

Practice Recommendations from Key Studies

Suicide risk not increased with SSRI antidepressants

Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. *Am J Psychiatry* 2003; 160:790-792.

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■ PRACTICE RECOMMENDATIONS

Depressed adult patients are no more likely to commit suicide while taking selective serotonin reuptake inhibitors (SSRIs) than any other class of antidepressants.

The low suicide rate in the non-SSRI category, which included tricyclic antidepressants (TCAs), reminds us that no evidence exists to consider tricyclics more dangerous than other antidepressants, despite what is commonly believed. Thus, clinicians who avoid prescribing any antidepressant because of risk of suicide may change their clinical practice. It is important to remember that these patients are adults and had mild to moderate depression without any significant comorbid conditions.

■ BACKGROUND

Several case reports and experts have speculated that SSRIs carry higher risks of agitation, suicidal ideation, and suicidal impulses. Media coverage and lawsuits involving patients who committed suicide while on antidepressants fueled the debate. Besides SSRIs, TCA and monoamine oxidase inhibitor (MAOI) medications may carry higher risk of suicide because of their toxicity in overdose.

The annual suicide rates for patients with major affective disorders is estimated to be 0.30% to 0.80%.¹ Psychiatric illness—including

major depression and bipolar disorder, chronic illness, alcohol abuse, and other factors—are associated with increased risk of suicide. This study attempted to determine whether SSRIs are dangerous in and of themselves.

■ POPULATION STUDIED

The study analyzed a US Food and Drug Administration (FDA) database to obtain suicide rates for 48,277 outpatients enrolled in controlled trials of antidepressants. The authors stated that antidepressant clinical trial participants tend to be mildly to moderately depressed and that studies tend to enroll patients who are not suicidal, do not have other psychiatric illnesses, and do not have known substance abuse problems.

■ STUDY DESIGN AND VALIDITY

This retrospective cohort study used FDA clinical trial data from 1985 to 2000 for 4 SSRIs (fluoxetine, sertraline, paroxetine, and citalopram) and 5 other antidepressants (venlafaxine, nefazodone, mirtazapine, sustained-release bupropion, and extended-release venlafaxine). Any suicides reported in the database were assigned to the antidepressant the patient was taking at the time they committed suicide.

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What is a POEM?

Each month, the POEMs (Patient-Oriented Evidence that Matters) editorial team reviews 105 research journals in many specialties, and selects and evaluates studies that investigate important primary care problems, measure meaningful outcomes, and have the potential to change the way medicine is practiced. Each POEM offers a Practice Recommendation and summarizes the study's objective, patient population, study design and validity, and results. The collected POEMs are available online at www.jfponline.com.

No significant differences in rates of suicide were found between SSRIs, non-SSRIs, and placebo

Many of the patients were taking an active control medication; therefore, data were obtained for another SSRI (fluvoxamine), 4 TCAs (imipramine, amitriptyline, mianserin, and dothiepin), and 2 other antidepressants (trazodone and maprotiline). The length of time patients were followed in the studies was between 4 and 8 weeks.¹

The study was adequately powered to detect a difference between the SSRI and non-SSRI antidepressant groups. Whether the population studied represents patients primary care physicians are likely to see in the office is unclear. The study did not summarize patient characteristics, report whether they were enrolled from specialty clinics, or assess the validity of the underlying individual studies.

OUTCOMES MEASURED

The study compared rates of completed suicide for the subjects taking SSRIs compared with the subjects taking non-SSRI antidepressants and placebo. Data were not available to assess whether suicidal ideation or attempts were different between the 2 groups.

RESULTS

The FDA database contained information for 48,277 patients enrolled in antidepressant trials. Of these, 26,109 were randomly assigned to SSRIs, 17,273 were assigned to non-SSRI antidepressants, and 4895 were given placebo. No statistically significant differences in rates of completed suicide were found between SSRIs, non-SSRIs, and placebo. Seventy-seven (0.15%) subjects committed suicide (0.15% of the SSRI group, 0.20% in the non-SSRI category, and 0.10% in the placebo group).

Similarly, analyzing the results by patient exposure years did not show a significant difference (0.59%, 0.76%, and 0.45% for SSRIs, non-

SSRIs, and placebo, respectively). The method of suicide was given for half of the suicides, but no clear differences in type of suicide or impulsivity could be drawn.

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Low-dose warfarin prevents recurrent thromboembolism

Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003; 348:1425-1434.

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PRACTICE RECOMMENDATIONS

Low-intensity warfarin (target international normalized ratio [INR], 1.5-2.0) effectively prevents recurrent venous thromboembolism without increasing the risk of major bleeding when used long-term for secondary prophylaxis. This is a reasonable approach following at least 3 to 12 months of full-intensity warfarin after the initial thromboembolic event.

