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INSIDE

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Malaria in the United States

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Four of the 1324 patients with malaria diagnosed in the United States and its territories in 2004, and reported to the CDC, died. Malaria was diagnosed in 30 pregnant women, and there were 3 cases of congenital malaria.*

Source: Skarbinski J, et al. Malaria Surveillance—United States, 2004. *MMWR Surveill Summ*. 2006;55:23-37.

THE CDC RECEIVED REPORTS OF 1324 PATIENTS WITH MALARIA IN the United States and its territories diagnosed in 2004; 4 patients died. This represented a 3.6% increase in cases from the previous year. US civilians accounted for 58.5% of cases. Of the 80.2% of cases in which species identification was accomplished, 49.5% were due to *P. falciparum*, 23.8% to *P. vivax*, 3.6% to *P. malariae*, and 2.0% to *P. ovale*; 1.3% of cases were due to mixed species infection.

Of the 4 autochthonous cases, one was laboratory-acquired and 3 were congenital. Of the remaining non-autochthonous cases, 68.0% were acquired in Africa, 14.5% in Asia, and 14.5% in Central and South America. Three US jurisdictions accounted for 35% of cases: the New York City Health Department reported 16.2% of cases, California 9.8%, and Texas 9.3%. Thirty cases of malaria occurred in pregnant women; only 10% took chemoprophylaxis. Four patients died.

Symptoms began < 1 month after arrival in the United States in 80.9% of *P. falciparum* infections and 43.0% of *P. vivax* infections. Of the patients for whom the information was available, 65.1% had taken no chemoprophylaxis, while 10.4% took inappropriate chemoprophylaxis. Of the 50 cases of *P. vivax* and 5 of *P. ovale* that occurred despite a history of having received appropriate chemoprophylaxis, 45.5% were consistent with relapsing infection occurring > 45 days after arrival in the United States. Nineteen cases were indeterminate due to lack of information. Only 11 cases, all caused

by *P. vivax*, occurred < 45 days after arrival in the United States, consistent with chemoprophylaxis failure, but only 4 of these reported compliance with their regimen. Fifty-eight cases of *P. falciparum* infection occurred in individuals given appropriate chemoprophylaxis, but only 13 reported compliance.

COMMENTARY

The major reason that cases of malaria continue to be seen in the United States is a lack of compliance with appropriate chemoprophylaxis during travel in endemic areas. A significant part of this problem is represented by travelers visiting family and friends, a group that comprised 52.6% of the patients with malaria. This is a group that unfortunately often eschews malaria prophylaxis.

There were 30 cases of malaria in pregnant women, and only 10% of these had taken chemoprophylaxis. The morbidity of malaria is increased in pregnancy and may, of course, affect the fetus, in addition to the mother. In general, pregnant women should avoid travel to malaria endemic regions. If they, nonetheless, elect to travel, in addition to taking measures to prevent mosquito bites, they should take chloroquine or mefloquine, depending upon the presence or absence of chloroquine resistance in the area visited. Atovaquone/proguanil, doxycycline, and primaquine should not be used. Febrile illness in neonates and infants born to mothers with a history of travel or emigration from a malaria endemic region, a history of malaria, or of illness compatible with malaria, should prompt examination of a peripheral blood smear.

Clinicians must remain alert to the diagnosis of malaria. In patients with a positive smear who have traveled to an area with chloroquine-resistant *P. falciparum*, treatment should be promptly initiated that is effective against these strains, even if the species cannot be immediately determined. ■

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VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER: Gerard Gemazian.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

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Leslie Hamlin,
Associate Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Cubicin® (Daptomycin): Treatment of *S. Aureus* Bacteremia/Endocarditis

SPECIAL FEATURE

By Erica Tam, Yanina Goykhman, Jessica C. Song, and Paul Hsiao

Erica Tam and Yanina Goykhman are PharmD Candidates, University of the Pacific, Paul Hsiao, PharmD, is Pharmacist Specialist, Santa Clara Valley Medical Center, and Jessica C. Song is Pharmacy Residency Coordinator, Santa Clara Valley Medical Center

Erica Tam, Yanina Goykhman, Jessica C. Song, and Paul Hsiao report no financial relationships relevant to this field of study.

Introduction

In recent years, S. aureus has been identified as the most common cause of infective endocarditis (IE). Risk factors for *S. aureus* IE include the presence of indwelling prosthetic devices and intravascular catheters.[1]

S. aureus-induced IE is a major problem in hospitals and communities alike. With the overuse of traditional antibiotic therapy such as nafcillin and oxacillin, there has been a surge of drug-resistant bacteria emerging for which β-lactam antibiotics are no longer effective.[1] Vancomycin is generally regarded as the mainstay of treatment for methicillin-resistant *S. aureus* (MRSA),[2] but cases of vancomycin-resistant or intermediate-resistant *S. aureus* strains have been reported.[3,4] In light of the recent emergence of reduced vancomycin susceptibility in *S. aureus*, the need for new antimicrobial agents with expanded indications is greater than ever.

Daptomycin, a cyclic lipopeptide produced by Streptomyces roseosporus has been of particular interest due to its activity against MRSA, MSSA (methicillin-susceptible *S. aureus*), vancomycin-resistant Enterococci

Table 1

Pharmacologic Properties of Cubicin® (Daptomycin)

