

Antidepressant Medication for Chronic Tension Headache

To the Editor: Dr Holroyd and colleagues¹ found that tricyclic antidepressants (TCAs) and stress management therapy (SMT) had similar modest effects in treating chronic tension headaches (CTHs). However, their study may have limited validity. In treating a cohort of patients with chronic tension-type headache with antidepressant medications, it is important to ensure that comorbid depression is not present. The authors state that comorbid psychiatric problems are common in patients with CTH. Since the exclusion criteria did not include evaluation for depressive symptoms (other than suicide risk), it is not clear if the beneficial effects of amitriptyline (up to 100 mg) or nortriptyline (up to 75 mg) were due to specific antiheadache effects or to their antidepressant actions.

Furthermore, as SMT was not compared to placebo therapy (ie, nontherapeutic clinical contact), all that can reliably be concluded is that SMT was better than placebo medication. It is unclear if this was due to the specific content of SMT rather than the extra 3 hours of clinical contact the patients received.

Finally, we question the authors' ability to conclude that SMT was a "viable alternative" to medication. Our reading of their results is that medication was more effective than placebo and that addition of SMT did not demonstrate any statistically significant improvement. The trial did not have sufficient power to assess subgroup analysis, and therefore the lack of detectable difference cannot be equated with clinical equivalence.

William Rifkin, MD
Laurie Ward, MD
Nassau University Medical Center
East Meadow, NY

1. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant therapy, stress management therapy, and their combination: a randomized controlled trial. *JAMA*. 2001;285:2208-2215.

In Reply: Drs Rifkin and Ward argue that patients with symptoms of depression should have been excluded from our trial to rule out the possibility that the mechanism of the TCAs' effect on CTH was their antidepressant activity. However, our goal was not to examine the mechanism of the effect of TCAs, but to address specific efficacy questions,¹ including whether a TCA treatment effect even exists. Excluding all patients with symptoms of depression would have compromised the external validity of our trial; the efficacy of the 3 treatments would have been evaluated in a clinically unrepresentative patient sample (in which no patient exhibited symptoms of depression).

We do have data on tertiary outcomes such as depression, but could not present these due to space limitations. The mechanism of the TCA effect on CTH was not their antidepressant

action; reductions in depression (Beck Depression Inventory [BDI])² scores did not differ between patients who received TCA vs placebo. Formal moderator analyses further revealed that baseline depression (assessed by either the BDI or by diagnosis of depression)³ did not moderate improvements in headache activity for any of the 3 active treatments. We are not aware of convincing evidence from any other trial to indicate that depression moderates the effect of TCAs on CTH.

We did not further complicate an already complex trial by adding a poorly defined "nontherapeutic clinical contact" group, for 2 reasons. First, in pragmatic trials such as ours, psychological treatment vs medication placebo and drug vs placebo comparisons effectively provide a "contemporary standard for definitive trials."⁴ Second, we do not believe that brief "nontherapeutic clinical contact" is an effective intervention for previously nonresponsive and longstanding (mean, 12 years) CTH.

Rifkin and Ward incorrectly assume that our power estimates were based on "comparison with placebo"; power estimates were based on the same a priori defined clinically meaningful difference (eg, 0.75 for Headache Index) for tests of all 5 hypotheses (ie, the pooled error term was used). It was not a lack of statistical power that led to the nonsignificant difference between TCAs and SMT at the primary end point, but rather the lack of a clinically meaningful difference in outcome: the effect size for the for the TCA vs SMT difference was minuscule ($\eta^2 = .002$) when compared with even a medium-sized treatment effect ($\eta^2 = .25$)⁵. In fact, differences between TCAs and SMT numerically "favored" each treatment on 2 of 4 outcome measures at the primary end point. We thus stand by our conclusion that in this trial "SMT appears to offer a viable alternative to [TCAs]."

Kenneth A. Holroyd, PhD
Michael Stensland, MS
Bruce W. Carlson, PhD
Department of Psychology
Ohio University
Athens

1. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chron Dis*. 1967;20:637-48.

2. Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depres-

GUIDELINES FOR LETTERS. Letters discussing a recent *JAMA* article should be received within 4 weeks of the article's publication and should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 500 words and 6 references. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors as space permits and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Letters will not be returned unless specifically requested. Also see Instructions for Authors (July 4, 2001). Letters may be submitted by surface mail: Letters Editor, *JAMA*, 515 N State St, Chicago, IL 60610; e-mail: JAMA-letters@ama-assn.org; or fax (please also send a hard copy via surface mail): (312) 464-5824.

Letters Section Editors: Stephen J. Lurie, MD, PhD, Senior Editor; Jody W. Zylke, MD, Contributing Editor.

sion Inventory: twenty-five years of evaluation. *Clin Psychol Rev*. 1988;8:77-100.

3. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study. *JAMA*. 1994; 272:1749-1756.

4. Klein DF. Control groups in pharmacotherapy and psychotherapy evaluations. *Prevention & Treatment* [serial online]. September 22, 1997;1. Available at: <http://journals.apa.org/prevention>. Accessibility verified September 27, 2001.

5. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

Who Should Be Screened for Osteoporosis?

To the Editor: Ms Cadarette and colleagues¹ evaluated 4 decision rules to determine who should be screened for osteoporosis by dual-energy x-ray absorptiometry (DXA). It is important to screen women at risk for osteoporosis because of the marked increase in morbidity and mortality associated with this disease, but also not to screen those women at low risk because of the increased cost.

The authors evaluated my decision rule (ABONE)² against other decision rules including their own screening tool. The authors determined that the sensitivity of ABONE was 79.1% (95% confidence interval [CI], 75.9%-82.3%) for identifying women with a T score of -2 or less compared with SCORE (sensitivity, 97.5%; 95% CI, 96.3%-98.8%) and ORAI (the authors' decision rule) (sensitivity, 94.2%; 95% CI, 92.3%-96.1%). ABONE found the least number of women with normal bone mineral density (BMD) at 35.8% (95% CI, 32.4%-39.2%), with SCORE identifying 69.2% (95% CI, 65.9%-72.5%) and ORAI identifying 56.3% (95% CI, 52.7%-59.8%) of patients with normal BMD. Cadarette et al concluded that ABONE was not a useful case-finding tool.

The ABONE rule was devised to determine which patients should be screened for osteoporosis. It was created to identify women with a T score of -2.5 or less, not -2.0 as the authors have used. Also, the authors eliminated 402 patients from analysis or 12.5% of the population studied; 382 of these patients had a diagnosis of osteoporosis. In the ABONE study,² 1610 women were consecutively studied with no exclusions. If Cadarette et al had included the 382 patients with osteoporosis in the evaluation of the ABONE criteria, I suspect that the sensitivity would have improved dramatically while still leaving ABONE with the lowest screening rate of normal patients. In this era of cost containment, avoidance of performance of an expensive unnecessary test is an important goal.

The criteria established by the original author should be used in evaluation of that work when compared with the work of another. I believe that ABONE is a simple tool to determine who will and who will not benefit from osteoporosis screening. Reevaluation of this study, including all the patients and statistical analysis using a T score of -2.5 or less, would substantiate the value of ABONE.

Louis Weinstein, MD
Department of Obstetrics and Gynecology
Medical College of Ohio
Toledo

1. Cadarette SM, Jaglal SB, Murray TM, McIsaac WJ, Joseph L, Brown JP, for the Canadian Multicentre Osteoporosis Study. Evaluation of decision rules for referring women for bone densitometry by dual-energy x-ray absorptiometry. *JAMA*. 2001;286:57-63.

2. Weinstein L, Ullery B. Identification of at-risk women for osteoporosis screening. *Am J Obstet Gynecol*. 2000;183:547-549.

To the Editor: Ms Cadarette and colleagues¹ compared the diagnostic properties of 4 different decision rules and the North Osteoporosis Foundation guidelines for selecting postmenopausal women for DXA testing, and estimated their sensitivity and specificity in the detection of low bone density. The diagnostic approaches mainly relied on age and body weight, with older age and lower body weight resulting in the highest probability of a obtaining a DXA scan indicating osteoporosis. This approach, although simple, appealing, and apparently efficacious, is limited by technical concerns.

A number of studies have shown that DXA is inherently inaccurate because it operates with 2 x-ray energies while the human body is composed of 3 main types of tissues: bone, muscle, and fat.² This "2-component limitation" can lead to an underestimate of bone density as high as 60%, particularly in frail older women with low bone mass, low percentage of body fat, and fatty bone marrow.² The decision rules evaluated by Cadarette et al are likely to identify exactly these frail older women, in whom the finding of a bone density under the diagnostic threshold for osteoporosis may merely reflect a high degree of inaccuracy of the measurement method, rather than a high sensitivity of the selection criteria. This measurement error is potentially compounded by the fact that DXA yields artifactually lower T-scores in subjects of shorter stature.³

Because these sources of inaccuracy are inherent to the DXA technology, they occur irrespective of the instrumentation, positioning, or conditions related to the patient (eg, obesity, extraskeletal calcifications), which would further increase the probability of measurement errors. For these reasons, we believe that criteria for identifying women to be screened for osteopenia by DXA should not be based on body size and weight. Peripheral quantitative computed tomography (pQCT), a recently developed technique that provides measurement of bone density independent of body size, as well as accurate assessment of bone cross-sectional geometry (an important and increasingly recognized component of bone strength), is a promising approach that may overcome the limitation intrinsic to the DXA technology.^{4,5} We have used the pQCT technique in an ongoing epidemiological study to assess age-associated changes in bone density, mass, and geometry.⁶

