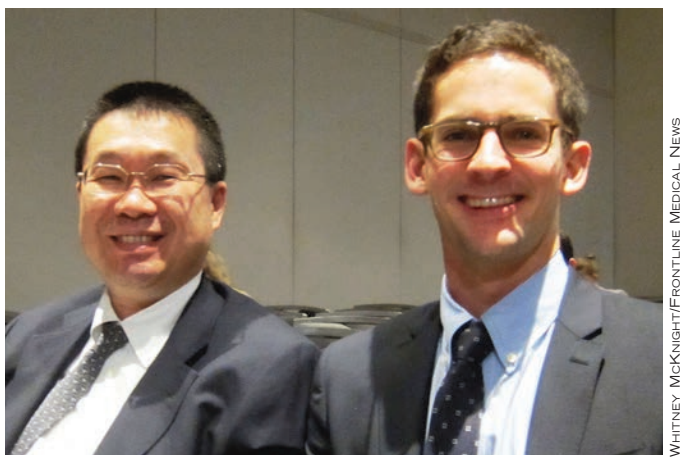
WHITNEY McKNIGHT/FRONTLINE MEDICAL NEWS

Scan the QR code to view our exclusive interview with Dr. Lewis Rubinson, of the R. Adams Cowley Shock Trauma Center at the University of Maryland, Baltimore.

ECMO plus CPR boosts survival seen with CPR only

AUSTIN, TEX. – Extracorporeal membrane oxygenation delivered during cardiopulmonary resuscitation allowed nearly twice as many patients to survive after discharge when compared against typical CPR-only procedures in a small, retrospective study.

"It's no secret that conventional CPR is not terrifically successful," Graham Peigh, a second-year medical student at Jefferson Medical College in Philadelphia, said during the Hot Topics in Pulmonary and Critical Care session at the annual meeting of the American College of Chest Physicians. "Extracorporeal membrane oxygenation [ECMO] gives patients a second chance at life."



WHITNEY McKNIGHT/FRONTLINE MEDICAL NEWS

Mr. Graham Peigh (right) is shown with Dr. Hitoshi Hirose of Thomas Jefferson University Hospital, Philadelphia.

Mr. Peigh and his colleagues retrospectively analyzed 100 ECMO procedures performed on adults at a single teaching hospital during 2010-2013 and found that when ECMO was added to CPR, the survival rate to discharge went from 15% as calculated in a previously reported meta-analysis (J. Gen. Intern. Med. 1998;13:805-16) to 29% (P = .04).

When an arrested patient does not respond to CPR, cannulation through the femoral artery and vein can be combined with compressions to improve chances of survival.

In their analysis, Mr. Peigh and his colleagues found that the survival rate with full neurologic recovery was 29% in the 24 cases in which ECMO was added to conventional CPR after the patients failed to respond to CPR alone.

ECMO support was delivered in a number of scenarios, ranging from acute myocardial infarction to malignant arrhythmia to at least one case each of drug overdose induced cardiac arrest, septic shock, postcardiotomy failure, and acute rejection.

The ECMO support was provided for a mean of 5 days. The mean age for all patients studied was 47 years, and 15 were male. All cases followed a 24-hour hypothermia protocol.

Six of the ECMO-CPR patients died post ECMO of anoxic brain injury, stroke, or sepsis while still in the hospital, but the remaining seven patients (54%) survived after discharge and made full neurologic recoveries. The other 11 died during ECMO-CPR.

Continued on page 10

Insights on genetic testing for anticoagulant therapy

WHITNEY McKNIGHT/FRONTLINE MEDICAL NEWS

To view our exclusive interview with Dr. Steven Hollenberg at CHEST 2014, scan the QR code or visit our video library at chestphysician.org.

AUSTIN, TEX. – Genetic testing holds promise for guiding the prescribing of antiplatelet therapies, particularly clopidogrel, but "we're not there yet" for the use of this testing in clinical practice, according to Dr. Steven Hollenberg, who is the director of the coronary care unit at Cooper University Hospital in Camden, N.J.

Genetic testing for clopidogrel responsiveness "certainly makes good sense, but I think we're going to have to wait for good data" that better inform clinical decision making.

Dr. Hollenberg discussed the implications of the negative results of the ARCTIC trial, which showed platelet function testing with antiplatelet therapy adjustment failed to improve clinical outcomes compared with standard unmonitored thienopyridine therapy in elective percutaneous coronary intervention.

Dr. Hollenberg also analyzed the results of other studies that are relevant to optimal antiplatelet and anticoagulant therapy, including the surprising outcomes of the WOEST trial.

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Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet 2403 mg/day in the three phase 3 trials had a higher incidence of elevations in ALT or AST (≥3× ULN) than placebo patients (3.7% vs 0.8%, respectively). Elevations ≥10× ULN in ALT or AST occurred in 0.3% vs 0.2% of patients in the Esbriet 2403 mg/day group and placebo group, respectively. Increases in ALT and AST ≥3× ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet 2403 mg/day in the three phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Most photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Instruct patients to avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: In clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported by patients in the Esbriet treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% vs 5.8% of patients in the 2403 mg/day group compared with the placebo group, respectively; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event vs 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea (36% vs 16%), rash (30% vs 10%), abdominal pain (24% vs 15%), upper respiratory tract infection (27% vs 25%), diarrhea (26% vs 20%), fatigue (26% vs 19%), headache (22% vs 19%), dyspepsia (19% vs 7%), dizziness (18% vs 11%), vomiting (13% vs 6%), anorexia (13% vs 5%), gastroesophageal reflux disease (11% vs 7%), insomnia (10% vs 7%), weight decreased (10% vs 5%), and arthralgia (10% vs 7%) in the Esbriet and placebo treatment groups, respectively.

Drug interactions: Pirfenidone is metabolized primarily (70% to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1.

The concomitant administration of Esbriet and fluvoxamine or other strong CYP1A2 inhibitors (eg, enoxacin) is not recommended because it significantly increases exposure to Esbriet. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of Esbriet and avoided during Esbriet treatment. If fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of Esbriet (ie, CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during Esbriet treatment.

The concomitant use of Esbriet and a CYP1A2 inducer may decrease the exposure of Esbriet, and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to Esbriet treatment and avoid concomitant use of Esbriet and a strong CYP1A2 inducer.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to InterMune at 1-888-486-6411.

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

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Continued from page 8

During ECMO-CPR, 11 patients died of anoxic brain injury, stroke, metabolic acidosis, bowel necrosis, and family withdrawal of life support. Predictors of ECMO death were a pre-ECMO creatinine level of 1.7 mg/dL (P = .02) and the presence of acidosis (P = .04).

The ECMO survivor cohort also had "encouraging" organ function results, with kidney and liver function remaining essentially unchanged after discharge. "Two of the patients who died of anoxic brain injuries were able to donate multiple organs for transplant," Mr. Peigh said.

Previously reported ECMO data have shown there is at least a 20% increase in survival without notable neurologic effect, compared with conventional CPR (Lancet 2008;372:554-61; Crit. Care Med. 2011;39:1-7).

However, since these data were derived from centers where code teams were available at all times to treat a high volume of cardiac arrest patients, Mr. Peigh said the results – although indicative of the procedure's value – "were not generalizable" to all institutions.

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Comorbidities in opioid users with sleep apnea

BY SHARON WORCESTER
Frontline Medical News

AUSTIN, TEX. – Any association between opioid use and death in patients with sleep apnea cannot be explained by sleep apnea alone, according to a retrospective analysis of data from the prospective observational DREAM study.

In 1,867 patients with moderate or severe sleep apnea who were on an opioid medication, no association was seen between opioid use and severity of sleep-disordered breathing, even with increasing doses, Dr. Husham Sharifi reported at the annual meeting of the American College of Chest Physicians.

Further, when opioid use was analyzed as an unadjusted variable, it was associated with an increase in mortality (odds ratio, 1.53), but this effect was attenuated by adjustment for sleep apnea (OR, 1.52), and was further attenuated – to the point where it was no longer statistically significant – by adjustment for both sleep apnea and Charlson Comorbidity Index (OR, 1.37), said Dr. Sharifi, who was an attending physician at Brigham and Women's Hospital, Boston, at the time of the research. He is now a fellow at Stanford (Calif.) University.

Sleep apnea remained an independent predictor of mortality even after adjustment for opioid use and Charlson Comorbidity Index, he said.

The DREAM study, which stands for Determining Risk of Vascular Events by Apnea Monitoring, includes a well-defined cohort of patients at three Veterans Administration sleep centers who were referred for overnight polysomnography for suspected sleep-disordered breathing between 2000 and 2004.

All patients had an Apnea-Hypopnea Index score greater than 15, indicating moderate to severe sleep apnea, and all were on opioid medication. The patients were followed for between 3 and 10 years, with follow-up ending Dec. 31, 2010.

Opioid use has boomed over the past 20 years – by more than 700%, Dr. Sharifi said. While there does not appear to be a significant impact of opioid use on daytime respiration, there are some limited data suggesting that it may be associated with sleep-disordered breathing.

The findings, though limited by the observational nature of the study and possible selection bias as the DREAM cohort is a referral population, suggest sleep apnea death is likely explained by an increased prevalence of risk factors in patients who take opioids and have sleep apnea.

