EFFECTIVENESS OF SIBUTRAMINE

TO THE EDITOR:

In their commentary on the article by Wirth and Krause,[1] Drs Stevenson, Trojian, and Jackson[2] questioned the use of sibutramine in races other than whites and the use of the drug beyond 1 year because long-term health and mortality benefits have not been established.

Regarding the former point, McMahon and colleagues[3] showed that the mean percentage change in body weight among blacks receiving sibutramine (–4.0%) is comparable to that among whites (–4.9%). Studies by Fanghitnel and colleagues[4,5] and Cuellar and colleagues[6] showed that sibutramine given for at least 6 months can induce significant loss of body weight and waist circumference in obese Hispanic patients compared with patients receiving placebo. These studies confirm that data exist to support the efficacy and safety of sibutramine in obese populations of diverse ethnic backgrounds.

Regarding long-term use, clinical studies that support the routine use and safety and efficacy of sibutramine administration for up to 1 year include those by Jones and colleagues[7] and Apfelbaum and colleagues.[8] The Sibutramine Trial of Obesity Reduction and Maintenance (STORM),[9] which was specifically designed to assess the safety and efficacy of sibutramine on maintenance of weight loss, showed that weight loss achieved with sibutramine can be maintained for up to 2 years and cause significant changes in high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, triglycerides, and uric acid exceeding those expected from weight loss alone. Adverse effects reported during the study were comparable to those seen with placebo. The small increases in blood pressure were counterbalanced by the beneficial effect on abnormal lipid levels and insulin resistance.

Although the long-term effect of sibutramine on obesity-associated mortality and morbidity has not been clearly established, the potential of developing coronary heart disease is directly related to the burden of risk factors present.[10] Modest weight loss can affect this cluster of risk factors and thus may produce health benefits for certain patients with chronic obesity who are at risk for other diseases. With the use of risk equations based on the Framingham Heart Study,[11] analyses of metabolic and cardiovascular responses from a number of sibutramine trials suggested a decrease in the absolute risk of events of coronary heart disease; patients at the highest risk (those with hypertension, diabetes, or dyslipidemia) showed the greatest risk reduction.[9,12] Use of sibutramine as an adjunctive modality for obesity management undoubtedly requires a risk-versus-benefit analysis for each patient. However, the opportunity to ameliorate risk factors and prevent or delay catastrophic events logically would seem to prevail over potential small changes in other cardiovascular parameters, unless the individual patient proves unable to tolerate these problems, if they occur.

Joseph A. Lieberman III, MD, MPH
Jefferson Medical College
Philadelphia, Pennsylvania
E-mail: jlieberman@jalmd.com

DRS JACKSON, STEVENSON, AND TROJIAN RESPOND:

We appreciate Dr Lieberman's input on the appropriate role of sibutramine in the long-term management of obesity. We limited our comments in the Recommendations for Clinical Practice section of our POEM article to white Europeans because this was the patient population studied by Wirth and colleagues.[1] We hope that the sample sizes of the studies cited by Dr Lieberman in support of the drug's effectiveness in other ethnic groups (American blacks and Hispanics) were similar to that of Wirth et al, which included 1001 subjects, 800 of whom received sibutramine.

The STORM trial[9] cited by Dr Lieberman to support the long-term safety and efficacy of sibutramine provided 2-year data on only 204 sibutramine-treated patients who completed the study. The beneficial effects reported for sibutramine on serum lipids were included as secondary outcomes in that study of the drug's effect on weight maintenance after weight loss. The statement by Dr Lieberman that small increases in blood pressure caused by the drug were counterbalanced by its beneficial effects on lipids is conjecture. One can only guess how different effects on heart disease risk factors might affect final outcomes such as coronary events. Notwithstanding the 2-year study period, because of the small sample size composed of relatively low-risk patients, the STORM trial was not designed to provide meaningful conclusions about important clinical outcomes such as morbidity, mortality, and drug safety.

Using risk equations to estimate the effect of weight loss achieved with sibutramine on the risk of coronary heart disease events is not an acceptable substitute for well-designed, truly long-term controlled trials studying final, rather than intermediate, outcomes. These studies should include a significant number of patients with other heart disease risk fac-

tors to improve the generalizability of the results. This is especially important for drugs such as sibutramine that provide beneficial effects on some risk factors (lipids) and detrimental effects on others (blood pressure and heart rate).

Given the known problems with other anorexiant drugs (eg, fenfluramine and dexfenfluramine) and the expense of sibutramine, clinicians should demand evidence of true clinical benefit and long-term safety before routinely prescribing sibutramine for treating obesity.