BACKGROUND

Prolonging the duration of full-intensity oral anticoagulation can decrease the recurrence of venous thromboembolism, but it often increases the rate of major bleeding above an acceptable risk-benefit ratio. This trial evaluated the efficacy and safety of long-term, low-intensity warfarin for the prevention of recurrent venous thromboembolism.

POPULATION STUDIED

This multicenter study included patients older than 30 years, with documented idiopathic venous thromboembolism who completed at least

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3 months of uninterrupted full-dose warfarin therapy (target INR, 2.0–3.0). The median age was 53 years; 47% were female, approximately 87% were white, and 9% were African American. More than 37% had at least 2 previous venous thromboembolisms, over 25% had either factor V Leiden or a prothrombin mutation, and all patients were treated with full-dose warfarin for an average of 6 months before enrollment.

Patients were excluded if they had lupus anticoagulant, antiphospholipid antibodies, or a history of metastatic cancer, major gastrointestinal bleeding, or hemorrhagic stroke. Patients were also excluded if their life expectancy was <3 years and if they were treated with antiplatelet therapies (other than aspirin 325 mg/d) or drugs that affect the prothrombin time.

■ STUDY DESIGN AND VALIDITY

This randomized, double-blind, placebo-controlled trial was conducted from July 1998 to December 2002. All patients were involved in a 28-day run-in phase to ensure that they could have their warfarin titrated to an INR of 1.5 to 2.0 without exceeding a daily dose of 10 mg. This run-in phase also identified and excluded patients with <85% adherence to the treatment regimen.

Following the run-in phase, eligible patients (n=508) were centrally randomized to receive warfarin or matching placebo, and were stratified according to the clinical site, time since the index event, and whether this was the patient's first venous thromboembolism. Every 2 months, clinical events were assessed and the INR was checked; doses were adjusted using a standard algorithm. INR results were transmitted in a double-blind fashion to the data coordinating center.

Analysis was by intention-to-treat. The study was designed to enroll 750 patients for an average follow-up of 4 years, but was terminated early by an independent data and safety monitoring board due to warfarin's significant benefit.

The National Heart, Lung, and Blood Institute supported this well-designed study. Bristol-Myers Squibb provided the study drug and placebo free

The study was terminated early by an independent board due to warfarin's significant benefit

of charge. Patients were typical outpatients, although they had an increased risk of venous thromboembolism based on the significant number with a history of previous events and thrombophilic mutations.

Central randomization allowed for concealed allocation to treatment assignment and physicians and patients were blinded to the true INR results by using a specially designed finger-stick device and adjusting doses in both treatment groups. Minor design weaknesses include a relatively small sample size and the use of a thromboplastin with an international sensitivity index of 2.0, instead of one closer to 1.0.

■ OUTCOMES MEASURED

The primary endpoint measured was recurrent venous thromboembolism. A composite endpoint was major hemorrhage (bleeding that required hospitalization or transfusion), recurrent venous thromboembolism, and death from any cause. New stroke events were also monitored.

■ RESULTS

Due to early termination, the mean duration of follow-up was 2.1 years and the median INR in the warfarin group was 1.7, compared with 1.0 for placebo. Low-intensity warfarin reduced the risk of recurrent venous thromboembolism by 64% (hazard ratio [HR]=0.36; 95% confidence interval [CI], 0.19–0.67; $P<.001$; number needed to treat [NNT]=22). Warfarin reduced the composite endpoint by 48% (HR=0.52; 95% CI, 0.31–0.87; $P=.01$; NNT=26).

No statistical difference existed in strokes, deaths, or major bleeding between the 2 treatment groups. Minor bleeding or bruising was reported more often with warfarin (HR=1.92; 95% CI, 1.26–2.93; $P=.002$; number needed to harm=16.4).

Steroids ineffective for pain in children with pharyngitis

Bulloch B, Kabani A, Tenebein M. Oral dexamethasone for the treatment of pain in children with acute pharyngitis: a randomized, double blind, placebo-controlled trial. *Ann Emerg Med* 2003; 41:601-608.

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■ PRACTICE RECOMMENDATIONS

In children with acute pharyngitis, oral dexamethasone does not provide clinically significant reductions in time to initial or complete pain relief. Reserve its use for children with group A β -hemolytic streptococcus pharyngitis who have moderate to severe pain, realizing that the benefit is of questionable significance.

■ BACKGROUND

Dexamethasone has been shown to be beneficial in several pediatric illnesses such as croup and asthma, and intraoperatively for adenotonsillectomy. Several studies of adults with acute pharyngitis reported relief of pain with use of corticosteroids. This study compared whether dexamethasone relieved pain from pharyngitis with group A β -hemolytic streptococcus and non-group A β -hemolytic streptococcus in children presenting to an emergency room in Canada.

