

## COMMENTS AND RESPONSE

## Screening for Colorectal Cancer

**TO THE EDITOR:** I hope that Pignone and colleagues (1) have countered the groundswell fostered by Lieberman and associates (2, 3) for screening colonoscopy in asymptomatic, average-risk adults. The latter studies demonstrated that six cases of colon cancer may have been missed by one-time stool card analysis and sigmoidoscopy in 3196 patients. However, widespread media coverage ignored the 10 serious complications of screening, which included a cerebrovascular accident and a myocardial infarction. At least one of the three deaths within 30 days of colonoscopy was probably the eventual result of a procedure complication. Lieberman and associates' study sample excluded patients with heart and lung disease, and experienced endoscopists performed all colonoscopies. To take this morbidity and mortality rate and expand it to a large sample being evaluated by less experienced endoscopists could be catastrophic.

*Colonoscopy* has become a household word since *Today* show anchor Katie Couric underwent the procedure on national television. The death of her husband, a 42-year-old man with no risk factors for colon cancer, was tragic. However, by undergoing this procedure at age 42, without symptoms or risk factors, to demonstrate its safety and acceptability, Ms. Couric may have sent the wrong message.

Private insurers are now following Medicare's lead in covering colonoscopy to screen for colon cancer in asymptomatic, average-risk adults. The expense of these procedures, combined with the resulting increase in use of pathologic services and follow-up procedures for trivial polyps, not to mention the expense of treating complications, can only begin to be calculated. Indeed, Pandora's box may contain a colonoscope.

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## References

1. Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;137:132-41. [PMID: 12118972]
2. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med.* 2000;343:162-8. [PMID: 10900274]
3. Lieberman DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med.* 2001;345:555-60. [PMID: 11529208]

**TO THE EDITOR:** Pignone and colleagues (1) claim that screening for colorectal cancer is cost-effective. I submit that this conclusion is not tenable. For colorectal cancer screening to save life-years, lives have to be saved. However, no trial of screening for colorectal cancer has shown a reduction in mortality. The combined results of the three published randomized, controlled trials of screening with fecal occult blood testing fail to show any trend toward mortality reduction; 25 609 of the 137 377 screened patients died, and 22 158 of the 121 348 unscreened patients died (2-4). Thus, there were 186.4

deaths per 1000 persons in the screened groups and 182.6 deaths per 1000 persons in the unscreened groups (relative risk, 1.02 [95% CI, 1.00 to 1.04]). There are no data from randomized, controlled trials regarding the effects of other screening methods on colorectal or all-cause mortality.

The conclusion seems unavoidable: Screening with the FOBT changes the way people die. It modestly reduces the rate of death from colorectal cancer, but it fails to save lives. There is no reliable evidence indicating that other screening methods reduce mortality or to what degree they change mortality, if indeed they do. The published evidence fails to support the claim that any life-years are saved by colorectal cancer screening or that screening is cost-effective. Since no lives are saved, the cost per year of life saved is incalculable.

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## References

1. Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;137:96-104. [PMID: 12118964]
2. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med.* 1993;328:1365-71. [PMID: 8474513]
3. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet.* 1996;348:1472-7. [PMID: 8942775]
4. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet.* 1996;348:1467-71. [PMID: 8942774]

**TO THE EDITOR:** Many gastroenterologists now spend half their days setting up colonoscopies and the other half performing them on standard-risk patients whose only fault is that they watch too much television. We welcome the clinical guidelines on colorectal cancer screening by the U.S. Preventive Services Task Force (1) and the accompanying summary by Pignone and colleagues (2), which place this subject in a reasonable perspective. The rush to universal colonoscopic screening of standard-risk patients was encouraged by various celebrities who gave the issue well-intentioned but in our opinion misguided publicity. As a result, it has become difficult for patients who really need colonoscopy to get it expeditiously.

The inconclusive studies that extol the virtues of screening colonoscopy in average-risk patients do not tell us whether finding polyps justifies the costs, risks, and discomfort of the procedure (2, 3). We would continue screening with total colonoscopy in patients who meet the currently accepted criteria for "high risk" for colorectal cancer and would use flexible sigmoidoscopy and fecal occult blood tests for patients at standard risk.

