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An Emerging Extended-Spectrum Triazole Antifungal: Noxafil® (Posaconazole)

SPECIAL FEATURE (PART 1 OF 2)

By Jean Yong Nam, PharmD Candidate, Rehan Noori, PharmD Candidate, and Jessica Song, MA, PharmD

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Introduction

MEDICAL ADVANCES IN RECENT YEARS HAVE RESULTED IN AN increased frequency of invasive fungal infections.[1] Patients undergoing solid organ transplantation, HIV/AIDS treatment, and invasive surgical procedures are especially susceptible to fungal pathogens, and are more likely to experience recurrent fungal infections.[2,3] Within the past 2 decades, escalating morbidity/mortality rates have been associated with Aspergillus and Candida infections among immunocompromised patients undergoing hematopoietic stem cell transplants.[4] Similarly, previously uncommon fungal infections such as Fusariosis and Zygomycosis are now becoming more prevalent, further supporting the need for newer, well-tolerated antifungal agents that demonstrate efficacy against these invasive and refractory fungal infections.[1,5]

Despite the availability of numerous antifungal agents, treatment options for invasive fungal infections are often limited by tolerability issues, and the potential for drug-drug interactions and resistance. Amphotericin B is the preferred antifungal for a variety of fungal infections, but its use is limited by its potential to induce nephrotoxicity.[6] In addition, resistance to fluconazole has been increasingly noted, and other triazoles, such as voriconazole and itraconazole interact with numerous drugs.[3,5] The risk of drug inter-

actions is especially increased in the immunocompromised, who often receive multiple medications.[7,8] The medications in the echinocandin class (eg, caspofungin) also have limitations because they are only available as intravenous formulations, which restricts outpatient utilization.[5]

Posaconazole is a second-generation extended-spectrum triazole antifungal agent, that is characterized by chemical properties that are most similar to both itraconazole and ketoconazole.[2,5] Like other triazoles, posaconazole works by inhibiting 14 -demethylase to block the synthesis of ergosterol, which is the primary structural unit in the fungal cell membrane.[9] The side chain of posaconazole is extended, and this is believed to improve binding affinity to 14 -demethylase, compared with fluconazole or other triazoles that lack this side group.[7]

As resistance to conventional antifungals continues to become widespread, further studies may extend posaconazole's spectrum of activity to include rare and difficult-to-treat fungal infections in patients with poor response to traditional therapy. This article will present a review of posaconazole's: 1) spectrum of activity, 2) pharmacokinetic properties, 3) clinical efficacy, and 4) comparison among other antifungal agents.

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Spectrum of Activity

Posaconazole has broad-spectrum antifungal activity with demonstrated in vitro potency against yeasts and molds, including: *Aspergillus* spp., *Zygomycetes* spp., *Candida* spp., and several other pathogens.[10,11,12] Posaconazole is also active against the less common but increasingly important emerging fungal pathogens including *Scedosporium* spp. and *Fusarium* spp.[1,5]

In an in vitro 2-year study by Diekema et al, a total of 448 filamentous fungi isolates were tested for susceptibility to triazoles (including itraconazole, posaconazole, ravuconazole, and voriconazole) as well as to caspofungin and amphotericin B.[10] The minimum inhibitory concentrations (MIC) for posaconazole, voriconazole, and amphotericin B against numerous fungal pathogens are shown in *Table 1*.

An additional small in vitro study highlighted posaconazole's activity against Zygomycetes (n = 37 isolates); *Mucor* spp, *Rhizopus* spp, *Absidia corymbifera*, *Cunninghamella* spp, *Apophysomyces elegans*, *Cokeromyces recurvatus*, and *Saksenaea vasiformis*.[11] The MIC_{90} values (µg/mL) for posaconazole were 1, 8, 0.25, 1, 2, 4, and 0.125, respectively. In comparison to other triazoles, posaconazole had MIC means 1.6-fold lower than itraconazole, 33-fold lower than voriconazole, and 47-fold lower than fluconazole. At present, susceptibility breakpoints for antifungal agents have not been established. Moreover, since standardized methods to test the susceptibility patterns of antifungals have yet to be established, MIC values should be interpreted with caution. A case report by Ide and associates also described effectiveness in a neutropenic male patient with breakthrough Zygomycosis while on voriconazole for a past Aspergillus infection.[13] The patient remained refractory to treatment with amphotericin B, but recovered successfully when switched to posaconazole 800 mg/day.

In a comparative study of in vitro activity against pathogenic yeasts, including strains of *C. neoformans* (n = 15), *C. parapsilosis* (n = 15), *C. lusitaniae* (n = 12), *C. albicans* (n = 23), *C. tropicalis* (n = 15), *C. krusei* (n = 15), and *T. glabrata* (n = 15), posaconazole and itraconazole displayed equivalent MIC_{90} to *C. neoformans* and *C. krusei* (60 ng/mL and 500 ng/mL, respectively).[14] However, all other strains were more susceptible to posaconazole (2-4-fold lower MIC_{90} values than itraconazole) except for *T. glabrata*, which had a comparably high MIC_{90} (> 1000 ng/mL) as itraconazole (1000 ng/mL). Similarly, an in vitro study (n = 3 strains) conducted by Perfect et al showed that posaconazole killed yeasts at a lower MIC_{90} (0.063 µ/mL) than either fluconazole or amphotericin B (2.0 µ/mL and 1.0 µ/mL, respectively), but was inferior to itraconazole (0.008 µ/mL).[15] A recent in vivo combination study of posaconazole with amphotericin B deoxycholate demonstrated additive effects of combination therapy (20.3% of 64 combina-

Table 1

In Vitro Minimum Inhibitory Concentrations of Select Triazoles to Filamentous Fungi

Filamentous fungi (no. isolates)	Posaconazole		Voriconazole		Amphotericin B	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
A. fumigatus (256)	0.25	0.5	0.25	0.5	1	1
A. flavus (30)	0.25	0.5	0.5	1	1	2
A. niger (29)	0.5	1	1	2	1	1
A. versicolor (20)	0.5	1	0.5	1	1	2
A. terreus (16)	0.12	0.25	0.25	1	2	2
Penicillium spp. (35)	0.5	1	0.5	2	1	2
Fusarium spp. (11)	> 8	> 8	4	> 8	1	2
Paecilomyces spp. (6)	0.12	--	0.25	--	0.5	--
Rhizopus spp. (5)	2	--	2	--	1	--
Mucor spp. (3)	1	--	2	--	0.5	--
All Aspergillus (372)	**0.25**	**0.5**	**0.5**	**1**	**1**	**1**
All filamentous fungi (448)	**0.25**	**1**	**0.5**	**1**	**1**	**2**

* MIC values are indicated in µ/mL

tions; 4 strains) versus *Candida albicans* (increased survival of mice).[16] In addition, no antagonism between posaconazole and amphotericin B was observed in this study.