VITALS

Key clinical point: Comorbid conditions may explain the link between opioid use, sleep apnea, and death.

Major finding: Opioid use was not significantly associated with mortality after adjustment for sleep apnea and comorbidities (odds ratio, 1.37).

Data source: A retrospective analysis of data for 1,867 patients from the prospective DREAM cohort.

Disclosures: Dr. Sharifi reported having no disclosures.

Observation is best for bronchiolitis

Guidelines *from page 1*

or chronic lung disease of prematurity (those born at less than 32 weeks' gestation who needed at least 21% oxygen for their first month). Premature infants who qualify for prophylactic palivizumab should get five monthly doses during respiratory synctial virus season.

VITALS

Key clinical point: Bronchiolitis should be diagnosed clinically and treated with support.

Major finding: Most treatments should not be administered because outcomes are not improved.

Data source: The findings are based on a review of the evidence in the Cochrane Library, Medline, and CINAHL from 2004 through May 2014.

Disclosures: Funding was provided by the American Academy of Pediatrics with travel support from CHEST, the American Academy of Family Physicians, the American Thoracic Society, and the American College of Emergency Physicians for their representatives.

Dr. Lieberthal noted in an interview that several other recommendations state that certain treatments should not be used at all rather than simply not being routinely used. These include albuterol, epinephrine, corticosteroids, chest physiotherapy, and antibiotics.

"Bronchiolitis is a self-limited viral illness," he said. Because it is diagnosed by signs and symptoms, no lab tests, oximetry, imaging, or other tests are needed, and treatment involves only support and observation. "None of the treatments that have been tested have been shown to affect the outcome of the illness," said Dr. Lieberthal, who practices general pediatrics and clinical pediatric pulmonology at Kaiser-Permanente in Panorama City, Calif.

Dr. Ralston noted in an interview that a new recommendation exists for using hypertonic saline to children who are hospitalized for bronchiolitis (although not in the emergency department), but the evidence for it is weak and its therapeutic value limited.

"This medication appears to have a slow onset and to provide a favorable response only in settings where patients are hospitalized for longer than is typical in most U.S. hospitals, as most of the studies were performed outside the U.S.," said Dr. Ralston, a pediatrician at Dartmouth-Hitchcock Medical Center, Lebanon, N.H.

The guidelines also note that clinicians "may choose not to administer supplemental oxygen if the oxyhemoglobin saturation exceeds 90%" in children, although the evidence for this recommendation is also weak. Children should receive nasogastric or intravenous fluids if they cannot maintain oral hydration.

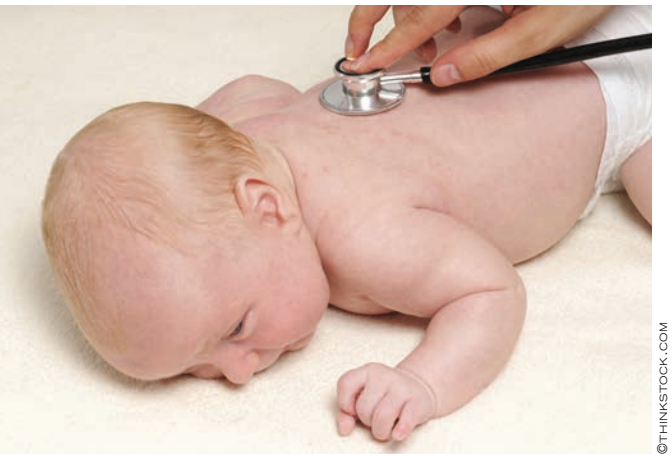
Parents should be advised that children who avoid secondhand tobacco smoke and are exclusively breastfed for at least 6 months have a reduced risk of bronchiolitis.

Further, anyone caring for a child with bronchiolitis should disinfect their hands using an alcohol-based rub or soap and water after direct contact with the child and the child's immediate environment.

Dr. Ralston said that important points stressed in both this recommendation and in the previous one include clinical diagnosis and avoiding exposure to tobacco smoke to reduce children's risk of bronchiolitis.

"This guideline is mostly about what you shouldn't do for the disease since, because of the high volume of the disease, bronchiolitis represents a major area of unnecessary medical intervention in children," Dr. Ralston said.

"We know that the vast majority of children will suffer only side effects from the medications or testing typically used in bronchiolitis care."



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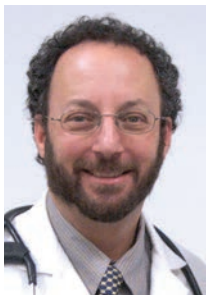
No medications except nebulized hypertonic saline are advised for infants hospitalized with bronchiolitis.

VIEW ON THE NEWS

Dr. Neil Skolnik comments: These guidelines, written with clarity, give incredibly direct and helpful direction on the diagnosis and treatment of bronchiolitis. It is great that these guidelines are coming out now, prior to RSV season.



Bronchiolitis is a clinical diagnosis and these guidelines reaffirm that there is not usually any need for x-ray or laboratory confirmation of the diagnosis.

The guidelines are primarily important for clarifying, based on the evidence, that many commonly used treatments, including albuterol, epinephrine, and steroids are not recommended for treatment of bronchiolitis as they are simply not helpful.

The guidance on administration of palivizumab is also important.

Palivizumab should not be administered in infants with a gestational age of greater than 29 weeks, and it should be reserved for infants in the first year of life who had a gestational age of less than 32 weeks and who had hemodynamically significant heart disease or chronic lung disease of prematurity.

Dr. Skolnik is professor of family and community medicine at Temple University in Philadelphia.

'Real-time' test will speed enterovirus D68 confirmation

BY LUCAS FRANKI
Frontline Medical News

A new lab test for enterovirus D68 is expected to speed up testing and confirmation of cases, according to a press release from the Centers for Disease Control and Prevention.

The new test is a "real-time" reverse transcription polymerase chain reaction and can identify all strains of EV-D68. The previous test could be used to detect almost any enterovirus, but was labor intensive to perform and not conducive to large-scale testing.

Of the 1,200 samples from 45 states sent to the CDC for EV-D68 testing between Aug. 1 to Oct. 10, less than 200 have been tested and about half have tested positive. The CDC now expects to be able to test around 180 samples a day and complete in 7-10 days the testing on samples received since mid-September. The new method will "reduce what would normally take several weeks to get results to a few days," Dr. Anne Schuchat, assistant surgeon general and director of the CDC's National Center for Immunization and Respiratory Diseases, said in the press release.

The new method will 'reduce what would normally take several weeks to get results to a few days.'

DR. SCHUCHAT

As with other enteroviruses, the CDC expects new cases of EV-D68 will decrease in the fall, but faster testing will more accurately show trends of the disease and will help to monitor changes in the outbreak as it winds down, according to the CDC press release.

VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: Enteroviral illness has always been one of the reasons for asthma exacerbations in August and September. Enterovirus D68 certainly was rampant and especially virulent this summer and fall in the United States. If an exact diagnosis is necessary for certain patients, this new lab test will be welcomed.

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Similar mortality at 6 months

Vitamin D *from page 1*

tients with serum vitamin D levels of 20 ng/mL or less. Patients received placebo or vitamin D_3 at a loading dose of 540,000 IU, followed by a monthly maintenance dose of 90,000 IU for 5 months, the researchers said (JAMA 2014 Sept. 29 [doi:10.1001/jama.2014.13204]).

Length of hospital stay averaged 20 days for patients who received vitamin D and 19 days for the placebo group. Among patients who received vitamin D_3, 28% died in the hospital, compared with 35% of the placebo group (hazard ratio, 0.81). Six-month mortality was 35% for the vitamin D_3 group, compared with 43% for the placebo group (HR, 0.78).

Among 200 patients with severe vitamin D deficiencies of 12 ng/mL or less, vitamin D_3 treatment was linked to a significant 44% drop in risk of dying in the hospital, the researchers said (28.6% vs. 46.1% for placebo; HR, 0.56). But length of hospital stay and 6-month mortality rates were similar between the two groups.

Drug maker Fresenius Kabi provided study medication and a grant to support the research. The European Society for Clinical Nutrition and Metabolism and the Austrian National Bank also funded the study. Dr Amrein and one of his colleagues reported receiving lecture fees from Fresenius Kabi.

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: This study demonstrates potential failings of the statistical approach more than the failing of the therapy.

The authors powered the study to detect a 2-day reduction from a 14-day length of stay. I cannot name any other single action – nor combinations of actions – that can reduce the length of stay of critically ill patients by 2 days. I believe the authors must have done so because it would take substantially higher numbers of patients to show smaller reductions in length of stay, and this is a single-center study.

I don't read this as a failure of vitamin D, so much as the authors' failure to adequately consider variability in the outcome of interest and their overestimation of the assumed effect of the treatment. There is enough positive result in this study to consider it a pilot and call for a multicenter trial of higher power.

Simvastatin shows no benefit for ARDS

BY AMY KARON
Frontline Medical News

Simvastatin did not improve clinical outcomes in adults with acute respiratory distress syndrome, compared with placebo in a multicenter, double-blind trial.