■ POPULATION STUDIED

The 184 children (aged 5 to 16 years) in this study presented to an emergency room with a chief complaint of sore throat,odynophagia, or dysphagia that began within the preceding 48 hours. They also had demonstrable erythema of the pharynx on exam. Children were excluded if they were immunocompromised, pregnant, already taking antibiotics, had used a corticosteroid recently, or had a peritonsillar or pharyngeal abscess.

■ STUDY DESIGN AND VALIDITY

This was a randomized, double-blind, placebo-controlled study. Initial allocation to treatment groups was concealed.

The children initially rated their pain from 1 to 10 ("no pain" to "most pain") on a validated 10-cm color analog scale. A reduction of 2 cm on the scale reflects a clinically significant difference in pain. The 85 patients with a positive test for group A β -hemolytic streptococcus received their first dose of antibiotic and a prescription for 10 days of penicillin V potassium in the emergency department, and either dexamethasone, dosed at 0.6 mg/kg to a maximum of 10 mg, or an identical placebo. All 99 patients with negative tests for group A β -hemolytic streptococcus underwent the same protocol as the positive group without the antibiotics.

The parents were shown how to administer the pain scale. All children could receive nonprescription analgesics. Research assistants blinded to treatment group telephoned patients at 24 and 48 hours. They asked the parents to determine the onset of pain relief and complete resolution to the nearest hour and administer the pain scale. Families were asked at 1 month to determine whether there were any relapses, treatment failures, or complications.

This study was well designed. The authors used a pain scale that was previously validated. The clinicians, patients, and outcomes assessors were all blinded to allocation assignment, and the analysis was performed on an intention-to-treat basis. Families were contacted every 24 hours, so we cannot be sure time to pain relief is accurate to the hour. Follow-up was adequate.

■ OUTCOMES MEASURED

The primary outcome measures were the time to initial pain relief and the time to complete pain relief.

■ RESULTS

Oral dexamethasone decreased the time to initial pain relief in children who tested positive for group

A β -hemolytic streptococcus, but not the time to complete pain relief. The mean time to initial pain relief in this group of children was 6 hours in the dexamethasone group vs 11.5 hours in the placebo group ($P=.02$; effect size of 5.5 hours; 95% confidence interval, 1–10 hours). The time to complete pain relief was approximately 1.5 days in either group. There was no significant difference in either time to initial pain relief or time to complete pain relief in children who tested negative for group A β -hemolytic streptococcus.

Do irbesartan and amlodipine reduce cardiovascular events in diabetic patients?

Berl T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. Ann Intern Med 2003; 138:542–549.

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■ PRACTICE RECOMMENDATIONS

When added to antihypertensive treatment in patients with diabetes and nephropathy, neither the angiotensin receptor blocker (ARB) irbesartan nor the calcium channel blocker amlodipine reduced the overall occurrence of cardiovascular events. However, irbesartan decreased the rate of heart failure and amlodipine reduced the rate of acute myocardial infarction.

■ BACKGROUND

Good control of blood pressure reduces microvascular and macrovascular complications in patients with diabetes more than control of blood glucose levels.¹ Further, the Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial (ALLHAT) demonstrated that diuretics should be first-line

therapy for all patients with hypertension, including those with diabetes.²

ARBs are currently recommended by the American Diabetes Association as first-line treatment in patients with type 2 diabetes with nephropathy.³

■ POPULATION STUDIED

This randomized, multinational study enrolled 1715 patients with type 2 diabetes, blood pressure >135/85 mm Hg, and frank nephropathy (mean 2.9 g/d of urinary protein). Two thirds of the patients also had retinopathy, nearly 30% had pre-existing cardiovascular disease, and over half took insulin. Patients were receiving multiple-drug antihypertensive regimens from their primary care physicians; those already taking ARBs, calcium channel blockers, or angiotensin-converting enzyme inhibitors were excluded.

■ STUDY DESIGN AND VALIDITY

In addition to their usual antihypertensive treatment, patients were assigned to receive either placebo, amlodipine (Norvasc) 10 mg/d, or irbesartan (Avapro) 300 mg/d. Allocation to treatment assignment was concealed, and patients and investigators were blinded to treatment assignment. Patients were followed for 2.5 years; loss to follow-up was less than 1%. Analysis was by intention-to-treat.

Goal blood pressure was defined as <135/85 mm Hg. During the study, the average blood pressure was 140/77 mm Hg in the irbesartan group, 141/77 in the amlodipine group, and 144/80 in the placebo group. Patients in the irbesartan and amlodipine groups each received a total of 3 additional antihypertensive drugs, and the placebo group received an average of 3.3 nonstudy antihypertensives. One third received diuretics and nearly half received beta-blockers.