Resistance of *Fusarium* spp. to several other triazoles led to an investigation of posaconazole as a treatment option for the eradication of this pathogen. A case report by Herbrecht et al showed successful treatment of *F. proliferatum* infection with posaconazole in a 62-year-old lung transplant patient.[1] The patient was not able to take amphotericin B because of renal insufficiency and, after susceptibility testing showed poor activity of itraconazole and fluconazole, posaconazole therapy resulted in successful eradication of the pathogen.

Meletiadis and colleagues' in vitro study displayed positive results against 55 clinical isolates of *S. prolificans* and 13 clinical isolates of *S. apiospermum*.[17] Although posaconazole showed efficacy against *Scedosporium* spp. isolates in this study (*S. prolificans* [$MIC_{50} \geq 8$ µ/mL, $MIC_{90} \geq 8$ µ/mL] and *S. apiospermum* [$MIC_{50} = 0.5$ µ/mL, $MIC_{90} = 1$ µ/mL]), voriconazole had lower MICs for both *Scedosporium* spp. isolates (*S. prolificans* [$MIC_{50} = 4$ µ/mL, $MIC_{90} = 4$ µ/mL] and *S. apiospermum* [$MIC_{50} = 0.125$ µg/mL, $MIC_{90} = 0.25$ µ/mL]). Voriconazole and other azoles, however, were also observed to exhibit cross-resistance, whereas posaconazole did not. Conversely, in an in vitro study performed by Carrillo and Guarro, posaconazole and voriconazole displayed equivalent MIC_{90} to *S. apiospermum* (11 isolates).[18] The disparity in the reported activities of posaconazole and voriconazole against *S. apiospermum* highlights the need for further study of the efficacy of triazoles against *Scedosporium* spp.

Pharmacologic Properties

Posaconazole, like the other azoles in clinical use for systemic treatment (fluconazole, itraconazole, voriconazole), is available as an oral suspension. The specific doses that will be marketed if FDA approval is granted for posaconazole have not been established. Phase III clinical trials with posaconazole in patients with graft-versus-host disease (GVHD), acute myelogenous leukemia (AML), or myelodysplastic syndrome (MDS), and in hematopoietic stem cell transplant (HSCT) recipients, evaluated a daily dose of 600 mg/d, divided in 3 doses.[4,12] Other clinical trials with posaconazole in patients with oropharyngeal candidiasis or refractory invasive fungal infections (IFI), evaluated daily doses of 100mg/d (200 mg loading dose), and 800 mg/d (divided in 2 or 4 doses), respectively.[5,19,20,21]

Posaconazole bioavailability increases with both nonfat meal and high-fat meal (2.6-fold and 4.0-fold, respectively), thereby supporting administration of this drug with food.[2,22] Unlike itraconazole and ketoconazole, whose absorption is affected by gastric pH, posaconazole is not affected and has consistent absorption patterns, regardless of the intestinal environment.[2] No dose adjustments are recommended for renal or hepatic insufficiency, as posaconazole is mainly excreted in the feces with minimal urinary excretion or hepatic metabolism.[23,24]

Posaconazole is metabolized via UDP-glucuronyl transferase (UGT) enzymes in the liver, is highly protein bound, and has a large volume of distribution, making it unnecessary to dose-adjust for patients undergoing hemodialysis.[3,5] Wexler and colleagues demonstrated that posaconazole is minimally inhibited by the cytochrome P450 isoenzyme (CYP), with inhibition of hepatic CYP3A4 occurring below micromo-

Table 2

Pharmacologic, Pharmacokinetic, Clinical Properties of Oral Posaconazole

Brand/Generic	Noxafil® (Posaconazole)					
Classification[7]	Second-generation, extended-spectrum triazole antifungal					
Mechanism of Action[5]	Inhibits the 14α–demethylase enzyme, ultimately blocking the synthesis of ergosterol, the primary fungal cell membrane sterol.					
Spectrum of Activity[5]	• Aspergillus (fumigatus, flavus, niger, terreus) • Candida (albicans, glabrata, parapsilosis, tropicalis, krusei, dubliniensis, lusitaniae, guilliermondii) • *Zygomycetes* spp. (only triazole with activity against this pathogen) • *Fusarium*, *Cryptococcus*, *Coccidioides*, *Histoplasma* spp.					
Possible Indications[4,5,12,19,20,21]	• Prevention of invasive fungal infections (IFI) in immunocompromised patients (HSCT, GVHD, AML, or MDS) • Oropharyngeal Candidiasis; Zygomycosis • Salvage therapy for patients with invasive fungal infections (Aspergillosis, Candidemia, Zygomycoses) refractory to or intolerant to other antifungals (amphotericin B-associated products, other triazoles (including voriconazole)					
Pharmacokinetics[8] (healthy volunteers) 400 mg tablet (q12h)	**Half-life (terminal)**	**Fecal excretion**	**Recovered unchanged in urine**	**V_d (L)**	**Protein Bound**	**Metabolism**
	31h	77%	Trace amounts	486 L	> 95%	Metabolized via the UDP-glucuronosyltransferase enzyme pathway.
Pharmacokinetics[19] (febrile neutropenia of refractory IFI) 400 mg suspension bid	**Half-life (terminal)**	**Fecal excretion**	**Recovered unchanged in urine**	**V_d (L)**	**Protein Bound**	**Metabolism**
	11.9	Not evaluated	Not evaluated	2447 L	Not evaluated	Metabolized via the UDP-glucuronosyltransferase enzyme pathway.
How Supplied[4,5,12,20,21]	**Not approved by FDA, but clinical studies have utilized oral suspensions (200 mg/5 mL)**					
Dosage[4,5,12,20,21]	For patients with proven or probable IFI who were refractory to, or were intolerant of, other antifungal therapy • Oral suspension, 800 mg/d (divided doses) • Treatment duration varied greatly, but some patients received up to 12 months of therapy For Oropharyngeal Candidiasis • Initial dose of 200 mg oral suspension on day 1, followed by 100mg/day x 13 days For salvage therapy in Zygomycosis • Oral suspension, 800 mg/d in divided doses (400 mg bid or 200 mg qid) • Treatment duration has ranged from 6 to 1005 days For HSCT/GVHD or AML/MDS patients (treated with chemotherapy) • Oral suspension, 200 mg tid • Treatment duration for HSCT patients approached 112 days					
Dosage Adjustment[5,24]	**Renal** No dosage adjustment required in renally impaired patients **Hepatic** No dosage adjustment required in hepatically impaired patients					
Administration[5]	Administration • Oral suspension should be given in divided doses • Oral suspension should be taken with food (preferably with a high-fat meal) • Able to be administered through a nasogastric tube					