Despite positive findings in early-phase studies, large clinical trials have failed to show that statins benefit patients with ARDS, said Dr. Daniel McAuley of Queen's University of Belfast, Northern Ireland, and his associates. The earlier studies used surrogate measures that do not clearly correlate with patient-specific outcomes, the researchers said. "Surrogate outcomes that more closely track patient outcomes need to be identified," they added (N. Engl. J. Med. 2014 Sept. 30 [doi: 10.1056/NEJMoa1403285]).

The multicenter, double-blind trial comprised 540 adults with ARDS

VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: Because of positive findings in early-phase studies, we continue to look for a viable role of statins in the treatment of ARDS. In this study, unlike the preceding SAILS trial, the cause of ARDS was not limited to sepsis. Despite a broader range of clinical diagnoses precipitating ARDS, the outcomes were similar. Currently, there are no data to support the routine use of statins in ARDS of any cause.

from 40 intensive care units in the United Kingdom and Ireland. Patients were randomized to enteral simvastatin or placebo, and the groups did not differ significantly in terms of number of ventilator-free days (12.6 vs. 11.5 days, respectively), days free of nonpulmonary organ failure (19.4 vs. 17.8 days), or 28-day mortality (22% vs. 26.8%). Adverse effects also were similar between the groups.

Continued on following page

Continued from previous page

The researchers recruited a heterogeneous cohort of patients with ARDS resulting from any cause so that findings would be generalizable.

Because recent research suggests that identification of specific phenotypes within ARDS may be possible, future studies "may identify a subpopulation of patients with ARDS who might have a greater response to simvastatin than was observed in our study," the researchers said.

The study was funded by the U.K. Efficacy and Mechanism Evaluation Programme, a joint partnership of the Medical Research Council and the National Institute for Health Research. Dr. McAuley has financial ties to GlaxoSmithKline as well as a patent-pending application related to a novel treatment for ARDS.

FDA clears glucose testing system for critically ill

For the first time, a blood glucose monitoring system has been cleared for use in critically ill hospitalized patients, the Food and Drug Administration has announced.

The device is the Nova StatStrip Glucose Hospital Meter System, which was cleared for use in 2006 for use in hospitals, but not in critically ill patients.

The expanded use applies to indications using arterial or venous whole blood, from patients "in all areas of a hospital with various conditions, including: trauma, cancer, sepsis and infection; cardiac, kidney, neurological, obstetric, gynecological, gastroenterological, endocrine, and lung issues; and people recovering from general or cardiothoracic surgery," the statement said.

The system is manufactured by Nova Biomedical.

–Elizabeth Mechatie

observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see **DRUG INTERACTIONS** and **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.3)].

Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see **OVERDOSAGE**]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see **DOSAGE AND ADMINISTRATION** and **USE IN SPECIFIC POPULATIONS**].

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see **WARNINGS AND PRECAUTIONS**].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **WARNINGS AND PRECAUTIONS**]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **WARNINGS AND PRECAUTIONS**]
- Immunosuppression [see **WARNINGS AND PRECAUTIONS**]
- Hypercorticism and adrenal suppression [see **WARNINGS AND PRECAUTIONS**]
- Growth effects in pediatric patients [see **WARNINGS AND PRECAUTIONS**]
- Glaucoma and cataracts [see **WARNINGS AND PRECAUTIONS**]

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.

Clinical Trials Experience in Asthma

Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment*	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 mcg N = 277 %**	**160/4.5 mcg N =124 %**	**80 mcg N =121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

* All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	**160/4.5 mcg N = 771 %**	**160 mcg N = 275 %**	**4.5 mcg N = 779 %**	**N = 781 %**
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Industry ties may bias neuraminidase inhibitor reviews

BY MARY ANN MOON
Frontline Medical News

In systematic reviews of research on neuraminidase inhibitors for either prevention or treatment of influenza, authors who had ties to drug manufacturers were much more likely to present the evidence as favorable and to recommend the drugs than were authors who had no such conflicts of interest, according to a report published in Annals of Internal Medicine.

"Reviewers with such conflicts of interest were also less likely to address issues with the underlying primary clinical evidence, such as publication bias and the lack of access to comprehensive study data," said Adam G. Dunn, Ph.D., of the Centre for Health Informatics, University of New South Wales, Sydney, and his associates (Ann. Intern. Med. 2014 Oct.6 [doi:10.7326/M14-0933]).

The findings suggest that "further measures may be necessary to ensure that industry collaborations do not compromise the scientific evidence," the investigators noted.

"If the benefits of neuraminidase inhibitors are eventually found to have been inflated, millions of patients will have been unnecessarily exposed to drugs that may be of little or no benefit," the researchers added.

Dr. Dunn and his colleagues observed that reviews of neuraminidase inhibitors had widely divergent conclusions, with some strongly endorsing the agents as influenza prophylaxis or treatment, while others questioned the drugs' safety and efficacy.

To examine whether industry influence may have contributed to these inconsistent conclusions, the investigators analyzed 26 systematic reviews. Thirteen assessed prophylaxis, and 24 assessed treatment; so, there were 37 distinct assessments. Seven of those were Cochrane analyses.

Two of the investigators read redacted copies of the reviews and rated them as favorable or unfavorable toward the use of neuraminidase inhibitors. Those copies showed no identifying information for the authors and no journal name or formatting clues. The agreement between the two investigators was "strong," at 86%.

At the same time, Dr. Dunn and his associates searched for all the financial conflicts of interest for all the authors of these reviews, paying special attention to ties to the pharmaceutical companies that made the neuraminidase inhibitors under review. To do so, they went beyond the affiliations and funding listed in the systematic reviews, examining the authors' personal and institutional websites, as well as disclosure lists provided by GlaxoSmithKline and Roche. They also performed Web searches combining the authors' names, drug names, and manufacturers' names.

Reviewers who had ties to the pharmaceutical industry rated neuraminidase inhibitors favorably in 88% (seven of eight) systematic reviews. In contrast, reviewers who had no such ties rated the drugs favorably

Continued on following page

Continued from previous page

in only 17% (5 of 29) of systematic reviews. That pattern persisted when prophylaxis and treatment were assessed separately.

Regarding prophylaxis, 100% (2 of 2) of the reviews with financial conflicts of interest were favorable, compared with only 9% (1 of 11) of those without conflicts of interest. Regarding treatment, 83% (5 of 6) of the reviews with financial conflicts of interest were favorable, compared with only 22% (4 of 18) of those without conflicts of interest.

In addition, reviewers who had ties to the pharmaceutical industry were less likely to include information about publication bias in their reports (14%, or only 1 of 7), compared with reviewers who had no such ties (79%, or 15 of 19), Dr. Dunn and his associates said.

The study findings indicate that financial conflicts of interest "are associated with product assessments favorable to the sponsors involved," the authors asserted.

Factors that may contribute to biased conclusions include "the design of the review, the patient populations and outcomes assessed, the selective inclusion of primary evidence, [and] the critical appraisal of evidence quality and provenance," the investigators noted. In addition, "the tone, emphasis, and interpretation provided by the authors may also influence the message that is conveyed," they said.

The Australian National Health and Medical Research Council funded the study. Dr. Dunn and his associates reported having no financial conflicts of interest.

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: A couple of decades ago, I received a stethoscope from a pharmaceutical company. The rep arrived one day in my office, and simply gave me a stethoscope, which prominently displayed the name of an antibiotic and the company. I kept the stethoscope in my office as a "spare," and bragged to colleagues that I wasn't biased, because I never prescribed the drug in question. None of us think that we are biased by industry gifts and payment for services. The fact is: We are.

Physicians who are the authors of systematic reviews concerning the use of neuraminidase inhibitors for the treatment of influenza were dramatically more likely to support use if they had industry ties. Investigators had to search authors' websites and curriculum vitae, and industry "sunshine" websites, to find relationships, as authors did not always report such connections. All of us use the information from systematic reviews and guidelines to inform our practice. Can we depend on this information? Only if we as authors are scrupulous about avoiding conflicts of interest and if we correctly report our potential conflicts.

Also required: Developers of evidence-based medicine tools must perform careful conflict of interest assessments of authors.

Cases of smoking-related conditions top 14 million

BY AMY KARON
Frontline Medical News

Cigarette smoking caused at least 14 million cases of major medical conditions among U.S. adults in 2009, investigators reported in JAMA Internal Medicine.

The statistic substantially exceeds a 2000 estimate by the Centers for Disease Control and Prevention of 12.7 million smoking-related conditions among 8.6 million individuals, said Brian L. Rostron, Ph.D., at the U.S. Food and Drug Administration, Silver Spring, Md., and his associates.

The discrepancy most likely stems from the fact that respondents in national health surveys tend to underreport chronic obstructive pulmonary disease (COPD), the leading medical consequence of smoking, the researchers said.

Using spirometry data, they estimated more than 7.4 million cases of COPD attributable to smoking in 2009, which was 70% higher than past statistics based on self-reported data, they said (JAMA Intern. Med. 2014 Oct. 13 [doi:10.1001/jamainternmed.2014.5219]).

For the study, the researchers used data from the 2009 U.S. Census Bureau, the 2006-2012 National Health Interview Survey, and the National Health and Nutrition Examination Survey to calculate the population-attributable risk of major smoking-related conditions among U.S. adults aged 35 years and older. Besides COPD, these conditions included diabetes mellitus, heart attacks, cancer, and stroke.