Virtual colonoscopy, stool DNA testing, and diverse other approaches may soon become acceptable screening mechanisms. Until then, we suspect that screening colonoscopy consumes too much physician time, endoscopy unit resources, and even health maintenance organization dollars. If we gastroenterologists would direct our

enthusiasm toward procedures with sound, evidence-based reasoning, we might be able to change our practices.

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#### References

1. Screening for colorectal cancer: recommendation and rationale. *Ann Intern Med.* 2002;137:129-31. [PMID: 12118971]
2. Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;137:132-41. [PMID: 12118972]
3. Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;137:96-104. [PMID: 12118964]

**IN RESPONSE:** We appreciate the comments from Drs. Kirkpatrick, Budenholzer, Rosson, and Spiro. We agree with Dr. Kirkpatrick that obtaining additional data on the safety of screening colonoscopy in real-world settings is important. Resource issues, such as the capacity for performing screening colonoscopy and potential effects on the availability of the procedure for diagnostic evaluations, must also be considered (1).

Dr. Budenholzer suggests that the effectiveness of colorectal cancer screening has not been demonstrated because the available randomized trials have not shown reductions in all-cause mortality. Colorectal cancer, however, accounts for fewer than 5% of all deaths, so demonstrating a reduction in all-cause mortality is difficult both in terms of the number of patients and the amount of follow-up time required. Cost-effectiveness models necessarily attempt to project the effects of screening over longer periods and for other means of screening that have not been evaluated in randomized trials. Although they do not have the same methodologic strength as individual randomized trials, they provide useful information for much less cost.

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#### Reference

1. Rex DK, Lieberman DA. Feasibility of colonoscopy screening: discussion of issues and recommendations regarding implementation [Editorial]. *Gastrointest Endosc.* 2001;54:662-7. [PMID: 11677497]

## RESEARCH LETTERS

### Acute Hepatocellular-Cholestatic Liver Injury after Olanzapine Therapy

**TO THE EDITOR:** *Background:* Olanzapine, a thienobenzodiazepine derivative, is an atypical antipsychotic agent indicated for the treatment of schizophrenia and related psychotic disorders (1, 2). Conventional, phenothiazine antipsychotics and older atypical antipsychotics have both been reported to cause acute hepatitis (3, 4). To

date, no cases of olanzapine-induced acute hepatitis have been described in the literature. This case in this letter has been reported to the manufacturer and to the U.S. Food and Drug Administration.

*Case Report:* A 78-year-old woman received a diagnosis of acute depression with psychotic features and was prescribed olanzapine, 10 mg/d. Thirteen days later, she developed fever associated with malaise, arthralgia, upper abdominal pain, anorexia, and nausea. The patient's only other medications were calcium-vitamin D, multivitamins, and occasional acetaminophen. The patient had no history of liver disease, alcohol intake, intravenous drug use, or blood transfusions.

On admission, physical examination of the patient was remarkable only for dry mucous membranes and a palpable, firm, and tender liver. Initial liver function tests showed an aspartate aminotransferase level of 361 U/L (normal range, 10 to 40 U/L), an alanine aminotransferase level of 204 U/L (normal range, 20 to 50 U/L), a total bilirubin level of 22  $\mu\text{mol/L}$  (1.3 mg/dL) (normal range, 2 to 21  $\mu\text{mol/L}$  [0.1 to 1.2 mg/dL]), and an alkaline phosphatase level of 189 U/L (normal range, 35 to 130 U/L). The leukocyte count was  $13.0 \times 10^9$  cells/L (normal range,  $4.4$  to  $11.3 \times 10^9$  cells/L), with 88% neutrophils and 0.5% eosinophils. Hemoglobin level, platelet count, prothrombin time, and levels of pancreatic enzymes and electrolytes were normal. Acetaminophen level was less than 7  $\mu\text{mol/L}$ . Results of serologic tests for hepatitis A, B, and C viruses; cytomegalovirus; Epstein-Barr virus; and antimitochondrial and antinuclear antibodies were negative. Hepatobiliary ultrasonography showed several gallbladder stones without dilatation of the biliary ducts or changes of acute cholecystitis.

On hospital day 3, the aspartate aminotransferase level increased to 964 U/L, the alanine aminotransferase level increased to 965 U/L, the total bilirubin level increased to 156  $\mu\text{mol/L}$  (9.1 mg/dL) (conjugated fraction, 7.9), and the alkaline phosphatase level increased to 488 U/L. On hospital day 4, the patient's symptoms resolved and results of liver function tests were remarkably improved. At follow-up 4 weeks later, the patient was asymptomatic and results of liver function tests had normalized.