Eric A. Jackson, PharmD
J. Herbert Stevenson, MD
Thomas Trojian, MD
University of Connecticut School of Medicine and Saint Francis Hospital and Medical Center
Hartford, Connecticut
E-mail: ejackson2@stfranciscare.org

REFERENCES

1. Wirth A, Krause J. Long-term weight loss with sibutramine: a randomized controlled trial. JAMA 2001; 286:1331–9.
2. Stevenson JH, Trojian T, Jackson EA. Does long-term use of sibutramine (Meridia) result in continued weight loss in short-term responders? J Fam Pract 2001; 50:1084.
3. McMahon FG, Fujioka K, Singh BN, et al. Efficacy and safety of sibutramine in obese white and African American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicenter trial. Arch Intern Med 2000; 160:2185–91.
4. Fanghanel G, Cortinas L, Sanchez-Reyes L, Berber A. Second phase of a double-blind study clinical trial on sibutramine for the treatment of patients suffering essential obesity: 6 months after treatment cross-over. Int J Obes Relat Metab Disord 2001; 25:741–7.
5. Fanghanel G, Cortinas L, Sanchez-Reyes L, Berber A. A clinical trial of the use of sibutramine for the treatment of patients suffering essential obesity. Int J Obes Relat Metab Disord 2000; 24:144–50.
6. Cuellar GEM, Ruiz AM, Monsalve MCR, Berber A. Six-month treatment of obesity with sibutramine 15 mg; a double-blind, placebo-controlled monocenter clinical trial in a Hispanic population. Obes Res 2000; 8:71–82.
7. Jones SP, Smith IG, Kelly F, Gray JA. Long term weight loss with sibutramine [abstract 071]. Int J Obes Relat Metab Disord 1995; 19(suppl 2):41.
8. Apfelbaum M, Vague P, Ziegler O, et al. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. Am J Med 1999; 106: 179–84.
9. James WPT, Astrup A, Finer N, et al, for the STORM Study Group. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. Lancet 2000; 356:2119–25.
10. Klein S. Outcome success in obesity. Obes Res 2001; 9(suppl 5):354S–8S.
11. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1990; 121:293–8.
12. Lauterbach KW, Evers T. The impact of sibutramine on CHD—a subgroup analysis [abstract]. Int J Obes Relat Metab Disord 2000; 24(suppl 1):S99.

EFFECTIVENESS AND SAFETY OF LIDOCAINE PATCH 5%

TO THE EDITOR:

As a recognized authority on neuropathic pain and as one of the primary academic investigators for the lidocaine patch 5% (Lidoderm), I would like to comment on the recently published article about treatment of postherpetic neuralgia (PHN).[1] Several erroneous statements regarding the lidocaine patch were made in the article that I would like to address.

First, the lidocaine patch has clearly demonstrated efficacy in randomized controlled trials.[2] The degree of pain relief demonstrated with topical lidocaine patch is comparable to that shown with systemic agents; eg, 53% of patients receiving lidocaine patch reported "moderate" or better pain relief, and 29% reported "a lot" or "complete" relief, comparable to gabapentin PHN study results. The lidocaine patch 5% remains the only drug that has been thoroughly evaluated by the US Food and Drug Administration (FDA) and granted an indication for the treatment of PHN, based on efficacy, safety, and tolerability. Second, unlike what is written in the article, lidocaine patch 5% can be used successfully for treating trigeminal PHN, based on personal experience and a prospective open-label trial (Katz NP, Davis MW, Dworkin RH. Topical lidocaine patch produces a significant improvement in mean pain scores and pain relief in treated PHN patients: results of a multicenter open-label trial. Presented at the American Pain Society 20th Annual Scientific Meeting, April 19–22, 2001, Phoenix, AZ).

Third, lidocaine patch 5% is a targeted peripheral topical analgesic that produces local analgesia without anesthesia and without any clinically meaningful systemic serum levels. No patient in any clinical study developed any cardiac adverse event deemed causally related to the lidocaine patch. No death or serious adverse event attributed to the lidocaine patch occurred in any clinical study. In addition, since its approval and availability in 1999, no systemic side effects have been associated with the drug when appropriately dosed. Moreover, recent pharmacokinetic studies have demonstrated that even with increased dosing to 4 patches continually administered every 12 hours, lidocaine serum levels (225 ng/mL) remain significantly below levels associated with cardiac arrhythmic effects and toxicity (cardiac activity begins at 1500 ng/mL and toxicity > 5000 ng/mL).