. . . *Table 2* continued on the next page.

lar concentrations, and with no inhibition of isoenzymes 1A2, 2A6, 2C9, 2C19, and 2D6.[3]

Table 2 summarizes the mechanism of action, spectrum of activity, pharmacokinetics, dosing/ administration, adverse effects, and the drug-interaction profile of posaconazole.

Clinical Efficacy

In July 2004, Schering-Plough Pharmaceuticals submitted a New Drug Application (NDA) to the US FDA, to market posaconazole for the treatment of IFIs in patients who are intolerant of other antifungals or with refractory disease. Additionally, the NDA also seeks US marketing approval of posaconazole for prophylaxis of serious IFIs in patients who are at high risk of acquiring these infections and for oropharyngeal *Candidiasis*.[2,25]

Although Schering-Plough Pharmaceuticals submitted an NDA for posaconazole to the FDA nearly 2 years ago, the majority of the Phase III clinical trial data are yet to be published. Trials were con-

Table 2

. . . continued from the previous page

Adverse Effects[4,5,12,20,21]	For patients with proven or probable IFI who were refractory to, or were intolerant of, other antifungal therapy • Nausea (9%), vomiting (6%), abdominal pain (5%) • Headache (5%), diarrhea (3%), elevated ALT or AST (3%), rash (3%) For oropharyngeal Candidiasis • Nausea (10%), diarrhea (8%), headache (7%), fever (6%), vomiting (6%) For HSCT or GVHD patients • Nausea (7%), vomiting (4%), diarrhea (3%) For AML/MDS patients (treated with chemotherapy) • Nausea (7%), diarrhea (7%), vomiting (5%)
Drug Interactions[3,5]	Posaconazole is a CYP3A4 inhibitor and has been shown to interact with: • Midazolam (AUC of this drug increased nearly 2-fold when co-administered with posaconazole) • Tacrolimus C_{max} and AUC increased by 121% and 358%, respectively, when co-administered with posaconazole • Cyclosporine dosage reductions of 14-29% were required in 3 of 4 heart transplant patients who received posaconazole • Phenytoin (may observe increased levels of this drug when co-administered with posaconazole) • Rifabutin (~ 2-fold increase in posaconazole clearance with concomitant administration of 2 drugs)
Pregnancy Category	Prescribing information is unavailable
Formulary Considerations	• Posaconazole, unlike other triazoles, has been shown to effectively treat infections caused by Zygomycetes • Unlike amphotericin B-associated formulations, which also are used to treat patients infected with Zygomycetes, posaconazole does not appear to induce nephrotoxicity • Posaconazole offers a superior drug-interaction profile (inhibitor of CYP3A4) compared with voriconazole (inhibitor/substrate of CYP3A4, CYP2C9, CYP2C19) and fluconazole (inhibitor of CYP2C9, CYP3A4) • Posaconazole has demonstrated potential in treating a wide variety of infections, including refractory IFI (failure to improve with other antifungals), oropharyngeal Candidiasis, Zygomycosis, and prevention of IFI in immunocompromised patients (HSCT, GVHD, AML, MDS)

ducted in the United States, Australia, Singapore, Europe, Canada, Latin America, and South Africa, and included over 1300 patients.[4,5,12,20,21] Detailed summaries of the clinical trials evaluating the efficacy of posaconazole in patients at high risk of developing IFIs can be found in *Table 3*.[4,12] See *Table 4* in the July issue, which will outline the key data regarding the efficacy of posaconazole in patients with oropharyngeal candidiasis and in patients with zygomycosis.

Ullman and colleagues compared the efficacy of posaconazole and fluconazole against Aspergillosis and other IFIs as prophylactic treatment in high-risk HSCT (or GVHD) patients (n = 600).[4] During the treatment period for patients given posaconazole and fluconazole (mean = 80.3 and 77.2 days, respectively), posaconazole resulted in lower incidences of proven/probable fungal infections for *Aspergillus* spp (P = 0.001) and all IFIs (P = 0.004). Similar results were shown during the primary time period (study period, 112 days) with lower incidences of *Aspergillosis* (P = 0.006) and all IFIs (P = 0.074) for the posaconazole-treated subjects. In addition to superiority in prevention of *Aspergillosis* spp and IFIs during the treatment period, posaconazole therapy prolonged the time to development of breakthrough infections compared with fluconazole therapy.

The results of another randomized, evaluator-blinded, active controlled, multi-center phase III clinical study by Cornely and colleagues support the use of posaconazole as prophylaxis to IFIs over fluconazole and itraconazole in neutropenic patients with AML or MDS undergoing myelosuppressive chemotherapy (n = 602).[12] Not only did posaconazole (n = 304) show a significant advantage over standard triazoles (n = 298) in regards to lower incidences of all IFIs during the treatment period (prophylaxis meanpos = 29 days, prophylaxis meanflu/itra = 25 days; P = 0.0001), but was also superior within 100 days post-randomization (P = 0.0031).