Cosimo Roberto Russo, MD
Fulvio Laurentani, MD
Francesca De Marco, MD
Luigi Ferrucci, MD, PhD
Laboratory of Clinical Epidemiology
Department of Geriatrics
National Institute of Research and Care on Aging
Florence, Italy

1. Cadarette SM, Jaglal SB, Murray TM, McIsaac WJ, Joseph L, Brown JP, for the Canadian Multicentre Osteoporosis Study. Evaluation of decision rules for referring women for bone densitometry by dual-energy x-ray absorptiometry. *JAMA*. 2001;286:57-63.
2. Bolotin HH, Sievanen H. Inaccuracies inherent in dual-energy X-ray absorptiometry in vivo bone mineral density can seriously mislead diagnostic/prognostic interpretations of patient-specific bone fragility. *J Bone Miner Res*. 2001;16:799-805.
3. Nielsen SP, Kolthoff N, Barenholdt O, et al. Diagnosis of osteoporosis by planar bone densitometry: can body size be disregarded? *Br J Radiol*. 1998;71:934-943.
4. Gasser JA. Assessing bone quantity by pQCT. *Bone*. 1995;17(suppl 4):145S-154S.
5. Schneider P, Butz S, Allolio B, et al. Multicenter German reference data base for peripheral quantitative computer tomography. *Technol Health Care*. 1995;3:69-73.
6. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc*. 2000;48:1618-1625.

In Reply: The primary objective of our study was to evaluate decision rules for identifying women who would benefit from initial BMD testing by DXA. Women with a diagnosis of osteoporosis prior to entry into the Canadian Multicentre Osteoporosis Study would not have been eligible for this case-finding study because they would have been previously diagnosed and managed.

The National Osteoporosis Foundation based their recommendations for treatment¹ on data from a comprehensive cost-effectiveness analysis² finding that treating women with a BMD T score less than -2.0 was cost effective to decrease fractures compared with lack of treatment. This outcome, termed the treatment threshold, was used as our primary outcome. Osteoporosis is defined clinically as a BMD T score of -2.5 or less, indicating that a woman is at high risk for fractures. It is important to identify women for whom treatment would be beneficial and not wait until the BMD becomes osteoporotic. We thus feel that evaluating decision rules to identify women below the treatment threshold is a fair primary outcome.

In response to Dr Weinstein's comment about identifying women with osteoporosis, we also evaluated the discriminatory performance of the decision rules to identify women with T scores of -2.5 or less, and presented these data in Tables 3 and 4 of our article. The ABONE rule missed 17% of these women (specificity, 83.3%; 95% CI, 78.5%-88.0%), 9% of those aged 65 or more years, and 50% of younger women. This is compared with ORAI (sensitivity, 97.5%; 95% CI, 95.5%-99.5%), and SCORE (sensitivity, 99.6%; 95% CI, 98.8%-100%). We concluded that further research is necessary, including a cost-effectiveness analysis to identify acceptable sensitivity and specificity, and an impact assessment to evaluate the usefulness of these decision rules in clinical practice.

Dr Russo and colleagues criticize the use of decision rules because of their reliance on DXA technology. At present, DXA is the generally recommended and accepted method for diagnosing osteoporosis, monitoring therapy, and assessing fracture risk.^{3,4} We do recognize that as technology changes and other methods become widely accepted to identify those who would benefit from treatment, criteria to facilitate the selection of women for testing may change. Until that time, how-

ever, decision rules may be used to facilitate the selection of women for testing by DXA.

Suzanne M. Cadarette, MSc
Susan B. Jaglal, PhD
Timothy M. Murray, MD
Warren J. McIsaac, MD, MSc
Osteoporosis Research Program
Women's College Ambulatory Care Centre
Sunnybrook and Women's College Health Sciences Centre
Toronto, Ontario

1. National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis*. Belle Mead, NJ: Excerpta Medica Inc; 1999.
2. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. *Osteoporos Int*. 1998;8(suppl 4):S7-S80.
3. Kanis JA, Glüer C-C. An update on the diagnosis and assessment of osteoporosis with densitometry. *Osteoporos Int*. 2000;11:192-202.
4. Genant HK, Cooper C, Poor G, et al. Interim report and recommendations of the World Health Organization task-force for osteoporosis. *Osteoporos Int*. 1999;10:259-264.

Violence in Children's Films and Video Games

To the Editor: The Entertainment Software Rating Board agrees with Dr Thompson and Mr Haninger¹ that parents should be involved with their children in selecting computer and video games. We also agree that parents should discuss game content with their children, and that pediatricians can play an important role in educating parents about the rating system.

