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NICK PIEGARI/FRONTLINE MEDICAL NEWS

Harvard intensivist Zara Cooper says bereavement care needs to extend to relatives, caregivers, and medical providers as well.

Palliative care is not just for the dying

BY SHERRY BOSCHERT
Frontline Medical News

SAN FRANCISCO – Palliative care is not just for the dying.

Understanding that premise is the first step to integrating palliative care into intensive care units, Dr. Zara Cooper said. Palliative care treats patient illness and can be delivered concurrently in the ICU with curative care that treats disease.

As options for curative treatment decrease, the role of palliative care may increase and does not stop at the patient's death. "It's important that we provide ongoing bereavement support not only to family members and survivors but also to caregivers and members of our medical team," added Dr. Cooper, an assistant professor of surgery at Harvard Medical School and a surgical intensivist at Brigham and Women's Hospital, Boston.

Getting intensive care colleagues to agree on a definition of palliative care is the first barrier to integrating palliative care into an ICU, Dr. Cooper said at the Critical Care Congress, sponsored by the Society for Critical Care Medicine. She paraphrased the World Health Organization's definition by saying, "Palliative care makes patients

See **ICU** • *page 10*

Aldosterone agonists earn new respect in HF guidelines

Cuts seen in hospitalizations, mortality.

BY BRUCE JANCIN
Frontline Medical News

SNOWMASS, COLO. – The latest heart failure guidelines from the American College of Cardiology/American Heart Association place a new emphasis on aldosterone antagonists as a central aspect of the management of symptomatic or previously symptomatic heart failure with reduced ejection fraction – while underscoring important caveats to their use.

Aldosterone antagonist therapy earns the strongest possible designation in the guidelines: a Class I/Level of Evidence A recommendation. This is based on data from multiple randomized trials showing that, used appropriately, these agents result in a 30% relative risk reduction in mortality and a 35% reduction in the relative risk of heart failure hospitalization, with a number needed to treat for 36 months of just six patients to prevent one additional death. Those figures place the aldosterone antagonists on a par with the other Class I/A heart failure medications – beta-blockers, ACE inhibitors or angiotensin receptor blockers, and hydralazine/isosorbide dinitrate in African Americans

See **Guidelines** • *page 9*

Low vitamin D – poor ICU outcomes

BY PATRICE WENDLING
Frontline Medical News

NAPLES, FLA. – Vitamin D deficiency is common in critically ill trauma patients and portends worse outcomes, a retrospective study suggests.

Among 200 trauma patients with available vitamin D levels, 26% were vitamin D deficient on ICU admission.

"These patients have a higher APACHE II score, have a longer ICU stay, and will likely be hospitalized greater than 2 weeks," Dr. Joseph Ibrahim reported at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

Long known to be essential for bone development and wound healing, recent studies have demonstrated that vitamin D deficiency is

See **Outcomes** • *page 14*

INSIDE

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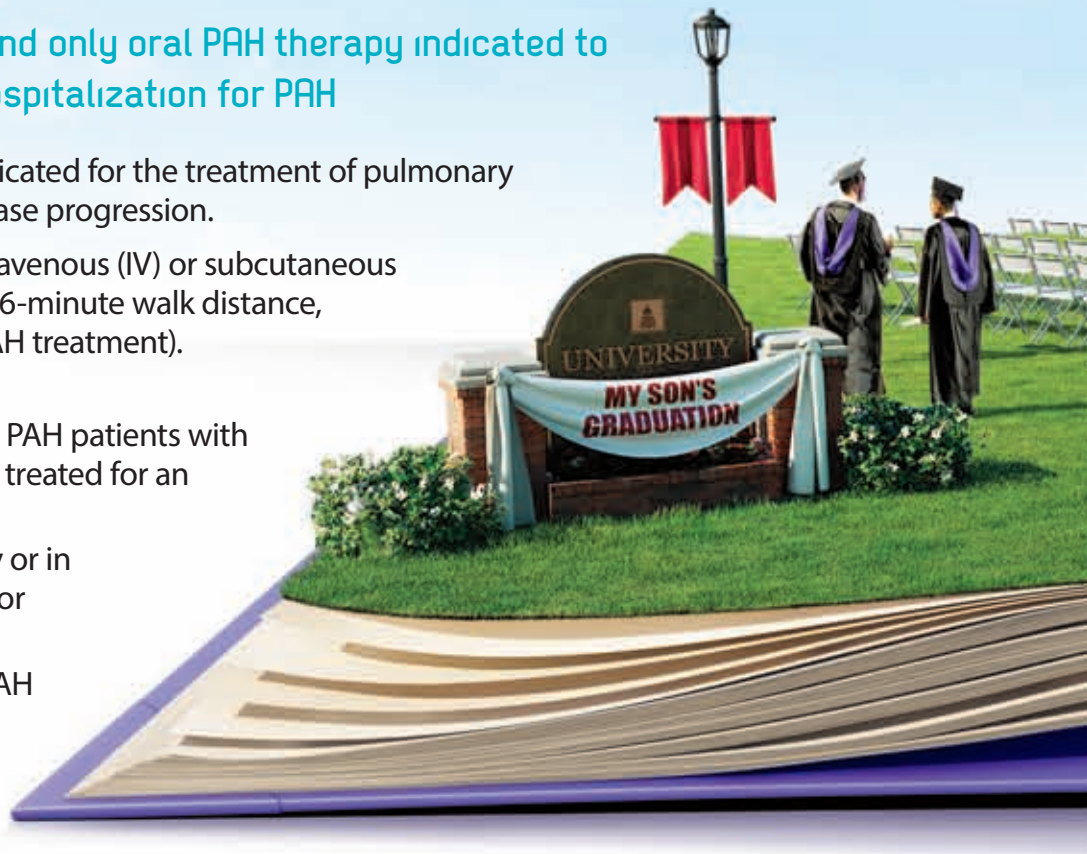
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

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.

FUTURE. FORWARD. | Opsumit®
macitentan tablets 10 mg

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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

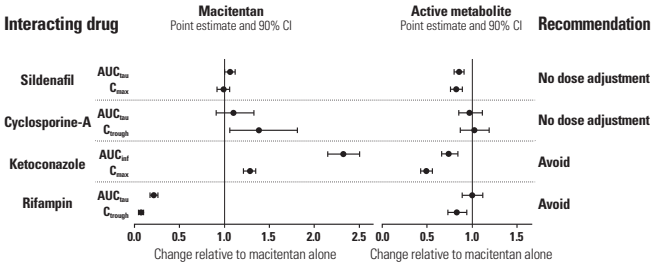
In vitro studies

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.

Sublingual therapy arriving for grass allergy

BY BRUCE JANCIN
Frontline Medical News

KEYSTONE, COLO. – Sublingual immunotherapy is finally coming.

Allergy therapy using rapidly dissolving oral tablets instead of subcutaneous injections has been approved in Europe for years. With Food and Drug Administration approval of sublingual immunotherapy tablets for the treatment of grass and ragweed allergies considered highly likely later this spring, the expectation is that patients, their referring physicians, and allergists will have many questions about this game-changing therapeutic innovation.

Dr. Harold S. Nelson, who closely follows developments in the field, provided answers and analysis at a meeting on allergy and respiratory diseases sponsored by National Jewish Health.

Among his key points:

► The effectiveness of sublingual immunotherapy (SLIT) for allergic rhinitis and allergic asthma is now thoroughly established. So are the optimal dosing regimens: SLIT tablets are dosed once daily at 30 times the optimal subcutaneous immunotherapy (SCIT) once-monthly maintenance dose. In other words, over the course of a month, a patient on SLIT will take a roughly 30 times greater dose of grass or ragweed allergen than will a patient on SCIT.

► SLIT, like conventional subcutaneous immunotherapy, is disease-modifying therapy, which prevents new sensitization and progression to asthma.

► SLIT for grass allergy will be approved for patients aged 5-65, while SLIT for ragweed will receive an indication for 18- to 65-year-olds.

► The optimal duration of SLIT is 3-4 years, which typically produces 7-8 years of persisting benefit before retreatment is needed.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► SCIT results in faster clinical improvement than does SLIT. And at least through the first 12-15 months, SCIT also appears to be significantly more effective.

► The big advantages SLIT offers over SCIT are convenience and safety. Although in U.S. clinical trials 1 in every 200-300 SLIT-treated patients experienced mild systemic reactions – typically with the first dose – no fatal or near-fatal anaphylactic reactions have occurred. That's why SLIT will be approved for at-home use after a first in-office observed dose. However, the FDA will mandate that SLIT prescriptions be accompanied by co-prescription of an epinephrine autoinjector, according to Dr. Nelson of National Jewish Health in Denver and professor of medicine at the University of Colorado at Denver.

Once SLIT products win FDA approval, the therapy will get a CPT code and become, for the first time, a billable treatment – a most welcome development. But Dr. Nelson emphasized that SLIT's approval will also create a new dilemma for physicians and their many patients with multiple allergies, say, to trees, dogs, and molds in addition to grasses or ragweed.

"Most of the companies have no plans to take SLIT beyond the standardized extracts, which means grass, ragweed, house dust mite, and cat. … And it seems unlikely that anyone is going to put a patient on tablets and injections at the same time. So it's a decision that will have to be made for every patient: whether the ability to treat grass and ragweed, and later, house dust mite and cat, is sufficient for that patient. Because if it's not, then probably the patient is still a candidate for SCIT," Dr. Nelson said.

The strategy of the companies developing SLIT is not that oral therapy is supposed to be a replacement for SCIT, but rather that it provides an immunotherapy option for patients who currently don't receive it because they balk at the inconvenience of monthly in-office injections, he continued.

"The idea is that if these people are told, 'You can just take a tablet at home,' they'll opt to get at least their allergies to grass and ragweed treated," Dr. Nelson explained.

In a soon-to-be-published report, Dr. Nelson has reviewed 11 random-

Continued on following page

IN THIS ISSUE


Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of *CHEST Physician*.

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Continued from previous page

ized head-to-head-comparison studies of SLIT versus SCIT and found them consistently uninformative. Most often, the deck was stacked against SLIT because it was given only three times per week and/or in too-low doses. In his view, there is only one enlightening comparative study, a recent randomized trial in which 40 Danish patients allergic to grass pollen received optimally dosed SLIT, SCIT, or neither for 15 months, with the same company's standardized injectable and tablet Timothy grass preparations being used.

After 15 months, both treatments were effective, clinically as well as immunologically, compared with the no-treatment controls, with the benefits becoming significant in the first 1-3 months. However, the improvements in IgG4, IgE-blocking factor, facilitated antigen presentation, and the basal activation test were generally twice as great in the SCIT group. Moreover, the symptomatic response to nasal challenge – the only measure of clinical response utilized in the study – was significantly better than in controls only with SCIT (Clin. Exp. Allergy 2014;44:417-28).

The effectivenss of sublingual immunotherapy for allergic asthma is now thoroughly established.

DR. NELSON

"This is the best comparative study we have, and it may be the best we'll get. Here both treatments are being given optimally, and it's very clear that at least in the first year, SCIT beats SLIT. It looks as though SLIT is trying to catch up late but doesn't quite get there through 15 months," Dr. Nelson said.

Of note, an analysis of seven phase III clinical trials totaling nearly 2,700 adults and children showed that roughly half of them experienced transient local adverse reactions to grass SLIT.

Grass allergies are the most common seasonal allergies in the United States. The three standardized SLIT products under FDA review, all of which have been approved in Europe for years, are Grastek, a Timothy grass extract; Ragwitek; and Oralair, a five-grass product developed by the French company Stallergenes. Oralair, to be marketed in the United States by Greer, contains Timothy grass allergen as well as extracts of four other temperate pasture grasses. Of note, Bermuda and Bahia grasses, common causes of seasonal allergy, aren't included in Oralair or Grastek.