Brand/Generic[8]	Cubicin® (Daptomycin)				
Classification[8]	Cyclic lipopeptide antibacterial agent				
Mechanism of Action[8]	Following binding to bacterial membrane, depolarization of the membrane potential occurs. The disruption of the membrane potential results in inhibition of protein, DNA/RNA synthesis, which results in bacterial cell death.				
Indications[8,9] (FDA labeled)	Cubicin® (Daptomycin) is indicated for the treatment of the following infections: • Complicated skin and skin-structure infections caused by susceptible strains of the following organisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. Equisimilis and *Enterococcus faecalis* (vancomycin-susceptible strains only). Consider a combination therapeutic regimen if the documented or presumed pathogens include anaerobic or Gram-negative organisms. • Cubist Pharmaceuticals Inc. received an Approvable Letter for the sNDA (label expansion to include *Staphylococcal aureus* bacteremia, including those with known or suspected infective endocarditis)				
Pharmacology (young, healthy adults)[8]	Half-life, normal renal function (h)	C_{max} (μ/mL)	T_{max} (h)	Protein bound (%)	Recovered unchanged in urine (%)
Dose 4 mg/kg 6 mg/kg	 8.1 8.9	 57.8 98.6	 0.8 0.5	 92% (for doses of 4-6 mg/kg)	 53.0% 47.4%
How Supplied	**Injection:** Pale yellow to light -brown lyophilized cake; single-use 250 mg and 500 mg/vials				
Dose[8,10,11]	skin/skin structure infections	4 mg/kg IV q 24h (CrCl ≥ 30 mL/min) **Duration for Phase III studies was 7-14d** 4mg/kg IV q 48h (CrCl < 30 mL/min; including hemodialysis or CAPD)	Adult patients (note: ages ranged from 18-85 in 2 pivotal clinical trials that included pts with diabetic foot infections)		
	Definite or possible MSSA/MRSA infective endocarditis (IE)	6 mg/kg IV q 24h Duration of treatment Left-sided IE (MSSA/MRSA): 28-42d Complicated right-sided IE (MSSA): 28-42d Complicated right-sided IE (MRSA): 28-42d Uncomplicated right-sided IE (MSSA): 14-28d	Note: The median age of daptomycin-treated patients was 45 years, with a mean (SD) of 46.7±15.7		
Dosage Adjustment[6]	**Renal Impairment:** • Increase dosing interval to 48 hours (refer to dose above) if CrCl < 30 mL/min (including HD or CAPD) • Should be given after hemodialysis on hemodialysis days **Hepatic Impairment:** • No dosage adjustment is required for mild-to-moderate hepatic insufficiency (Child-Pugh Class B) • Use in severe hepatic insufficiency has not been adequately evaluated				
Storage/Administration[8]	**Storage:** • Store vials at refrigerated temperatures (2°-8°) • Reconstituted solutions stable for 12h at room temperature, 4h when refrigerated • Diluted solutions stable for 12h at room temperature, 48h when refrigerated • Combined time (vial and infusion bag) should not exceed 12h at room temperature, 48h refrigeration **Administration:** • Reconstitute 500 mg vial with 10 mL normal saline (incompatible with dextrose-containing solutions) • Further dilute reconstituted solution with normal saline and infuse over a period of 30 minutes				
Monitoring Requirements[8]	• Monitor serum creatine phosphokinase (CPK) levels weekly during daptomycin therapy • DC daptomycin if patient experiences unexplained signs/symptoms of myopathy				
Contraindications[8]	Hypersensitivity to daptomycin or any other component of the formulation				

. . .Table 1 continued on the next page

Table 1

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Warnings/Precautions[8,11]	• **Myopathy** has been documented with daptomycin use; monitor CPK weekly • **Pseudomembranous colitis** has been reported with most antibiotics, including daptomycin
Adverse Effects[8,11]	**Adverse effects occurring in ≥ 5% patients with skin/skin structure infections:** constipation, nausea, diarrhea, and headache **Serious adverse effects:** In the S. aureus bacteremia (including IE patients) study,[11] 21 measurements of CPK levels in excess of 500 were reported, compared with 3 measurements from 3 different comparator-drug-treated patients
Drug/Food Interactions[8,11]	HMG CoA Reductase Inhibitors • Of the 11 (out of 120) daptomycin-treated patients in the S. aureus bacteremia study[11] with CPK > 500, 4 (36.4%) received prior or concomitant therapy with simvastatin/atorvastatin • Consider suspending the use of HMG CoA Reductase Inhibitors during daptomycin therapy
IV Solution Compatibility[8]	**Incompatible when admixed:** Dextrose-containing solutions
Pregnancy Category[8]	**B**
Lactation[8]	Excretion in human milk unknown, use caution

Daily Cost of Therapy for a 70 kg Patient[a]	Daptomycin 6 mg/kg	Vanco 1 g IV q 12h	Nafcillin 2 g IV q 4h	Cefazolin 2 g IV q 8h	Linezolid 600 mg IV q 12h[b]
	$135.98	$16.00	$69.42	$5.99	$145.00

[a] Pricing derived from SCVMC Inpatient Purchasing Department (excluding bag charges and labor costs)

[b] The daily cost of linezolid 600 mg po q 12h is $108.22. Tigecycline is not indicated for the treatment of *S. aureus* IE, but the daily cost of 100 mg IV/d is

Table 2

American Heart Association Recommendations for the Treatment of *Staphylococcus aureus* Infective Endocarditis

Type of Infection	Regimen	Duration
Oxacillin-susceptible strains (absence of prosthetic valve)	Nafcillin or oxacillin 12 g/24h IV in 4-6 equally divided doses ± Gentamicin sulfate, 3 mg/kg per 24h IV/IM in 2-3 equally divided doses	6 week 3-5 days
For penicillin-allergic (non-anaphylactoid type); absence of prosthetic valve; MSSA	Cefazolin 6 g/24h IV in 3 equally divided doses ± Gentamicin sulfate, 3 mg/kg per 24h IV/IM in 2-3 equally divided doses	6 week 3-5 days
Oxacillin-resistant strains (absence of prosthetic valve)	Vancomycin 30 mg/kg per 24h IV in 2 equally divided doses	6 week
Oxacillin-susceptible strains, prosthetic valve[a]	Nafcillin or oxacillin 12 g/24h IV in 4-6 equally divided doses + Rifampin 900 mg per 24h IV/PO in 3 equally divided doses + Gentamicin sulfate, 3 mg/kg per 24h IV/IM in 2-3 equally divided doses	≥ 6 weeks ≥ 6 weeks 2 weeks
Oxacillin-resistant strains, prosthetic valve	Vancomycin 30 mg/kg per 24h IV in 2 equally divided doses + Rifampin 900 mg per 24h IV/PO in 3 equally divided doses + Gentamicin sulfate, 3 mg/kg per 24h IV/IM in 2-3 equally divided doses	≥ 6 weeks ≥ 6 weeks 2 weeks

[a] Consider cefazolin for non-immediate-type hypersensitivity to penicillin

(VRE), and linezolid-resistant *E. faecium* strains.[5,6] Its unique mechanism of action sets it apart from other antibiotics currently on the market, as its bactericidal action appears to be through inhibition of amino acid transport and membrane disruption.[5] Unlike other available agents, such as vancomycin, quinupristin/dalfopristin, and linezolid, daptomycin offers once daily dosing and rapid in vitro bactericidal activity against VRE and MRSA.[7]

At present, daptomycin is indicated for use in the treatment of complicated skin/skin structure infections caused by susceptible strains of *S. aureus* (including MRSA), *Streptococcus pyogenes*, S*treptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *Equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible strains only).[8] Cubist Pharmaceuticals Inc. received an Approvable Letter for the supplemental New Drug Application (label expansion to include *S. aureus* bacteremia, including those with known or suspected IE) on March 24, 2006.[9] This article will review daptomycin's: 1) spectrum of activity, pharmacological and pharmacokinetic properties; 2) safety profile; 3) dosage, interaction, and resistance patterns; and 4) clinical efficacy in IE patients.