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Because many respondents to health surveys underreport COPD, previous CDC estimates of smoking-related illness were too low, according to a new study.

This approach yielded an estimate of 6.9 million adults in the United States with at least one major medical condition secondary to smoking (95% confidence interval, 6.5-7.4 million), with a total of 10.9 million conditions identified (95% CI, 10.3-11.5 million), the researchers said.

To better estimate the burden of COPD secondary to smoking, the investigators then used self-reported and spirometry data from the National Health and Nutrition Examination Survey. This analysis identified 14 million smoking-attributable conditions overall, including more than 7.4 million cases of COPD, they said. Notably, COPD was 3.78 times more common among current female smokers than never smokers, and four times more common among male smokers than never smokers, they said.

The results are "generally conservative, owing to the existence of other diseases and medical events that were not included in these estimates," the researchers wrote, adding that "the International Agency for Research on Cancer has concluded, for example, that ovarian cancer, specifically mucinous tumors, is caused by smoking." Current estimates also do not capture the prevalence of cardiovascular surgeries, congestive heart failure, peripheral arterial disease, rheumatoid arthritis, and macular degeneration attributable to smoking, said the investigators.

Descriptions of medical diagnoses were self-reported and therefore might not always be accurate, Dr. Rostron and associates noted. They reported no funding sources or conflicts of interest.

FDA panel: Keep Chantix boxed warning ... for now

BY ELIZABETH MECHCATIE
Frontline Medical News

SILVER SPRING, MD. – The boxed warning about the risk of serious neuropsychiatric effects linked to the smoking cessation drug varenicline should remain on the drug's label, and the need for the warning can be reevaluated when results of a postmarketing safety study are available next year, the majority of a Food and Drug Administration advisory panel decided.

At a joint meeting of the FDA's Psychopharmacologic Drugs and the Drug Safety and Risk Management Advisory committees, 11 of the 18 panelists voted to retain the boxed warning about neuropsychiatric symptoms and suicidality.

Pfizer, which manufactures the nicotinic receptor partial agonist in a tablet formulation as Chantix, is doing a prospective, randomized, double-blind study comparing neuropsychiatric events in 8,000 smokers, with and without a psychiatric history, treated with varenicline, nicotine replacement therapy, bupropion, or placebo. Results are expected in 2015. The company maintained that the boxed warning is no longer justified and can be put in the warnings and precautions section, based on analyses of observational studies and randomized clinical trials that were submitted to the FDA earlier this year.

The warning states that the serious events include but "are not limited to" depression, suicidal ideation, suicide attempts, and completed suicides; and that some cases "may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking." The boxed warning is used for this drug because there is a "serious adverse reaction that can be prevented or reduced in frequency or severity," the FDA said.

Removal of the warning might be seen as an 'endorsement of safety and that has not been demonstrated.'

DR. PERRONE

The panelists cited weaknesses in the observational studies and the meta-analysis.

Six panelists voted to modify the language in the warning, and most recommended that lines about the health benefits of quitting smoking be removed, citing a promotional tone. Several panelists recommended adding sleep disruption and disorders, and recognized adverse events of the drugs.

Dr. Jeanmarie Perrone, director of medical toxicology in the emergency medicine department at the University of Pennsylvania, Philadelphia, who voted to retain the warning, said there was biologic plausibility for these events. Removal of the warning might be seen as "an endorsement of safety and that has not been demonstrated," she said.

The FDA usually follows the recommendations of its advisory panels, which are not binding. Serious adverse events should be reported to MedWatch at www.fda.gov/Safety/MedWatch/default.htm.

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November is PH Awareness Month

Now is the time to make sure your patients receive V/Q* scans

To learn more, visit CTEPH.com and PHAssociation.org/CTEPH

NOVEMBER 18TH IS THE FIRST ANNUAL CTEPH AWARENESS DAY

Join Bayer, the Pulmonary Hypertension Association, and others in celebrating PH Awareness Month

*V/Q=ventilation/perfusion

Pneumonia readmissions dived under QI initiative

BY SHARON WORCESTER
Frontline Medical News

AUSTIN, TEX. – A multidisciplinary intervention, including implementation of a diagnostic scoring system and daily interdepartmental meetings to review cases, significantly decreased readmission rates for patients at a tertiary care center who were discharged with a diagnosis of pneumonia.

VITALS

Key clinical point: A scoring system and multidisciplinary effort improved pneumonia patient readmission rates and diagnostic accuracy.

Major finding: All-cause and pneumonia-related readmission rates declined from 20.7% to 13.2%, and from 10.5% to 3%, respectively.

Data source: A retrospective study of the charts of 463 patients.

Disclosures: Dr. Hussein reported having no disclosures.

From November 2012 to January 2013 – a 3-month period after implementation of the quality improvement (QI) initiative – the all-cause readmission rates among 227 patients discharged with a diagnosis of pneumonia declined by 7.5 percentage points, compared with the all-cause readmission rates among 236 patients discharged during the same period in the prior year, before implementation of the initiative (from 20.7% to 13.2%), Dr. Hussein Hussein, a fellow at the University of Oklahoma Health Sciences Center, Oklahoma City, reported at CHEST 2014.

A similar reduction was seen for pneumonia-related readmissions, which declined from 10.5% to 3% during the same period, said Dr. Hussein, who was with Yale New Haven (Conn.) Hospital, at the time the research was conducted.

Further, after implementation of the scoring system – a modified Clinical Pulmonary Infection Score (MCPIS) calculated based on patient temperature, white blood cell count, sputum cultures, oxygen requirements, and radiographic appearance, which was administered at admission and again at 32 hours – the accuracy of pneumonia diagnoses appeared to improve; the mean MCPIS scores among patients with a discharge diagnosis of pneumonia increased significantly after implementation (from 4 to 6); the proportion of patients considered unlikely to have pneumonia decreased from 42.6% to 3.6%; the proportion considered to probably have pneumonia decreased from 31.9% to 17.9%; and the number deemed likely to have pneumonia increased from 25.5% to 78.6%.

All of the changes were statistically significant, and the improved accuracy of diagnosis was likely a result of provider education that led to increased use of sputum cultures, Dr. Hussein noted.

Pneumonia is the second most common discharge diagnosis among Medicare beneficiaries, and nearly 20% of these patients are readmitted within 30 days at a cost exceeding

$17 billion annually.

"This is why the Centers for Medicare & Medicaid Services is penalizing poor-performing hospitals with high rates of readmission," he said.

The MCPIS was implemented in 2012 as a quality improvement tool. Based on the scores, patients were categorized as unlikely to have pneumonia (score of 3 or less), probably having pneumonia (score of 4-5), and likely to have pneumonia (score of 6 or greater). The daily meetings during which patients admitted with pneumonia were reviewed involved participation of physicians from different medical divisions and representatives from nursing, social work, and continuing care.

The primary goal of these rounds was to ensure timely follow-up after discharge, Dr. Hussein explained, adding that if the diagnosis was felt to be incorrect, the case was discussed with the team that was caring for the patient.

To assess the effects of this intervention, he and his colleagues conducted a retrospective chart review of all patients discharged with a diagnosis of pneumonia during each of the two assessment periods.

Vaccine slashes the odds of flu hospitalizations

PHILADELPHIA – Receiving a flu shot cut the odds of influenza hospitalizations by 56% among older adults during the 2010-1011 flu season, surveillance data show.

Vaccine effectiveness was consistent across all age groups, even among those aged 75 years or older.

"Continued emphasis on the importance of influenza vaccination among older adults is crucial," Dr. Fiona Havers said at ID Week.

She reported on 364 adults, aged 50 years and older, who received a flu shot at least 14 days prior to hospital admission for laboratory-confirmed influenza during the 2010-2011 season. Cases were admitted to one of 11 sites participating in the Emerging Infections Program, now FluSurv-Net, and were matched by age and county to 773 controls.

Cases were significantly more likely than were controls to be of nonwhite race (31% vs. 15%), to be Hispanic (7% vs. 2%), to have an annual income less than $35,000 (52% vs. 33%), to have high school or lower-level education (44% vs. 27%), and to have at least two chronic conditions (72% vs. 36%).

Estimates of influenza vaccine effectiveness in preventing hospitalization was 33% for all ages, 33% for ages 50-64 years, 45% for ages 65-74 years, and 21% for those 75 years and older, reported Dr. Havers of the influenza division of the Centers for Disease Control and Prevention.

After adjustment for age, gender, race/ethnicity, income, education, recent hospitalization, functional status, and chronic medical conditions, vaccine effectiveness estimates were 56%, 64%, 61%, and 57%, respectively.

The investigators also looked at influenza subtype and found that after adjustment, vaccination was associated with a significant reduction in the risk of hospitalizations for influenza A H3N2 (51%) and influenza B (95%).

ID Week comprises the annual meetings of the Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, HIV Medicine Association, and Pediatric Infectious Diseases Society.