The companies have pursued different dosing strategies. ALK recommends taking Grastek continuously year-round. Stallergenes recommends starting Oralair a few months before the start of grass allergy season and stopping when the pollen season is over (J. Allergy Clin. Immunol. 2011;128:559-66).

Dr. Nelson's prediction that these three SLIT products are headed for FDA approval this spring stems from enthusiastic endorsements by the agency's Allergenic Products Advisory Committee. The SLIT grass allergy products were recommended unanimously, and the ragweed SLIT also received a strongly favorable vote.

He reported serving as a consultant to Merck, Pearl Therapeutic, and Circassia.

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Advanced clinical providers proving their mettle

BY PATRICE WENDLING
Frontline Medical News

NAPLES, FLA. – Complication rates are similar for advanced clinical practitioners and resident physicians performing key routine procedures in the ICU or trauma setting, a retrospective study found.

Advanced clinical practitioners (ACPs) performed 555 procedures with 11 complications (2%), while resident physicians (RPs) performed 1,020 procedures with 20 complications (2%).

Procedures consisted of arterial lines, central venous lines, bronchoalveolar lavage, thoracotomy tubes, percutaneous endoscopic gastrostomy (PEG), and tracheostomies, Massanu Sirleaf, a board-certified acute care nurse practitioner, said at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

VITALS

Major finding: The complication rate was 2% for advanced clinical providers (11/555) and resident physicians (20/1,020).

Data source: A retrospective study of 1,575 invasive procedures.

Disclosures: Ms. Sirleaf and her coauthors reported having no financial disclosures.

No differences were observed between the ACP and RP groups in mean ICU length of stay (3.7 vs. 3.9 days) or hospital stay (13.3 vs. 12.2 days).

Mortality rates were also similar for ACPs and RPs (9.7% vs. 11%; $P = .07$), despite significantly higher age (mean 54.5 years vs. 49.9 years) and APACHE III scores for the ACP group (mean 47.7 vs. 40.8).

"Our results demonstrate that ACPs have become a very important part of our health care team and substantiate the safety of ACPs in performing surgical procedures in critically ill patients," Ms. Sirleaf said.

Restrictions in resident work hours have imposed workload challenges on trauma centers, leading some to recruit nurse practitioners and physician assistants to care for critically ill patients in the ICU and to perform invasive procedures previously done exclusively by physicians, she observed. Very few studies, however, have addressed ACPs' procedural competence and complication rates.

The retrospective study included all procedures performed from January to December 2011 in the trauma and surgical ICUs at the F.H. "Sammy" Ross Jr. Trauma Center, Carolinas Medical

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Center in Charlotte, N.C. Eight ACPs performed invasive procedures for surgical critical care patients under attending supervision, while three postgraduate year two (PGY2) surgical and emergency residents performed procedures for trauma patients.

Invited discussant Dr. Jeffrey Claridge, director of trauma, critical care, and burns at MetroHealth Medical Center in Cleveland, agreed with the study's conclusion that complications were similar between ACPs and RPs, but went on to say that 2% is extremely low and that "something is missing or oversimplified."

In particular, he pressed Ms. Sirleaf on where the procedures were performed, the level of supervision provided to ACPs, and how extensive the review of complications was other than procedural notes. For example, did the authors look at whether chest tubes fell out within 24 hours because they were inappropriately secured, PEG or tracheostomy sites that got infected, or breaks occurred in sterile technique.

Ms. Sirleaf replied that in addition to reviewing postprocedural notes, radiologists looked for complications 24 hours after chest tube placement and patients with a tracheostomy were followed for complications for 7 days by the attending.

Urgency of the procedure was not evaluated since the procedures were elective and most were performed at the bedside.

Work-hour restrictions have led some centers to recruit NPs and PAs to care for critically ill patients.

MS. SIRLEAF

"For the ACPs with a level of competency, just like interns at the beginning, they assisted the attending and as they got better, the majority of the procedure was performed by the ACP at the bedside with the attending scrubbed in," she said.

At the time of the study, three ACPs had 1 year of experience, with up to 7 years' experience in the remaining ACPs. Senior ACPs provided training along with the attendings, and both ACPs and RPs underwent quarterly simulation lab training on procedures. To maintain competency, Carolinas Medical Center also requires ACPs perform a set number of each type of procedure on a yearly basis and have these procedures witnessed and signed off on by an attending, said Ms. Sirleaf, now with Sharp Memorial Hospital, San Diego.

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Aldosterone agonists central in HF

Guidelines *from page 1*

– in terms of benefits (see chart).

"These data are quite striking," Dr. Clyde W. Yancy observed in presenting highlights of the 2013 ACC/AHA guidelines at the Annual Cardiovascular Conference at Snowmass.

"For many years, we've functioned in a space where we thought there's not that much we can do for heart

'Only a handful of patients need to be exposed to these therapies to derive a significant benefit on mortality.'

DR. YANCY

failure, and I would now argue stridently against that. You can see the incredibly low numbers needed to treat here. Only a handful of patients need to be exposed to these therapies to derive a significant benefit on mortality. These are data we should incorporate in our clinical practice without exclusion," declared Dr. Yancy, who chaired the heart failure guideline-writing committee.

The important caveat regarding the aldosterone antagonists is that they should be used only in patients with an estimated glomerular filtration rate greater than 30 mL/min per 1.73 m^2 and a serum potassium level below 5.0 mEq/dL. Otherwise that Class I/A recommendation plummets to III/B, meaning the treatment is inappropriate and potentially harmful, continued Dr. Yancy, professor of medicine and of medical social sciences and chief of cardiology at Northwestern University, Chicago.

The guidelines emphasize the imperative to implement what has come to be termed guideline-directed medical therapy, known by the abbreviation GDMT. The panel found persuasive an analysis showing that heart failure patients with reduced ejection fraction who were on two of seven evidence-based, guideline-directed management interventions had an adjusted 38% reduction in 2-year mortality risk compared with those on none or one, while those on three interventions had a 62% decrease in the odds of mortality and patients on four or more had mortality reductions of about 70% (J. Am. Heart Assoc. 2012;1:16-26).

The seven interventions are beta-blockers, ACE inhibitors or ARBs, aldosterone antagonists, anticoagulation for atrial fibrillation, cardiac resynchronization therapy, implantable cardioverter-defibrillators, and heart failure education for eligible patients.

The guidelines advise strongly against the combined use of an ACE inhibitor and ARB. It's an either/or treatment strategy. Studies indicate there is no additive benefit with the combination, only an increased risk of side effects.

An important innovation in the guidelines is the new prominence afforded to heart failure with preserved ejection fraction, known as HFpEF (pronounced heff-peff).

"What's most different in the new heart failure guidelines is that we have uploaded HFpEF to the front page," said Dr. Yancy. "We want you to appreciate how important it is. We recognize that there's no evidence-based intervention that changes its natural history; rather, the focus is on identification and treatment of the comorbidities. It's important to emphasize that this is a novel way of thinking about heart failure for a very important iteration of that disease."

Among the other highlights of the guidelines is a clarification of the current role for biomarker-guided heart failure therapy. B-type natriuretic peptide (BNP) or N-terminal pro-BNP measurements are deemed useful in making the diagnosis of heart failure as well as in establishing prognosis.

Serial measurements can be used to titrate GDMT to optimal doses. But there are as yet no data to show that using the biomarkers to titrate GDMT to higher doses improves mortality.

The 2013 ACC/AHA Guideline for the Management of Heart Failure was developed in collaboration with the American Academy of Family Physicians, the American College of Chest Physicians, the Heart Rhythm Society, and the International Society for Heart and Lung Transplantation (J. Am. Coll. Cardiol. 2013;62:e147-239).

Dr. Yancy reported having no financial conflicts.

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Benefits of guideline-directed medical therapy for heart failure

Drug	Relative risk reduction in mortality	Number needed to treat to prevent one death in 36 months	Relative risk reduction for heart failure hospitalization
Hydralazine/ isosorbide dinitrate	43%	7	33%
Beta-blocker	34%	9	41%
Aldosterone antagonist	30%	6	35%
ACE inhibitor or angiotensin receptor blocker	17%	26	31%

Source: Dr. Yancy

VIEW ON THE NEWS

Dr. Jun Chiong, FCCP, comments: The new 2013 ACCF/AHA Guideline for the Management of Heart Failure provides a fresh and comprehensive guide to evaluation and management of heart failure patients. The guideline has new areas that are going to be quite helpful for the providers. The indications for aldosterone antagonists are broadened for symptomatic HFpEF patients NYHA class II, III, and IV patients. Creatinine values needed to be = 2.5 mg/dL in men or = 2.0 mg/dL in women, and potassium =5.0 mEq/L are highlighted along with the necessity for careful monitoring of potassium, renal function, and diuretic dosing at initiation follow-up. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is considered potentially harmful and is not recommended.

PALLIATIVELY SPEAKING: Reconsidering comfort care

BY LEIGH FREDHOLM, M.D., AND STEPHEN BEKANICH, M.D.

Recently, members of our palliative care team participated in the care of a man approaching the end of his life. The patient had suffered an in-hospital cardiac arrest 4 weeks earlier, and though he had survived the immediate event, it resulted in anoxic encephalopathy, which rendered him incapable of making decisions.

When it became clear that the patient was declining despite full support, the hospital's ethics committee was convened to determine goals of care and next steps, as the patient had no family or surrogate decision maker. After determination that the hospital staff had exercised due diligence in attempting to locate a surrogate, the physicians involved reviewed the patient's case and recommended a change in goals to comfort care. More than one member of the committee expressed confusion as to what interventions are and are not included in comfort care, including medically administered nutrition and hydration (MANH).

DR. FREDHOLM

DR. BEKANICH

Comfort care has traditionally included medications for distressing symptoms (pain, dyspnea, nausea), personal care for hygiene, and choice of place of death (home, hospital, nursing facility), usually with the assistance of a hospice agency.

As the number and complexity of interventions used near the end of life expand, clinicians and hospital staff report confusion about whether these interventions, generally considered to be life-sustaining treatments, can also be considered comfort care. We generally find that when interventions are considered in the context of the patient's goals of care, the dilemma is clarified. Often the situation is made more complicated by considering the interventions before settling on goals. Broadly speaking, goals of care are derived from a careful consideration (by patient, physician, and family) of the natural history of the illness, expected course and prognosis, and patient preferences.

In the case of the above-referenced patient, we were unable to ascertain his goals because of neurological impairment. We did know, however, that the patient had steadfastly avoided hospitals and medical care of any kind. The attending hospitalist, pulmonologist, and palliative care physician agreed that the patient's clinical status was declining despite all available interventions, and that his constellation of medical problems constituted a terminal condition. The physicians agreed that future ICU admission, resuscitation, and other new interventions would only prolong his dying process, but not permit him to live outside the hospital. At that time, the patient was receiving nutrition and hydration via a Dobhoff tube, and was tolerating enteral nutrition without excessive residuals or pulmonary secretions.

As with other interventions,

Continued on following page

Palliative skills critical to ICU care

ICU *from page 1*

feel better." It is specialized medical care that focuses on preventing and relieving symptoms, pain, and stress associated with life-threatening illness – whatever the diagnosis – and is appropriate at any stage in a serious illness.

Typically provided by a team, palliative care may involve physicians, nurses, social workers, pharmacists, chaplains, pain experts, ethicists, rehabilitation therapists, psychiatry consultants, and bereavement counselors. The team can take a load off busy intensivists by handling the often lengthy conversations with patients and families facing life-threatening illness, she said.

Palliative care providers can be embedded in ICUs or in a team that's available as consultants. "I think we have to do both" models, depending on the needs of individual institutions, said Dr. Cooper.

Once a definition is agreed upon, the next steps to convincing colleagues and administrators to make better use of palliative care are to make it relevant for them and to normalize its presence in the ICU, she said. "Palliative care is just as essential as med management, antibiotics, pharmacology – it's part of what we do well."