Pharmacology/In Vitro Studies

A summary of the pharmacologic, pharmacokinetic, and clinical properties of daptomycin can be found in *Table 1.*

Studies assessing the effectiveness of daptomycin in animal model *S. aureus* IE suggest that it is as effective or better than vancomycin, penicillin, and semi-synthetic penicillins, such as nafcillin and cloxacillin.[12,13] Cantoni and colleagues compared daptomycin to cloxacillin in the treatment of rats with *S. aureus* IE,[13] and found that daptomycin was as effective in low-bacterial count infections, but more effective against high-bacterial count infections. Also, Cantoni et al demonstrated that earlier treatment resulted in a faster recovery.

Of particular importance is the finding that daptomycin is effective against glycopeptide-intermediate-resistant-*S. aureus* (GISA) infections.[3,4] This finding is clinically significant because vancomycin, a glycopeptide, has been used excessively since the development of methicillin-resistant strains. Due to this overuse, vancomycin-resistant strains have developed.

Data from 2 studies revealed the superior efficacy of daptomycin in combination with gentamicin, compared with daptomycin monotherapy, for the treatment of in vitro pharmacodynamic models of *S. aureus* IE.[14,15] LaPlante et al[14] showed that the time-to-achieve bactericidal activity against MSSA and MRSA was 3-fold faster with combination therapy (daptomycin 6 mg/kg + gentamicin 1.3 mg/kg q 12h) compared with daptomycin monotherapy. Synergistic activity against GISA was attained within 48 hours of starting combination therapy. Tsuji and colleagues[15] reported that a combination regimen of daptomycin 6 mg/kg and a single-dose of gentamicin 5 mg/kg reduced the time-to-kill by 6- to 8-fold, compared with daptomycin monotherapy, with less toxicity.

Current Endocarditis Guidelines

Current American Heart Association (AHA) guidelines for the treatment of *S. aureus* IE highlight the therapeutic options for patients lacking prosthetic valves and for prosthetic valve patients.[1] In addition, therapeutic regimens were further subdivided according to the causative pathogen (MSSA or MRSA). *Table 2* summarizes the AHA recommendations for the treatment of *S. aureus* IE.

Case Studies

A review of published literature showed that most reports of daptomycin use for the treatment of IE patients have been presented as retrospective analyses or as case reports.[16-18] Segreti and colleagues conducted a retrospective analysis of 31 daptomycin-treated patients with bacteremia ± IE, most of whom failed previous antimicrobial therapy.[16] Of the 30 bacteremic patients, 9 were classified as IE patients. MRSA, VRE, and MSSA represented the most commonly implicated pathogens in this study. Clinical cure rates for patients infected with MRSA, MSSA, and VRE were 100% (11/11), 86% (6/7), and 45% (5/11), respectively. Six of the 9 IE patients were successfully treated with daptomycin. Six of the 7 deaths were attributed to incurable VRE infection. Daptomycin was generally well-tolerated, but 3 of 31 patients experienced elevations in creatine kinase (CK) levels in excess of 10 times the baseline level. However, CK elevations were attributed to recent surgical procedures.

Veligandla and colleagues described the case of a patient experiencing severe myalgia associated with daptomycin use.[17] In this report, a 26-year-old African-American woman with MRSA IE was administered intravenous daptomycin due to intolerance to vancomycin and quinupristin/dalfopristin. Although her CK level was well below the level associated with significant myopathy symptoms, the patient nevertheless experienced significant muscle pain that subsided shortly (few days) after treatment discontinuation.

Table 3

Key Features of the Phase III Daptomycin Study[11]

Patient Population	Study Definitions	Treatment Groups
Patients: • *S. aureus* bacteremia, including those with known/suspected IE (n = 315 intent-to-treat patients) • Infective Endocarditis (Daptomycin group, n = 28 intent-to-treat patients) • LIE, 32.1% • RIE (uncomplicated): 21.4% • RIE (complicated): 46.4% • Infective Endocarditis (Comparator group, n = 25 intent-to-treat patients) • LIE, 36% • RIE (uncomplicated): 16% • RIE (complicated): 48% • Baseline pathogen • MSSA, 53.6-56.0% • MRSA, 44.0-46.4% **LIE = Left-sided IE** **RIE = Right-sided IE**	**Complicated *S. aureus* right-sided IE** • Definite or possible IE according to modified Duke Criteria; and • Echocardiographic evidence indicating no predisposing pathology or active involvement of either the mitral valve or the aortic valve; and • Any of the following additional criteria: patient was not an IV drug abuser, evidence of extra-pulmonary sites of infection, serum creatinine ≥ 2.5 mg/dL, or blood cultures yielded MRSA **Complicated *S. aureus* bacteremia** • Patient did not have IE according to the Modified Duke Criteria; and • *S. aureus* was isolated from blood cultures obtained on at least two calendar days up through Day 5 (one blood culture must have been obtained from a fresh venipuncture site and one blood culture must have been obtained on the calendar day of or on the day immediately preceding the first dose of study medication); and/or •Metastatic foci of infection (deep tissue involvement) was present including, for example, septic arthritis, deep tissue abscess, or infection involving prosthetic material including intravascular foreign material not removed by Day 4.	**Dosing of Study Drugs** Daptomycin 6 mg/kg IV q 24h Vancomycin 1 g IV q 12h Semi-synthetic penicillin **Left-sided IE Daptomycin Regimen** 1. MSSA: Daptomycin x 28-42 days + Gentamicin first 4 days (or until blood culture negative x 48h) 2. MRSA: Same as MSSA **Complicated RIE Daptomycin Regimen** 1. MSSA: Daptomycin x 28-42 days 2. MRSA: Daptomycin x 28-42 days or 14-28 days if only complicating factor was MRSA **Uncomplicated RIE Daptomycin Regimen** 1. MSSA: Daptomycin x 14-28 days **Complicated *S. aureus* Bacteremia** 1. MSSA: Daptomycin x 28-42 days 2. MRSA: Same as MSSA **Note: Vancomycin dosing was adjusted for renal failure** **Clinical success defined as resolution of signs and symptoms such that no further antibiotic Rx was required, or improvement of signs/symptoms**

Rybak and colleagues assessed the efficacies of daptomycin (3 mg/kg IV q 12h) and vancomycin for the treatment of 12 intravenous (IV) drug users with Gram-positive bacteremia and right-sided IE.[18] Clinical failures occurred with daptomycin therapy, and were most likely due to insufficient dosing regimens.