However, we disagree with the overly broad conception of violence used in the study. The authors see violence where most Americans would not—for example, in games as innocuous as *Ms Pac-Man* (apparently because players receive points for “eating” ghosts) and *The Smurfs*.

In a similarly flawed study, Thompson and Yokota² identified “acts of violence” in every available G-rated animated film, including *The Care Bears Movie*, *A Boy Named Charlie Brown*, and *Snoopy, Come Home*. An example of a “violent” act cited in this study is the flying elephant Dumbo “shooting” peanuts through his trunk during a circus performance. Clearly, this conception of violence is well outside the mainstream.

A survey conducted by Peter D. Hart Research Associates found that 84% of US residents agree with ratings assigned under the Entertainment Software Ratings Board (ESRB) system (unpublished data, 2000). That is because ESRB ratings and content descriptors are applied to each video game by 3 trained raters (from a pool of more than 150), including retired educators, parents, and consumers from all walks of life. These raters have no ties to the computer and video game industry, reflect our nation's diversity, and are not regular game players.

The level of detail provided in the ESRB's content-based system is one of the reasons that Senator Joseph Lieberman (D, Conn) has described the ESRB system as “the most comprehensive system of any entertainment medium in the country.”

Nonetheless, the ESRB agrees with Thompson and Haninger more than it disagrees. And we join with them in urging parents to learn more about computer and video game ratings, use ESRB ratings and content descriptors to find out about

a game's content, actively participate in computer and video game selection, and discuss game content with their children.

Arthur I. Pober, EdD
Entertainment Software Rating Board
New York, NY

1. Thompson KM, Haninger K. Violence in E-rated video games. *JAMA*. 2001; 286:591-598.
2. Yokota F, Thompson KM. Violence in G-rated animated films. *JAMA*. 2000; 283:2716-2720.

In Reply: We believe that any scientific study must be specific about definitions and apply them consistently. We defined violence as "physical acts where the aggressor makes or attempts to make some physical contact with the intention of causing injury or death."¹ We also defined violence as "intentional acts where the aggressor makes or attempts to make some physical contact that has potential to inflict injury or harm."² We believe that these definitions are consistent with standard dictionary definitions and lie well within the US mainstream, although they exclude unintentional acts (eg, natural disasters, accidents, objects not attributed to a character) and expected physical acts by sports games characters that are not intended to injure (eg, tackling, checking). Recognizing the breadth of these definitions, we reported on the intent to injure² and on whether injuring characters was either rewarded or required for advancement.¹

In applying these definitions consistently, we included some intentional acts by characters that some people might not perceive as violent. Addressing the video games cited by Dr Pober, we counted as violent the game play in *The Smurfs*, where the screen instructs the player to "destroy all three monsters before proceeding," requiring the player to throw explosives wrapped as presents at the creatures who then yelp and die. For *Ms Pac-Man*, an arcade game that we played but did not include in our statistical analysis, we counted as violent only those parts of the game play where the ghosts try to kill the player or vice-versa. For the movies, we included as violent the scene where Dumbo shoots peanuts with a machine gun sound at the elephants that had previously taunted him as well as the scenes depicting physical fighting between characters in *A Boy Named Charlie Brown*, *The Care Bears Movie*, and *Snoopy, Come Home*. To see examples at the other extreme end of the spectrum, watch *Quest for Camelot* or *The Lion King*, or play *Nuclear Strike 64* or *Goemon's Great Adventure*.

Our experience playing the games and independently reviewing game and movie content using standard definitions provides a different perspective than the subjective assessment that an average US adult might get from reviewing video game excerpts or watching a movie once. We believe that game raters should experience playing the games as part of the rating process, or at least watch someone else play them.

Kimberly M. Thompson, ScD
Kevin Haninger, BA
Fumie Yokota, MS
Harvard School of Public Health
Boston Mass

1. Thompson KM, Haninger K. Violence in E-rated video games. *JAMA*. 2001; 286:591-598.
2. Yokota F, Thompson KM. Violence in G-rated animated films. *JAMA*. 2000; 283:2716-2720.

Clinical Description of Nail Clubbing

To the Editor: In their article on clubbing, Drs Myers and Farquhar¹ imply that "advanced" and "early" clubbing might be used as quantitative terms. However, the terms to describe the clubbing are not standardized. Should we just use early and advanced (does early clubbing mean that it will become advanced with time?) or grade the clubbing like heart murmurs? It might be useful to have some standard rather than, for example, "present" or "absent," or "acute" and "chronic." Once present, does clubbing often go away? I have seen clubbing in a patient with lung cancer and when the cancer was "cured" with surgery, the clubbing disappeared only to return with recurrence of the tumor.