Posaconazole has been studied in the treatment of IFIs characterized by refractoriness or intolerance to other antifungal agents. The results of the first Phase III trial of posaconazole were presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington DC, in September 2004.[5] In this open-label study, 330 patients received 800 mg/day posaconazole suspension (divided doses) and 279 external control patients received other antifungal agents (primarily amphotericin B deoxycholate). The study population was primarily comprised of patients infected with *Aspergillus* (posaconazole, 45%; con-

Table 3

Phase III Clinical Trials of Posaconazole (Prevention of IFIs in Immunocompromised Patients)

<table>
<tr><th>Study Characteristics</th><th>Ullman et al[4]</th><th>Cornely et al[12]</th></tr>
<tr><td>Patients</td><td>• 600 allogeneic Hematopoietic Stem Cell Transplant (HSCT) or Graft-Versus-Host Disease (GVHD) patients
<table>
<tr><th></th><th>Posaconazole</th><th>Fluconazole</th></tr>
<tr><td>No. of pts.</td><td>301</td><td>299</td></tr>
<tr><td>Median age (yrs.)</td><td>43.0</td><td>41.0</td></tr>
</table></td><td>• 602 patients with AML or MDS treated with chemotherapy
<table>
<tr><th></th><th>Posaconazole</th><th>Standard Azole</th></tr>
<tr><td>No. of pts.</td><td>304</td><td>298</td></tr>
<tr><td>Median age (yrs.)</td><td>49</td><td>50</td></tr>
<tr><td>1[0] diagnosis, n (%)
AML
MDS</td><td>
255 (84)
49 (16)</td><td></td></tr>
<tr><td colspan="3">• includes itraconazole (n = 58) and fluconazole (n = 240)</td></tr>
</table></td></tr>
<tr><td>Design</td><td>• Prospective multicenter, randomized, double-dummy study</td><td>• Prospective multicenter, randomized, open-label, active controlled, evaluator-blinded trial</td></tr>
<tr><td>Inclusion Criteria</td><td>• Male or female HSCT patients at least 13 years old
• Acute or chronic extensive graft versus host disease (GVHD)
• Treatment with immunosuppressive agents
° High dose corticosteroids (at least 1 mg per kg per day of methylprednisolone or equivalent
° Antithymocyte globulins for therapy of acute GVHD
° ≥ 2 immunosuppressive agents (including tacrolimus, mycophenolate mofetil, or other steroid-sparing immunosuppressive regimen</td><td>• Adults or adolescents (ages > 13 years) and weight > 34 kg, of either gender with either acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS)
• Patients likely to develop neutropenia (absolute neutrophil count [ANC] ≤ 500 cells/mm[3]) within 3-5 days that would last at least 7 days
• Female subjects of childbearing potential must have a negative serum pregnancy test (beta-hcG)</td></tr>
<tr><td>Exclusion Criteria</td><td>• History of proven or probable mould infection or IFI prior to treatment
• Clinically significant hepatic/renal impairment
• Hypersensitivity reactions to azole medications
• Interaction of azoles with current medication use
° Potential serious side effects
° Leading to decrease in azole levels
• Use of other antifungal or investigational agents</td><td>• Females nursing, pregnant, or intending to become pregnant
• Patients previously treated with amphotericin B, fluconazole, itraconazole, or any drugs known to interact significantly with study azoles within 30 days of entry
• Use of other investigational drugs or biologic agents other than chemotherapy agents within 30 days of entry
• Subjects with renal insufficiency (CrCl < 20 mL/min or require dialysis during study), ECG with prolonged QTc interval (> 450 m/sec for men and > 470 m/sec for women), or liver dysfunction at baseline (AST, ALT, or alkaline phosphates > 5 times ULN, or total bilirubin > 3 times ULN)</td></tr>
</table>

Table 3 continued on the next page

trol, 40%). Other patients were infected with *Candida* (posaconazole, 10%; control, 14%), *Fusarium* (posaconazole, 8%; control, 2%), *Cryptococcus* (posaconazole, 13%; control, 29%), and *Zygomycetes* (posaconazole, 5%; control, 4%). Success, defined as a complete or partial response, was seen in 42% of posaconazole-group compared with 26% of control-group patients with *Aspergillosis*. This difference was significant in favor of posaconazole ($P = 0.006$). Of note, a successful outcome was reported for 3 of 6 patients with voriconazole-refractory invasive *Aspergillosis*.

To date, one pivotal, randomized, evaluator-blinded study has compared the efficacy of posaconazole to that of fluconazole for the treatment of oropharyngeal candidiasis.[20] The primary efficacy measure used in this study was complete or partial resolution of the signs and symptoms of oropharyngeal *Candidiasis*. The primary end point was achieved by 91.7% and 92.5% of the posaconazole- and fluconazole-treated patients, respectively (absolute difference, -0.8%, 95% CI, -6.61% to 5.04%). In addition, sustained mycologic success at 28 days post-treatment was achieved by a greater number of posaconazole-treated patients compared with the fluconazole group ($P = 0.038$). ■