In conclusion, I am hopeful that these points of clarification will contribute to improved understanding of the data pertaining to the lidocaine patch 5% and will demonstrate its effectiveness and safety for treating one of the most refractory neuropathic pain conditions, PHN. I hope they will also show why the lidocaine patch is recommended as a first-line therapy for PHN by many neuropathic pain authorities,[2] as reflected by a recent *New England Journal of Medicine* editorial.[3]

Bradley S. Galer, MD
Vice President, Scientific Affairs
Endo Pharmaceuticals, Inc.
Chadds Ford, Pennsylvania
University of Pennsylvania School of Medicine
Philadelphia
E-mail: galer.bradley@endo.com

REFERENCES

1. Alper BS, Lewis PR. Treatment of postherpetic neuralgia: a systemic review of the literature. J Fam Pract 2002; 51:121–8.
2. Argoff CE. New analgesics for neuropathic pain: the lidocaine patch. Clin J Pain 2000; 16:S62–6.
3. Watson CP. A new treatment for postherpetic neuralgia. N Engl J Med 2000; 343:1563–5.

DRS ALPER AND LEWIS RESPOND:

We appreciate Dr Galer's commentary and the opportunity to respond. The only published randomized controlled trial (RCT) of lidocaine patch to meet our inclusion criteria and demonstrate efficacy over placebo was an "enriched enrollment study" of 32 subjects who had previously demonstrated moderate to complete pain relief in an open-label compassionate use protocol.[1] An FDA reviewer[2] identified the limitations of applying results from this small, highly selected population and recommended further studies in PHN patients who had not previously been treated with the lidocaine patch.

The largest placebo-controlled RCT (150 subjects) in relatively unselected patients demonstrated insufficient difference between treatment groups to warrant FDA approval of the new drug application.[3] The fact that we could not discover this trial in a conventionally published format is to us a glaring example of publication bias. Upon further investigation, we found that the manufacturer's application was initially denied with the need for "one additional efficacy study," and was then subsequently approved based on the enriched enrollment study above.[4]

Dr Galer states that lidocaine patch can be successfully used to treat trigeminal PHN. We do not have RCT evidence to support or refute this statement, noting that the larger trial did not enroll subjects with trigeminal PHN, and the enriched enrollment study did not state the location of PHN.

We concur that the patient death in the larger unpublished trial was likely unrelated to use of the patch, although a lidocaine blood level was not obtained. According to its product labeling, Lidoderm should be used with caution in patients with severe hepatic disease and in those receiving antiarrhythmic or local anesthetic drugs. It is not clear that the pharmacokinetic data cited by Dr Galer are generalizable to patients with PHN and multiple comorbidities.

In summary, we do not find convincing evidence that lidocaine patch is more effective than placebo for unselected patients with PHN and believe that further clinical investigation is warranted. Some patients have had no response from multiple therapies and have benefited from the lidocaine patch. The resourceful and compassionate clinician should consider the lidocaine patch when confronted with a patient with refractory PHN who is intolerant of or a poor candidate for therapies with a stronger evidence basis (tricyclic antidepressants, topical capsaicin, gabapentin, and oxycodone).

Brain S. Alper, MD, MSPH
Columbia, Missouri
E-mail: alperb@health.missouri.edu
Peter R. Lewis, MD
Hershey, Pennsylvania

REFERENCES

1. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain 1999; 80:533–8.
2. Lidoderm (lidocaine) patch. Center for Drug Evaluation and Research application number: NDA 20-612. Medical reviews. Washington, DC: US Food and Drug Administration, Center for Drug Evaluation and Research. Submitted June 1, 1998. Available at: http://www.fda.gov/cder/foi/nda/99/20612_medr_P6.pdf; pp. 9–12. Accessed April 23, 2002.
3. Lidoderm (lidocaine) patch. Center for Drug Evaluation and Research application number: NDA 20-612. Medical reviews. Washington, DC: US Food and Drug Administration, Center for Drug Evaluation and Research. Submitted June 11, 1996. Available at: http://www.fda.gov/cder/foi/nda/99/20612_medr_P1.pdf; pp. 6–ff. Accessed April 23, 2002.
4. Lidoderm (lidocaine) patch. Center for Drug Evaluation and Research application number: NDA 20-612. Administrative documents. Washington, DC: US Food and Drug Administration, Center for Drug Evaluation and Research. Available at: http://www.fda.gov/cder/foi/nda/99/20612_medr_P1.pdf; p. 12. Accessed April 23, 2002.