Predicting which patients will die, and when, is difficult. Patient preferences for care or end-of-life treatment often are unclear. The goals of treatment depend on the patient's condition and must be dynamic. "Is it end-of-life care if we don't know the patient is dying?" she asked.

One way to consider which ICU patients might benefit from palliative care is to ask, "Would I be surprised if this patient died within a year?" even if discharged from the ICU or the hospital, she suggested.

Four studies in the medical literature separately reported that 20% of Americans die in the hospital after an ICU admission, 80% of deaths in ICUs occur after life support is withdrawn or withheld, nearly half of dying patients receive unwanted therapy, and a majority of dying patients experience pain and suffering, Dr. Cooper said. Five other studies reported high mortality rates in patients with sepsis, acute respiratory distress syndrome, ICU stays longer than 14 days, admission to long-term acute care, or initiation of dialysis in the elderly.

A recent study of 25,558 elderly patients undergoing emergency surgery reported 30-day mortality rates of 37% in those with preexisting do-not-resuscitate (DNR) orders and 22% in those without DNR orders. Major complications occurred in more than 40% in each group (Ann. Surg. 2012;256:453-61). Risk factors increase the likelihood of death, but "all of these patients are experiencing serious illness" and would benefit from palliative care, Dr. Cooper said.

One recent study of 518 patients in three ICUs found good adherence to only two of nine palliative care processes – pain assessment and management. Interdisciplinary family meetings had been held by day 5 in the ICU for less than 20% of patients, and adherence to six other palliative care practices ranged from 8% to 43% (Crit. Care Med. 2012;40:1105-12).

Normalizing palliative care in the ICU means adopting the attitude that "it's just part of what we do, the same way that we manage our vents, etc." Dr. Cooper said.

Adopting proactive screening criteria (patient factors) that trigger palliative care consultations would reduce utilization of ICUs without increasing mortality, and would increase the availability of palliative care for patients and families, according to a recent report from the Improving Palliative Care in the ICU Project's advisory board (Crit. Care Med. 2013;41:2318-27).

The triggers should be specific to each ICU and patient population and developed through a process with stakeholders, with outcomes evaluated. "This is not a one-size-fits-all strategy," Dr. Cooper said. "The triggers in the MICU [medical ICU] and the SICU [surgical ICU] cannot be the same. It won't work. I've actually seen that in my own institution," Dr. Cooper said.

The triggers also shouldn't focus only on the patients most obviously likely to die or they will perpetuate the misconception that palliative care is only for the dying, she added.

To integrate palliative care into an ICU, "just do it," she said. "Commit yourself" to intensive symptom management and multidisciplinary family meetings within 72 hours of ICU admission. Institute an intensive communication plan to provide emotional, educational, and decision support for patients and families. Offer pastoral and psychosocial support. Start end-of-life-care discussions sooner, and provide bereavement services when patients die.

Lastly, don't hesitate to bill insurers for these services, Dr. Cooper said. In-person or phone meetings about treatment options when the patient lacks the capacity to decide can be billed as critical care, as can discussions about DNR codes. Also bill for treating acute pain, agitation, delirium, and other life-threatening symptoms as critical care.

Dr. Cooper reported having no financial disclosures.

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If you're interested in more about this topic, you can join a discussion within the Critical Care e-Community. Simply log in to ecommunity.chestnet.org and find the Critical Care group. If you're not part of the Critical Care NetWork, log in to chestnet.org and add the Critical Care NetWork to your profile. Questions? Contact communityadmin@chestnet.org.

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whether or not to consider MANH a part of comfort care is individualized. In this patient's case, in the absence of evidence that he would not want MANH, it was continued. Other patients have expressed the wish that they would under no circumstances accept MANH while receiving comfort care. Both are correct as long as they reflect that patient's wishes.

With respect to other interventions – including but not limited to BiPAP, inotrope infusion, chemotherapy, radiation therapy, and transfusions – whether or not they provide comfort is a decision to be made jointly by the patient and physician(s). As advances in medicine allow patients to live longer with serious illness, the definition of comfort care must also expand.

Dr. Fredholm and Dr. Bekanich are codirectors of Seton Palliative Care, part of the University of Texas Southwestern Residency Programs in Austin.

"Palliatively Speaking," appears monthly at ehospitalistnews.com.

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP: Dr. Fredholm and Dr. Beckanich adeptly discuss how to weigh possible life-sustaining measures in terms of whether they are providing comfort for patients and how to ensure that such treatments are discussed with patients in that context.

Additionally, they provide a very nice example of how to proceed when patients cannot communicate for themselves and have no family or other surrogates to speak for them.

Join us in the Critical Care NetWork's eCommunity.

Relatively few in ICUs get end-of-life dialogue training

BY SHERRY BOSCHERT
Frontline Medical News

SAN FRANCISCO – Despite training recommendations, half of physicians and less than a third of nurses surveyed in adult intensive care units at 56 California hospitals reported receiving formal training in talking with patients and families about the end of life.

DR. ANSTEY

A 2008 consensus statement by the American College of Critical Care Medicine included a recommendation for end-of-life communication skills training for clinicians to improve the care of patients dying in ICUs (Crit. Care Med. 2008;36:953-63).

Dr. Matthew H.R. Anstey and his associates approached 149 California hospitals to gauge the extent of implementation of this recommendation. At 56 hospitals, doctors and nurses who work in adult ICUs voluntarily completed an anonymous web-based survey. Eighty-four percent of the 1,363 respondents were nurses, he reported in a poster presentation at the Critical Care Congress, sponsored by the Society for Critical Care Medicine.

Overall, 32% of the respondents said they had received formal training in communication skills. A significantly higher percentage of doctors had undergone training (50%) compared with nurses (29%), said Dr. Anstey, who is currently a

Continued on following page

VITALS

Major finding: Half of doctors and 29% of nurses in ICUs said they had received formal training in end-of-life communications.

Data source: A voluntary web-based survey of 1,363 doctors and nurses working in adult ICUs in 56 California hospitals.

Disclosures: Dr. Anstey reported having no financial disclosures. His research was in conjunction with a Commonwealth Fund Harkness Fellowship in Health Care Policy and Practice, for which he was placed at Kaiser Permanente in California.

Palliative care shortens ICU, hospital stays, review shows

BY SHERRY BOSCHERT
Frontline Medical News

SAN FRANCISCO – Palliative care in the intensive care unit reduces the length of stay in the ICU and the hospital without changing mortality rates or family satisfaction, according to a review of the literature.

Although measurements of family satisfaction overall didn't change much from palliative care of a loved one in the ICU, some measures of components of satisfaction increased with palliative care, such as improved communication with the physician, better consensus around the goals of care, and decreased anxiety and depression in family members, reported Dr. Rebecca A. Aslakson of Johns Hopkins University, Baltimore, and her colleagues.

Dr. Aslakson presented the findings at the Critical Care Congress, sponsored by the Society for Critical Care Medicine.

Dr. Aslakson and her associates were unable to perform a formal meta-analysis of the 37 published trials of palliative care in the ICU because of the heterogeneity of the studies, which looked at more than 40 different outcomes.

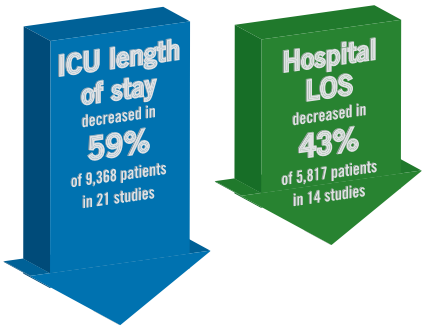
Instead, their systematic review grouped results under four outcomes that commonly were measured, and assessed those either by the number of studies or by the number of patients studied.

ICU length of stay decreased with palliative care in 13 of 21 studies (62%) that used this outcome and in 59% of 9,368 patients in those studies.

Hospital length of stay decreased with palliative care in 8 of 14 studies (57%) and in 43% of 5,817 patients.

Family satisfaction did not decrease in any studies or families and increased in only 1 of 14 studies (7%) and in 2% of families of 4,927 patients, Dr. Aslakson and her colleagues reported (J. Palliat. Med. 2014;17:219-35).

Benefits of palliative care in the ICU



Note: Data are based on a systematic review of 37 published trials.

Source: Dr. Aslakson

Frontline Medical News

Mortality rates did not change with palliative care in 14 of 16 studies (88%) that assessed mortality and in 57% of 5,969 patients in those studies. Mortality increased in one small study (6%) and decreased in one larger study (6%).

"Talking about big-picture issues and goals of care doesn't lead to people dying," Dr. Aslakson said.

"No harm came in any of these studies." Some separate studies of palliative care outside of ICUs reported that this increases hope, "because people feel that they have more control over their choices and what's happening to their loved ones," she added.

Integrative vs. consultative model

Dr. Aslakson and her associates also reviewed studies based on whether the interventions used integrative or consultative models of palliative care.

Generally, consultative models bring outsiders into the ICU to help provide palliative care, and integrative models train the ICU team to be the palliative care providers. In reality, the two models may overlap. For this review, the investigators applied mutually exclusive definitions to 36 of the studies.

In 18 studies of integrative interventions, members of the ICU team were the only caregivers in face-to-face interactions with the patient and families. In 18 studies of consultative interventions, palliative care providers included others besides the ICU team.

In the studies of integrative palliative care, ICU length of stay decreased with palliative care in four of nine studies (44%) that measured this outcome and in 52% of 6,963 patients in those studies, she reported. Hospital length of stay decreased in two of five studies (40%) and in 24% of 3,812 patients. Family satisfaction changed in none of 15 studies, and mortality decreased in 1 of 5 studies (20%) and in 34% of 3,807 patients.

In the studies of consultative care, ICU length of stay decreased with palliative care in 9 of 12 studies (75%) that measured this outcome and in 79% of 2,405 patients in those studies. Hospital length of stay decreased in six of nine studies (67%) and in 79% of 2,005 patients. Family satisfaction increased in one of four studies (25%) and in 21% of 429 patients. Mortality increased in 1 of 11 studies (9%) and in 5% of 2,162 patients.

One model isn't necessarily better than the other, Dr. Aslakson said. Integrative palliative care may work best in a closed ICU with perhaps four or five intensivists in a relatively small unit. An integrative approach can be much more difficult in open or semiopen ICUs that have "40 different doctors floating around," she said. "We tried that in my unit, and it didn't work that well."

Continued on following page

VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: Dr. Aslakson and colleagues' systematic review adds to the body of literature that demonstrates no mortality increase when palliative care measures are initiated in the ICU. Shorter lengths of stay both in the ICU and hospital were other positive outcomes noted without a significant change in patient or family satisfaction. These findings were independent of whether an integrative or consultative approach to palliative care was undertaken. This should encourage physicians to examine their practice setting and determine which approach meets the needs of their ICU and begin to utilize palliative care earlier and more aggressively without fear of increasing mortality.

Continued from previous page

lecturer in anesthesia at Harvard Medical School, Boston.

Sixty-six percent of all respondents agreed that "nurses are present during the communication of end-of-life information to the family" at their institution. Nurses were significantly more likely to agree with this statement (69%) than were doctors (52%).

Both doctors and nurses were very supportive of the idea of formal communication training for ICU providers. When asked about possible strategies to reduce inappropriate care for ICU patients, 91% of respondents said communication training would have a positive effect, Dr. Anstey reported.

This could be accomplished by requiring ICU physicians to complete a communication training module for ongoing credentialing, he said in an interview. Either individual hospitals could require this as part of credentialing for privileges to work in the ICU, or state medical boards could require it, similar to the California Medical Board's requirement that physicians obtain some continuing medical education in pain management, he suggested.

VIEW ON THE NEWS

Dr. Paul A. Selecky, FCCP, comments: Physicians are notorious about not doing a good job of communicating with patients in general, and when you focus on a vital subject as end-of-life care, it is of even greater importance. The findings in this study are not surprising. The unanswered question is how to fix it.