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Table 3

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Study Characteristics	Ullman et al[4]	Cornely et al[12]
Evaluation	• Primary end point ° Incidence of proven or probable IFI during primary time period for all randomized subjects • Secondary end points °Incidence of proven or probable: • Aspergillosis during primary time period • Breakthrough IFIs during treatment • Breakthrough Aspergillosis during treatment ° Mortality	• Primary end point ° Frequency of proven/probable IFI during treatment phase (randomization to 7 days after final dose of drug) • Secondary end points ° Frequency of IFIs caused by Aspergillosis spp during treatment period ° Frequency of IFIs from randomization to 100 days ° Mortality at 100 days after randomization ° Clinical outcome during treatment phase • Failure defined as proven/probable IFI during treatment phase or patients who were randomized but did not receive treatment
Results	• Completion of study (high discontinuation rate 2^0 to severity of underlying disease) ° Posaconazole (n = 55) ° Fluconazole (n = 48) • Incidence of proven/probable IFI during primary time period for all randomized subjects ° Aspergillosis spp (P = 0.006) • Posaconazole-7 • Fluconazole-21 ° All IFIs (P = 0.074) • Posaconazole-16 • Fluconazole-27 • Mean (days) to breakthrough IFI from first dose (P = 0.048) ° Posaconazole (102) ° Fluconazole (88) • No significant difference in all-cause mortality (25% posaconazole, 28% fluconazole, P = 0.847) • Significant difference in mortality due to IFIs (P = 0.041, 1% posaconazole, 4% fluconazole)	• Completion of study ° Posaconazole group: 64% (n = 195) ° Standard azole group: 54% (n = 160) • Incidence of proven/probable IFIs during Tx phase, n (%) ° Invasive Aspergillosis: (P = 0.0001, 95.13% CI, -9.05% to -3.05%) • Posaconazole: 2 (1%), standard azoles: 20 (7%) ° All IFIs (P = 0.0009, 95.13% CI, -9.68% to -2.50%) • Posaconazole: 7 (2%); standard azoles: 25 (8%) • Incidence of probable or proven IFIs within 100 days post-randomization, n (%), P = 0.0031, 95.13% CI, -10.76% to -2.71% ° Posaconazole: 14 (5%) ° Standard Azoles: 33 (11%) • Overall number of deaths in posaconazole group was 16% (n = 49) versus 22% (n = 67) in the standard azole group (P + 0.048, chi-square test) ° Out of these 116 deaths, 21 were deemed IFI-related deaths (5 in posaconazole group vs 16 in standard azole group, P = 0.0128, chi-square test)

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Seroreversion in Patients Receiving Antiretrovirals During Early HIV Infection

ABSTRACT & COMMENTARY

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

Synopsis: *All 5 patients who had seroreversion and eventually stopped ART experienced virologic rebound and antibody evolution.*

Source: Hare CB, et al. Seroreversion in Subjects Receiving Antiretroviral Therapy during Acute/Early HIV Infection. *Clin Infect Dis*. 2006;42:700-708.

This paper from the Gladstone Institute at the University of California, San Francisco represents a substudy of intensively studied patients who were enrolled in the Options Project. This study enrolled patients within the first 12 months of HIV infection using a variety of criteria to define the approximate time of infection, and included both acutely infected patients (with negative/indeterminate antibody tests) and early infection (those who were antibody positive at the time of study entry). Patients chosen for this retrospective substudy were those who initiated ART within 28 days of study enrollment and maintained an undetectable HIV RNA level for at least 24 weeks while receiving continuous ART. A battery of anti-HIV antibody tests was used to evaluate serial specimens. These included 2 second generation viral lysate-based ELISA's, a recombinant peptide HIV-1/HIV-2 EIA, and a third generation peptide-based HIV-1/HIV-2 EIA. Two different anti-HIV-1 Western blot assays and a detuned anti-HIV ELISA assay were evaluated as well. In addition, cellular immune responses to various HIV-1 peptide antigens were assessed using an ELISPOT assay which measures IFN-gamma production by antigen-specific CD4+ and CD8+ T cells.

As summarized above, only 12 patients likely had acute HIV infection as defined by a negative second generation anti-HIV EIA at screening, and all seroconverted, although one unequivocally seroconverted only on a third generation recombinant peptide-based assay. Six patients out of the entire cohort of initially seronegative and seropositive patients seroreverted by at least one EIA test while receiving ART. Five of the 6 patients who seroreverted stopped ART; all of these patients experienced virologic rebound and subsequent antibody evolution. Cytotoxic T lymphocyte responses to HIV gag peptides were detected in 4 of the 5 seroreverters who were tested.

COMMENTARY

This paper is of interest for 2 reasons: It has implications for diagnosis of HIV infection, and it has interest from a pathogenesis standpoint on ART of acute/early HIV infection.

Due to the not infrequent referral of HIV-uninfected patients to the public hospital HIV clinic where I work in San Jose, it is our standard procedure to confirm with anti-HIV EIA and Western blot all new patients referred to our clinic, regardless of treatment status. Although clearly rare, the well-documented seroreversion (to second generation anti-HIV EIAs) described in this paper of 7% of patients who received ART for acute/early HIV infection could result in patients falling out of care or transmitting HIV to others while believing they were HIV-negative. While it would be wrong to suggest changing the current HIV testing algorithm (where EIA precedes confirmatory testing with Western blot), this rarely demonstrated cause of false-negative anti-HIV EIA results needs to be excluded by history (of ART for acute/early HIV infection) and brought to the attention of an attending physician so either a third generation EIA or Western blot can be ordered. It is of note that all 6 of the seroreverting patients retained at least equivocal antibody reactivity to gp160 at all time points studied. Again, it remains inappropriate to order Western blot assays routinely on EIA-negative patients since as many as one-third of normal healthy blood donors will have an indeterminate Western blot (usually with gag reactivity).[1] It is also important to point out that routine

ordering of HIV RNA by either RT-PCR or bDNA is also inappropriate since low-titer, false-positive HIV RNA levels are also commonly seen.

From a pathogenesis perspective, this study is interesting. It has been postulated that early institution of ART in patients with acute/early HIV infection may prove beneficial in by restricting viral evolution[2] and, potentially, decrease the rate of disease progression.[3,4] While this hypothesis remains unproven and should be tested in larger prospective randomized controlled trials, this study does show that the benefits of this approach appear to be limited since all seroreverting patients who discontinued ART experienced virologic rebound and antibody evolution once antiretrovirals were stopped. ■

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Amebic Encephalitis—More Common Than You Might Think

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Antibody testing successfully identified 7 patients whose encephalitis was due to the free-living amoeba, Balamuthia mandrillaris, a pathogen that should be suspected in individuals with soil contact, high CSF protein, and mass-like or ring-enhancing brain lesions.*

Source: Schuster FL, et al. Detection of Antibodies Against Free-Living Amoebae *Balamuthia mandrillaris* and Acanthamoeba Species in a Population of Patients with Encephalitis. *Clin Infect Dis*. 2006;42:1260-1265.