Phase III *S. Aureus* Bacteremia/Endocarditis Study

One multicenter, randomized, open-label, Phase III study has assessed the efficacy of daptomycin in patients with *S. aureus* bacteremia, including those with known or suspected *S. aureus* IE.[11]

Cubist Pharmaceuticals compared daptomycin to vancomycin and semi-synthetic penicillins in the treatment of 246 patients with *S. aureus* bacteremia. A summary of the therapeutic drug regimens and patient population characteristics can be found in *Table 3*.

The primary end point of clinical success was assessed 38-46 days after the final dose of study medication for patients who achieved a successful outcome at the end of therapy. The FDA efficacy analysis of the overall intent-to-treat patient population showed non-inferiority of daptomycin, compared with vancomycin/semi-synthetic penicillins, with identical success rates of 38.3% (95% CI for difference in success rates, 0.1% [-12.4, 12.5]; using a non-inferiority margin of -20.

Fifty-three of the 246 patients with *S. aureus* bacteremia comprised the subgroup patient population with IE. Of those, 50% (3/6) of uncomplicated right-sided IE were cured, compared with 25% (1/4) of those in the comparator arm. Clinical success rates achieved by daptomycin-

and comparator drug-treated patients with complicated right-sided IE were 38.5% (5/13) and 50% (6/12), respectively. Only 11% (1/9) of daptomycin-treated patients and 22% (2/9) of comparator-treated patients with left-sided IE were cured. Since the study was not powered to detect statistical differences between the 2 treatment arms in patients with IE, descriptive statistics were used to report the data.

The FDA's Anti-Infective Drugs Advisory Committee expressed concern that increasing minimal inhibitory concentrations (MIC), a surrogate measure of resistance, were associated with treatment failures among the patients (overall group and IE group) enrolled in this study. The rate of persistent and relapsing bacteremia, as reported by the FDA, was higher for daptomycin-treated patients (21/120 overall, 8/28 IE), compared with the rates observed in the comparator group (11/115 overall, 5/25 IE). Of the 8 IE patients who developed daptomycin MICs 2 m/mL, 6 experienced persisting/relapsing bacteremia, with equal distribution of infections due to MRSA and MSSA.

While the incidence of adverse events was comparable between treatment groups, there was concern about higher CK levels in the daptomycin arm versus the comparator arm. In particular, of the subset of 44 patients who received concomitant or prior statin therapy, nearly 17% of daptomycin-treated patients developed CK levels in excess of 500 U/L, whereas none of the patients on comparator treatment achieved such levels. Despite the high frequency of CK elevation observed during daptomycin treatment, only one report of daptomycin-associated rhabdomyolysis was noted in this study.

Resistance Concerns and Safety

As previously reported, the development of reduced susceptibility to daptomycin (MIC 1 µ/mL) was observed in the Phase III study of bacteremic patients, including those with known or suspected IE.[11] In addition, recently published case reports have described the emergence of daptomycin-resistant *S. aureus* isolates during treatment of vertebral osteomyelitis and MRSA bacteremia.[19,20]

Because of its distinct mechanism of action, daptomycin has a low propensity for cross-resistance with other antibiotics, and it has a low frequency of spontaneous development of in vitro resistance.[11] Nevertheless, data included in the FDA briefing report for daptomycin highlighted numerous other resistance issues, including the development of diminished susceptibility during daptomycin treatment, evidence of a trend towards decreasing activity against Staphylococci over the past few years, and the increased likelihood of exhibiting isolates with higher daptomycin MICs among patients experiencing persistent/relapsing bacteremia.

Daptomycin has been reported to have the potential for inducing myositis (muscle pain + CK elevation) in various reports[11,17] and, more recently, 2 published reports described cases of rhabdomyolysis occurring during treatment.[21,22] Consequently, the manufacturer recommends weekly CK level monitoring during therapy.

Conclusion

Daptomycin appears to be an effective alternative to vancomycin and semi-synthetic penicillins against ID due to various strains of *S. aureus*. In light of the growing resistance to standard treatment options, future comparative clinical studies enrolling a large number of *S. aureus* IE patients are warranted, in order to verify the safety and efficacy of daptomycin use for the treatment of these patients. However, the acquisition cost of daptomycin is considerably higher than those of comparator agents, such as vancomycin, cefazolin, and semi-synthetic penicillins. Consequently, semi-synthetic penicillins and vancomycin should probably continue to be used as first-line agents for the treatment of *S. aureus* IE, unless there is known resistance to these agents.

Cubist Pharmaceuticals submitted its response to the FDA Approvable letter on March 27, 2006.[7] The final FDA recommendation for label expansion is pending. ■

References

1. Baddour LM, et al. Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Statement for Healthcare Professionals From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394-e434. Erratum in: *Circulation*. 2005;112:2373.
2. Appelbaum PC. The Emergence of Vancomycin-Intermediate and Vancomycin-Resistant *Staphylococcus aureus*. *Clin Microbiol Infect*. 2006;12:16-23.
3. Akins RL, Rybak MJ. Bactericidal Activities of 2 Daptomycin Regimens Against Clinical Strains of Glycopeptide Intermediate-Resistant *Staphylococcus aureus*, Vancomycin-Resistant *Enterococcus faecium*, and Methicillin-Resistant *Staphylococcus aureus* Isolates in an In Vitro Pharmacodynamic Model with Simulated Endocardial Vegetations. *Antimicrob Agents Chemother*. 2001;45:454-459.
4. Cha R, Rybak MJ. Daptomycin Against Multiple Drug-Resistant Staphylococcus and Enterococcus