The characteristics of participating hospitals were similar to those of nonparticipating hospitals in the sizes of the hospitals and ICUs, their regional location in California, and the proportions of hospitals that are teaching facilities.

The 93 nonparticipating hospitals were significantly more likely to be for-profit hospitals (59%) compared with participating hospitals (7%), and significantly less likely to be part of a hospital system containing more than three hospitals (54%) compared with participating hospitals (75%).

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Different ICUs need palliative care models that fit them. "Look at your unit, the way it works, and who the providers are, then look at the literature and see what matches that and what might work for your unit," she said.

Outcomes of better communication

A previous, separate review of the medical literature identified 21 controlled trials of 16 interventions to improve communication in ICUs between families and care providers. Overall, the interventions improved emotional outcomes for families and reduced ICU length of stay and treatment intensity (Chest 2011;139:543-554), she noted.

Yet another prior review of the literature reported that interventions to promote family meetings, use empathetic communication skills, and employ palliative care consultations improved family satisfaction and reduced ICU length of stay and the adverse effects of family bereavement (Curr. Opin. Crit. Care 2009;15:569-77).

Dr. Aslakson reported having no financial disclosures.

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Low vitamin D – poor ICU outcomes

Outcomes *from page 1*

a significant predictor of 30- and 90-day all-cause mortality in critically ill patients, even after adjustment for such factors as age, Charlson/Deyo index, sepsis, and season (Crit. Care Med. 2012;40:63-72). It also has been shown to significantly predict acute kidney injury in the critically ill (Crit. Care Med. 2012;40:3170-9).

For the current analysis, vitamin D levels were drawn upon ICU admission, at 72 hours, and every 7 days until hospital discharge in 200 of 234 consecutive adult trauma patients admitted to the ICU at the Level 1 Orlando Regional Medical Center during a 4-month period. Deficiency was defined as 25-hydroxyvitamin D of 20 ng/mL or less. All patients received nutritional support using a standard protocol, but not vitamin D supplementation.

Median vitamin D ICU admission levels in the 51 vitamin D–deficient patients were significantly lower than for nondeficient patients (16 ng/mL vs. 28 ng/mL; *P* less than .001). Levels decreased a median of 4 ng/mL at 72 hours in both groups, but only the sufficient group returned to admission baseline levels at week 2, reported Dr. Ibrahim, a critical care surgeon with the medical center.

We have to supplement patients with much higher doses than are provided in enteral formulas.

DR. IBRAHIM

"This demonstrates that if we wish to obtain normal vitamin D levels in these patients, we will have to supplement them with much higher doses than what we are providing with standard enteral formulas," he said in an interview.

Patients with vitamin D deficiency spent more time than did nondeficient patients in the ICU (median 3 days vs. 2.7 days) and hospital (median 8.4 days vs. 7.1 days), but these trends did not reach statistical significance.

Significantly more deficient patients, however, remained in the hospital for at least 2 weeks (37% vs. 20%).

The investigators were unable to show a difference in mortality between the deficient and nondeficient

Continued on following page

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: This is an interesting and provocative report associating vitamin D deficiency with worse outcome among trauma patients. As noted in the article, we have currently observed only an association, not cause and effect, so it is too soon to suggest routine measurement and/or supplementation of vitamin D in this patient population. However, given the known immunomodulating effects of vitamin D, there is biological plausibility in these findings, and I suspect that a story is about to unfold.

Continued from previous page

groups (16% vs. 12%; $P = .51$), possibly because the study was underpowered, he said.

Deficient and sufficient patients did not differ in age (median 48 years vs. 44 years), body mass index (26.2 kg/m^2 vs. 25.7 kg/m^2), admission ionized calcium (1.06 mmol/L for both), or Injury Severity Score (14 vs. 13). Only APACHE II scores were significantly higher in deficient patients (20 vs. 15).

"It makes sense that with the significant difference in APACHE II score, one would expect to see a similar difference in mortality, but again we were unable to show this with this study," Dr. Ibrahim said.

Prehospital factors significantly associated with low vitamin D status were African American race, diabetes, and lack of vitamin D supplementation.

Vitamin D supplementation may be helpful in critically ill trauma patients during hospitalization, but more research is needed, Dr. Ibrahim said. The group is planning a supplementation study, looking at vitamin D dosing and frequency of testing.

"Our first goal was to demonstrate a significant incidence, which we did," he said. "It should be noted that the incidence was in a location with probably one of the highest amounts of sunshine in the country and that the findings may underestimate what one would find in other areas of the United States."

Dr. Oscar Guillamondegui, of Vanderbilt University Medical Center in Nashville, Tenn., who proctored the poster session, said he would expect vitamin D levels to be lower in acutely sick patients requiring ICU management because production of vitamin D–binding protein, a subprotein in the albumin family of proteins involved in vitamin D transport and storage, is decreased in high stress situations to allow for the increase in acute phase protein production.

"Although the data are intriguing, as a retrospective study, it is too early to suggest that supplementation is essential," he said.

Dr. Ibrahim and Dr. Guillamondegui reported having no financial disclosures.

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If you're interested in more about this topic, you can join a discussion within the Critical Care e-Community. Simply log in to ecommunity.chestnet.org and find the Critical Care group. If you're not part of the Critical Care NetWork, log in to chestnet.org and add the Critical Care NetWork to your profile. Questions? Contact communityadmin@chestnet.org.

POINT/COUNTERPOINT

Another surgeon's error – Must you tell the patient?

Patients have a right to honest information.

BY DR. SUSAN D. MOFFATT-BRUCE

Surgeons have a moral and ethical obligation to inform a patient when a medical error has occurred, including cases when the error was made by another surgeon.

Principles that support complete and honest disclosure to the patient and/or the patient's family in such cases include professional obligation on the part of both the surgeon who made the error and the surgeon who discovered the error, the integrity of both surgeons, the patient's right to informed care throughout the continuum of care, and the patient's right to informed consent.


DR. MOFFATT-BRUCE

With respect to the first, the American Medical Association's code of ethics provides a framework for disclosure; it clearly states that situations occur in which a patient experiences significant complications that may have resulted from a physician's mistake or judgment and that the physician is ethically required to inform the patient of all facts necessary to ensure understanding of the error that occurred.

The American College of Physicians' ethics manual also states that physicians should disclose to patients information about procedural or judgment errors made during the course of care, as long as that information is pertinent and material to the patient's well-being.

Errors do not necessarily imply negligence or unethical behavior, but failure to disclose may.

As for patients' rights, I think that patients are entitled to honest information. They shouldn't bear the burden of determining how they came to be in another surgeon's care.

Patients with complications may have impactful financial burdens that result from the additional treatment that is needed, and without all pertinent information, they may have difficulty understanding the benefits, such as deferment of payments, to which they are entitled.

The patient is entitled to informed consent, and this requires an understanding of the conditions under which they arrived in another surgeon's care. If a second procedure is required, the patient must be made aware of potential complications – including how the effects of the initial error might impact outcomes.

Although surgeons have an ethical obligation to disclose errors made by another surgeon, this is admittedly a difficult task. Pressures from society and medical professionals can make disclosure difficult, but the benefits of disclosure are very real; studies show that open, honest communication improves patient satisfaction, strengthens the physician-patient relationship, and can ultimately improve outcomes.

Disclosure also has the potential to improve the well-being of the surgeons involved, through relieving feelings of guilt, and satisfying the need to fulfill one's obligations. Furthermore, data suggest that error disclosure reduces long-term litigation and costs. Admittedly, however, there are few data on how disclosure of another surgeon's errors might result in reduction of litigation and costs.

Ultimately, supporting a just culture allows us to emphasize the importance of disclosing errors and to be accountable in setting a standard that involves exploring errors rather than ignoring them; it must be remembered, though, that this process of disclosure involves obtaining facts to help both surgeons and patients understand what truly happened.

Surgeon-to-surgeon discussions can be productive and can facilitate disclosure. However, if the doctor who made the error declines to be part of the disclosure process, one still has an obligation to disclose the error and to answer the patient's questions honestly.

This approach requires a commitment to support surgeons in their efforts to promote transparency, and it requires a clear understanding of our obligations and the role of disclosure during training; we need to engage medical students and residents in the very important role of health care advocacy.

Dr. Moffatt-Bruce is an associate professor of thoracic surgery at the Ohio State University, Columbus.

Discuss the error with the responsible physician.

BY DR. CHADRICK E. DENLINGER

Surgeons do not have an obligation to disclose to a patient another surgeon's possible medical error.

A consensus has been reached in medicine about our ethical duty to inform patients about our own medical errors. Although nondisclosure has previously been rationalized by concerns about invoking anxiety or confusion in the patient, this approach has largely been discredited; disclosure preserves patient trust and bolsters the physician-patient relationship.


DR. DENLINGER

However, it is an entirely different story when it comes to disclosing another surgeon's mistake – a situation that is quite common. A recent survey showed that two-thirds of respondents had encountered a similar dilemma in the past 6 months (Qual. Saf. Health Care 2009;18:209-12).

The approach that physicians have previously taken when faced with this dilemma is an important measure of what they believe represents an ethical or just response. A poll of many of my colleagues across the country and at my own institution suggests that the preferred approach is to provide appropriate care for the patient and to answer their questions honestly, but to not proactively disclose the perceived medical error.

In fact, this was the preferred approach of every surgeon who responded.

WAVEBREAK MEDIA/THINKSTOCK

A recent article in the New England Journal of Medicine addressed this very topic. The authors noted that there is little guidance available regarding the reporting of another physician's error (2013;369:1752-7).

Among the challenges inherent in disclosing another's mistake is the difficulty in determining exactly what happened. Uncertainty inevitably exists regarding the conversations that took place between the patient and the surgeon, and also about what actually defines a medical error. Incidents regarded as medical errors may comprise a large spectrum, ranging from "not what I would have done – but within the standard of care," to "blatant negligence."

Several studies suggest that highly trained physicians and surgeons routinely disagree about whether negligence has occurred in a given case. In one study, two reviewers disagreed 38% of the time as to whether appropriate care was provided.

Physicians have difficulty judging if the standard of care has been met. Therefore, it is not acceptable for each of us to assume we are the medical expert capable of rendering an opinion of whether previous care was appropriate and informing patients of our opinion.

Physicians overwhelmingly report that in the event they are responsible for a medical error discovered by another physician, they would prefer that the physician come to them first to discuss the matter. In fact, 93% of 400 respondents in one survey reported this preference.

The most acceptable approach when dealing with a peer's medical error is to discuss the error with the responsible physician and to encourage the physician to disclose any error with the patient.

If there is disagreement as to whether an error occurred, institutional guidance should be applied. Only a collaborative approach can appropriately meet the needs of the patient and family after harmful medical errors.

Dr. Denlinger is an associate professor at the Medical University of South Carolina, Charleston.

Breath test could improve lung cancer screening

BY SHARON WORCESTER
Frontline Medical News

ORLANDO – The presence of certain carbonyl volatile organic compounds in exhaled breath can aid in the detection of early lung cancer, according to Dr. Michael Bousamra.

An analysis of volatile organic compounds (VOCs) in the exhaled breath of 10 lung cancer patients and 88 controls, including 45 who were smokers and 43 who were nonsmokers, identified four carbonyl VOCs that occurred significantly more often in the lung cancer patients' breath samples than in the control samples: 2-butanone, 3-hydroxy-2-butanone, hydroxylacetaldehyde, and 4-hydroxyhexenal.

Further study of 151 patients with suspicious lung nodules found no single VOC marker that was independently predictive of lung cancer, but when the levels of three or more were elevated in a single patient, the sensitivity and specificity for lung cancer were 60% and 95.2%, respectively. When the levels of at least two of the VOCs were elevated, the sensitivity and specificity were 84.7% and 81%, respectively, and when at least one was elevated, the sensitivity and specificity were 93.8% and 45.2%, respectively.