Lawrence Scharer, MD
Pulmonary/Critical Care Division
St Luke's/Roosevelt Hospital Center
New York, NY

1. Myers KA, Farquhar DR. Does this patient have clubbing? *JAMA*. 2001;286: 341-347.

In Reply: Although we agree with Dr Scharer that the terms used to describe clubbing are not standardized, it was not our intention to propose an ordinal grading system for clubbing. The purpose of our article was to review and synthesize the available evidence that might assist clinicians in establishing the presence of clubbing in individual patients using quantitative techniques, such as measurement of the nailfold angles and phalangeal depth ratio. Since the digital abnormalities in patients with "early" or "mild" clubbing can be subtle, we felt that these quantitative techniques would be most useful in these patients. Although systems that grade clubbing have been proposed,^{1,2} we were unable to identify any studies that linked the various grades of clubbing (eg, I through IV) to numerical cut-points for the nailfold angles or phalangeal depth ratios.

Regression of clubbing has been documented in numerous instances, for example following treatment of suppurative pulmonary diseases³ and inflammatory bowel disease.⁴ Whether all diseases associated with clubbing can lead to so-called "advanced" clubbing (usually characterized by what many clinicians have described as "drumstick" fingers) is not clear.

We also agree that a more precise and reproducible grading system for clubbing, perhaps using the quantitative indices described in our article, would be clinically useful. Given the paucity of published evidence, such a grading system might best be developed by consensus agreement of a group of clinicians with particular interest in this topic.

Kathryn A. Myers, MD, EdM, FRCPC
Donald R. E. Farquhar, MD, SM, FRCPC
Department of Medicine
Hotel Dieu Hospital/Queen's University
Kingston, Ontario

1. Beaven DW, Brooks SE. Color atlas of the nail. In: *Clinical Diagnosis Yearbook*. London, England: Wolfe Medical Publications Ltd; 1984:128-129.
2. Ogilvie C. *Chamberlain's Symptoms and Signs in Clinical Medicine: Respiratory System*. 10th ed. Bristol, England: John Wright & Sons Ltd; 1983.
3. Dickinson CJ. The aetiology of clubbing and hypertrophic osteoarthropathy. *Eur J Clin Invest*. 1993;23:330-338.
4. Kitis G, Thompson H, Allan RN. Finger clubbing in inflammatory bowel disease. *BMJ*. 1979;2:825-828.

Linezolid and Reversible Myelosuppression

To the Editor: In their Research Letter, Dr Green and colleagues¹ reported 3 cases of myelosuppression with red cell hypoplasia that occurred during linezolid therapy. We report here a case of reversible sideroblastic anemia that appeared within 2 months of linezolid treatment.

A 61-year-old man with chronic leg osteomyelitis due to *Staphylococcus aureus*, *Enterococcus faecalis*, and *Morganella morganii* was treated by debridement surgery and antibiotics including linezolid (600 mg twice daily) and ofloxacin (400 mg twice daily) for 60 days. He was also receiving ranitidine. During this period, platelet and leukocyte counts remained stable while hemoglobin concentration progressively decreased from 15.4 to 7.8 g/dL. Anemia was microcytic (mean corpuscular volume 83 fL), with a reticulocyte count of $28 \times 10^3/\mu\text{L}$. Vitamin B12, folate, and ferritin serum levels were normal. Serum iron was increased at 219 $\mu\text{g/dL}$ (normal, $<175 \mu\text{g/dL}$) and transferrin level was reduced at 150 mg/dL (normal, $>200 \text{ mg/dL}$). Bone marrow examination showed dyserythropoiesis with megaloblastosis, vacuolated proerythroblasts, and more than 15% of pathognomonic ringed sideroblasts. The administration of linezolid was interrupted and ranitidine was replaced by omeprazole. The patient also received 2 units of packed red blood cells. Three weeks after linezolid discontinuation, hemoglobin level was normal with a marked increase of reticulocytosis ($150 \times 10^3/\mu\text{L}$).

Acquired sideroblastic anemia (ASA) is usually idiopathic, but may also be associated with exposure to drugs and toxins. In our patient, there was a strong temporal relationship between linezolid introduction and the appearance of ASA, as well as between treatment interruption and resolution of ASA. Although given concomitantly, ranitidine had been administered for more than a year without adverse effects, and this drug is not known to be myelotoxic. Furthermore, 3 cases of reversible myelosuppression and 1 case of mild leukopenia due to linezolid have been described.^{1,2} In the linezolid-compassionate protocol, anemia has also been recorded (0.8%) but mostly in critically ill patients receiving multiple medications.³ Accordingly, we believe that linezolid should be added to the list of drugs potentially causing ASA. Linezolid is an oxazolidinone analog with significant activity against resistant gram-positive pathogens.²⁻⁴ Consequently, linezolid is an oral alternative to parenteral glycopeptides and is expected to be widely used in the near future.⁴ We believe that clinicians should be aware of this serious complication and closely moni-

tor hematologic parameters in patients receiving long-term linezolid therapy.