–Patrice Wendling

For your patients with chronic obstructive pulmonary disease (COPD) who require maintenance bronchodilator treatment

Help Your Patients Breathe Better With ANORO ELLIPTA

Indication

- ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
- ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol.**
- **The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

ANORO ELLIPTA significantly improved trough (predose) FEV_1 by 167 mL vs placebo (*P*<0.001) at Day 169[1]

A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared the efficacy and safety of ANORO ELLIPTA (n=413) and placebo (n=280), each administered once daily by the ELLIPTA inhaler. The primary endpoint was trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168).[1]

Once-daily ANORO ELLIPTA

The first and only FDA-approved product for patients with COPD combining 2 long-acting bronchodilators in 1 inhaler

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO ELLIPTA (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO ELLIPTA, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic exposure to vilanterol and cardiovascular adverse effects may occur.
- ANORO ELLIPTA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Reference: 1. Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107(10):1538-1546.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA on the following pages.

ANORO ELLIPTA was developed in collaboration with Theravance

ANORO™ ELLIPTA™
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

ANORO™ ELLIPTA™
(umeclidinium and vilanterol inhalation powder)
FOR ORAL INHALATION USE

The following is a brief summary only; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full Prescribing Information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes

ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.

ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists

ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.

5.5 Paradoxical Bronchospasm

As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.

5.7 Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.8 Coexisting Conditions

ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.9 Worsening of Narrow-Angle Glaucoma

ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.10 Worsening of Urinary Retention

ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.11 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*

The following adverse reactions are described in greater detail in other sections:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions With ANORO ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Reaction	Placebo (n = 555) %	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %
Infections and infestations				
Pharyngitis	<1	2	1	2
Sinusitis	<1	1	<1	1
Lower respiratory tract infection	<1	1	<1	<1
Gastrointestinal disorders				
Constipation	<1	1	<1	<1
Diarrhea	1	2	<1	2
Musculoskeletal and connective tissue disorders				
Pain in extremity	1	2	<1	2
Muscle spasms	<1	1	<1	<1
Neck pain	<1	1	<1	<1
General disorders and administration site conditions				
Chest pain	<1	1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than with placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.

12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when

considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.9, 5.10), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ANORO ELLIPTA.

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

Nonteratogenic Effects: *Umeclidinium:* There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA: It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium: It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol: It is not known whether vilanterol is excreted in human breast milk. However, other beta$_2$-agonists have been detected in human milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of ANORO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.2 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for individual components, umeclidinium and vilanterol, as described below.

Umeclidinium: Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vivo* rat bone marrow micronucleus assay, *in vivo* rat unscheduled DNA synthesis (UDS) assay, and *in vitro* Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the *in vitro* mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Asthma-Related Death: Inform patients that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists: Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

Risks Associated With Beta-Agonist Therapy: Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ANORO ELLIPTA was developed in collaboration with Theravance.

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Malpractice premiums remained flat in 2014

BY ALICIA GALLEGOS
Frontline Medical News

Malpractice premiums stayed mostly the same in 2014, with 65% of liability insurance rates steady nationwide, according to the Medical Liability Monitor's annual survey.

Trends of slow lawsuit frequency and low plaintiff payouts contribute to the steady market, said Chad C. Karls, editor of the 2014 Annual Rate Survey and a principal and consulting actuary for Milliman in Brookfield, Wis.

There are large verdicts, "but when we take it across all claims, the vast majority don't have a verdict attached to them," Mr. Karls said in an interview. "The vast majority get settled. "

But unchanging insurance rates can mean misery or relief depending on practice locations. Internists in southern Florida will pay a high of $47,707 for malpractice insurance this year, while those in South Dakota will pay $3,697. Ob.gyns. in the New York counties of Nassau and Suffolk will pay $214,999 in premiums, but in Central California, they will pay $16,240. General surgeons in southern Florida will dish out $190,829 in 2014, while Wisconsin surgeons will pay $10,868.

Premiums increased in some areas. Indiana physicians saw the highest increase at 4.5%.

Nevada doctors saw a 34.8% decrease, the largest drop. Nevada's rate decline is not surprising, said Dr. Warren Volker, trustee-at-large for the Clark County (Nev.) Medical Society and chair of Premiere Physician Insurance Company in Nevada. Doctors there have seen a stable medical liability climate for the last decade, he said. "Our premiums have gone down dramatically, across the board," Dr. Volker said in an interview. He attributed the declines to tort reform in 2002, including a $350,000 noneconomic damages cap in medical malpractice cases. Since then, the number of lawsuits has gone down and competition among liability insurers has increased, he said.

Legal reforms such as Nevada's have contributed to the overall decrease in lawsuits and payout severity across the country, Mr. Karls said. Patient safety initiatives and better risk management within medical practices also have an impact.

Industry analysts have not seen an impact by the Affordable Care Act on malpractice insurance rates, Mr. Karls said. There might be fewer claims if the ACA results in proactive approaches to medical errors and less acute care, but in the short term, more patients covered under the ACA could mean a rise in lawsuits and premiums.

Dr. Volker said he expects the trend of practice mergers and acquisitions to continue as more physicians seek to escape high premium costs and regulatory burdens. "What you're going to see in the hotbeds is more migration," said Dr. Volker, who practices in Nevada, California, Florida, and Arizona. "More doctors [will be] giving up their individual practices and joining larger groups."

The MLM survey, published in October, gathered July 1 data from major malpractice insurers and examined rates for mature, claims-made policies with $1 million/$3 million limits for internists, general surgeons, and ob.gyns.

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On Twitter @legal_med

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: One of the most painful aspects of practicing medicine is paying malpractice insurance premiums. But based on the Medical Liability Monitor's 2014 annual survey, some sunshine has crept into this field, with the finding of flat malpractice premiums nationwide. States such as Nevada credit tort reform legislation with noneconomic damage limits as the reason lawsuits are down and premiums are flat. Also, the consolidation of medical practices with better risk management may have had a positive effect. Still to be determined is the effect of the Affordable Care Act on the frequency of malpractice lawsuits with increasingly more patients getting care from the same number of physicians.

Survey: Many physicians plan to reduce their workload

BY ALICIA GALLEGOS
Frontline Medical News

Nearly 45% of physicians plan to cut back on seeing patients, to take on fewer patients, or to retire within the next 3 years.

Increased workloads, regulatory burdens, and changes to the health care system are drivers of the anticipated career moves, according to a survey of 20,088 physicians commissioned by the Physicians Foundation, a nonprofit research organization.

The 2014 Survey of America's Physicians: Practice Patterns and Perspectives, released by Merritt Hawkins, is based on responses from physicians nationwide from March to June of 2014. The survey found 81% of physicians described themselves as overextended or at full capacity, up from 75% in 2012. Within the next 1-3 years, 18% of doctors said they plan to reduce their hours, 10% plan to seek a nonclinical job, 9% will retire, and 8% plan to reduce the number of patients seen. Also, 39% said they will accelerate their retirement plans because of changes in the health care system.

Twenty-nine percent of respondents gave the Affordable Care Act a C grade as a vehicle for health reform; 21% gave ita D, and 25% issued an F. Just 4% gave the law an A; 22% gave it a B.

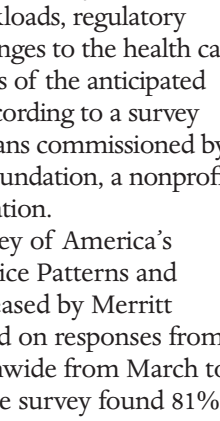
Dr. Walker Ray, vice president of the Physicians Foundation, said the results suggest a looming physician shortage and decreased quality care.

Electronic medical records have been adopted by 85% of physicians, up from 70% in 2012, the survey found. But 46% of respondents said that EMRs have reduced their efficiency, while 24% say the systems have improved their efficiency. Doctors worked an average of 53 hours a week in 2014, the same number of hours reported in 2012. Physicians spent an average of 20% of their time on nonclinical paperwork in 2014.

Fifty-three percent were hospital or medical group employees, up from 44% in 2012 and 38% in 2008. In 2014, 35% said they were independent practice owners, down from 49% in 2012.

VIEW ON THE NEWS

Dr. James A.L. Mathers Jr., FCCP, comments: Most of the numbers cited here are in the ballpark with similar surveys and reflect the impact of policies that limited medical school enrollment and funding for postgraduate training in the 1990s and early 2000s. Statistics show that about 42% of practicing physicians in this country are older than 55 and about 21% are over 65. The HITEC Act and the ACA increased CMS control over Medicare spending but also substantially increased the administrative burden on physicians. This increased burden, both in the costs and time commitment of maintaining a practice, is taking its toll.



CHEST Foundation targets cancer, COPD awareness

November is National Awareness Month for lung cancer and COPD, two of the leading causes of death in the United States. In observance of the month, CHEST Foundation, with grant support, launched three unique campaigns to raise awareness and to educate people living with lung cancer or COPD.

'Lung Cancer Care: A Team Approach' reinforces importance of multidisciplinary team for optimal lung cancer care

www.LungCancerTeam.com

With support from Genentech, a member of the Roche Group, this campaign aims to encourage pulmonologists to engage other lung cancer specialists in providing multidisciplinary, patient-centered care.