The absence of VOC elevation was predictive of benign disease in 80% of cases, Dr. Bousamra of the University of Louisville, Ky., reported at the annual meeting of the Society of Thoracic Surgeons.

Notably, the concentrations of three of four VOCs in samples from lung cancer patients decreased to the level found in healthy controls after resection, he explained.

Continued on following page

VITALS

Major finding: Finding three or more specific carbonyl VOCs in exhaled breath was 95% predictive of lung cancer, while no elevation was 80% predictive of benign nodules.

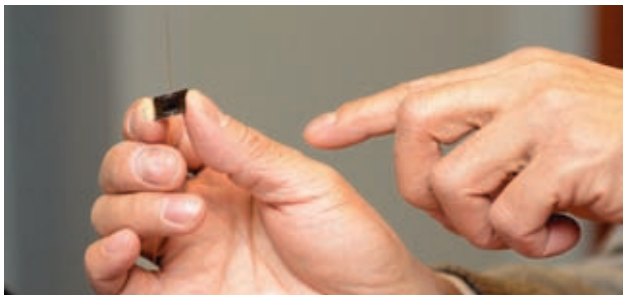
Data source: An analysis of VOCs in the exhaled breath of 151 patients with suspicious lung lesions.

Disclosures: Dr. Bousamra reported having no disclosures.

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: Current lung cancer screening recommendations remain quite controversial, and no matter one's stance on the data, it would have to be agreed upon that further guidance on the appropriate screening population and further reduction in CT false positives are needed. In the near future, biomarker and exhaled breath phenotypes will dramatically change our screening for lung cancer and lead to earlier diagnoses.

The microchip used in the study detected four carbonyl volatile organic compounds that appeared more often in the breath samples of lung cancer patients.



Courtesy University of Louisville Health Sciences Center

Continued from previous page

This finding "lends credence to the notion that these carbonyl markers really aren't indicators of something other than cancer," Dr. Bousamra said.

Of the 151 patients in the study, 109 were diagnosed with lung cancer and 42 with benign nodules. Of those who had lung cancer, 1 had stage 0 disease, 47 had stage I, 18 had stage II, 26 had stage III, and 17 had stage IV.

The exhaled breath samples were collected using a 1-L Tedlar bag and were analyzed by investigators who were blinded to the preoperative di-

agnosis and pathology, he said.

The findings suggest that these specific VOCs in exhaled breath could be used as an adjunct to computed tomography (CT) for the diagnosis of early lung cancer. In this study, the VOCs were also useful for distinguishing benign from malignant nodules, Dr. Bousamra noted at the meeting.

'When three or four carbonyl markers were elevated, the probability of cancer was very high; when no carbonyl markers – or even one – was elevated, associated pulmonary disease was likely benign.'

"When three or four carbonyl markers were elevated, the probability of cancer was very high; when no carbonyl markers – or even one – was elevated, associated pulmonary disease was likely benign. I think that clinical decision making could be assisted in these instances," he said.

Carbonyl VOC testing, however, is not quite ready for prime time, he noted.

Exhaled breath has long been considered a promising noninvasive tool for the diagnosis of early lung can-

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cer, but the studies conducted to date have failed to achieve clinical significance because of a lack of specificity and challenges associated with complex volatile mixtures.

Although the findings of the current study advance the possibility of using exhaled breath in lung cancer diagnosis and clinical decision making, the study was limited by an inadequate control group. In addition, further study is needed in patients who have pulmonary nodules and benign pulmonary disease, as well as in patients following resection, Dr. Bousamra said.

The possibilities for this type of testing are exciting, and this work represents a window into the future of lung cancer screening and diagnosis.

The study also lacked a specific look at patients with chronic obstructive pulmonary disease and other interstitial lung disease common in patients with lung cancer, he noted.

He estimated, however, that VOC testing could be in place to help with

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.

the diagnosis of lung cancer within 2 years.

The possibilities for this type of testing are exciting, and the work of Dr. Bousamra and his colleagues represents a window into the future of lung cancer screening and diagnosis, according to the invited discussant, Dr. Tom Varghese Jr., who is with the University of Washington in Seattle.

Lung cancer is the leading cause of cancer deaths worldwide, with higher mortality than the next three leading causes of cancer death combined, Dr. Varghese said.

A large screening trial showed that using low-dose CT for screening could reduce mortality by 20% – a finding that led to the recent endorsement by the U.S. Preventive Services Task Force of low-dose screening CTs for patients who are at high risk.

Such a screening program, if it were applied using strict criteria, "would avert 12,000 lung cancer deaths today," he asserted.

Adding measurement of VOCs in exhaled breath to the screening protocol could result in fewer invasive procedures for abnormal screening results, and VOC measurement could thus prove to be a simple, straightforward cost-saving measure, Dr. Varghese added.

PRESIDENT'S REPORT: New Year's resolution reboot?

BY DR. MICHAEL H. BAUMANN, FCCP

As I write this article, I am looking out a hotel window at a very cold Chicago landscape (I'm talking really cold for a guy from Mississippi). We just completed a very productive CHEST 2014 Executive Program Committee meeting to plan our annual program for this October in Austin, Texas. This effort was expertly led by Dr. Mark Metersky and his vice-chairs, Drs. Alex Niven and Jean Bourbeau, with great contributions by a superb group of executive committee members and the CHEST staff. We have an exciting program planned for you this year in Austin! The planning meeting was followed by the traditional "thank you" dinner for the planning committee participants. One of my New Year's resolutions went flying out the window, yet again: eating sensibly! Hard for me to resist great food.


DR. BAUMANN

I bet I'm not alone. I am more than 2 months into the yearly "resolution game." Not one of my resolutions is intact – as usual. Like many of you, I bet, I set my sights a bit too high. My plans included eating more sensibly (not really that tough of a target, except cheese curls and french fries are irresistible), getting more regular exercise (my Nordic Track® often sits unused – yes, I'm that old – I actually own a Nordic Track), get home earlier each evening (there's always something coming up at work), and not working as much on the weekends, or better yet, not at all (guess when I'm writing this).

Time for a resolution reboot! Yep, I "borrowed" that term from *Headline News* where I heard the phrase one early morning when the Nordic Track and I were getting reacquainted. I'd like to offer you several resolution ideas that should be easy to accomplish, and, yes, involve CHEST.

1 Come to CHEST World Congress in Madrid, March 21-24 (www.chestworldcongress2014.org/). I realize by the time this is published, time may be short. This is a fantastic program in collaboration with our partner, the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and offers great and innovative content in a wonderful setting. Be sure to take advantage of the beautiful treasures of Madrid! One of those great treasures is the food! (There goes my resolution again.) Yes, this suggested CHEST resolution may be the hardest to accomplish, but the effort will be well rewarded.

2 Make your plans now to attend CHEST 2014 in Austin, Texas, (chestmeeting.chestnet.org). As noted, we just completed our program planning to include hands-on simulation, interactive sessions, and many more unique learning opportunities. Austin is a great city with much to offer, including world famous music, great barbecue, and other cuisine (food again – I better reboot that resolution, or just boot it).

3 Submit an abstract to CHEST 2014! This is a great way to show off the great care you have been providing for your patients!

4 Our new global headquarters opened in February. This fantastic facility offers an Innovation, Simulation, and Training Center that includes six simulation labs looking just like ICU rooms. Plan to attend one of our many new simulation offerings this year covering a myriad of topics, including ultrasound and mechanical ventilation. Look for even more exciting offerings over the year, as we take full advantage of this wonderful new resource, and sign up (www.chestnet.org/Education/Products/Live-Learning).


CHEST

Dr. Thomas Fuhrman (front) and Dr. Steve Simpson discuss possible CHEST 2014 sessions at the CHEST 2014 Executive Program Committee planning meeting.

5 Join our e-Community or become even more active in the e-Community (www.chestnet.org/NetWorks/eCommunity). Start your own discussion with your questions or opinions on a topic of most interest to you. This is a global connection that can provide you with great perspectives and new ideas.

6 Get social! Join other CHEST members on Twitter, Facebook, or Instagram (www.chestnet.org/Get-Involved/Connect-with-Us/Get-Social). This is a great way to connect with your colleagues. If you aren't sure about how to do this (as I was not sure), connect with our Public Relations Specialist, Kristi Bruno at kbruno@chestnet.org. Being a bit of an "old dog," I'm still learning some of the new tricks about social networking from Kristi. She is a great resource!

7 Make a contribution to The CHEST-Foundation (www.chestnet.org/About/Overview/Foundation-and-OneBreath). The foundation is the philanthropic arm of CHEST, providing resources to our members to help our patients. Your donation can be targeted to the Beyond Our Walls Capital Campaign, helping to support our new global headquarters.

8 Last but not least, if you are not yet a member, join up (www.chestnet.org/Get-Involved/Membership/Join)!

Numbers 1-7 are just a few of the great opportunities you will have as part of the CHEST community. Good luck rebooting your resolutions! Now it's time to work on one of my resolutions, less work on the weekends.

FROM THE EVP/CEO: 'Global' – more than a name for our new HQ

BY PAUL A. MARKOWSKI, CAE

After months of planning and much anticipation, we have moved to our new location in Glenview, Illinois. February 18 marked the first day in our new space, and there's much to be proud of in this building. It won the prestigious "Green Development of the Year Award" for 2013 from the Commercial Real Estate Development Association, the premier organization for real estate professionals in metropolitan Chicago, and it's under review for Silver LEED certification. It houses our state-of-the-art Innovation, Simulation, and Training Center, with an auditorium, eight breakout rooms, six simulation suites, and wet and dry labs to supplement training. Behind the scenes is an enhanced technological infrastructure to support digital learning. More than a beautiful structure with impressive features, this building is the resource we need to be the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care. It's fitting we have named our new building CHEST Global Headquarters.

For us, being global extends well beyond a name for the building. It's what we are. A timely testament to this is our CHEST World Congress, taking place this month in Madrid, Spain, where more than 1,500 attendees and faculty from all regions of the world are sharing best clinical practices. We've partnered with the Spanish Society of Pneumology and Thoracic Surgery to develop the scientific program, ensuring topics presented are of educational value to an

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international audience. And, to keep the momentum of the congress going, we're already thinking about and planning for CHEST World Congress 2016.

Our other education programs, intended to have meaningful impact on global lung health and patient care, consistently prove to have high value for an international audience as well. Our CHEST annual meeting is always well attended by health professionals from around the world. CHEST 2013 was no exception, with 28% – or 1,450 – of the attendees coming from outside the United States and Canada. And, with CHEST endorsement currently being sought for education activities in other countries, from India to Italy, our global impact continues to reach beyond our annual meeting.

MR. MARKOWSKI

As part of our new brand promise to be an essential connection at a critical time, we are committed to delivering knowledge in formats that meet the needs of busy clinicians worldwide. *CHEST* Journal is an ideal medium for this, and more than 21,000 subscribers around the world receive it either in print or online. Various international editions have been published, including those for Brazil, China, Greece, India, Italy, the Middle East, Spain, and Turkey. These editions are published in each country's native language, allowing health-care professionals to read and study the research in a language that is familiar and easily understood.

Our membership reflects our strong representation around the world. We have members in more than 100 countries, and almost 20% of our total membership is from outside the United States and Canada. Our Council of Global Governors, in place to promote leadership opportunities for international members, is operating strong at almost 30 governors. These leaders work to expand our education programs and membership, promote relationships with international industry partners, recruit attendees for CHEST activities, and more. This global community means more ideas, perspectives, and opportunities to collaborate and advance chest medicine around the world.

Over the next few months, we'll be settling into our new CHEST Global Headquarters and establishing ourselves in our new neighborhood. Our presence across the world is already established, and I look forward to watching that grow as we leverage the resources available in our new building. Follow me on Twitter (@PMarkowskiACCP) to read our progress. And, if you're in the Glenview, Illinois, area, stop by our new building. We'll be happy to show you around.