This was a valid study, but the sample size was not adequate to rule out a small but clinically relevant benefit of irbesartan. This was a secondary analysis of the Irbesartan Diabetic Nephropathy Trial, which evaluated renal protection. Reporting

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Nearly 25% of patients discontinued treatment early due to complications, protocol violations, or hypertension

outcomes not part of the study design makes interpretation difficult, because statistically significant findings are likely to occur by chance alone if the investigators make numerous comparisons.

OUTCOMES MEASURED

The combined outcome was the occurrence of at least 1 of the following: any acute myocardial infarction, unplanned coronary revascularization procedure, heart failure, stroke, or fatal coronary heart disease. Each outcome was also examined individually.

RESULTS

Differences were small among the groups at baseline, but the investigators appropriately accounted for these differences in the analysis. Nearly one quarter of the patients discontinued the assigned treatment prematurely (mostly due to complications of therapy, protocol violations, or uncontrolled hypertension).

Overall, more than one third of patients experienced 1 of the cardiovascular endpoints. For the combined cardiovascular outcome, a trend toward benefit from irbesartan (hazard ratio [HR]=0.90) was not statistically significant. Heart failure was reduced among patients receiving irbesartan (HR=0.72; 95% confidence interval [CI], 0.52–1.00; number needed to treat [NNT]=15).

No benefits were seen in the combined outcome among patients receiving amlodipine, but myocardial infarctions were reduced (HR=0.58; 95% CI, 0.37–0.92; NNT=26) and, compared with irbesartan, heart failure was increased.

Adverse events were similar in all 3 groups, except that more hyperkalemia was seen in the patients receiving irbesartan.

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Low-dose doxycycline moderately effective for acne

Skidmore R, Kovach R, Walker C, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. Arch Dermatol 2003; 139:459–464.

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PRACTICE RECOMMENDATIONS

The authors propose that moderate acne may be treated with doxycycline in subantimicrobial doses (20-mg tablets taken twice daily). This regimen was well-tolerated, moderately effective in reducing skin lesions, and did not have a detectable effect on the antibiotic resistance of skin flora.

The cost of Periostat (the only form of doxycycline 20 mg available in the US) is about \$55 per month, while generic doxycycline 100 mg is about \$10.¹ This study has some significant flaws, but a trial of low-dose doxycycline in an adult with acne severe enough to warrant antibiotics would still seem a reasonable, albeit expensive, option.

BACKGROUND

Doxycycline, when used in doses that are below its antimicrobial threshold, is effective in treating adult chronic periodontitis. Doxycycline

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hyclate 20 mg twice daily (Periostat) is believed to work by decreasing inflammation and does not appear to create bacterial resistance to itself. Given the role of host inflammatory response in acne, the researchers tested sub-antimicrobial dosing of doxycycline in adults with moderate acne.

■ POPULATION STUDIED

The subjects were 51 adults with moderate acne (defined as 6–200 comedones, 10–75 papules, and <6 nodules) drawn from 2 university-based outpatient clinics. Thirty-five (69%) were white, and the mean age was 23 years.

Subjects could not have used acne therapy for 6 weeks prior to enrollment and could not be on hormonal contraception. Forty of these patients completed the 6-month study. Of the patients not completing the study, 5 were lost to follow-up, 4 did not follow the study protocol, and 2 had possible adverse reactions to the study drug.

■ STUDY DESIGN AND VALIDITY

In this double-blind randomized study, patients were given either oral doxycycline hyclate 20 mg twice daily (n=26) or a matching placebo (n=25). Patients were assessed at baseline and at 2, 4, and 6 months.

The authors do not describe how the study participants were recruited into the study, and no information is given regarding allocation concealment. After randomization, the groups were not well-balanced, in that there were approximately twice as many men in the placebo group than the treatment group. Since androgens play a significant role in acne, this unequal distribution of men into the placebo group may partly be responsible for the better results found in the treatment group. It raises further doubt as to whether allocation assignment was concealed from the enrolling researchers.

Analyses appeared to be per protocol and not by intention-to-treat. The study was supported by the makers of Periostat.

Low-dose doxycycline in adult acne cases severe enough for antibiotics would be reasonable but expensive

■ OUTCOMES MEASURED

The primary outcomes measured were the number of lesions present at each evaluation. Secondary outcomes included the clinician global assessment and the patient self-assessment scores using a 7-point qualitative scale. Forehead skin flora samples were collected at baseline and at 6 months to assess for changes in microflora or resistance patterns.

■ RESULTS

Six months after baseline, the doxycycline group showed a greater decrease in inflammatory lesions (50.4% fewer vs 30.2% fewer for placebo; $P=.04$) and comedones (53.6% fewer vs 10.6% fewer; $P=.01$). The clinician's global assessment, however, was an improvement of only 0.4 on a 7-point scale at 6 months, a barely clinically significant difference ($P=0.03$). The change in patients' global assessment was also towards improvement, but was not statistically significant.