As part of the California encephalitis project (CEP), more than 250 serum samples from selected patients were screened for antibodies to amebic pathogens, particularly *Balamuthia mandrillaris*. Overall, the CEP has tested samples for > 1800 cases submitted for extensive testing in attempts to determine the etiology of encephalitis in patients without severe immunocompromise. Samples from individuals with a history of occupational contact with soil, or of swimming or camping, as well as elevated CSF protein level and pleocytosis, hydrocephalus, ring-enhancing lesions, or space-occupying lesions were selected for indirect immunofluorescent antibody testing (IFA) against Balamuthia.

While no cases had elevated IFA to Acanthamoeba species or to *Naegleria fowleri*, serum samples from 7 patients had IFA titers against *B. mandrillaris* of > 1:64, and all 7 were subsequently proven to have balamuthia encephalitis by direct examination of brain tissue obtained at postmortem examination. The latter methods included hematoxylin-eosin staining, immunostaining, and polymerase chain reaction for detection of 16 rRNA. The median CSF protein concentration of 5 patients with Balamuthia infection was 1247 mg/dL, compared to 93 mg/dL ($P < 0.001$) in the seronegative group, while glucose levels (47 mg/dL vs 61 mg/dL) and WBC (106/mm^3 vs 63/mm^3) were not significantly different. All 7 patients with proven balamuthiasis were of Hispanic ethnicity.

One patient with confirmed *Acanthamoeba encephalitis* was identified during the course of the study, but that patient who was receiving corticosteroid therapy for systemic lupus erythematosus had what were considered to be negative antibody titers to this organism.

■ COMMENTARY

Despite enormous diagnostic efforts, the CEP reported several years ago that the etiology of encephalitis remained unknown in at least 62% of cases.[1,2] This report identifies a small, but significant number of cases that proved to be due to the free-living amoeba, *B. mandrillaris*. A number of additional patients with borderline titers could not be adjudicated because of lack of availability of brain tissue for examination, either because no postmortem examination was performed or the patient survived and was lost to follow-up. Nonetheless, the number of identified cases of encephalitis due to this pathogen exceeded the number of cases of human rabies during a similar time frame. Since the amoebal infection has greater potential for successful therapy[3,4] directed against it than does rabies, *Balamuthia encephalitis* is, at least from one viewpoint, a clinically more important disease. Unfortunately, most cases of *Balamuthia encephalitis* are

first diagnosed at post-mortem examination. In California, there were 2 survivors[3] among 12 human cases identified from 1990-2005. The demonstration that infection may be identified by serum antibody testing provides hope that, with improved clinician awareness, cases will be more likely to be diagnosed antemortem in the future.

The onset of *Balamuthia encephalitis* is subacute, with months of symptoms prior to diagnosis or death. In addition to the progressive focal and non-focal central nervous system symptoms and findings, CSF examination generally reveals mild, predominantly lymphocytic pleocytosis, with normal or low glucose concentration, and protein concentrations that commonly exceed 1000 mg/dL. A case of amebic encephalitis due to Acanthamoeba has been diagnosed by visualization of the organism on cytological examination of CSF.[4] Space-occupying mass-like lesions and multiple ring-enhancing lesions may be seen. As pointed out by Schuster and colleagues, initial presumptive diagnoses have included tuberculosis, neurocysticercosis, viral encephalitis, bacterial brain abscess, tumor and atypical disseminated encephalomyelitis. Balamuthia are free-living amoebae that are present in soil, and individuals such as construction and agricultural workers, among others, should be considered at increased risk.

At least 3 survivors have been identified. After identification of the organism in skin and brain biopsy specimens of a 64-year-old man, treatment involved 5-fluorocytosis, fluconazole, pentamidine isethionate, sulfadiazine, and clarithromycin, with subsequent improvement. There was worsening after discontinuation of fluconazole, with improvement once again after its reinitiation. The patient was then chronically maintained on therapy with fluconazole and sulfadiazine. A similar initial regimen was associated with improvement in a 5-year-old patient with confirmed brain infection.[3] A 72-year-old apparently immunocompetent woman was successfully treated with pentamidine, sulfadiazine, fluconazole, and clarithromycin.[5]

Be the first on your block to make this diagnosis and save a life!

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CME Questions

11. Which is correct?

a. *Balamuthia mandrillaris* is a fungal pathogen of Balamuthia monkeys.
b. *Balamuthia mandrillaris* causes an acute neutrophilic meningitis with rapid progression to death.
c. *Balamuthia mandrillaris* is transmitted by the bite of mosquitoes.
d. Infection with *Balamuthia mandrillaris* is potentially treatable.

12. Which is correct?

a. Posaconazole is primarily metabolized by cytochrome P450 enzymes.
b. Posaconazole acts by binding to ergosterol in the fungal cell membrane.
c. Posaconazole is primarily excreted in the feces of healthy volunteers.
d. Posaconazole is active in vitro against both many Aspergillus isolates, as well as many zygomycetes.

13. Which is correct?

a. Posaconazole inhibits fungal ergosterol synthesis.
b. Posaconazole is inactive in vitro against non-albicans species of Candida.
c. The gastrointestinal absorption of posaconazole is markedly affected by gastric pH.
d. Posaconazole is neither an inhibitor nor an inducer of the CYP450 enzyme, CYP3A4.

Answers: 11. (d); 12. (c); 13. (a)

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:

Posaconazole (Part 2)

UPDATES

By Carol A. Kemper, MD, FACP

Scrub That Lettuce!

Sposton EL, Macrae M, Ogden ID, et al. Slugs: Potential Novel Vectors of *Escherichia coli* 0157. *Appl Environ Microbiol*. 2006;72:144-149.

On my first walk through a redwood forest after moving to California, I came across numerous slimy yellow creatures along the trail that looked like snails without shells. These were banana slugs, creatures that are currently the official mascots of the University of Califonia, Santa Cruz.