This Month in *CHEST*: Editor's Picks

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

The Utility of Nodule Volume in the Context of Malignancy Prediction for Small Pulmonary Nodules. *By Dr. H. J. Mehta et al.*

Experiences of Racism and the Incidence of Adult-Onset Asthma in the Black Women's Health Study. *By Dr. P. F. Coogan et al.*

TOPICS IN PRACTICE MANAGEMENT

Copy, Paste, and Cloned Notes in Electronic Health Records: Prevalence, Benefits, Risks, and Best Practice Recommendations. *By Drs. J. M. Weis and P. C. Levy.*
Accompanying Editorial
Illusions and Delusions of Cut, Pasted, and Cloned Notes: Ephemeral Reality and Pixel Prevarications. *By Dr. R. Koppel.*

SPECIAL FEATURE

Radiation Risks in Lung Cancer Screening Programs: A Comparison With Nuclear Industry Workers and Atomic Bomb Survivors. *By Drs. R. J. McCunney and J. Li.*
Accompanying Editorial
Radiation Risk From Lung Cancer Screening: Glowing in the Dark? *By Dr. D. C. Christiani.*

NETWORKS: Seasonal disasters, e-cigs in smoke-free times, celebrating transplant anniversaries

Disaster Response

Disaster events related to the winter season

In this winter season we have seen snow, freezing rain, below zero temperatures, and ice storms along with high winds. This makes us more vigilant about the weather and its consequences both outside and inside our homes. This is especially true when ice storms disrupt powerlines, and large areas are without electricity or telephone service.

The first line of defense for storms is preplanning both for places of safety (warming centers, shelters, alternate care sites) and for a public awareness to reach these sites early before conditions become dangerous. A set of winter disaster materials (ie, extra blankets, boots, gloves, hats, flashlights, water, power bars, etc) should be already in place for both home and car. If your car becomes stranded on the highway, it is advised to stay with your car rather than hiking to find help. Mark your car so that highway patrol or snowplow drivers will see you.

FEMA/Aaron Skolnik

The high-risk populations of the elderly and very young should always be suspected of some degree of hypothermia, frostbite, and carbon monoxide exposure if in a confined space indoors. Hypothermia can be classified as mild, moderate, or severe. The classification relates to the core body temperature (range 35-28 degrees C.).

Arrhythmias, including fibrillation and bradycardia, along with tachycardia and hypotension, can be seen. Removal of wet clothing, rewarming, and following ACLS guidelines are starting points for care. Carbon monoxide poisoning should be treated with 100% oxygen.

Preparation and preplanning can be your best outcome in these winter months.

Reference: Sisitsky, A. Winter storm. In: Ciottone GR, ed. *Disaster Medicine.* 3rd ed. Philadelphia, PA: Mosby/Elsevier; 2006:499-501.

Alan Roth, MS, NPS, RRT
Steering Committee Member

Women's Health Network

ENDS of a smoke-free era

The crux of the concern regarding unrestricted access of e-cigarettes to minors is this: potential nicotine addiction. Adolescents have increased susceptibility to nicotine addiction (Dwyer et al. *Pharmacol Ther.* 2009;122[2]:125). The proliferation of e-cigarettes or ENDS (electronic nicotine-delivery systems) challenges decades of efforts to limit marketing to youth and public use of tobacco products (Fairchild et al. *N Engl J Med.* 2014;370[4]:293). Efforts to prevent hard won gains from being undermined have been initiated. Locally, hospitals and college campuses have added e-cigarettes to smoke-free policies. Nationally, the US Food and Drug Administration has been asked to regulate e-cigarettes as tobacco products.

ENDS may have a role as a smoking

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NetWorks' abstract winners – CHEST 2013

For the past 2 years at CHEST, the NetWorks have identified and recognized outstanding abstracts.

This year, the NetWorks recognized 15 outstanding affiliate abstracts in the clinical areas of Allied Health, Cardiovascular Medicine and Surgery, Chest Infections, Clinical Pulmonary Medicine, Critical Care, Disaster Medicine, Interventional Chest/Diagnostic Procedures, Interstitial and Diffuse Lung Disease, Pediatric Chest Medicine, Pulmonary Physiology, Function, and Rehab, Pulmonary Vascular Disease, Respiratory Care, Sleep Medicine, Thoracic Oncology, and Transplant.

Their contributions to clinical research were recognized at the NetWork Featured Lectures during CHEST 2013.

NetWork: Allied Health
Abstract Title: Improving the Specificity of D-Dimer in Pulmonary Embolism
Presented to: Dr. Thomas Murphy

NetWork: Cardiovascular Medicine and Surgery
Abstract Title: Left Ventricular Diastolic Dysfunction Predicts Presence of Pleural Effusion Better Than Left Ventricular Ejection Fraction in Congestive Heart Failure
Presented to: Dr. Amita Kalra

NetWork: Chest Infections
Abstract Title: Characteristics and Outcomes Following Pulmonary Cryptococcosis in Solid Organ Transplantation: Comparison With Nonsolid Organ Transplant Patients
Presented to: Dr. Angel Brown

NetWork: Clinical Pulmonary Medicine
Abstract Title: The Prevalence of Obstructive Lung Pattern on Pulmonary Function Tests in Patients With Congestive Heart Failure
Presented to: Dr. Larry Ladi

NetWork: Critical Care
Abstract Title: Outcomes of Patients in the Marked Interval Recovery After Critical Illness With Low Expected Survival (MIRACLES) Study
Presented to: Dr. James Louisell

NetWork: Disaster Response
Abstract Title: A Quality Improvement Project to Reduce Congestive Heart Failure Mortality With Intensive Case Management
Presented to: Dr. Pratik Dalal

NetWork: Interventional Chest/Diagnostic Procedures
Abstract Title: Pharmacokinetics of Paclitaxel Delivery for the Airway by a New Endobronchial Drug Delivery Catheter: Experimental Study
Presented to: Dr. Hisashi Tsukada

NetWork: Interstitial and Diffuse Lung Disease
Abstract Title: Hypersplenism and Polyarthritis Are Strong Risk Factors for Common Variable Immunodeficiency Related Granulomatous-Lymphocytic Interstitial Lung Disease
Presented to: Dr. Richard Hedelius

NetWork: Pediatric Chest Medicine
Abstract Title: Delay to Diagnosis and Delay to Treatment in South African Children With MDR-TB and HIV
Presented to: Dr. Alfredo Lee Chang

NetWork: Pulmonary Physiology, Function, and Rehab
Abstract Title: The Effect of 6-Week Pulmonary Rehabilitation in COPD: A Randomized Control Study
Presented to: Dr. Deepu Cheriamane

NetWork: Pulmonary Vascular Disease
Abstract Title: Hemodynamic Effects of First-Line Bosentan and Slidenafil Combination Therapy for Pulmonary Arterial Hypertension
Presented to: Dr. Jason Weatherald

NetWork: Respiratory Care
Abstract Title: Positional Changes in Oxygen Saturation at High Altitude
Presented to: Dr. Chandra Patel

NetWork: Sleep Medicine
Abstract Title: Treatment Response in Patients With Opioid-Related Central Sleep Apnea
Presented to: Dr. Roopika Reddy

NetWork: Thoracic Oncology
Abstract Title: The Impact of Microscopically Positive Final Pathologic Margins Identified Days After Surgery in Resected Non-small Cell Lung Cancer (NSCLC)
Presented to: Dr. David Odell

NetWork: Transplant
Abstract Title: Diffuse Alveolar Hemorrhage in Hematopoietic Stem Cell Transplant Recipients: 10-Year Experience in a Single Center
Presented to: Dr. Raolat Abdulai

Continued from previous page

cessation device for current smokers but needs to be studied. Long-term safety of e-cigarettes requires long-term follow-up—unless preliminary evidence is found demonstrating biochemical or molecular effects of exposure to inhaled and environmental "vapors." ENDS are touted as less harmful than burnt or chewed tobacco products, but without data, this is speculation and far from being deemed safe (Schober et al. *Int J Hyg Environ Health*. 2013;Dec 6 [Epub ahead of print]).

Unscientific marketing hype characterizes concerns about ENDS as being paternalistic, overbearing, and causing harm to smokers (Ross G. www.forbes.com; 2/16/2012). In the real world, an encouraging note was the knowledge evinced by savvy fourth graders we met during the ACCP Industry Advisory Council and CHEST Foundation Community Outreach Event at Tonti Elementary School in Chicago during CHEST 2013. They not only knew about e-cigarettes but lumped them with traditional tobacco products into the same health threat bucket. Moving forward, we may need to add "vape" to the pledge not to "smoke" but for now – they got it right.

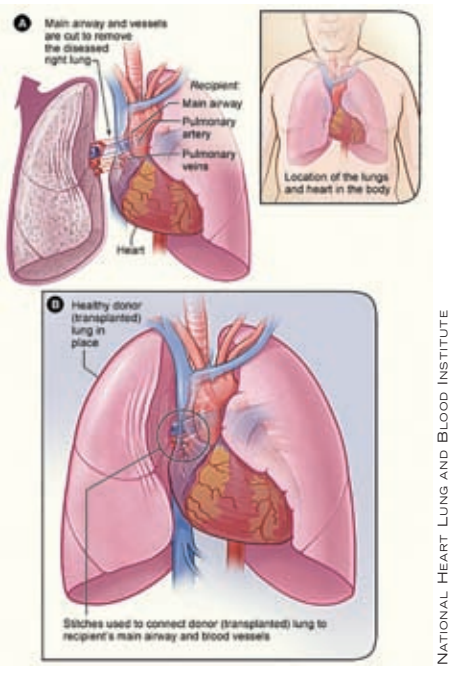
Dr. Linda S. Efferen, FCCP
Steering Committee Member

Transplant

Lung transplantation: golden or pearl anniversary

It has been more than 50 years since the first attempt at human lung transplantation and over 30 years since the first success. The initial obstacles of graft preservation, surgical technique, and immunosuppression have been surmounted with continued refinement and ongoing identification of new challenges. Overall survival is 82% at 1 year, 55% at 5 years, and 31% at 10 years as reported in the October 2013 Registry Report of the International Society of Heart and Lung Transplantation.

This registry reported over 3,700 lung transplants performed annually worldwide (in 2011) and a cumulative total of 40,000 since 1988. Close to 1,800 lung transplants are performed annually in the United States. This volume 10 years ago was approximately 1,000; 20 years ago, 700; and 25 years ago, 33 (Organ Procurement and Transplant Network Data as of February 7, 2014). Improved outcomes, increasing organ utilization, and more efficient and equitable allocation are evidence of success in this field. In clinical practice, the 5-, 10-, and 20-year "well-patient" visits are the reminders.



National Heart Lung and Blood Institute

A large part of this success reflects the ongoing improvements in the "craft" of transplantation and the maturation of a true multidisciplinary field encompassing surgery, medicine, anesthesia, critical care, nursing, radiology, pathology, immunology, pharmacology, social work, nutrition, respiratory therapy, and many others. Yet, the current survival statistics, as well as waiting-list volume and mortality, clearly demonstrate that we still have a long way to go.

Our knowledge of immune function and alloimmunity has grown exponentially. The relatively small number of lung transplants and limited funding pose significant challenges for the translational and clinical research critically necessary to evaluate outcomes and the application of scientific advances in the clinical arena. Lung transplantation occurs at a predictable volume and at a relatively small number of centers, and, thus, multicenter studies are feasible. As lung transplantation moves into its next half century, we must strive to pursue the learning and research opportunities necessary to achieve optimal and equitable allocation and outcomes.

Dr. Jeffrey D. Edelman, FCCP
Steering Committee Member

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Bringing you the latest pulmonary medicine news.

Look to **COPD Hub** for all the cutting-edge news from medical meetings, the FDA, and medical specialty journals.