Isolates in an In Vitro Pharmacodynamic Model with Simulated Endocardial Vegetations. *Diagn Microbiol Infect Dis*. 2003;47:539-546.
5. Lamp KC, et al. In Vitro Pharmacodynamic Effects of Concentration, pH, and Growth Phase on Serum Bactericidal Activities of Daptomycin and Vancomycin. *Antimicrob Agents Chemother*. 1992;36:2709-2714. Erratum in: *Antimicrob Agents Chemother*. 1993;37:930.
6. Piper KE, et al. In Vitro Activity of Daptomycin Against Clinical Isolates of Gram-Positive Bacteria. *J Infect Chemother*. 2005;11:207-209.
7. Furuya EY, Lowy FD. Antimicrobial Strategies for the Prevention and Treatment of Cardiovascular Infections. *Curr Opin Pharmacol*. 2003;3:464-469.
8. Daptomycin (Cubicin®) Prescribing Information. Lexington, MA: Cubicin Pharmaceuticals Inc.: June 2005.
9. Pharmaceuticals has Submitted Response to FDA Approvable Letter Received on Friday: Action Anticipated by late May. Website accessed on June 1, 2006. www.salesandmarketingnetwork.com/news_release.php?ID=2010582
10. Lipsky BA, Stoutenburgh U. Daptomycin for Treating Infected Diabetic Foot Ulcers: Evidence from a Randomized, Controlled Trial Comparing Daptomycin with Vancomycin or Semi-Synthetic Penicillins for Complicated Skin and Skin-Structure Infections. *J Antimicrob Chemother*. 2005;55:240-245.
11. Cubicin (Daptomycin for Injection) for the Treatment of *Staphylococcus aureus* Bacteremia, Including Those with Known or Suspected Infective Endocarditis. FDA Briefing Document for Anti-Infective Drugs Advisory Committee Meeting. March 6, 2006.
12. Kennedy S, Chambers HF. Daptomycin (LY146032) for Prevention and Treatment of Experimental Aortic Valve Endocarditis in Rabbits. *Antimicrob Agents Chemother*. 1989;33:1522-1525.
13. Cantoni L, et al. Comparative Efficacy of Daptomycin, Vancomycin, and Cloxacillin for the Treatment of *Staphylococcus aureus* Endocarditis in Rats and Role of Test Conditions in this Determination. *Antimicrob Agents Chemother*. 1990;34:2348-2353.
14. LaPlante KL, Rybak MJ. Impact of High-Inoculum *Staphylococcus aureus* on the Activities of Nafcillin, Vancomycin, Linezolid, and Daptomycin, Alone and in Combination with Gentamicin, in an In Vitro Pharmacodynamic Model. *Antimicrob Agents Chemother*. 2004;48:4665-4672.
15. Tsuji BT, Rybak MJ. Short-Course Gentamicin in Combination with Daptomycin or Vancomycin Against *Staphylococcus aureus* in an In Vitro Pharmacodynamic Model with Simulated Endocardial Vegetations. *Antimicrob Agents Chemother*. 2005;49:2735-2745.
16. Segreti JA, et al. Daptomycin for the Treatment of Gram-Positive Bacteremia and Infective Endocarditis: A Retrospective Case Series of 31 Patients. *Pharmacotherapy*. 2006;26:347-352.
17. Veligandla SR, et al. Muscle Pain Associated with Daptomycin. *Ann Pharmacother*. 2004;38:1860-1862.
18. Rybak MJ, et al. Pharmacokinetics and Bactericidal Rates of Daptomycin and Vancomycin in Intravenous Drug Abusers Being Treated for Gram-Positive Endocarditis and Bacteremia. *Antimicrob Agents Chemother*. 1992;36:1109-1114.
19. Marty FM, et al. Emergence of a Clinical Daptomycin-Resistant *Staphylococcus aureus* Isolate During Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia and Osteomyelitis. *J Clin Microbiol*. 2006;44:595-597.
20. Skiest DJ. Treatment Failure Resulting from Resistance of *Staphylococcus aureus* to Daptomycin. *J Clin Microbiol*. 2006;44:655-656.
21. Papadopoulos S, et al. Rhabdomyolysis During Therapy with Daptomycin. *Clin Infect Dis*. 2006;42:e108-e110.
22. Kazory A, et al. Rhabdomyolysis and Acute Renal Failure in a Patient Treated with Daptomycin. *J Antimicrob Chemother*. 2006;57:578-579.

Efavirenz is not Depressing

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center, Clinical Professor of Medicine, Stanford University School of Medicine

Dr. Winslow is a consultant for Bayer Diagnostics and Pfizer/Agouron, and is on the speaker's bureau for Pfizer/Agouron.

Synopsis: *In a randomized trial of efavirenz (EFV) vs protease inhibitor (PI)-containing highly active antiretroviral therapy depressive disorder was encountered no more frequently in the EFV group than in the PI group.*

Source: Journot V, et al. Use of Efavirenz is not Associated with a Higher Risk of Depressive Disorders: A Substudy of the Randomized Clinical Trial ALIZE-ANRS 099. *Clin Infect Dis*. 2006;42:1790-1799.

ALIZE-ANRS WAS A 48 WEEK RANDOMIZED CONtrolled trial in which 355 virologically-suppressed,

HIV-infected patients receiving PIs were randomized to a continuation regimen containing EFV vs PI. The trial's adverse event database and a self-administered depression scale questionnaire were used to assess depressive disorder. Depressive disorder or suicide attempt occurred in 7% of the PI-treated patients and 8% of the EFV-treated patients ($P = .56$).

COMMENTARY

The non-nucleoside reverse transcriptase inhibitor (nnRTI) efavirenz has been an important component of HAART since its regulatory approval in the late 1990s. I was very fortunate to be working at the DuPont Company in the Viral Diseases Drug Discovery Group during the late 80s through mid-90s when our company in-licensed from Merck its most promising L-drug, nnRTI, which we designated as DMP 266 during its development (later given the generic name efavirenz). Our group in Discovery Research verified its amazing in vitro potency,[1] while other colleagues in preclinical development demonstrated its favorable pharmacokinetic characteristics, great safety and tolerability in animals. We did learn from these studies that CNS effects were seen in non-human primates at high doses and were seen in the range of blood levels we would likely see in humans dosed at 600 mg daily, so CNS side effects in humans were anticipated before we started our clinical trials. It was an exciting time to be engaged in antiretroviral research. Due to the sudden resignation of the Director of Oncology in Clinical Research and the impending initiation of clinical trials of DMP 266, I gave up most of my laboratory research and took over the job of running the clinical trials of 2 oncology drugs and designing the clinical development plan for DMP 266. We initiated single, followed by multiple, dose pharmacokinetic studies in humans in late 1995, Phase II/III studies (including 003 and 006) and drug interaction studies in early 1996, worked with the ACTG to get DMP 266 in several additional clinical trials, and the rest is history. After I left DuPont in early 1996, Nancy Ruiz and her team did a wonderful job completing those trials and filing the NDA.