Slugs, like snails, are molluscs, but they lack shells and come in a variety of sizes, including some which make their presence much less obvious than that of the banana slug. Instead, they are soft, slimy creatures that necessarily hang out in dark, moist places, such as the underside of lettuce leafs in the field. Lettuce and other leafy vegetables commonly retain a complement of these creatures and, unless removed by vigorous cleaning, they and their feces may be ingested along with the arugula and other raw items in modern salads. Vegetables such as these may also be carry snails, and these fellow gastropods are known to be intermediated hosts for a number of parasitic infections affecting humans, such as fascioliasis.

Sposton and colleagues have now provided evidence demonstrating the potential for slugs to transmit at least one enteric pathogen, *Escherichia coli* 0157. The major reservoir for these enteropathogens is the gastrointestinal tract of farm ruminants who shed the organism in their feces. Slugs, which are ubiquitous agricultural pests that continuously infest soil and its associated bacteria. Sposton et al identified verotoxin gene-positive *E. coli* 1057 in 0.21% of gray field slugs, a frequent contaminant of leafy salad vegetables, from a farm in Aberdeenshire, Scotland. The bacteria were genetically indistinguishable from those recovered from sheep on the farm, 7% of whom were estimated to be carrying it. They demonstrated that the slug, which can travel up to 12 meters a night, could carry viable *E. coli* on its external surface for as long as 14 days, and the microorganism persisted for up to 3 weeks in excreted slug feces.

Thus, slugs have the potential to act as vectors of transmission of verotoxin positive *E. coli* 0157. This, however, could be prevented by careful cleaning of leafy salad vegetables before ingestions.

An aside: Slugs are hermaphroditic, having the "unenviable task of being a father and a mother at the same time."[1] Some slugs enhance their reproductive success by the use of love darts, which are hard, needle-like structures produced in the dart-sac for the express purpose of dart shooting, which results in increased success in spermatozoa reaching their trarget.[1] This raises the bizarre question: could *E. coli* 0157 infection be a sexually transmitted disease in slugs? ■

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Ketek's Troubled History

Wall Street Journal, Monday May 1, 2006, page A1; Response Statement from Sanofi Aventis dated May 10, 2006.

Reports of severe, life threatening and even fatal cases of severe liver damage in patients receiving telithromycin (Ketek®, Sanofi Aventis), some of which were recently reviewed in the *Annals of Internal Medicine*, has prompted a deeper analysis of events leading up to FDA approval of this agent in the United States. According to the FDA, they are presently aware of 10 cases of hepatic failure following administration of telithromycin, although the relationship to drug is under investigation.

Telithromycin was first submitted to the FDA for approval in 2000, and eventually received formal approval for use in sinusitis, bronchitis and community acquired pneumonia in April 2004. During the FDA's initial drug eval-

uation, it was felt that there was insufficient data regarding the risks of visual blurring, hepatic toxicity, and other side events, and drug interactions and requested additional data. The company complied, embarking on a large clinical trail in 24,000 adult outpatients (Study 3014). The study was performed in the usual care setting, with more than 400 sites throughout the United States.

Unfortunately, subsequent events have shed doubt on the validity of Study 3014 data provided by at least 3 of the investigators (these 3 sites enrolled a total of 872 patients). The most egregious case was a female physician in Alabama who "enrolled" 407 patients, who is subsequently serving a 4-year sentence in Federal prison for defrauding the company (in an interesting twist, she pled guilty to mail fraud for sending falsified data through the mail). Another physician lost his license for gross negligence and drug possession shortly after enrolling the final patient at his site. And another physician admitted to inadequate record keeping.

The hullabaloo surrounds the issue of whether and when the parent company may have recognized irregularities and deficiencies at some sites, and whether this was adequately reported to the FDA. Only an independent FDA audit of these sites, conducted simply because of the large numbers of patients enrolled, revealed serious problems, including patients who received study drug for inappropriate indications (eg, weight loss), patients who reported never receiving study drug, fabrication of data, and failure to report adverse events.

Despite suspicions and concerns raised about Study 3014 sites in ongoing FDA investigations, an FDA Advisory Committee Panel convened in January 2003 to-re-evaluate telithromycin for approval. Inexplicably, the panel was not made aware of the above concerns, and recommended the drug for approval. The FDA rejected the Advisory Committee's recommendation, indicating that additional data from Study 3014 and overseas post-marketing experience was still needed.

In the meantime, increasingly available post-marketing data from Europe and other countries suggested the drug had an adequate safety record. The FDA ultimately decided that Study 3014 was too flawed to be relied upon, but nonetheless approved the drug in April 2004 for the treatment of sinusitis, bronchitis and community acquired pneumonia.

The Senate Finance Committee and 2 congressmen are now examining these events. While the company admits that "deviations occurred at some sites, and in one case, actual fraud by one the site investigators was ultimately identified in an FDA criminal investigation", they continue to vigorously defend Study 3014 data as reflecting the broader experience of community based research, and believe it provides useful safety data. They "remain confidant that Ketek is a safe and effective first-line therapy" for respiratory tract infections. Indeed, the drug has broader activity against many respiratory bacterial pathogens than many other currently available agents, and continues to be evaluated in clinical trails of pediatric otitis.

The company is to be credited for their efforts at new drug development in the face of increasing bacterial resistance, something that few pharmaceutical companies have elected to pursue.

None of this addresses many primary care physicians concerns regarding the potential drug interactions with this telithromycin, including agents commonly received by many elderly. These include interactions with CYP 3A4 inducers, such as rifampin, coumadin (with an increased risk of bleeding), some of the statins, several antiarrhythmic agents, and drugs with the potential to prolong the QT interval. Feedback from physicians in the community suggests that concerns regarding drug interactions (and just trying to remember them all) may be the more material limitation to the broader use of this agent.

However, it may be telling that a local dermatologist scared the beejeebers out of patient recently seen in consultation for disabling chronic bronchiectasis. Although he had received telithromycin without problem on at least one prior occasion, the dermatologist urged him to stop his current course of therapy before it "damaged his liver." ■

Financial Disclosure:

Dr. Carol A. Kemper, MD, FACP, is on the speaker's bureau for Sanofi Aventis.

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.