*Discussion:* Several features of our case support olanzapine as the cause of hepatic injury. According to a diagnostic validation scale for drug-induced hepatitis (5), our case had a high score (16 out of 20), favoring a diagnosis of olanzapine-induced liver injury. The pathophysiologic mechanism of this adverse event remains unclear. However, the absence of acute hepatitis in reports of patients with overdose of the drug (6) indicates that olanzapine-induced hepatitis is probably not dose dependent. We performed a MEDLINE literature search (from October 1996 to April 2002) using the terms *olanzapine*, *hepatitis*, *antipsychotics*, and *adverse effects*. No reports of acute hepatitis related to olanzapine were found.

The safety and tolerability of olanzapine were evaluated in phase II and III clinical trials (1, 2). Liver enzymes showed transient elevation in 9.4% of olanzapine-treated patients, and none of these patients showed signs or symptoms of acute hepatitis. In premarketing testing, only 2% of olanzapine-treated patients had elevated liver enzyme levels and none experienced jaundice or clinical hepatitis (7).

Gómez and colleagues (8), in their study of more than 2000 patients treated with olanzapine, reported no cases of jaundice or clinical hepatitis at 6 months' follow-up. In one international, multicenter double-blind study of 1336 olanzapine-treated patients (9), 7.9% developed a modest elevation in hepatic enzyme levels without signs or symptoms of acute hepatitis. These studies suggest that olan-

zapine may be associated with nonicteric, generally mild, transient hepatocellular injury. Because of the potential for serious liver injury induced by olanzapine, we suggest that patients taking this drug should undergo periodic assessment of liver function and should be observed for signs and symptoms of acute hepatitis. The pathophysiologic mechanism and incidence of olanzapine-induced acute hepatitis remain unknown.

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#### References

1. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology*. 1996;14:111-23. [PMID: 8822534]
2. Beasley CM Jr, Sanger T, Satterlee W, Tollefson G, Tran P, Hamilton S. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. *Psychopharmacology (Berl)*. 1996;124:159-67. [PMID: 8935812]
3. Kellner M, Wiedemann K, Krieg JC, Berg PA. Toxic hepatitis by clozapine treatment [Letter]. *Am J Psychiatry*. 1993;150:985-6. [PMID: 8494085]
4. Krebs S, Dormann H, Muth-Selbach U, Hahn EG, Brune K, Schneider HT. Risperidone-induced cholestatic hepatitis. *Eur J Gastroenterol Hepatol*. 2001;13:67-9. [PMID: 11204814]
5. Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology*. 1997;26:664-9. [PMID: 9303497]
6. Gerber JE, Cawthon B. Overdose and death with olanzapine: two case reports. *Am J Forensic Med Pathol*. 2000;21:249-51. [PMID: 10990286]
7. Zyprexa [package insert]. Indianapolis, IN: Eli Lilly; 1997.
8. Gómez JC, Sacristán JA, Hernández J, Breier A, Ruiz Carrasco P, Antón Saiz C, et al. The safety of olanzapine compared with other antipsychotic drugs: results of an observational prospective study in patients with schizophrenia (EFESO Study). *Pharmacoepidemiologic Study of Olanzapine in Schizophrenia. J Clin Psychiatry*. 2000;61:335-43. [PMID: 10847307]
9. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry*. 1997;154:457-65. [PMID: 9090331]

### Furosemide Challenge in Patients with Heart Failure and Adverse Reactions to Sulfa-Containing Diuretics

**TO THE EDITOR:** *Background:* Diuretics have an important role in managing symptomatic fluid overload in severe heart failure and are used in 85.8% of patients (1). Two patients in our 500-patient practice had reported a distant history of an adverse reaction to sulfa-containing diuretics and had been successfully managed with oral ethacrynic acid. However, the recent discontinuation of ethacrynic acid tablets by the manufacturer (Merck & Co., West Point, Pennsylvania) created a dilemma in managing these patients.