LUNG CANCER CARE
A TEAM APPROACH

"Pulmonologists play a key role in diagnosing, staging, and treating patients with lung cancer," said CHEST Medical Director Mark J. Rosen, MD, Master FCCP. "As early intervention improves survival, upon patient diagnosis, we encourage pulmonologists to collaborate with oncologists, thoracic surgeons, and other lung cancer specialists on multidisciplinary efforts that may result in better patient outcomes."

'Tome Un Respiro' provides Spanish-language COPD resources

www.TomeUnRespiro.com

Sunovion Pharmaceuticals Inc. is supporting CHEST Foundation's

TAKE A BREATH
Tome Un Respiro

Spanish-language COPD campaign, "Tome Un Respiro" ("Take a Breath") to reach the US Hispanic community. The foundation's website now features Spanish-language content about COPD symptoms, causes, testing and diagnosis, treatment, and other resources.

"We saw a need to address the lack of Spanish-language COPD resources available to the Hispanic community," said Henry McMillan, Director for Respiratory Marketing at Sunovion Pharmaceuticals Inc. "We were honored to support CHEST to provide COPD information to the Hispanic community through this campaign."

'Live Well' advocates for healthy behaviors in COPD population

www.TakeControlLiveWell.com

"You Can Live Well With COPD" is the overarching message of this campaign made possible through a charitable grant from AstraZeneca. The "Take Control. Live Well." message encourages people living with COPD to adopt healthy lifestyle behaviors for better management of their illness and to improve their quality of life. Clinicians can now find resources on the website for sharing with their COPD patients, including a "COPD Lifestyle Management Tool" and "Living Well With COPD" booklet.

TAKE CONTROL. LIVE WELL. COPD

The campaigns will continue throughout November targeting health-care providers, patients, family members, and caregivers. Visit chestnet.org/Foundation and follow us on Twitter, Facebook, and LinkedIn for more information. All three campaigns support the foundation's goal to make an impact on world health, one community at a time.

Code acute bronchiolitis using ICD-10-CM

Time is short to learn the new diagnosis coding system.

BY RHONDA BUCKHOLTZ, CPC, VICE PRESIDENT OF ICD-10 TRAINING AND EDUCATION AT AAPC

Effective October 1, 2015, we face a massive change: the implementation of ICD-10-CM and ICD-10-PCS. Chest coders must learn a completely new diagnosis coding system. To illustrate the documentation specificity necessary to code in ICD-10, consider the following ICD-10 coding snapshot using a case of an infant diagnosed with acute bronchiolitis.

Chief complaint: *Increased work of breathing*

A 3-month-old girl was brought to the ED by her mother. She became ill about a week ago. Her mother says she was using the vaporizer and thinks it helped. The patient's cough gradually worsened, and 3 days ago it increased significantly, with increased congestion. Two days ago, she was brought to the ED and was given levalbuterol, 2 puffs every 4 to 6 h, but her mother states this did not help. Today, she had difficulty breathing. She gagged and vomited with feedings, had a temperature of 101°, and mother has brought her back.

ROS: Otherwise negative.

Medications: Levalbuterol

Family history: Mother, father, and brother all have asthma. Father smokes in the presence of child.

To illustrate the documentation specificity necessary to code in ICD-10, consider this snapshot using a case of an infant diagnosed with acute bronchiolitis.

Physical examination: Normal vital signs, but patient fussy. Respiratory rate around 36-45 breaths per minute; oxygen saturation, 100% on oxygen at 0.5 L/min; 89% breathing room air. HEENT: normal. Chest: Symmetrical expansion and retractions. Lungs: diffuse crackles bilaterally, some wheezing, no rhonchi. Cardio: 2/6 systolic ejection murmur. Abdomen: normal.

Labs in urgent care today: CBC: WBC of 20.8/cu mm, with 88% neutrophils, 2% bands, and 7% monocytes. Hemoglobin of 10.7 g/dL, hematocrit of 31.3%, platelet count of 715,000 g/dL, urinalysis normal, CRP 2.0. Chest radiograph shows bronchial thickening, unchanged from prior radiograph.

Assessment: Acute bronchiolitis. Patient will be admitted and put on bronchiolitis pathway, providing aggressive suctioning and supplemental oxygen as needed. Due to strong family history of asthma and exposure to tobacco smoke, we will monitor the patient closely.

ICD-10-CM code(s):

J21.9 Acute bronchiolitis, unspecified

Z77.22 Contact with and (suspected) exposure to environmental tobacco smoke (acute) (chronic)

Z82.5 Family history of asthma and other chronic lower respiratory diseases

Rationale: Since the child is diagnosed with acute bronchiolitis, the presence of coughing, difficulty breathing, and posttussive emesis are not coded separately. The family history of asthma and the exposure to smoke are both important to code as they relate to the patient's respiratory issue. You are instructed, when applicable, to use additional codes to identify exposure to tobacco. This exposure is identified in codes representing environmental tobacco smoke, history of tobacco use, occupational exposure to environmental tobacco smoke, tobacco dependence, and tobacco use.

This month in *CHEST*: Editor's picks

BY DR. RICHARD S. IRWIN, MASTER FCCP.
Editor in Chief

Simultaneous Assessment of Hepatocyte Growth Factor and Vascular Endothelial Growth Factor in Epithelial Lining Fluid From Patients With COPD.
By Dr. H. Kanazawa et al.

Laterality Defects Other Than Situs Inversus Totalis in Primary Ciliary Dyskinesia: Insights Into Situs Ambiguus and Heterotaxy.
By Dr. A. J. Shapiro et al.

Long-term Outcomes Following Development of New-Onset Atrial Fibrillation During Sepsis.
By Dr. A. J. Walkey et al.

Detection of Fibroproliferation by Chest HRCT Scan in Resolving ARDS.
By Dr. E. L. Burnham et al.

GIANTS IN CHEST MEDICINE
Richard W. Light, MD.
By Dr. J. H. Newman.

MEDICAL ETHICS
Physician Strikes.
By Dr. S. L. Thompson and J. W. Salmon.

CHEST Clinical Trials Registry is a path to more participation

Are you a clinical trials investigator with unused capacity?

The CHEST Clinical Trials Registry is a free service that connects physicians to information about clinical trials in respiratory disease conducted by participating pharmaceutical companies.

Ongoing groundbreaking research could have a measurable impact on patient care, but a lack of clinical trial participants is significantly slowing research and threatening the development of new treatments. Recruiting and retaining trial participants are the greatest challenges to developing the next generation of treatment options.

Participation in clinical trials provides an opportunity to advance and accelerate medical research and contribute to an improved health outlook for future generations. Use our registry to get immediate information on how you can be involved in a clinical trial.

Learn more at chestnet.org.

Shanghai ahead: Announcing CHEST World Congress 2016

CHEST World Congress 2016 will be held in Shanghai, China, in April 2016. Clinicians specializing in pulmonary, critical care, and sleep medicine from around the world are expected to participate in the event, offered with support of the Chinese Thoracic Society.

Delegates who attend CHEST World Congress 2016 in Shanghai will participate in a variety of educational experiences ranging from hands-on simulation training and keynote addresses to presentations by leading health-care experts and reports on the latest research in chest medicine.

More details coming soon!

Guidelines Methodology

March 12-13

Innovation, Simulation, and Training Center
Glenview, Illinois

Who Should Attend?

Guideline developers at novice or intermediate levels who want to improve their skills and knowledge of guideline development techniques and evidence review methodologies are encouraged to attend. Guidelines implementers, clinical decision tool designers, electronic health record programmers, performance measure developers, medical educators, and health policy makers are also encouraged to attend.

Gain the knowledge, skills, and tools needed to develop evidence-based clinical practice guidelines and consensus statements. In this interactive course, you will:

- Advance your level of expertise in guideline development.
- Learn the difference between evidence-based guidelines and consensus statements and how to apply the different methodologies across a range of clinical topics.
- Learn how to conduct a systematic evidence review and develop evidence-based clinical practice guidelines.

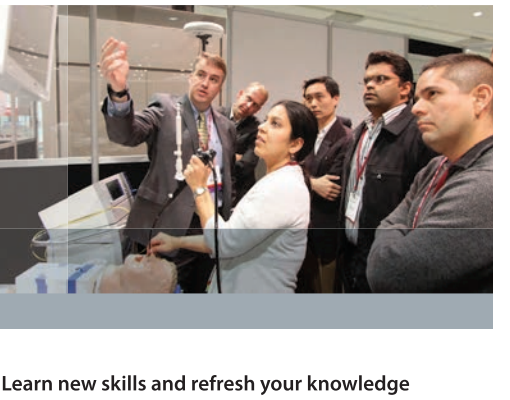
CHEST AMERICAN COLLEGE of CHEST PHYSICIANS

> Register Now
chestnet.org/live-learning

Comprehensive Bronchoscopy With EBUS

February 19-21

Innovation, Simulation, and Training Center
Glenview, Illinois



CHEST AMERICAN COLLEGE of CHEST PHYSICIANS

Who Should Attend?

Pulmonologists, physicians, intensivists, advance practice nurses, respiratory therapists, and physician assistants from critical care medicine, intensive care medicine, and thoracic medicine are encouraged to attend.

Learn new skills and refresh your knowledge with experts in bronchoscopy and procedure-related training.