Gastric Acid Secretion and the Absorption of Thyroxine

The absorption of thyroxine is strongly influenced by stomach acidity, according to new study. Researchers from Italy looked at 248 patients with multinodular goiter who were treated with thyroxine with a goal thyrotropin (TSH) level of 0.05 to 0.20 mU/L. Of these patients, 53 had *Helicobacter pylori* related gastritis and 60 had atrophic gastritis of the stomach. The reference group comprised 135 patients with multinodular goiter and no gastric disorders. The study also included 11 patients who were infected with *H. pylori* during the study and 10 patients who were treated with omeprazole and had no gastroesophageal reflux. Patients with *H. pylori*-related gastritis, atrophic gastritis, or both had a daily requirement of thyroxine that was 22-34% higher than the reference group. In the 11 patients who became infected with age by lower *H. pylori* during the study, thyrotropin levels increased significantly (P = 0 .002), an effect that was nearly reversed with eradication of *H. pylori*. Treatment with omeprazole also increased serum thyrotropin levels (median 1.70mU/L increase in thyrotropin; P = 0.002), requiring a 37% increase in thyroxine dose.

The authors conclude that normal gastric acid secretion is necessary for effective absorption of thyroxine, and factors that impair acid secretion including atrophic gastritis, *H. pylori* gastritis, and treatment with omeprazole require increased doses of thyroxine (*N Engl J Med*. 2006;354:1787-1795). This study has important implications, given millions of patients who take thyroxine, the frequency of *H. pylori* infections in this country, and frequency of use of OTC and prescription proton pump inhibitors.

Can Plavix Add to the Efficacy of Aspirin?

Does clopidogrel (Plavix) add to the efficacy of low aspirin in patients with vascular disease? No, according to new study published in the April 20th *New England Journal of Medicine*. CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) is a multinational study which randomized 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75-162 mg/d) or placebo plus low-dose aspirin for median of 28 months. The efficacy primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The rate of this end point was 6.8% with the combined drug treatment versus 7.3% with aspirin plus placebo (P = 0.22) for the subgroup of patients with multiple risk factors, the rate of the primary end point was lower for aspirin plus placebo (5.5% aspirin plus placebo versus 6.6% aspirin plus clopidogrel; P = 0.20) and the rate of death from cardiovascular causes was also higher with clopidogrel plus aspirin vs aspirin plus placebo (3.9% versus 2.2%; P = 0.01).

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.

In the subgroup with clinically evident atherothrombosis, there was a slight benefit for aspirin plus clopidogrel (6.9% versus 7.9%, P = 0.46).

The authors conclude that overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease (*N Engl J Med*. 2006;354:1706-1717). An accompanying editorial acknowledges that there were many subgroups within CHARISMA that showed varying outcomes with clopidogrel plus aspirin, but cautions against differentiating patients along the lines used in the study. The editorialists find that "these data showed no significant benefit associated with long-term clopidogrel therapy in addition to aspirin." (*N Engl J Med*. 2006;354:1744-1746).

Prevention of Hypertension?

Prehypertension is defined as blood pressure in the range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic. Since JNC-VII, there has been increased interest in prehypertension since it has been associated with excess morbidity and deaths from cardiovascular causes. A new study suggests that pharmacologic intervention in patients with prehypertension may help prevent progression to hypertension. The Trial of Preventing Hypertension (TROPHY) looked at 809 patients with prehypertension. A total of 409 patients were randomly assigned to candesartan or placebo for 2 years, followed by 2 years of placebo for both groups. When a study participant reached the study end point of stage I hypertension, they were treated with antihypertensive agents.

Both treatment and placebo groups were instructed in lifestyle changes to reduce blood pressure throughout the trial. During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 in a candesartan group ($P < 0.001$). After 4 years, hypertension had developed in 240 participants in the placebo group and 208 in the candesartan group (relative risk reduction 15.6%; $P < 0.007$). Serious adverse events were slightly higher in the placebo group.

The authors conclude that treatment of prehypertension with candesartan was well-tolerated and reduced the risk of incident hypertension during the study period (*N Engl J Med*. 2006;354:1685-1697). In an accompanying editorial, it is pointed out the prehypertension is present in the about 70 million Americans, and is estimated to decrease average life expectancy by as much as 5 years. Despite this, the author urges caution in recommending wholesale treatment of all patients with prehypertension until more information is available on which drugs are most effective and the best duration of therapy. In the meantime, lifestyle changes, which benefit all risk factors, should be recommended for all patients with prehypertension (*N Engl J Med*. 2006;354:1742-1744).

Estrogen Alternatives

Since publication of the Women's Health Initiative (WHI), many postmenopausal women have discontinued estrogen, and most newly menopausal women are considering alternatives. A recently published paper systematically reviews clinical trials of nonhormonal treatments for hot flashes. More than 4000 studies were considered. Forty-three trials met inclusion criteria, including 10 trials of antidepressants, 10 trials of clonidine, 6 trials of other medications, and 17 trials of isoflavone extracts. In the antidepressant group, both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) were effective in decreasing the daily number of hot flashes compared to placebo (mean difference -1.13; 95% CI, -1.70 to -0.57). Clonidine was also somewhat effective (-0.95; 95% CI, -1.44 to - 0.47), as was gabapentin (-2.05; 95% CI, -2.80 to -1.30). Red clover isoflavone extracts were not effective, and mixed soy isoflavones had mixed results. The authors conclude that SSRIs, SNRIs, clonidine, and gabapentin provide evidence for some efficacy; however, none are as effective as estrogen (*JAMA*. 2006;295:2057-2071).

FDA Actions

In April, the FDA issued a statement rejecting the medical use of marijuana, citing past evaluations by several US government agencies that showed that "no animal or human data supported the safety or efficacy of marijuana for general medical use." The statement supports the Drug Enforcement Agency's approach to treating all use of marijuana as a criminal act.

Zanamivir (Relenza), GlaxoSmithKline's inhaled anti-influenza drug has received a new indication for prophylaxis of influenza in patients age 5 years and older. The approval was based on 4 large-scale, placebo-controlled trials which showed that the drug was effective in reducing spread of influenza among household members and in community outbreaks. ■