SNAKE OIL OR SOUND MEDICINE

TO THE EDITOR:

I was a bit dismayed by the article by Arroll and colleagues[1] and the editorial by Little[2] in the April issue of *the Journal of Family Practice* promoting delayed prescriptions as a way of decreasing usage of antibiotics for viral upper respiratory infections. I certainly applaud any effort to reduce unnecessary use of antibiotics; but is this the right method?

When patients seek medical care they should reasonably be able to expect that the physician will use his or her best judgment in prescribing the most appropriate care. To let the patient decide is just an abdication of responsibility by the physician. To say, "You don't need a prescription for an antibiotic, but here is your prescription for an antibiotic" sends a mixed message to the patient. I believe a mixed message is worse than no message. Each time an antibiotic is prescribed for a cold, either immediately or delayed, it will only reinforce that behavior and make it that much more difficult for the next physician the patient sees to prescribe rationally.

Although prescribing appropriately can be difficult sometimes, it is now easier than before. Guidelines for appropriate treatment of respiratory infections were published in the *Annals of Internal Medicine* in March 2001.[3] Since the publication of these guidelines I have followed them as closely as possible. I have been surprised how few patients object to symptomatic treatment of their colds when I spend just a few extra moments explaining the rationale of my decision to not prescribe antibiotics. For patients very resistant to my views, they are often convinced

if I explain that better guidelines are now available for prescribing antibiotics for respiratory infections than in the past, and I offer to provide the literature reference if they are interested.

Arroll and colleagues[1] reported that by giving delayed prescriptions for antibiotics to patients with common colds, antibiotic use was reduced from 89% to 48%. At the risk of appearing too simplistic, may I point out that if only those physicians had done their duty, antibiotic use would have been reduced to 0%.

Promoting the irrational use of antibiotics makes us no better than the snake oil salesmen of years ago. Actually, it makes us worse. Many of the snake oil salesmen believed their remedies worked, but we know better.

Charles G. Young, MD
McKinley Health Center
University of Illinois at Urbana-Champaign
E-mail: cgyoung@mhc.uiuc.edu

REFERENCES

1. Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce the use of antibiotics for the common cold? A single-blind controlled trial. J Fam Pract 2002; 51:324–8.
2. Little P. Where next with antibiotics and respiratory tract infections? J Fam Pract 2002; 51:337–8.
3. Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims, and methods. Ann Intern Med 2001; 134:479–86.

DRS LITTLE RESPOND:

Is delayed prescribing irrational and the stuff of snake charmers? Unlike with snake charmers' wares, a body of emerging evidence supports the judicious use of delayed prescribing. In some situations, delayed prescribing can be useful:

In response to patient pressure and expectation. If a physician believes antibiotics are of little benefit, then he or she should advise against using them, and discuss their disadvantages. However, if patients are adamant that they want antibiotics, then the delayed prescribing approach combined with a discussion of patients' concerns and expectations can be a useful way to avoid long, antagonistic, and counterproductive encounters with patients, and to convey the message that antibiotics may not be essential. Good evidence has suggested that if physicians use a delayed prescription, patients' beliefs in the importance of antibiotics and their subsequent reconsultation rate are the same or better than if nothing is prescribed,[1] and only a minority use their prescriptions.[2]

Where the evidence is not clear cut. For most respiratory tract infections—rhinosinusitis, bronchitis, sore throat, and otitis media (ie, the vast majority of RTIs)—the evidence is not simple: systematic reviews in the Cochrane library suggest a modest benefit from antibiotic use on average, and most patients' symptoms will settle quickly, but a proportion do benefit. Furthermore, we cannot easily identify patients with bacterial infections, infections that will not settle quickly, or the few patients who go on to develop complications. Should all patients be offered antibiotics or none? In face of this uncertainty, it is perfectly reasonable and safe to advise patients that their symptoms are extremely likely to settle during the next few days, that it is wise not to use antibiotics unless absolutely necessary, and only if severe symptoms persist then to use antibiotics. Such clear guidance to patients does not therefore need to give mixed messages and has been applied successfully in large cohorts3 (as in the Dutch guidelines for antibiotics in otitis media) and several recent trials.[2,4]

Paul Little, MD
Southampton University
Aldermoor Health Center
Southampton, England
E-mail: p.little@soton.ac.uk

REFERENCES

1. Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. BMJ 1997; 315:350–2.
2. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. BMJ 1997; 314:722–7.
3. van Buchem FL, Peeters MF, van 't Hof MA. Acute otitis media: a new treatment strategy. Br Med J (Clin Res Ed) 1985; 290:1033–7.
4. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. BMJ 2001; 322:336–42.

JFP