Two patients in the doxycycline group dropped out due to possible adverse drug reaction. One patient had a gastric ulcer with bleeding, which was not attributed to the medication. Another had a recurrence of yeast vaginitis, which was thought to be related to the antibiotic. No significant change was detected in the composition of the skin flora or in antibiotic susceptibility in those patients taking antibiotics.

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Selective aldosterone blockade reduces mortality after MI

Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348:1309–1321.

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■ PRACTICE RECOMMENDATIONS

Eplerenone, a selective mineralocorticoid receptor antagonist currently approved by the Food and Drug Administration for treatment of hypertension, reduces mortality following myocardial infarction (MI) in patients with left ventricular dysfunction and clinical signs of congestive heart failure. Previous research by the same group established that spironolactone does the same at lower cost than eplerenone.¹

■ BACKGROUND

Family physicians commonly manage patients with congestive heart failure following acute MI. This trial examined the effects of selective aldosterone blockade on morbidity and mortality in patients who suffered an acute MI complicated by left ventricular dysfunction and clinical signs of congestive heart failure.

■ POPULATION STUDIED

This industry-sponsored study enrolled 6642 patients at medical centers in 37 different countries. Inclusion criteria included acute MI (diagnosed according to “standard criteria”) within the previous 2 weeks; left ventricular dysfunction (ejection fraction <40%), and heart failure as documented by clinical findings of pulmonary rales, radiographic changes, or a third heart sound.

Exclusion criteria included the use of potassium-sparing diuretics, a baseline serum creatinine over 2.5 mg/dL, or baseline serum potassium over

5.0 mmol/L. The average patient age was 64 years; 70% were male and 90% were white. The average left ventricular ejection fraction at the time of enrollment was 33%.

More than 80% of study patients were taking angiotensin-converting enzyme (ACE) inhibitors, 75% were taking beta-blockers, 60% were taking diuretics, and nearly 50% were on statin therapy. This degree of medical therapy is higher than generally cited^{2,3} and thus might impact generalizability.

■ STUDY DESIGN AND VALIDITY

Subjects were randomized to receive either eplerenone 25 mg/d titrated to a maximum of 50 mg/d (n=3391), or placebo (n=3313). All patients concurrently received “optimal medical management” that included ACE inhibitors, beta-blockers, diuretics, aspirin, statins, and coronary reperfusion therapy. Endpoints were analyzed using the Cox proportional-hazards regression and the time to event was summarized using standard Kaplan-Meier curves. All final data analysis was performed by the study sponsor.

The study design was good: it was well-powered to detect an 18% difference in death from any cause between groups. Randomization was stratified according to clinical site and statistical analysis was performed using the appropriate models. Weaknesses include no mention of concealed subject allocation, which could lead to an overestimation of the magnitude of treatment effect.

■ OUTCOMES MEASURED

Primary endpoints were time to death from any cause and time to death or hospitalization for cardiovascular events (stroke, MI, heart failure, or arrhythmia). Secondary endpoints were the absolute presence of death or hospitalization. Endpoints were adjudicated by blinded assessors.

■ RESULTS

Groups were similar at baseline. Patients were followed every 3 months for an average of 16 months. Mortality from all causes was lower

in the eplerenone group (14.4% vs 16.7%; $P<.01$; number needed to treat [NNT]=44). Cardiovascular death and hospitalization were also reduced in the eplerenone group (26.7% vs 30%; $P<.01$; NNT=33).

Patients in the eplerenone group were more likely to discontinue medication use (528 vs 493) and more likely to have serious hyperkalemia (5.5% vs 3.9%; $P<.01$; number need to harm=63).

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Blood cultures not helpful for community-acquired pneumonia

Campbell, SG, Anstey R, Ackroyd-Stolarz S. The contribution of blood cultures to the clinical management of adult patients admitted with community-acquired pneumonia. Chest 2003; 123:1142–1150.

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■ PRACTICE RECOMMENDATIONS

Blood cultures rarely contribute to the management of uncomplicated community-acquired pneumonia. A positive blood culture has no relation to the severity of the illness or to patient outcomes. Physicians should order blood cultures only for those patients with severe illness and for those in whom initial therapy fails.

■ BACKGROUND

Many clinical guidelines recommend routine blood cultures in the initial evaluation of community-acquired pneumonia. Previous research cast doubt on this approach.¹

■ POPULATION STUDIED

The researchers recruited adults presenting with community-acquired pneumonia to 19 Canadian hospital emergency departments between January and July 1998. Patients were eligible if they had 2 or more signs or symptoms—including temperature $<38^{\circ}\text{C}$, productive cough, chest pain, dyspnea, and crackles on auscultation—and a chest radiograph showing an opacity compatible with acute pneumonia.