Due to the autoinduction of metabolism (by the cytochrome P450 system) by EFV, which occurs in the first 2 weeks of therapy, CNS side effects are generally most prominent in the first few weeks of treatment. In patients who experience these side effects, the most common symptoms include insomnia, often bizarre and vivid dreams, and sometimes jitteriness during the day. Most clinicians find that, if forewarned of these potential side effects, most patients find that these effects become much less severe if they hang in there for a couple of weeks. However, most of us have had a few patients where these CNS side effects are so severe that the EFV must be discontinued. The relationship between EFV side effects and plasma EFV levels is fairly impressive, and the association of reduced metabolism of EFV in certain individuals including those with certain cytochrome P450 2B6 polymorphisms has recently been demonstrated.[2]

Due to the high prevalence of mood disorders in most HIV-infected populations, concern was raised early on that EFV could exacerbate depression. The registrational trials did not support this concern, but anecdotal experience after regulatory approval and widespread use raised this concern in the minds of many practitioners. A handful of publications in mainly non-peer reviewed publications were purported to show an association between EFV use and depression, and many practitioners started thinking it was inappropriate to prescribe efavirenz in patients with a history of psychiatric disease. The majority of post-registrational, controlled trials did not show such an association.[3]

This well-controlled trial by ANRS (essentially the French ACTG) dispels the concern about a significant causal association between EFV and new onset of depression or exacerbation in patients with pre-existing depression. While this should reassure providers that EFV can be safely used in patients with stable depression, I still take somewhat of a pragmatic approach and tend to use EFV with caution, or chose a PI in the rare patient who has poorly controlled underlying psychiatric illness (either mood disorder or thought disorder/psychosis). This is because supporting a patient who is already struggling through the initial 2-3 weeks of therapy when CNS side effects are most severe often requires a tremendous expenditure of effort and resources, which is multiplied in the presence of pre-existing poorly controlled psychiatric disease.

It may be of interest to some of the readers that efavirenz was almost not developed. The entire class of Merck L-drug nnRTIs was shelved by Merck management after rapid selection of high-level resistance was observed in vivo as a result of single amino acid substitutions in RT when these drugs were studied as

monotherapy in the late 1980s. When the DuPont Merck joint venture was created in 1991, a few believers transferred from the Merck to DuPont organization, including Paul Friedman who came on board at DuPont Merck as President of R&D. Paul knew that antiretrovirals with a low genetic barrier to development of resistance (like the nnRTIs) needed to be studied as part of combination therapy—a concept which was still controversial in the early 1990s; however, this seemed obvious to me, hence the design of our registrational studies. It may also be of interest to some readers that DuPont (the company which discovered the angiotensin receptor blocker, losartan) had probably the premier HIV protease inhibitor discovery program in the world in the late 1980s and early 1990s, and culminated in the discovery using computer-assisted drug design technology of the small molecule cyclic urea compounds.[4] Unfortunately after the DuPont Merck joint venture was formed, DuPont's protease inhibitor program was disbanded since it was viewed by Merck management as competing with indinavir, which was entering into Phase II/III trials at that time. ■

References

1. Winslow DL, et al. Selection Conditions Affect the Evolution of Specific Mutations in the Reverse Transcriptase Gene Associated with Resistance to DMP 266. *AIDS*. 1996;10:1205-1209.
2. Haas D, et al. A Common CYP2B6 Variant is Associated with Efavirenz Pharmacokinetics and Central Nervous System Side Effects. AACTG Study NWCS 214. 11th Conference on Retroviruses and Opportunistic Infections; Feb 8-11, 2004; San Francisco. Abstract 133.
3. Clifford DB, et al. Impact of Efavirenz on Neuropsychological Performance and Symptoms in HIV-Infected Individuals. *Ann Intern Med*. 2005; 143:714-721.
4. Lam PY, et al. Cyclic HIV Protease Inhibitors: Synthesis, Conformational Analysis, P2/P2' Structure-Activity Relationship, and Molecular Recognition of Cyclic Ureas. *J Med Chem*. 1996;39:3514-3525.

CME Question

4. **Which of the following antimalarials is believed to be safe in pregnancy?**
   a. Chloroquine
   b. Atovaquone/proguanil
   c. Doxycycline
   d. Primaquine

5. **Which of the following is correct?**
   a. Daptomycin is an aminoglycoside antibiotic.
   b. Daptomycin's antibacterial activity is limited to aerobic Gram negative bacilli.
   c. Daptomycin administration may be associated with elevation of creatine phosphokinase in some patients.
   d. Daptomycin commonly causes severe nephrotoxicity.

6. **Which of the following is correct?**
   a. Efavirenz use frequently causes depression.
   b. Efavirenz-associated central nervous system side (CNS) effects are generally most prominent in the first weeks of treatment.
   c. The most frequently encountered CNS side effect associated with efavirenz use is the occurrence of generalized seizures.
   d. Efavirenz inhibits its own metabolism so that blood levels gradually increase over time.

Answers: 4. (a); 5. (c); 6. (b)

CME Objectives

The objectives of *Infectious Disease Alert* are:

• To discuss diagnosis and treatment of infectious diseases;

• To present current data regarding use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• To present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests;

• To discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy...■

In Future Issues:

Rotavirus Vaccine

UPDATES

By Carol A. Kemper, MD, FACP

WNV Update—2006

ProMED-mailpost, June 27, 2006; www.promedmail.org

As we plunge into the late summer months, thoughts turn again to West Nile Virus. July and August are typically the hottest months for WNV. As of the end of June, 22 states in the continental United States have reported avian, animal, or mosquito WNV infections for the year. Three states (Colorado, Mississippi, and Texas) have reported 5 cases of human infection, all of whom were suffering from the more severe neuroinvasive form of the disease (not just WNV fever).

All blood donations are being pooled and screened for WNV infection. Based on these data, an estimated 1.2 to 1.3 million human infections have occurred in the United States since WNV first made its debut here in 1999. The majority of these have been asymptomatic or minimally symptomatic and clinically unrecognized. An estimated 8300 people may have developed more severe neurologic symptoms, and nearly 800 have died.

In January 2006, the CDC, in collaboration with the US Geological Service, established a website for reporting and tracking WNV and other mosquito-born diseases, called ArboNET. Detailed county-level human, avian, animal, and mosquito data are updated weekly. Now is the time to distribute literature and guidelines to patients: eg, canvas your yard and surrounding areas for pools and crevices key to the survival of mosquito larva; save and report any dead birds to the local health department; use appropriate mosquito clothing and precautions, etc. Interestingly, although dead crows may be the "canary that does not sing," other songbirds in the backyard, such as robins and sparrows, can develop high levels of WNV viremia without dying—creating a reservoir of ready infection for mosquitoes in your own backyard. ■

Does HCV Really Go Away?

Carreño V, et al. Detection of Hepatitis C Virus (HCV) RNA in the Liver of Healthy, Anti-HCV Antibody-Positive, Serum HCV RNA-Negative Patients with Normal Alanine Aminotransferase Levels. *J Infect Dis*. 2006:194:53-60.