Pascale A. Abena, MD
 Valérie G. Mathieux, MD
 Jean-Marie Scheiff, MD, PhD
 Lucienne M. Michaux, MD, PhD
 Bernard C. Vandercam, MD
 Department of Internal Medicine and Laboratory of Hematology
 Saint-Luc University Hospital
 Brussels, Belgium

1. Green SL, Maddox JC, Huttenbach ED. Linezolid and reversible myelosuppression. *JAMA*. 2001;285:1291.
2. Chien JW, Kucia ML, Salata RA. Use of linezolid, an oxazolidinone, in the treatment of multidrug-resistant gram-positive bacterial infections. *Clin Infect Dis*. 2000;30:146-151.
3. Clemett D, Markham A. Linezolid. *Drugs*. 2000;59:815-827.
4. Livermore DM. Quinupristin/dalfopristin and linezolid: where, when, which and whether to use? *J Antimicrob Chemother*. 2000;46:347-350.

To the Editor: Dr Green and colleagues¹ discuss 3 cases described as reversible myelosuppression that may be associated with linezolid treatment. Pharmacia, which manufactures linezolid, asked independent hematologists to review the histories and bone marrow pathology of the first 2 cases. The third case was not reported to us as of March 14, 2001.

In the first case, independent hematologists indicated that a low reticulocyte count, the presence of early erythroid precursors with decreased maturation of the red cell series, reversibility, and hypocellularity were incompatible with the diagnosis of erythroid aplasia. These findings were considered to be compatible with anemia in a 70-year-old patient with underlying diseases and chronic infection. According to the hematologists, the appearance of the bone marrow biopsy of the second case was normal for a patient with a hemoglobin concentration of 12.8 g/dL. In both cases, anemia resolved after drug discontinuation.

In preclinical studies, linezolid demonstrated a predictable dose- and time-dependent reversible myelosuppression. Data from controlled clinical trials conducted prior to approval (April 2000) showed that linezolid was associated with a slight (1%) increased cumulative incidence of thrombocytopenia after 2 weeks of therapy. There was no increased risk of anemia or neutropenia.

Pharmacia monitors adverse events worldwide. We have received 30 spontaneous reports of reversible anemia in patients treated with linezolid, including the 2 cases referred to above. All cases developed in patients with underlying diseases predisposing them to anemia who received prolonged linezolid therapy. These patients often received concomitant medications associated with anemia. No clinically significant events were reported.

We agree with Green et al that it is important for the medical community to be aware of this information. Since March 5, 2001, a "Dear health care professional" letter has been posted on the US Food and Drug Administration (FDA) Web site (<http://www.fda.gov/>). Pharmacia has also mailed the letter to US health care providers. The letter provides information on

the risk factors associated with the development of these hematological adverse events and gives guidelines for blood monitoring. This information has also been added to the linezolid (Zyvox) package insert.

None of the 3 cases in the letter by Green et al is compatible with a diagnosis of pancytopenia. This makes any comparison to chloramphenicol toxicity, either the "dose-dependent reversible pancytopenia" referred to by Green et al or the irreversible aplastic anemia, difficult to understand. Genotoxicity by interference with DNA synthesis is the mechanism implicated in chloramphenicol associated aplastic anemia.² Linezolid is not genotoxic and has not been associated with aplastic anemia.

Felix M. Arellano, MD
Vice President and Chief Safety Officer
Pharmacia Corporation
Peapeck, NJ

1. Green SL, Maddox JC, Huttenbach ED. Linezolid and reversible myelosuppression. *JAMA*. 2001;285:1291.
2. Yunis AA. Chloramphenicol toxicity: 25 years of research. *Am J Med*. 1989;87(suppl 3N):44N-48N.

To the Editor: Dr Green and colleagues¹ reported serious but reversible myelosuppression in patients receiving more than 2 weeks of therapy with linezolid, with bone marrow changes that appear similar to those seen in reversible chloramphenicol toxicity. The structure and mechanism similarities between linezolid and chloramphenicol suggest there may be a shared mechanism for this adverse effect. Linezolid shares with chloramphenicol an antibacterial mechanism involving binding to the ribosomal RNA of the 50s subunit. They also have structural similarities, including the nitro group hypothesized to be the feature of chloramphenicol responsible for aplastic anemia.²

Chloramphenicol has recognized hematologic toxicity including a reversible, dose-dependent anemia that is usually observed after 2 weeks of therapy, a much less common but often fatal aplastic anemia with acellular marrow and pancytopenia, and leukemia. Continued intensive postmarketing surveillance of linezolid for further occurrences of myelosuppression including aplastic anemia or even leukemia is clearly needed.