Patients were excluded if they required intensive care or had immune deficiency, alcohol addiction, chronic renal failure, were in shock, or were pregnant or nursing.

■ STUDY DESIGN AND VALIDITY

This was a prospective observational study that used data gathered from a prior multicenter clinical trial, conducted to determine the effects of a clinical pathway for community-acquired pneumonia.² Patients were assigned, using cluster randomization, to a conventional or study arm.

The conventional group had blood cultures drawn at the discretion of the attending physician. The study group had 2 blood cultures drawn at admission. Using chart reviews, the investigators evaluated the microbiological yield of blood cultures and whether the results influenced physician prescribing or treatment changes.

This well-designed study evaluated a large population from varied locations, and included both community and teaching hospitals. Demographics were typical for an urban setting.²

The study's weaknesses: no blinding or concealed allocation was used; the authors did not explain explicitly how they determined whether positive blood cultures were contaminated, or whether antibiotic changes were appropriate; and they did not perform independent chart reviews.

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■ OUTCOMES MEASURED

Investigators reported the percentage of positive blood cultures, how the results led to a change in antibiotic therapy, and whether the changes were appropriate. They also determined if blood cultures correlated with severity of illness, using the Pneumonia Severity Index Scores (PSIS).

■ RESULTS

A total of 1743 patients met inclusion criteria and 1022 were admitted. Of these, 716 were randomized to the intervention arm and 1027 to the conventional arm. Blood cultures were drawn on 760 (74.4%) patients. Forty-three (5.66%) had positive blood cultures with significant organisms. The pathogens cultured were the usual pneumonia organisms—*Streptococcus pneumoniae* (68%), *Staphylococcus aureus* (11%), and *Hemophilus influenzae* (11%), with small percentages of *Escherichia coli*, Enterobacteraceae, and *Klebsiella pneumoniae*. The cost of 2 blood cultures was \$41.70, yielding a total cost of roughly \$31,000, or \$2000 (Canadian) per positive blood culture that lead to a change in therapy.

In 23 of the 43 (53.5%) patients with positive blood cultures, the class of treatment was either not changed or changed to a broader-spectrum antibiotic, even though the positive blood cultures indicated acceptability of a more narrow spectrum or less expensive choice. In 14 cases (32.6%), a less-expensive regimen was appropriately chosen.

In only 3 cases did positive blood cultures lead to increases in therapy to provide better antibiotic coverage. Based on PSIS, the severity of illness correlated poorly with the blood culture yield—positive in 6.2% of risk class I and II (less severe), and 5.2% in risk class V (most severe).

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Zonisamide effective for weight loss in women

Gadde KM, Franciscy DM, Wagner HR, Krishnan KRR. Zonisamide for weight loss in obese adults. A randomized controlled trial. *JAMA* 2003; 289:1820–1825.

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■ PRACTICE RECOMMENDATIONS

Zonisamide (Zonegran), in conjunction with a reduced-calorie diet (deficit of 500 kcal/d), resulted in an additional mean 5-kg (11-pound) weight loss compared with diet alone. This regimen was well-tolerated in obese female patients. Further evaluation of long-term side effects and continued weight loss beyond 32 weeks is needed.

■ BACKGROUND

Zonisamide is an antiepileptic medication with a common side effect of causing significant weight loss. This study was conducted to assess the efficacy of using zonisamide for weight loss alone in obese adults.

■ POPULATION STUDIED

Sixty adults from an outpatient clinic population and those responding to flyers were enrolled. Participants were aged 21 to 50 years, with a mean body-mass index of 36.3 and mean age of 37 years. Subjects were 92% female; 48% were African Americans and 52% Caucasians.

Exclusion criteria included endocrine-related obesity; serious/unstable medical illness; major psychiatric disorder; drug or alcohol abuse; recent weight fluctuations >4 kg; prior obesity surgery; and use of medications, herbs, or supplements that effect weight or significantly effect the cytochrome P450 system. Also excluded were women of childbearing age who were not on acceptable forms of contraception,

pregnant or breastfeeding women, and those deemed unable to follow study procedures.

■ STUDY DESIGN AND VALIDITY

Subjects were randomized in a double-blind fashion (allocation assignment concealed) to receive either zonisamide or identical placebo. All participants were also prescribed a hypocaloric diet (500 kcal/d deficit). Zonisamide therapy was started at 100 mg/d orally and gradually titrated to 600 mg/d.

The study was conducted in 2 phases. Phase 1 consisted of treatment for 16 weeks with patients, study investigators, and assessors of outcomes blind to treatment group assignment (triple-blinding). A total of 51 (85%) of participants completed this phase. During phase 2, participants were allowed to continue their current medication for an additional 16 weeks, with only patients remaining blind to treatment group assignment.