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FRONTLINE
MEDICAL COMMUNICATIONS

CHEST 2014 opportunities

Abstracts and case reports – free submission

Submit an abstract of your original investigative work or a case report for presentation at the meeting. Categories are available for health professionals at all stages of their careers, including students and residents. Both domestic and international submissions are invited, and submission is free.

Call for abstracts

Submission deadline: April 1

Submit an abstract of your original investigative work for presentation at the meeting. Accepted abstracts will be published in an online supplement to *CHEST*. Three types of abstracts will be considered:

► Slide Presentations
► Poster Presentations
► NEW! Poster Discussions

Learn more and submit at chestmeeting.chestnet.org.

Call for case reports

Submission deadline: April 1

Submit case reports for presentation during special sessions. Accepted case reports (excluding clinical case puzzlers) will be published in an online supplement to CHEST. Four types of case reports will be considered:

► Affiliate Case Reports
► Medical Student/Resident Case Reports
► Global Case Reports
► Clinical Case Puzzlers

Learn more and submit at chestmeeting.chestnet.org.

The CHEST Foundation 2014 Grants and Awards Program

Application deadline: May 31

The CHEST Foundation tradition of recognizing and rewarding healthcare professionals for scholarly projects, and clinical/translational research continues. Grants for both leaders in chest medicine and young investigators are available, including:

► GlaxoSmithKline Distinguished Scholar in Thrombosis—$150,000 over 3 years
► The CHEST Foundation Clinical Research Grant in Pulmonary Arterial Hypertension—$50,000 1-year grant
► The CHEST Foundation and the Pulmonary Fibrosis Foundation Clinical Research Grant in Pulmonary Fibrosis—$30,000 1-year grant
► CHEST Diversity Committee Young Investigator in Pulmonary, Cardiovascular, Critical Care, or Sleep Research Grant—$25,000 1-year grant
► Humanitarian/Community Service Grants

See which grants you are eligible for, and apply today at chestnet.org/grants.

Play CHEST Challenge

Game ends: May 30

CHEST affiliate members, play CHEST Challenge to test your knowledge of pulmonary, critical care, and sleep medicine while competing for prizes.

The three top-scoring programs will compete in the CHEST Challenge Championship at CHEST 2014. All championship players will receive:

► Airfare and registration to CHEST 2014 in Austin, Texas
► Complimentary hotel
► Cash prizes

Game on! Log on and learn more at chestchallenge.org.

Something new is in store – a new way to give to The CHEST Foundation

The next time you visit the online CHEST Store to register for a course, download an app, or purchase self-study materials, make sure to visit the new CHEST Foundation page. You will find the "Make A Gift" link at the bottom of the Bookstore Section. You can also access it directly at www.chestnet.org/store/donate.

Your unrestricted donations will help support the advancement of chest medicine through our ongoing programs and activities, including:

► Clinical research grants and awards.
► Youth tobacco prevention programs.
► Patient and public education.
► Community service and humanitarian programs.

Join your colleagues and friends, and become a member of The CHEST Foundation Annual Giving Club. You will receive special recognition and benefits based on your level of giving.

Please visit the CHEST Store today, and make a donation to become a member!

Questions about making a gift to The CHEST Foundation? Please contact Patti Steele, Annual Fund Manager, at 224/521-9527 or psteele@chestnet.org.

Road to ICD-10: What you should do to prepare

BY JEANNA STOVALL, MSA, RHIA
CHEST Regulations & Reimbursement Director

The October 1, 2014 deadline for ICD-10CM/PCS implementation is less than 8 months away. Whether your health centers ICD-10 preparations are on schedule, or if you are lagging behind, this article will provide useful information no matter what level of preparation your office has completed.

First, identify next steps:

Have you completed an analysis of business impacts, to include end-to-end solutions for the following areas?

► Coding training, billing, EHR (electronic health records), benefits and coding determinations, reimbursement, managed care contracts and auditing.
► Talk with your payers about how ICD-10 implementation might affect your commercial managed care contracts. Since ICD-10 codes are much more specific, payers may modify terms of contracts, payment schedules, reimbursement, and coverage determinations.
► Ensure the EHR system captures the correct ICD-10 code.
► Go to https://implementicd10.noblis.org/ for detailed planning guides.

Do you use billing software, clearinghouse, or billing service to submit claims? Or are you in the process of purchasing and/or contracting with a vendor? Is the vendor using HIPAA version 5010?

► Call the vendor to determine level of compliance to ICD-10 standards, when upgrades and testing will be done (either at cost or no cost).
► Schedule internal testing with the vendor to ensure your practice is able to send and receive transactions with ICD-10 codes.

Review internal standard operating procedures and policies to ensure all practice documents are up-to-date.

Second, see the chart below for a few translated ICD-9 to ICD-10 codes to begin the journey to success.

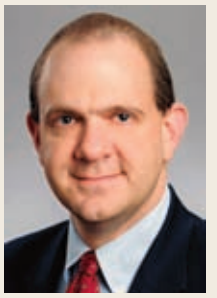
ICD-9	ICD-10
491.21 COPD	J44.0 COPD with acute lower respiratory infection J44.1 COPD with acute exacerbation J44.9 COPD unspecified
481 Pneumonia	J18.0 Bronchopneumonia, unspec. organism J18.1 Lobar pneumonia unspec. organism J18.2 Hypostatic pneumonia unspec. organism J18.8 Other pneumonia, unspec. organism J18.9 Pneumonia, unspec. organism
415.13 Pulmonary embolism	I26.01 Septic pulmonary embolism with acute cor pulmonale I26.02 Saddle embolus of pulmonary artery with acute cor pulmonale I26.09 Other pulmonary embolism with acute cor pulmonale I26.90 Septic pulmonary embolism without acute cor pulmonale I26.92 Saddle embolus of pulmonary artery without acute cor pulmonale I26.99 Other pulmonary embolism without acute cor pulmonale
327.21 Sleep apnea	G47.30 Sleep apnea, unspecified G47.31 Primary central sleep apnea G47.32 High-altitude periodic breathing G47.33 Obstructive sleep apnea (adult) (pediatric) G47.34 Idiopathic sleep-related nonobstructive alveolar hypoventilation G47.35 Congenital central alveolar hypoventilation syndrome G47.36 Sleep-related hypoventilation in conditions classified elsewhere G47.37 Central sleep apnea in conditions classified elsewhere G47.39 Other sleep apnea

FRONTLINE MEDICAL NEWS

SLEEP STRATEGIES: Targeting the neuromuscular disease patient

BY DR. LISA F. WOLFE, FCCP

EDITOR'S NOTE



Dr. Wolfe reports on advances in sleep medicine therapeutics that have improved the ability of sleep specialists to manage patients with neuromuscular disease. In many practices (including my own), patients with hypercapnia of all etiologies are referred to sleep specialists because of our greater familiarity with devices used for noninvasive ventilation, even though their disease state is not specific to sleep and their management is not routinely covered during sleep medicine training. The group with neuromuscular disease is the most challenging of these populations, since they have additional needs that most labs and specialists are unprepared to meet. Dr. Wolfe argues that the challenge of managing these patients is best seen as an opportunity, since many of them have been orphaned by other specialists; changes in the finances of our practices and the technologies available for home ventilation may strengthen our ability to manage the weak.

Dr. David Schulman, FCCP
Section Editor

The provision of home-based ventilatory support has been the purview of the pulmonologist for more than 50 years. Before the birth of sleep medicine as a dedicated specialty, the focus of home ventilation was on the care of patients with neuromuscular disease (NMD), who were required to use full-sized mechanical ventilators, nonvented masks, and bulky tubing sets with double-lumen active circuits served by an external pressure line, since this was the only equipment available at the time. These large devices were cumbersome and limiting in their lack of portability but were well suited to the needs of patients with NMD. They used volume-cycled ventilation, ensuring full ventilatory support with a guaranteed inspiratory time and respiratory rate. Although effective, they lacked many of the conveniences that are now the norm, including integrated humidifiers and a wide range of mask options.

In the 1980s, continuous positive airway pressure (CPAP) became widely available as therapy for OSA (Shepard et al. *J. Clin. Sleep Med.* 2005;1[1]:61). The large number of patients with OSA spawned a revolution in home respiratory therapy, driven by a rapid expansion in resources, including the development of outpatient facilities dedicated to diagnosing and treating sleep-related breathing disorders, smaller and lighter equipment with novel ventilator modes, improved options for facial appliances, and other comfort-oriented features. While a new generation of practitioners pursued training in the management of sleep-disordered breathing, it was largely focused on OSA, with very limited experience managing the special needs of the NMD patient population.

Sleep laboratories often lacked the necessary amenities and frequently performed inappropriate diagnostic studies that delayed the time to initiation of noninvasive ventilation (NIV) (Boitano and Benditt. *Respir. Care* 2011;56[6]: 878). Titration studies were often performed without defined protocols that would guarantee adequate patient ventilation; the first such protocol for sleep labs to use as a guide to titrating patients with NMD was not published until 2010. (Berry et al. *J Clin. Sleep Med.* 2010;6[5]:491).

For years, many clinicians caring for NMD patients avoided referring them to sleep programs, trying to provide care with minimal support from pulmonary physicians.

In addition to the issues related to a lack of resources, there were other barriers delaying the marriage between sleep medicine and these patients. For example, although the American Academy of Neurology recommends the use of NIV as standard of care for patients with amyotrophic lateral sclerosis, they do not recommend the involvement of a sleep laboratory, choosing instead to rely upon guidance from pulmonary function testing (Miller et al. *Neurology.* 2009;*739*[15]:1218). This recommendation is based on several studies, including a prominent randomized control trial, which demonstrated a mortality and quality of life benefit from NIV, though it did not use polysomnography to optimize the treatment (Bourke et al. *Lancet Neurol.* 2006;5[2]:140). For years, many clinicians caring for NMD patients avoided referring them to sleep programs, trying to provide care with minimal support from pulmonary physicians. In a survey of Muscular Dystrophy Association clinics from 2000, polysomnography was only provided by a third of programs; the authors subsequently call the procedure unnecessary, as well as "uncomfortable and often painful" (Bach and Chaudhry. *Am. J. Phys. Med. Rehabil.* 2000;79[2]:193).

Advances in sleep medicine therapeutics

New developments seem likely to bring these previously discordant groups into a more harmonious relationship, driven by changes on two fronts. First, the role of the sleep lab is changing, as home sleep testing combined with auto-titrating CPAP machines play a larger role in the management of OSA. For brick-and-mortar labs needing to reinvent themselves, one option is to expand care to aggressively address the needs of those with non-OSA forms of sleep-disordered breathing, including nocturnal hypoventilation due to NMD. Though less prevalent, these conditions will continue to require in-lab sleep testing, although labs will need to adapt to meet the additional needs of these patients, as outlined in Table 1. The physical design of the lab will need to better accommodate power chairs, with additional space for caregivers. Polysomnographic technologists will need to have equipment to facilitate bed-to-chair transfers. Respiratory assist device options will need to be expanded to include those more capable of supporting ventilation, while study montages will need to include parameters to better assess ventilation, work of breathing, and/or accessory muscle use. Lastly, labs will need to develop more productive relationships with durable medical equipment providers to help them understand that patients with NMD have different needs than those with OSA.