Attend to experience:

- Hands-on training, including techniques for conventional TBNA, EBUS-guided TBNA, foreign body removal using flexible bronchoscopic techniques, and more.
- Cognitive and skills testing on issues essential to conventional and EBUS-TBNA, EBUS scope and processor knobology, endobronchial brushings and biopsy, managing airway bleeding, and foreign body aspiration.
- Case-based, interactive sessions to encourage honest, individual responses. Group responses will allow faculty to focus on both group and individual learning needs.

> Register Now chestnet.org/live-learning

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Also available at MedJobNetwork.com

PROFESSIONAL OPPORTUNITIES

NORTHERN CALIFORNIA

Established Pulmonary /Critical Care group is seeking BC/BE Pulmonary/ Critical Care associate.

Group also constitutes the local 300-bed hospital's Intensivist Program. Focus on patient care without competition.

Hospital has new state-of-the art ICU, Level II Trauma Center in beautiful Northern Californian "University-City" which has national recognition for its quality of life.

1st year salary guarantee with full partnership in 2nd year without buy-in. Group-owned PFT and Sleep Labs onsite.

90th percentile earnings potential in a family friendly community with distinguished schools, university, and beautiful, sunny location!

H1-B VISA sponsorship available.

Please respond with CV to
brett.crane@enloe.org
or call (530) 332-3959

FLORIDA Pulmonologist/ CCM Physician

Join a respected, established and busy pulmonary group in the Orlando/Winter Park area.

Excellent opportunity for a dynamic BC/BE Pulmonary/Critical Care physician (BC/BE in Sleep Medicine a plus).

We serve one hospital location in addition to our office practice and 4-bed sleep lab. Academic affiliation and teaching opportunities available.

Excellent schools and recreational activities - just minutes away from either coast!

Competitive compensation and benefits. Partnership track available, if desired.

Please email your CV along with any questions you may have to:

MSimmons@PCCFL.com
or fax your CV to 407.539.2786.

Moving? Look to Classified Notices for practices available in your area.

Kentucky

8 person well established Pulmonology group in Louisville, KY seeking pulm/cc/ sleep physician.

Competitive salary, incentive bonus and partnership track.

Opportunity to practice both inpatient/ outpatient pulmonary medicine.

Sleep medicine available but not a must.

Please send CV to:
kvanderpool@kpadocs.com

BRONSON

MICHIGAN

Pulmonologists Needed for Perm and Locums Positions

Bronson Healthcare Midwest has an exciting opportunity for a Board Certified Pulmonologist to join an established pulmonary group. Group provides inpatient consults and maintains an outpatient pulmonary practice, which is located on the campus of Bronson Methodist Hospital. Evening coverage is provided by the Bronson Adult Critical Care service. This would be an employed position offering a competitive salary and bonus structure with comprehensive benefits and relocation.

Bronson Healthcare Midwest in Kalamazoo, Michigan, is also seeking a Board Certified Pulmonologist to provide locums work a week or weekend per month for their established pulmonary group. The group provides inpatient consults and maintains an outpatient pulmonary practice, which is located on the campus of Bronson Methodist Hospital. Evening coverage is provided by the Bronson Adult Critical Care service. This would be an employed contracted position covering travel, meals and malpractice insurance.

Bronson Healthcare Midwest is a subsidiary of Bronson Healthcare Group in Kalamazoo, Michigan. The practice operates within Bronson Methodist Hospital which is an award winning, tertiary healthcare system serving 10 counties in southwest Michigan. With a workforce of more than 7,000, Bronson is one of the area's largest employers. We offer a full range of services from primary care to advanced critical care and have multiple service locations in Kalamazoo, Calhoun and Van Buren counties. Kalamazoo, located midway between Detroit and Chicago, is a diverse university town with highly rated public schools and affordable real estate. Offering art, symphony, theater, museums and year round festivals, there are many activities for the whole family including numerous parks, lakes, fine dining and Lake Michigan is less than an hour's drive away.

For more information about Bronson or Kalamazoo
visit **www.bronsonhealth.com** or **www.kalamazoomi.com**

Interested candidates my contact **Cadace Lee at 269-341-8631** or **leeca@bronsonhg.org**

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CHA Cambridge Health Alliance

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Division Chief Pulmonary/Critical Care with Sleep

Cambridge Health Alliance, a nationally recognized, award-winning health system, is currently seeking a Division Chief for the Department of PUL/CC. Our health care system is comprised of three campuses and an integrated delivery system of primary and care specialty care sites in Cambridge, Somerville and Boston's metro north region.

Ideal candidate will have at least 5 years post fellowship experience with progressive leadership experience. Candidates need to be BC in both pulmonary and critical care medicine and possess additional training in sleep medicine. A strong interest in resident and medical student teaching is required. Excellent clinical/communication skills as well as a strong commitment to serve our multicultural underserved patient population is essential. This position has both inpatient/ambulatory responsibilities and is an excellent opportunity for both personal and professional growth. We offer a supportive and collegial environment with a strong infrastructure, inclusive of a fully integrated electronic medical record system.

Cambridge Health Alliance is a teaching affiliate of Harvard Medical School (HMS) and offers excellent opportunities for research and teaching. This position will have a faculty appointment to Beth Israel Medical Center and HMS commensurate with academic rank. At CHA we strongly encourage women and minorities to apply.

Please forward CV's to **Laura Schofield, Senior Director of Physician Recruitment**, Cambridge Health Alliance, 1493 Cambridge Street, Cambridge MA 02139. **Telephone** (617) 665-3553, **Fax** (617) 665-3553 or via **e-mail**: Lschofield@challiance.org. EOE. www.challiance.org

GR14_194

South Florida Critical Care Medicine - Nocturnist

An MHS representative will be attending the CHEST2014 Conference, visit us at booth#740

About the Opportunity:
Memorial Healthcare System's Intensivist program is expanding. The program is currently comprised of 21 full time intensivists, providing 24/7 ICU coverage at multiple locations within The Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple Board Certifications including infectious diseases, pulmonology, surgery and neuro-critical care. This is a full-time employed position with competitive benefits and compensation package, "sovereign immunity", paid CME, state of the art equipment (including EPIC EMS, digital Olympus bronchoscopes, intubation scopes, Glidescopes, Sonosite Ultrasounds etc)

Qualifications & Responsibilities:
The program is seeking four (4) dedicated critical-care nocturnists to join the existing team. The nocturnists will integrate into the existing operational structure as the program expands to cover additional critical care units. Critical care coverage is provided in 12 hour in–house shifts, 7pm to7am – averaging approximately 15 shifts per month. The successful candidates will have excellent clinical skills, a broad knowledge base in critical care and be dedicated to providing high quality, evidence based care. Candidates must be BC/BE.

About Memorial Healthcare System:
Memorial Healthcare System is a 1,900-bed healthcare system located in South Florida and is highly regarded for its exceptional patient- and family-centered care. Memorial's patient, physician and employee satisfaction rates are among the most admired in the country, and the system is recognized as a national leader in quality healthcare.

About South Florida:
South Florida offers quality of life, is rich in cultural and recreational amenities, and offers pristine beaches, top-rated golf courses, museums and world-class dining. The greater Ft. Lauderdale area offers numerous communities in which to raise a family. In addition, Florida has no state income tax.

To inquire about this opportunity, visit www.memorialphysician.com

Live
Work
Play

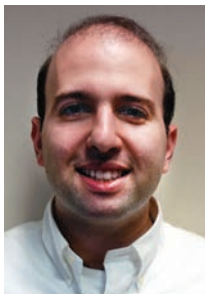
Memorial Healthcare System

The how and where of telemedicine

Sleep Strategies *from page 1*

fashion to be a worthwhile endeavor within our ever-evolving field. Below, I discuss some practical considerations for current and future sleep telemedicine providers.

The backdrop



DR. FIELDS

Telemedicine is defined as "the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status" (www.americantelemed.org). This definition is intentionally broad, allowing a wide range of telecommunication modalities to fall under its umbrella. We can counsel patients over the telephone, review their sleep testing results via secure computer networks, and assess their CPAP data remotely.

Technology now allows us to examine patients from across the country. Clinical video telehealth (CVT) allows real-time video and audio communication between patients and their providers. This patient care technique is already used in other medical specialties, with one meta-analysis showing CVT to be less costly and at least as effective as in-person care (Wade et al. *BMC Health Services Research*. 2010;10[10]:233). While CVT for OSA has not been well-studied, one small trial showed equivalent patient satisfaction and CPAP adherence between in-person and CVT study arms (Parikh et al. *Telemed J E Health*. 2011;17[8]:609). Our challenge – and one that faces any potential telemedicine provider – is translating technologic capability into effective, feasible clinical care.

The resources

The technology needed for sleep telemedicine is readily available with more companies producing related products each passing year. Multiple manufacturers produce CVT consoles with a mounted high-definition camera for patient ("originating site") interviews, mobile cameras for detailed examination (eg, modified Mallampati score assessment), and electronic stethoscopes, with other new accessories constantly being added. Software links a distant-site provider's webcam and computer monitor to the originating site; I have found these interviews to be every bit as effective as in-person encounters. My center's program also employs an originating-site telemedicine technician who obtains vital signs, assists the distant-site provider with a modified physical examination, and troubleshoots any technological issues. Dovetailing nicely with these CVT encounters is remote CPAP adherence and effectiveness monitoring via online "clouds" (eg, Respironics EncoreAnywhere™ and Resmed AirView™). These store-and-forward platforms allow data transmission from CPAP machines to the Internet via modem or Bluetooth technology. Results can be shared with the patient during a CVT follow-up encounter.