A total of 36 (60%) of participants completed the full 32 week trial. Data analysis was by intention-to-treat.

Strengths of the study included triple-blind randomization with concealed allocation. Weaknesses included a small sample size and short follow-up, making it difficult to assess long-term safety and outcomes. Only 5 men were enrolled in this trial and all received zonisamide. Thus, we cannot reliably extrapolate study conclusions to men.

■ OUTCOMES MEASURED

The primary outcome measured was change in absolute body weight. Secondary outcomes included percent weight change and the number of participants in each group to reach a weight loss of at least 5% and 10% of baseline body weight. Other measures included adverse treatment effects and an Impact of Weight on Quality of Life (IWQOL) questionnaire.

■ RESULTS

In the initial phase of the trial, the zonisamide group lost significantly more weight than the placebo group (mean 5.9 kg vs 0.9 kg; $P<.001$). A total of 57% of patients in the zonisamide group

vs 10% in the placebo group lost at least 5% of their initial body weight, and 23% of those in the zonisamide group vs 0% in the placebo group lost at least 10% of initial body weight ($P=.05$). After the extension phase, the zonisamide group had a mean weight loss of 9.2 kg vs 1.5 kg for the placebo group.

As measured by the IWQOL questionnaire, health, work, mobility, and activities of daily living were all significantly improved in the zonisamide group at both 16 and 32 weeks. Ten patients in the zonisamide reported fatigue vs 1 patient in the placebo group. Otherwise, no adverse effects were reported differentially between the groups.

Continuous use of oral contraceptives reduces bleeding

Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. Obstet Gynecol 2003; 101:653-661.

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■ PRACTICE RECOMMENDATIONS

This study provides good evidence that continuous use of combination oral contraceptives for 1 year decreases bleeding without clinically important changes in blood pressure, weight, or hemoglobin when compared with cyclic users. Clinicians should consider offering this option to their patients, while continuing to look for evidence that addresses long-term sequelae, as well as patients of color or those with less than a college education.

■ BACKGROUND

Most clinicians in the US prescribe oral contraceptives that are given cyclically for 21 days, followed by 7 days of no therapy, to mimic

CONTINUED

By the end of the trial, 72% of users of continuous oral contraception were without any bleeding

natural cycling, signal the absence of pregnancy, protect against endometrial cancer, and prevent irregular bleeding. This randomized controlled trial compared continuous and cyclic contraceptives with respect to bleeding pattern and side effects.

■ POPULATION STUDIED

The investigators recruited 79 subjects at a university-affiliated research clinic. They excluded women who intended to become pregnant, were aged <18 years or >45 years, had standard contraindications for oral contraceptives, had hemoglobin <9 g/dL, or had a diagnosis of uterine infection or cervical dysplasia.

The average age of subjects was 28 years, the average body-mass index was 25, and the majority were prior oral contraceptive users. Most (88%) were white and more than 70% had a college education. Subjects were probably similar to those in a typical family practice, but providers should be cautious in generalizing the results to patients of color or those with less than a college education.

■ STUDY DESIGN AND VALIDITY

After an initial 28-day run-in period, women were randomized to receive either 21-day cycles (with 7 days of placebo) or continuous treatment with a 20- μ g ethinyl estradiol/100- μ g levonorgestrel formulation for 1 year. Allocation was concealed, but after randomization, masking was limited due to differences in pill color.

After randomization, all subjects were offered ultrasound and endometrial biopsy during months 1 and 9. Subjects returned every 3 months for weight, blood pressure, pill counts, and diary review, and they filled out questionnaires on level of satisfaction, symptoms, bleeding, and pregnancy concern.

The methodology was good. Major strengths included randomization with concealed allocation and intention-to-treat analysis. Weaknesses were relatively minor, and included loss to follow-up of about a quarter of subjects, incomplete masking, the small sample receiving endometrial biopsies, lack of power for rare but important consequences such as pregnancy or thrombosis, lack of correction for multiple comparisons, and lack of follow-up beyond 1 year.

■ OUTCOMES MEASURED

The primary outcome was the number of bleeding and spotting days; secondary outcomes were adherence to regimen, patient satisfaction, symptoms, and physiologic parameters such as weight and blood pressure. Cost and provider satisfaction were not addressed.

■ RESULTS

Study groups were similar after randomization, and the follow-up rate was >75%. Bleeding was significantly less in continuous users than in cyclic users, with an average of 3 vs 10 days for cycles 1–3 and 0 vs 9 for cycles 10–12, respectively (all comparisons $P<.001$.) Spotting was significantly greater in continuous users in cycles 1–3 (median 6 vs 4 days, $P<.001$), but no difference was found by the end of the trial.