Mathew C. Lawyer, JD
Southern Illinois School of Medicine
Springfield
Edward Z. Lawyer, MS
University of Illinois Medical School
Champaign

1. Green SL, Maddox JC, Huttenbach ED. Linezolid and reversible myelosuppression. *JAMA*. 2001;285:1291.
2. Jimenez JJ, Arimura GK, Abou-Khalil WH, Isildar M, Yunis AA. Chloramphenicol-induced bone marrow injury: possible role of bacterial metabolites of chloramphenicol. *Blood*. 1987;70:1180-1185.

In Reply: Since our letter was published, we have observed 10 additional patients with anemia, reticulocytopenia, and increasing iron saturation. These patients ranged in age from 24 to 81 years (7 women, 3 men), and all received linezolid (600 mg twice per day) for at least 2 weeks. Some of these patients were taking several medications and others received only lin-

ezolid. In all cases, the iron saturation and reticulocyte count returned to normal when linezolid was discontinued. Dr Abena and colleagues observed this same effect in their patient with sideroblastic anemia while receiving linezolid.

We disagree with Dr Arellano's assertion that our first 2 patients did not have serious suppression of erythropoiesis. At the request of Pharmacia, we provided clinical data and marrow slides on the first 2 patients. The first patient had 30% marrow cellularity, an myelocyte to erythrocyte ratio of 174:1, and a reticulocyte count of 0%. These changes reversed quickly after linezolid was stopped. The second patient consented to bone marrow examination 5 days after discontinuing linezolid, by which time there had been significant recovery in erythropoiesis, and the microscopic features were much less dramatic.

Vacuolization of early erythroblast precursors is a characteristic finding in patients with reversible chloramphenicol-induced myelosuppression. Likewise, rising serum iron and increasing saturation of iron binding capacity are well-described features of reversible chloramphenicol toxicity. As described by Messrs Lawyer and Lawyer, the structural and functional similarities of these 2 drugs may reflect their similar adverse effects.

Arellano mentions "30 spontaneous reports of reversible anemia in patients treated with linezolid. . . ." Pharmacia Corporation issued a drug warning letter to all physicians specifically mentioning "myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia . . .)."¹ The effect on iron kinetics, which may herald the development of the other hematologic effects, was not mentioned.

From the cases we reported and others subsequently collected, we stand by our original conclusion that linezolid has the potential to cause reversible myelosuppression in patients on long-term therapy in a manner similar to chloramphenicol. It would be of interest to study a larger series of patients to determine the temporal relationship between the duration of drug administration and the development of anemia and abnormal serum iron studies. We hasten to add, however, that linezolid is an important drug in the armamentarium against highly drug-resistant gram-positive cocci. Our intention is to highlight safety concerns and offer a means for monitoring potential toxicity.

Stephen L. Green, MD
John C. Maddox, MD
Riverside Regional Medical Center
Newport News, Va

1. Peterson J. *Important Drug Warning: Letter to Health Care Professionals*. Peapeck, NJ: Pharmacia Corp; March 5, 2001.

RESEARCH LETTER

Electrophysiological Correlates of Personality Influences in Visceral Perception

To the Editor: Because perception thresholds to gastrointestinal distension can be affected by stress,¹ psychological factors may play an important role in visceral perception. The ce-

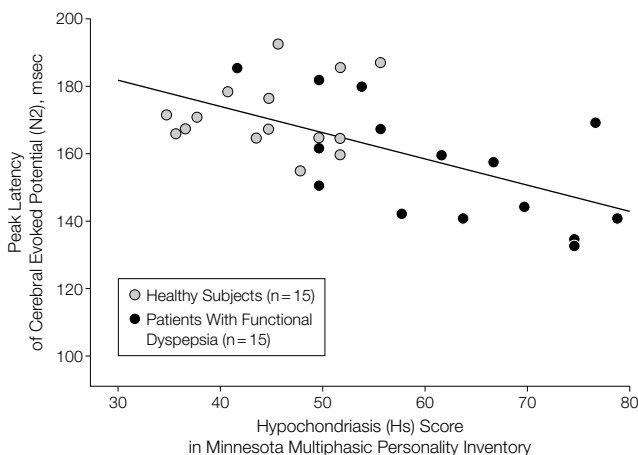
rebral evoked potential (CEP), which originates from the processing of afferent neural pathways, may reflect such higher-level processing of painful stimuli. Topographic study suggests that early peaks of CEP originate from deep central brain structures, whereas later peaks originate from the cortex.² We have previously found that patients with functional dyspepsia have shorter peak latency of the late CEP component by esophageal electrical stimulation (ES), suggesting that patients with dyspepsia may have an altered central processing of visceral perception.³ Although Shagass and Schwartz⁴ reported a relationship between neuroticism and peak latencies for somatosensory evoked potentials, it is not clear how CEP responses may relate to visceral perception. We investigated the hypothesis that late CEP responses to visceral stimulation may be related to personality traits.