The second major development that may allow sleep providers to better service these patients is the advent of new technology for home-based ventilation. Many of the advantages previously available only with CPAP devices have now been made available for use with noninvasive ventilators. These new NIV devices are smaller, and use lighter, single-lumen passive circuits that can utilize any of the commonly available CPAP masks instead of requir-

Continued on page 31

Table 1: Sleep lab redesign for NMD

Physical redesign	Technology redesign	DME redesign
Power chair space • Hallways • Bathrooms • Scales **Chair to bed transfers** • Hoyer lift • Hospital bed • Sliding boards **Respiratory support** • Nebulizer • Suction devices **Caregivers** • Space to sleep • Allow caregivers to provide nonsleep medical care	**Monitoring devices** • End tidal and/or transcutaneous CO_2 • Accessory respiratory muscle monitoring (i.e., diaphragm or intercostal EMG) **Respiratory devices** • Bilevel ST and/or PC • VAPS device • Home-based MV **Titration algorithm** • Tidal volume goals • Respiratory rate goals • Support inspiratory time • Use ventilatory changes rather than supplemental oxygen to address desaturation • Consider adding daytime titrations for mouthpiece ventilation	**Diagnostic sleep testing** • May not be needed • Testing with FVC/MIP/CO_2/Overnight oximetry should be used to qualify the patient for NIV **Report diagnosis** • Sleep reports should state NMD and possibly central but not obstructive sleep apnea as the diagnosis **DME support** • When choosing an ST, PC, or VAPS device, confirm the DME has: ◦ The device available ◦ Been trained in the use and care of the device

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Tennessee

Pulmonary Program Director James H. Quillen College of Medicine seeks candidates at the Associate/Full Professor level with M.D. and active ABIM certification in Pulmonary and Critical Care Medicine to serve as Fellowship Director. Candidates must have an established record of scholarship and mentoring of junior faculty. ETSU is an AA/EOE employer.

View position summary and apply at **https://jobs.etsu.edu/applicants/jsp/shared/Welcome_css.jsp**

South Florida Critical Care Medicine - Nocturnist

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 memorialphysician.com

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Pregabalin improves RLS with less augmentation

BY MARY ANN MOON
Frontline Medical News

Oral pregabalin significantly improved symptoms of moderate to severe restless leg syndrome, compared with both placebo and pramipexole, in an industry-sponsored, international randomized trial.

Just as important, pregabalin was associated with significantly less iatrogenic worsening, or augmentation, of symptoms than was pramipexole, Richard P. Allen, Ph.D., of the department of neurology at Johns Hopkins University, Baltimore, and his associates reported in the New England Journal of Medicine.

Pregabalin also was associated with lower rates of nausea, vomiting, and headache than pramipexole, but patients taking pregabalin had higher rates of suicidal ideation, dizziness, somnolence, and weight gain – "factors that may limit its long-term use," the investigators said.

Dopaminergic drugs such as pramipexole are known to be associated with augmentation in which symptoms intensify and may involve more parts of the body and start earlier in the day than before treatment. Pregabalin is a nondopaminergic agent with analgesic and anticonvulsant activity, and was recently reported to be effective against restless leg syndrome.

Dr. Allen and his colleagues assessed both agents in a study involving 719 adults with moderate to severe primary restless leg syndrome. The patients did not undergo an objective assessment of sleep.

In the double-blind trial sponsored by Pfizer, the manufacturer of pregabalin, these patients were randomly assigned to receive 0.25 mg pramipexole, 0.5 mg pramipexole, 300 mg pregabalin, or matching placebo capsules every day for 12 weeks. At that time, all patients receiving placebo were randomly reassigned to one of the three active treatments for the remainder (40 weeks) of the 1-year study. The mean age of the patients ranged from 54 to 57 years in the groups.

Periodically, participants reviewed with clinicians their daily symptom logs and completed the International RLS (IRLS) Study Group Rating Scale, which measures subjective symptom severity on a 0-40 scale, with higher scores indicating worse symptoms.

Clinicians also assessed patients' symptoms using the Clinical Global Impression of Improvement (CGI-I) scale, and they assessed possible augmentation using their clinical judgment, scores on the Augmentation Severity Rating Scale, and scores on the Structured Interview for the Diagnosis of Augmentation instrument.

At 12 weeks, patients who received pregabalin showed significantly greater improvement in IRLS scores than did those who received placebo, improving from 22.3 to 10.9 for pregabalin-treated patients and from 22.4 to 15.5 for placebo-treated patients. Pregabalin-treated patients also were more likely to have "very much improved" or "much improved" ratings on the CGI-I, compared with placebo (71.4% vs 46.8%).

Patients who received pregabalin also reported greater improvement in several sleep parameters, including waking after sleep onset, quality of sleep, and total sleep time, compared with those who received placebo. These measures also were significantly better for patients treated with 0.5 mg pramipexole when compared with placebo-treated patients, but not for those taking 0.25 mg pramipexole.

The finding that pregabalin is effective for RLS even though it has no direct effect on dopaminergic systems calls into question the rationale for dopaminergic therapies. Dopaminergic treatments have been predicated on the assumption that RLS results primarily from dopamine abnormalities, Dr. Allen and his associates noted (N. Engl. J. Med. 2014 Feb. 12 [doi:10.1056/NEJMoa1303646]).

Pregabalin was associated with significantly less augmentation than the 0.5-mg dose of pramipexole, but not the 0.25-mg dose. "Among patients receiving active treatment over the entire 52-week study period, augmentation occurred in 3 of 176 patients receiving pregabalin (1.7%), 11 of 167 receiving 0.25 mg of pramipexole (6.6%), and 16 of 178 receiving 0.5 mg of pramipexole (9.0%)," the investigators wrote.

Dr. Allen reported ties to Pfizer, UCB Pharma, Impax Pharmaceuticals, Luitpold Pharma, Xenoport, GlaxoSmithKline, and Pharmacosmos. His associates reported ties to Pfizer and numerous industry sources. Four authors are employees of Pfizer.

VIEW ON THE NEWS

This carefully conducted study is one of a few head-to-head studies of two classes of medications that have been reported for the treatment of restless leg syndrome. It presents compelling evidence for the efficacy of a nondopaminergic drug in the treatment of RLS and thereby implicates a role for nondopaminergic pathways in the disease, said Dr. Sudhansu Chokroverty.

Although augmentation occurred significantly more often with pramipexole, patients who took pregabalin still had a rate of 1.7%, which "raises the question of whether augmentation is related to medication, is intrinsic to RLS, or is related to individual patient characteristics," he noted.

Dr. Chokroverty is with the department of neurology at the New Jersey Neuroscience Institute, JFK Medical Center, Edison. He reported no relevant financial conflicts of interest. These remarks were taken from his editorial accompanying Dr. Allen's report (N. Engl. J. Med. 2014 Feb. 12 [doi:10.1056/NEJMe1313155]).

FDA approves tasimelteon for sleep-wake disorder

BY ALICIA AULT
Frontline Medical News

The U.S. Food and Drug Administration approved tasimelteon (Hetlioz) for sleep disturbances in the blind.

The drug, a melatonin receptor agonist, is indicated only for totally blind individuals who have chronic non-24-hour sleep-wake disorder.

With non-24, as it is called, the circadian rhythm is disrupted, causing difficulty with the timing of sleep. People who have the condition sleep when they should not and can't sleep when they should.

"Non-24-hour sleep-wake disorder can prevent blind individuals from following the normal daily schedule that we all take for granted," said Dr. Eric Bastings, deputy director of the division of neurology products in the FDA's Center for Drug Evaluation and Research, Silver Spring, Md. "Hetlioz can improve the ability to sleep at night and to be active during the day."

The FDA and tasimelteon's maker, Vanda Pharmaceuticals, estimate that 80,000-100,000 blind individuals have non-24 disorder.

Tasimelteon was given priority review by the FDA because it was deemed to have the potential to significantly improve patients' lives. Non-24 also is considered a rare condition, so tasimelteon received orphan-drug designation by the FDA, which gives it additional years of market exclusivity.

"Totally blind people have struggled with the problems brought on by non-24-hour sleep-wake disorder, sometimes for their entire life, without understanding what causes it and without being able to do anything about it," said Steven W. Lockley, Ph.D., of the sleep medicine division at Brigham and Women's Hospital, Boston, and an investigator for Vanda. The approval "means that, for the first time, these patients have access to an approved, safe and effective treatment for their difficult debilitating disorder," Dr. Lockley said in a statement issued by Vanda.

'For the first time, [blind people] have access to an approved, safe and effective treatment.'

DR. LOCKLEY

The company evaluated tasimelteon's effectiveness in 104 participants in two clinical trials of totally blind individuals with non-24 disorder. Patients receiving the therapy had significantly increased nighttime sleep and decreased daytime sleep duration, compared with placebo, according to the FDA.

The most common side effects were headache, elevated liver enzymes (alanine aminotransferase), nightmares or unusual dreams, disturbed night's sleep, upper respiratory or urinary tract infection, and drowsiness. To reduce the risk of decreased mental alertness, the agency said, tasimelteon should be taken at the same time every night before bedtime and activities should be limited after taking the drug.

Vanda said that tasimelteon should be available within a few months as a 20-mg capsule. The company also has studied the drug for chronic insomnia and depression. It ended the depression studies in early 2013 and is not currently actively pursuing the insomnia indication.

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ing a nonvented mask. By eliminating the complex circuitry and limited mask choices of traditional home-based mechanical ventilators and replacing them with systems that are familiar to sleep medicine physicians and durable medical equipment providers, access to care becomes more realistic for all patients with NMD.

The implementation of standardized protocols for VAPS titration would require a fundamental shift in the way polysomnographic technologists understand positive airway pressure treatments.

New NIV devices are designed to specifically address problems of hypoventilation; these devices allow provisions for assured inspiratory times and respiratory rates, just like home-based mechanical ventilators. This is important because diaphragmatic fatigue, due to muscle weakness in neuromuscular patients, may present with either failure to initiate breaths or premature termination of breathing efforts. To completely support the work of breathing, these devices must be able to control the frequency and length of breath delivery. The new NIV devices have also been fitted with microprocessors and servo-motors that allow them to target specific volumes and minute ventilations. Referred to as volume-assured pressure support devices (VAPS, see Table 2), these machines offer a fresh perspective on autotitration technology; rather than targeting patency of the upper airway just as traditional autotitrating PAP devices do, VAPS software measures markers of ventilation and augment support until pre-set targets are achieved.

Table 2: Options in Volume Assured Pressure Support (VAPS)

Device	Manufacturer	Modes	Target of Ventilation	Unique Options
Average volume assured pressure support	Philips Respironics	S, ST, and PC	Tidal volume	Rate of change is adjustable
Intelligent volume assured pressure support	ResMed	ST	Alveolar ventilation	Trigger and cycle adjustments
SOMNOvent auto-ST	Weinmann	S/ST	Upper airway patency, respiratory rate, and tidal volume	Not available in the U.S.
Trilogy	Philips Respironics	S, ST, PC, MPV, and AVAPS-AE	Tidal volume (upper airway patency with AE)	Integrated battery backup

S = spontaneous, ST = spontaneous timed, PC = pressure control, MPV = mouthpiece ventilation

FRONTLINE MEDICAL NEWS

The implementation of standardized protocols for VAPS titration would require a fundamental shift in the way polysomnographic technologists understand positive airway pressure treatments, targeting an adequate ventilation rather than patency of the upper airway. Such a protocol would require the technologist to set a pressure support range with a target tidal volume, inspiratory time, and respiratory rate. In addition, end-tidal carbon dioxide levels and respiratory muscle effort would need to be monitored throughout the study, with subsequent tweaking of the range of pressure support and expiratory pressure for hypoventilation and upper airway obstruction, respectively. Once the titration is complete, implementation of VAPS at home should help to compensate for fluctuations in disease severity and variability of hypoventilation with sleep stage and body position (Jaye et al. *Eur Respir J.* 2009;*33*[*3*]:566). These devices also have internal batteries allowing for daytime use and can support noninvasive ventilation in a portable fashion using a mouthpiece, which can be set to deliver breaths on demand, allowing "off time" for coughing, swallowing, or speech.

Conclusion

Advancements in technology will foster a healthier relationship between sleep medicine and providers that treat neuromuscular disease, ushering in a new generation of sleep specialists and labs that can address sleep-related breathing disorders other than obstructive sleep apnea. While caring for these individuals will initially be a challenge to some of us who have been in practice for years, it is a natural extension of the medicine we have always practiced and will lead to improved provision of care to and quality of life for some of our sickest patients.

Dr. Wolfe is Associate Professor in Medicine - Pulmonary and Neurology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

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