A small number (5% to 15%) of fortunate people who become acutely infected with HCV appear to clear their infection with no residual evidence of HCV viremia and normal transaminases. Suspicions are, however, being cast on whether HCV can ever be, in fact, completely cleared from the body. Studies have shown that patients successfully treated with antiviral therapy who achieve sustained undetectable levels of plasma HCV RNA may still harbor occult intrahepatic virus. Other investigators have identified HCV RNA in the peripheral blood mononuclear cells (PBMC) of a few patients who apparently cleared their viremia and developed anti-HCV antibodies, either naturally or in response to antiviral treatment.

Carreño and colleagues in Madrid, Spain, examined liver biopsies from 12 patients with anti-HCV antibodies by recombinant immunoblot assay and negative serum HCV RNA (Amplicor HCV, version 2.0, Roche Diagnostics). Two of the patients had a remote history of blood transfusion more than 25 years earlier. The remaining patients had no history of hepatitis and no risk factor for HCV. During a mean follow-up of 29 ± 20 months, none of the patients developed clinical or laboratory evidence of HCV infection. Serum transaminases remained normal; they continued to have undetectable plasma HCV RNA, and all 12 remained HCV antibody positive.

Surprisingly, despite this lack of evidence for residual HCV infection, 10 of 12 (83%) liver biopsies were positive for genomic HCV RNA. All 10 of these specimens also demonstrated positive antigenomic HCV RNA strands, indicating occult replication. All 10 individuals had genotype 1b, raising concerns about possible cross-contamination in the lab, but nucleotide sequencing revealed distinct clones.

Genomic HCV RNA was also detected in the PBMCs of 6 of 12 patients (50%) (all of whom had positive liver biopsies); anti-genomic RNA was identified in 5 of these.

Despite a lack of clinical or other laboratory evidence of infection, histopathology in one patient revealed chronic active hepatitis and stage 1 fibrosis. Other potential causes of liver disease were ruled-out in this individual. Three patients had steatohepatitis or steatosis (2 were overweight and one was diabetic). The remaining 6 patients with positive intrahepatic HCV RNA had normal or

minimal histologic changes. ■

Predicting Discordance in CD4 and HIV RNA

Goicoechea M, et al. Determinants of CD4+ T Cell Recovery During Suppressive Antiretroviral Therapy: Association of Immune Activation, T Cell Maturation Markers, and Cellular HIV-1 DNA. *J Infect Dis*. 2006:194;29-37.

Goicoechea and colleagues examined immunologic factors affecting CD4 T cell recovery in HIV+ patients who had achieved successful virologic control with a non-nucleoside containing antiretroviral (ART) regimen. These patients were part of a clinical trial enrolling patients with baseline CD4 ≥ 100 cells/mm^3 and with viral loads ≥ 5000 particles/mL, 162 of HIV plasma RNA at weeks 24 and 48. The other 88 were missing data or failed to achieve virologic suppression. The 162 patients were divided into 2 groups: those with concordance virologic responses to ART, with a ≥ 100 CD4 cells/mm^3 increase from baseline at 48 weeks, and those with discordant responses with CD4 cell increases at 48 weeks. Those with concordant responses gained an average of 111 CD4 cells/mm^3, and those with discordant responses gained an average of 22 cells/mm^3 over the 48-week study.

Measures of cellular and plasma HIV DNA levels and T cell immunophenotypes were compared between the 2 groups. Increased CD4 and CD8 T cell activation at baseline was a significant independent predictor of CD4 T cell recovery. The odds of developing an increasing number of CD4 cells fell by 20% for every 5% increase in activated CD4 cells. In particular, the presence of high memory (CDRA-CD62L-) CD8+ cells at baseline was a significant predictor of poor CD4 cell count recovery.

A greater portion of naïve CD4 T cells at baseline was associated with a concordant increase in CD4 counts and virologic suppression. Such patients also had significantly better recovery of naïve CD4 cells and CD8 cells than did discordant subjects at week 12, as well as weeks 24 and 48. This suggests that naïve CD4 cells not only play a role in the early recovery CD4 phase, eg, the first 3 months after initiation of ART, when extrathymic cells are being redistributed into the circulation. But these concordant subjects continue to display increased regeneration capacity, presumably from thymic expansion for up to 48 weeks. Neither cell-associated HIV DNA levels at baseline or at week 48 were predictive of outcome. Interestingly, progressive age was associated with poorer CD4 count recovery, perhaps reflecting the duration of progressive HIV disease and naive CD4 cell depletion. Identification of patients with immunophenotypic markers of immune system activation and naive CD4 cell depletion may provide a rationale for earlier initiation of ART. ■

Raw Food Pet Treats: Good for Them, Bad for You?

ProMED-mailpost, June 29, 2006; www.promedmail.org

Earlier outbreaks of human salmonellosis related to feeding your pet pig ears or a nice undercooked hamburger patty off the grill have been discussed in this column. This account is the third published report of human salmonellosis associated with pet treats in North America. Investigations have confirmed that raw beef and salmon-containing pet treats were responsible for 9 cases of human salmonellosis in Western Canada and Washington state in 2004-2005. Six of the 9 patients from British Columbia, Washington State, and Alberta recalled feeding pet treats to their dogs prior to onset of illness, and another 2 owned dogs. This is likely just the tip of what really occurred, since studies suggest that for every clinically identified case of salmonella infection, 38 unrecognized cases occur in the community.

Stool cultures yielded *S. thompson*, which was indistinguishable by pulse field gel electrophoresis from strains found in dog and salmon pet treats. Samples of salmon and beef pet treats manufactured at the Washington plant and those collected at the BC plant by Canadian authorities yielded a variety of organisms, predominately S. thompson. Up to 80,000 colony-forming units of salmonella per gram of salmon treats were discovered. Other Salmonella serotypes, including Montevideo, Newport, Give, Meleagridis, Cerros, Muenster, Agona, and Anatum were also found in treats from both the British Columbia and Washington plants. The treats are made from dehydrated, then rehydrated, raw beef and salmon. No irradiation or heat treatment intended to destroy bacteria was employed. No warning labels on the packages advised pet owners to wash their hands after handling. This article serves as a reminder that hand washing is important when handling any kind of raw foods or meats, even if it comes nicely packaged. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

The Safety of Long-Acting Beta Agonist Inhalers

Do long-acting beta agonist inhalers increase the severity of asthma? Yes, according to the results from a large meta-analysis recently published in the *Annals of Internal Medicine*. Pooled data from 19 trials with nearly 34,000 participants found that the long-acting beta agonists salmeterol, formoterol, and eformoterol were associated with higher rates of asthma exacerbations, requiring hospitalization, (odds ratio 2.6 [95% CI, 1.6-4.3]) and life-threatening exacerbations (odds ratio 1.8 [CI, 1.1-2.9]), compared to placebo. In subgroup analyses, the odds ratio for hospitalizations was 1.7 for salmeterol and 3.2 for formoterol. The risk of hospitalization was especially high in children on long-acting beta agonists (odds ratio 3.5 [CI, 1.3-9.3]). The odds ratio for adults was 2.0 (CI 1.1-3.9). Although the rate of death was low, the odds ratio for asthma-related death was 3.5 (CI, 1.3-9.3).