Methods. Subjects were 15 patients (6 men, 9 women; mean age, 26 years) randomly selected from those who consulted the Tohoku University Hospital, who satisfied the Rome criteria⁵ for functional dyspepsia, and who had not taken any medication, and 15 healthy control subjects (7 men, 8 women; mean age, 22 years) who were randomly recruited from the Tohoku University campus. The study was approved by the Tohoku University Ethics Committee, and written informed consent was obtained from all subjects. Subjects were exposed to esophageal ES (1 Hz and 200 μ sec-square wave) at 37 cm from the nostril by gradual increase in 2 mA steps at 5-minute intervals. Subjects were asked to report the first sensation of any new sensation (sensory threshold) and of any definite unpleasant sensation (discomfort threshold) in the chest. CEP responses were recorded and averaged across 20 repetitions. The peak latencies were determined as the time difference from the onset to the peak (negative; N) or troughs (positive; P) of CEP waves. The early (N1, P1) and late (N2) latencies and the perception thresholds were measured, as were the neurotic subscales (hypochondriasis [Hs]; depression [D]; and hysteria [Hy]) on the Minnesota Multiphasic Personality Inventory (MMPI).⁶

Results. The patients with dyspepsia had significantly higher scores of Hs (62 vs 45, $P < .01$), D (44 vs 32, $P < .01$) and Hy (60 vs 49, $P < .01$). In univariate tests, all 3 peak latencies were significantly associated with sensory and discomfort thresholds. The late latency of N2 was negatively associated with the scores of Hs ($r = 0.61$, $P < .001$; FIGURE), D ($r = 0.41$, $P < .05$), and Hy ($r = 0.43$, $P < .02$), while the earlier latencies (N1, P1) were not. Stepwise multiple regression analysis revealed that the earlier latencies were significantly related to discomfort threshold (N1: $R^2 = 0.33$, $P < .001$; P1: $R^2 = 0.17$, $P < .05$) while the latency of N2 was related to Hs ($R^2 = 0.37$, $P < .001$). Age, sex, and body mass index made no significant contribution to the regression model.

Comment. Our results suggest that neurotic personality traits may be related to central processing of visceral perception, and

Figure. Relationship Between the Peak Latency of Cerebral Evoked Potentials (N2) and the Score of Hypochondriasis (Hs) in MMPI



A significant negative correlation between the late peak latency of CEP (N2) and the score of hypochondriasis in MMPI among healthy subjects and patients with functional dyspepsia ($r = -0.61$, $P < .001$) in the univariate analysis with linear regression. CEP indicates cerebral evoked potential; MMPI, Minnesota Multiphasic Personality Inventory.

that CEP recording may be a useful method for assessing whether visceral perception is related to these traits. Our results also suggest that cognitive patterns associated with some personality variables might promote visceral hypersensitivity via cortical processing.

Motoyori Kanazawa, MD

Shin Fukudo, MD

Department of Behavioral Medicine

Taisuke Nomura, MD

Department of Psychosomatic Medicine

Michio Hongo, MD

Department of Comprehensive Medicine

Tohoku University School of Medicine

Sendai, Japan

Funding/Support: This research was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, and Cultures of Japan.

1. Delvaux MM. Stress and visceral perception. *Can J Gastroenterol*. 1999;13 (suppl A):32A-36A.
2. Hollerbach S, Kamath MV, Fitzpatrick D, et al. The cerebral response to electrical stimuli in the oesophagus is altered by increasing stimulus frequencies. *Neurogastroenterol Motil*. 1997;9:129-139.
3. Kanazawa M, Nomura T, Fukudo S, Hongo M. Abnormal visceral perception in patients with functional dyspepsia: use of cerebral potentials evoked by electrical stimulation of the oesophagus. *Neurogastroenterol Motil*. 2000;12:87-94.
4. Shagass C, Schwartz M. Personality and somatosensory cerebral evoked responses. *Science*. 1965;48:1359-1360.
5. Talley NJ, Colin-Jones D, Koch KL, et al. Functional dyspepsia: a classification with guidelines of diagnosis and management. *Gastroenterol Int*. 1991;4:145-160.
6. Hathaway SR, McKinley JC. The Minnesota Multiphasic Personality Inventory manual. Revised. New York, NY: Psychological Corporation; 1951.