Though these technologies for performing sleep telemedicine exist, do we have the economic means to implement them? Telemedicine carries a significant start-up price tag with ongoing maintenance-of-service costs. Major expenses include a telemedicine "cart" or console at the originating site (up to $20,000), fees for space at that site, software to stream data to the provider, and compensation for the telemedicine professional at the originating site (eg, technician or nurse). Lost in-person visit revenue during telemedicine encounters should also be considered, particularly if compensation for these services is insufficient.

Continued on following page

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Continued from previous page

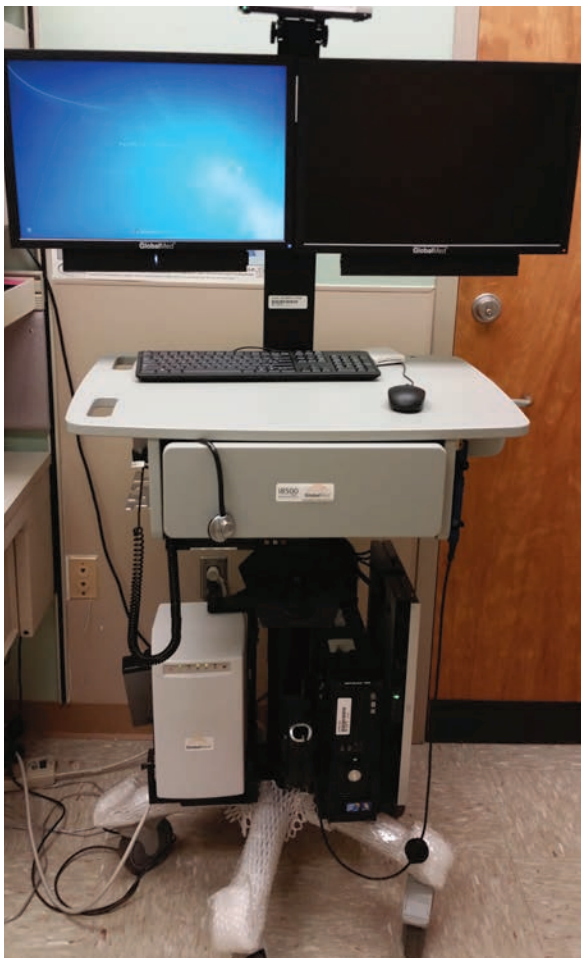
Adequate reimbursement is essential to any telemedicine program's viability. Private insurance coverage rules vary greatly by the originating site's state. As of 2014, only 20 states require insurers to pay for telemedicine visits at parity with in-person visits; each state's status is available online at www.americantelemed.org. State-to-state Medicaid reimbursement also varies significantly, and the National Conference of State Legislatures provides a useful summary of coverage (www.ncsl.org/research/health/state-coverage-for-telehealth-services.aspx). Currently, Medicare only reimburses real-time, CVT encounters when the originating facility is located in a health professional shortage area (HPSA) – defined as having a primary care to patient ratio of at most 1:3,500 – or in a county outside of a metropolitan statistical area as defined by the US Office of Management and Budget. These criteria, in addition to Medicare's excluding home-based telemedicine, can significantly limit the number of patients eligible for telemedical care. You can learn if a particular originating site is eligible for Medicare telehealth coverage through the US Department of Health and Human Services' website, available at datawarehouse.hrsa.gov/telehealthAdvisor/telehealthEligibility.aspx.

The clinical drivers

Is the financial investment and time commitment required to start a sleep telemedicine program balanced by a sufficient benefit to our patients? Available data suggest a robust "yes." New analyses from the Wisconsin Sleep Cohort show OSA to be a burgeoning public health challenge. The prevalence of moderate-to-severe OSA is now 3% among women and 10% among men between 30 and 49 years old. In those between 50 and 70, the prevalence is markedly higher, at 9% of women and 17% of men (Peppard et al. *Am J Epidemiol*. 2013;177[9]:1006). Most of these individuals remain undiagnosed, exposing them to the well-described sequelae of untreated sleep-disordered breathing (Kapur et al. *Sleep Breath*. 2002;6[2]:49).

One factor contributing to OSA underdiagnosis is a lack of access to care; more than 59 million Americans live in medical HPSAs with limited primary care resources. Specialists are generally even harder to access in these areas. While the sleep specialist shortage is difficult to quantify, an Association of American Medical Colleges (AAMC) report found patient-to-pulmonologist and patient-to-neurologist ratios of 24,673:1 and 23,928:1, respectively (AAMC. Physician Specialty Data Book. 2012). Since many of these providers do not practice sleep medicine (and despite some other specialists who do), a large supply-and-demand disparity likely exists. Fortunately, telemedicine is already being used to narrow that gap. Outlying facilities have developed telemedicine agreements with academic medical centers, allowing sleep specialists direct consultation with medically underserved patients (Spaulding et al. *J Telemed Telecare*. 2011;17[7]:346).

Similar challenges exist within the VA system. In my own VA Southeast Network, approximately 48% of veterans live in rural areas. These individuals account for almost 1.5 million outpatient visits annually, contributing to significant wait times and driving up VA travel reimbursement costs. While we have just begun instituting CVT in some specialty clinics (including sleep), other VA Medical Centers have already seen telemedicine's benefits come to fruition. The Richard L. Roudebush VA Medical Center in Indianapolis reports a $662,264 reduction in travel reimbursements in the first 3 years of its multispecialty CVT program, with an average of 90 miles saved per veteran and overall patient satisfaction at 96% (Wennergren et al. *Int J Clin Med*. 2014;5:711).



Courtesy of Dr. Barry Fields

A sleep telemedicine cart features a high-definition camera, video monitors, and a telestethoscope, which allow for real-time interaction with patients.

The opportunities

As previously noted, Medicare's restrictive policies have stifled efforts to expand telemedicine, but a new opportunity may soon lower those hurdles. The proposed Medicare Telehealth Parity Act of 2014 expands coverage to millions of Americans. Over the next 4 years, this legislation would remove geographic coverage restrictions, cover care originating from a patient's home, and add coverage for store-and-forward technologies (eg, PAP download reviews). This could mean the difference between telemedicine viability and insolvency within the private sector. As of this writing, final approval looks like it will wait until after the 2014 midterm elections.

Another opportunity for telemedicine expansion exists secondary to changes in state medical licensing rules. Telemedicine practitioners caring for out-of-state patients often need a medical license in each of those patients' states. These licensing requirements particularly impact sleep medicine; each provider within a group practice who shares sleep study interpretation responsibilities would need additional licensing to serve any out-of-state patients. Fortunately, the Federation of State Medical Boards is finalizing its Interstate Medical Licensure Compact. Scheduled to be released in 2015, the Compact would be a legally binding agreement among states, allowing physicians to have a rapid, streamlined mechanism for interstate licensing approval. While individual state governments would need to enact the Compact, it was recently touted as "herald[ing] a major reform in medical licensing" (Steinbrook et al. *JAMA*. 2014;312[7]:695).

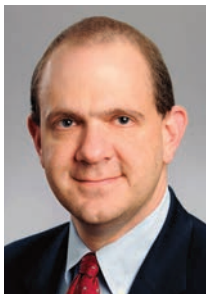
Concluding remarks

Sleep telemedicine is in its infancy, and significant growing pains remain. There is little precedent to chart its course, and even less research to inform its implementation. Nevertheless, existing resources, clinical drivers, and growth opportunities only heighten my conviction that it will serve an important role in our growing field.

Dr. Fields is Assistant Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care, Emory University; and Staff Physician, Division of Sleep Medicine, Atlanta Veterans Affairs Medical Center, Atlanta, Georgia.

EDITOR'S NOTE

This month in Sleep Strategies, Dr. Fields discusses what may be one of the most important technological advances in the management of sleep apnea in quite some time. Patients often ask me about new advances in CPAP machines or interfaces that will make their therapy easier to use; the reality is that only a small minority of patients will benefit meaningfully from the new devices, and the recently-developed CPAP masks are not reliably better than the ones we have been using for years. Telemedicine, on the other hand, has the possibility of being a game-changer, allowing us to diagnose and monitor patients with sleep apnea who had previously been inaccessible due to distance or immobility. Combined with the availability of home sleep testing and adherence monitoring databases, we may soon enter an era in which sleep providers can treat a greater number of patients more rapidly and reliably than is currently feasible.



DR. SCHULMAN

Adoption of telemedicine by sleep apnea practices will not be without its challenges. In an era of shrinking remuneration for sleep specialists, the start-up costs are going to be a major impediment to implementation, and insurers will need to commit to compensating us for time spent on clinical care, even if we are unable to physically touch the patients we are managing. However, given the growing imbalance between sleep apnea prevalence and the availability of qualified sleep-medicine providers, telemedicine may be just the tool we need to keep the ramifications of untreated sleep apnea at a greater distance from our patients.

Dr. David A. Schulman, FCCP
Section Editor

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