In the largest of the studies included in the meta-analysis, the Salmeterol Multicenter Asthma Research Trial (SMART), in which 26,000 patients were followed for 6 months on salmeterol or placebo, there was a 2-fold increase in life-threatening asthma exacerbations and a 4-fold increase in asthma related deaths. The authors conclude that long-acting beta agonist use increases the risk of hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. The authors also conclude that inhaled corticosteroids cannot adequately protect against the adverse effects of these drugs (*Ann Int Med*. 2006;144:904-912).

An accompanying editorial suggests that physicians should follow current guidelines which emphasize use of inhaled corticosteroids as the first-line treatment for patients with mild-to-moderate persistent asthma. Only after maximal corticosteroid doses have been reached should long-acting beta agonist be considered (*Ann Int Med*. 2006;144:936-937).

The FDA met one year ago to discuss long-acting beta agonist and required black box warnings on the labeling for these drugs; however, there usage has changed very little in the ensuing year.

Treating Chronic Primary Insomnia

Cognitive behavioral therapy is more effective than zopiclone for the treatment of chronic primary insomnia in older adults, according to a new study from Norway. In a randomized, double-blind, placebo-controlled trial, 46 adults (mean age, 60.8; 22 women) with chronic primary insomnia were randomized to cognitive behavioral therapy, sleep medication with zopiclone 7.5 mg each night, or placebo for 6 weeks. The cognitive behavioral therapy consisted of 6 weekly sessions lasting 50 minutes that covered sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, and progressive relaxation techniques. The main outcome was

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

polysomnographic data and sleep diaries, which were used to determine total wake time, total sleep time, sleep efficiency, and slow-wave sleep.

Cognitive behavioral therapy (CBT) resulted in improved short-term and long-term outcomes compared with zopiclone on 3 of 4 outcome measures. CBT improved sleep efficiency from 81.4% to 90.1% at 6-month follow-up compared to a decrease from 82.3% to 81.9% with zopiclone. CBT resulted in better sleep architecture and less time awake during the night. Total sleep time was similar in all 3 treatment groups but, at 6 months, patients receiving CBT had better sleep efficiency than those taking zopiclone. The authors conclude that cognitive behavioral therapy is superior to zopiclone for management of insomnia, both in the short term and long-term. For most outcomes, zopiclone did not differ from placebo (*JAMA*. 2006;295:2851-2858).

Zopiclone is a new generation sleep medication available in Europe. The active isomer of zopiclone has been available in the United States since April 2005 (eszopiclone - Lunesta).

New Breakthrough in Smoking Cessation?

Varenicline, Pfizer's new smoking cessation drug, is the subject of 3 articles in the July 5 issue of *JAMA*. The drug, which is a partial agonist of the 4 2 nicotinic receptor, blocks the action of nicotine but provides a lower level of stimulation of dopamine release to reduce craving and withdrawal symptoms. Two of the 3 articles compared varenicline to bupropion and placebo in combination with behavioral counseling over 12 weeks of treatment. In both studies, varenicline was significantly more effective than placebo or bupropion (*JAMA*. 2006;296:47-55, 56-63). In the third study, 12 more weeks of varenicline was found to be significantly more effective than placebo in maintaining abstinence. This study also found that after 24 weeks of treatment, the benefit of the drug was maintained up to one year (*JAMA*. 2006;296:64-71). An accompanying editorial points out that while the studies of varenicline are promising and the drug represents a new agent with a different mechanism of action, it is not a panacea for smoking cessation, with quit rates still under 50% in these studies (*JAMA*. 2006;296:94-95). These studies could not come at a better time for Pfizer, as the company plans to market the drug within the next few months under the trade name Chantix.

FDA Actions

The FDA has given Biogen-Idec approval to resume marketing natalizumab (Tysabri) for the treatment of relapsing forms of multiple sclerosis. The monoclonal antibody was initially marketed in November 2004, but was withdrawn four months later, after three patients developed progressive multifocal leukoencephalopathy (PML) in clinical trials. Subsequent trials have not shown any additional cases of PML, but the drug is limited to use in patients who have failed or have not tolerated alternative therapies for multiple sclerosis. The re-approval is a restricted distribution program which includes registration of patients, prescribers, infusion centers, and pharmacies and includes patient education materials. Patients are also required to have a brain MRI prior to initiation of therapy. More information is available at: www.fda.gov/cder/drug/infopage/natalizumab/default.htm.

Duramed Pharmaceuticals have received approval to market a new 91 day birth control regimen consisting of 84 days of levonorgestrel 0.15 mg with ethinyl estradiol 0.03 mg, and seven days of ethinyl estradiol 0.01 mg (Seasonique). This product differs from the company's other 91 day birth control regimen (Seasonale) in that it incorporates estradiol rather than placebo for the last seven days in order to reduce bloating and breakthrough bleeding. Both products result in four menstrual periods per year.

The FDA has approved Genentech's ranibizumab (Lucentis) for the treatment of neovascular (wet) age-related macular degeneration (AMD). The drug, which is injected intraocularly, inhibits vascular endothelial growth factor A which is thought to contribute to proliferation, vascular leakage, and angiogenesis. Many ophthalmologists have been using Genentech's other anti-angiogenesis drug bevacizumab (Avastin) for the treatment of AMD, although it is not approved for this indication. Compounded bevacizumab injected intraocularly is approximately $17 per dose. Ranibizumab marketed as Lucentis is projected to cost approximately $2000 per dose.

Two former blockbuster drugs are making the switch to generics. Sertraline (Zoloft- Pfizer) will be available later this year in both generic pill and liquid form. In 2005, Zoloft was the most popular antidepressant in the US. The FDA has also approved a generic form of simvastatin (Zocor) Merck & Co.'s enormously popular statin for the treatment of hypercholesterolemia. Generic simvastatin is currently available 5, 10, 20, 40, and 80 mg strengths. ■