By the end of the trial, 72% of the continuous users were without any bleeding or spotting. No subjects became pregnant, and no differences were seen in other symptoms. Ten subjects had endometrial biopsies at cycles 1 and 9; none had endometrial hyperplasia or neoplasia.

No difference existed in physiologic parameters, with the exception that continuous users had a significantly higher systolic blood pressure (average, 115.6 mm vs 107.9 mm; $P<.02$). No differences existed in patient satisfaction and recommendation about future methods. At the end of the trial, about one fifth of each group wanted to switch to the other group.

Clindamycin for vaginosis reduces prematurity and late miscarriage

Ugwumadu A, Manyonda I, Reid F, Hay P. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomized controlled trial. Lancet 2003; 361:983-988.

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■ PRACTICE RECOMMENDATIONS

Using oral clindamycin to treat women with asymptomatic bacterial vaginosis during their second trimester (between 12 and 22 weeks estimated gestational age) reduces the number of premature births and late miscarriages. The study did not demonstrate a difference in the number of neonatal intensive care unit admissions, mean birth weight, or gestational age.

This is the first study demonstrating benefits in treating asymptomatic bacterial vaginosis early in pregnancy. It still needs to be determined, in larger trials, whether generalized screening and treatment for asymptomatic bacterial vaginosis in the early second trimester is beneficial and cost-effective.

■ BACKGROUND

Bacterial vaginosis is associated with premature delivery and late miscarriage. In 2 previous randomized controlled trials, metronidazole did not reduce preterm delivery in low-risk pregnancies when used to treat bacterial vaginosis at 23 to 24 weeks estimated gestational age. Another randomized controlled trial showed an 18% absolute risk reduction in premature deliveries when metronidazole and erythromycin were used to treat bacterial vaginosis in pregnant women with preexisting risk factors for premature delivery.¹

This study set out to determine whether treating bacterial vaginosis earlier (before 22 weeks estimated gestational age) with oral clindamycin

would reduce the number of premature births and late miscarriages.

■ POPULATION STUDIED

This British, 2-center study enrolled 6120 of 11,189 pregnant women in their early second trimester—between 12 and 22 weeks estimated gestational age—who agreed to screening for bacterial vaginosis or abnormal vaginal flora. Slides were gram-stained, and 2 independent investigators assessed the slides with the Nugent scoring system (0–10).

The investigators excluded 246 of 740 women who had a positive screening test because of various reasons, including symptomatic bacterial vaginosis; age <16 years; multiple gestations; had or needed cervical cerclage or cone biopsy; demonstration of a cervical, uterine, or fetal anomaly; diabetes mellitus, hypertension, or collagen vascular disease.

■ STUDY DESIGN AND VALIDITY

The 494 women who met diagnostic criteria for bacterial vaginosis or abnormal vaginal flora were randomly assigned by computer to receive either clindamycin 300 mg orally twice daily for 5 days or matching placebo. Allocation was concealed, and the study was double-blinded.

The women were followed-up in clinic 2 to 4 weeks after treatment to assess side effects and pregnancy status. Data were extracted from hospital records for the outcomes.

The methodology was very strong. Strengths include randomization, double-blinding, power for primary outcome of 90%, sufficient follow-up rate, and sensitivity analysis for 9 lost follow-ups.

Weaknesses were relatively minor, and included lack of power for secondary outcomes and a mild imbalance between treatment and placebo group. The placebo group had a slightly increased history of previous miscarriages (primarily first trimester) but not preterm deliveries. The authors postulated that this discrepancy was not likely to affect the overall results because a history of first-trimester

miscarriage does not increase the risk of future premature delivery or late miscarriage.

■ OUTCOMES MEASURED

The primary endpoint of the study was the number of late miscarriages (between 13 and 24 weeks gestation) and preterm deliveries (between 24 weeks and 37 weeks gestation). Secondary outcomes included admission to neonatal intensive care unit, birth weight, and number of weeks gestation at delivery.

■ RESULTS

Women treated with clindamycin had a statistically significant reduced rate of late miscarriages or spontaneous preterm deliveries compared with women in the placebo group (5.3% vs 15.8%). Ten (95% confidence interval,

6–20) women positive for bacterial vaginosis would need to be treated to prevent 1 late miscarriage or preterm delivery.

Overall, 120 women would need to be screened, with all women treated who were positive for bacterial vaginosis, to prevent 1 of these outcomes. There was no statistically significant difference in mean birth weight, gestational age at delivery, or need for admission to the neonatal intensive care unit. The small sample size of the study limited its power to show a possible statistically significant difference in the secondary outcomes.

REFERENCE

1. Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *N Engl J Med* 1995; 333:1732–1736.