*Objective:* We performed a MEDLINE search using the terms *furosemide, bumetanide, torsemide, diuretics, sulfamyl diuretics, thiazide diuretics, hypersensitivity, allergy, and allergic reaction* but did not identify any reports describing a drug rechallenge protocol. Therefore, we created a furosemide rechallenge protocol based on a method describing a rechallenge with a sulfa-containing anti-infective agent (2).

**Table. Furosemide Desensitization**

Day of Treatment	Solution Volume, mL	Dose, mg
Furosemide, 0.05 mg/mL		
1	1	0.05
2	2	0.1
3	4	0.2
4	8	0.4
5	10	0.5
6	20	1
7	40	2
Furosemide, 10 mg/mL		
8	0.4	4
9	0.8	8
10	2	20

*Methods:* The initial dose of furosemide, 0.05 mg, was prepared by using furosemide oral solution (Table). Patients were admitted to the cardiac intermediate care unit, placed on telemetry monitors, and given intravenous ethacrynic acid during the furosemide rechallenge.

*Case 1:* A 73-year-old man was evaluated for heart failure management. A dermatologist evaluated the patient in 1997 for the development of urticarial plaques on his trunk, extremities, and face secondary to bumetanide treatment. He tolerated the furosemide rechallenge protocol without any problem and was discharged on furosemide, 40 mg orally twice daily. At an 8-month follow-up visit, he was free of any signs or symptoms of urticarial plaques, hives, or rash.

*Case 2:* A 70-year-old woman was admitted to the hospital with symptoms of increasing shortness of breath and exacerbation of heart failure. She reported a distant history of pancytopenia caused by furosemide and bumetanide. On admission, her leukocyte count was  $2.9 \times 10^9$  cells/L, hemoglobin level was 123 g/L (12.3 mg/dL), hematocrit was 0.35, and platelet count was  $139 \times 10^9$  cells/L. The leukocyte count and platelet count decreased during hospitalization. The leukocyte nadir was  $2.2 \times 10^9$  cells/L on day 7, and the platelet nadir occurred on day 3. The patient continued to follow the protocol and was discharged after 10 days on furosemide, 40 mg orally twice daily. At 5 weeks after discharge, her complete blood count had returned to preadmission values.

*Conclusion:* Drug hypersensitivity reactions, such as urticaria and rash, have been reported with furosemide and bumetanide (3, 4). Angioedema and lichenoid eruptions have been reported with torsemide (5, 6). Cross-allergy has occurred with furosemide and other sulfa drugs (7). The overall incidence of drug hypersensitivity reactions is rare (<0.5%) (4); however, since approximately 5 million patients have heart failure (8), physicians may be faced with treating patients who present with serious adverse reactions to loop diuretics.

The case series describing the trimethoprim-sulfamethoxazole rechallenge excluded patients with anaphylactic reactions (2). In addition, 10 of 28 patients reported recurrence of rash on follow-up (2). Neither of the two patients presented here had any history of life-threatening anaphylactic reaction to sulfa-containing drugs. An alternate treatment option would be to administer intravenous ethacrynic acid through a peripherally inserted central catheter on an outpatient basis. This option is expensive and carries the risk for mechanical and infectious complications but may be preferred in the presence of life-threatening reactions to sulfa-containing diuretics.

We believe this protocol may benefit numerous other patients with heart failure until equipotent alternative diuretics become available. Many investigational agents, such as the vasopressin inhibitors, may be alternatives in the future.

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#### References

- Cohn JN, Tognoni G, Glazer R, Spormann D. Baseline demographics of the Valsartan Heart Failure Trial. Val-HeFT Investigators. *Eur J Heart Fail.* 2000;2:439-46. [PMID: 11113722]
- Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol.* 1994;93:1001-5. [PMID: 8006304]
- Lasix [package insert]. Bridgewater, NJ: Aventis Pharmaceuticals; 2001.
- Bumex [package insert]. Basel, Switzerland: Roche; 2001.
- Demadex [package insert]. Basel, Switzerland: Roche; 2001.
- Byrd DR, Ahmed I. Photosensitive lichenoid reaction to torsemide—a loop diuretic. *Mayo Clin Proc.* 1997;72:930-1. [PMID: 9379695]
- Hansbrough JR, Wedner HJ, Chaplin DD. Anaphylaxis to intravenous furosemide. *J Allergy Clin Immunol.* 1987;80:538-41. [PMID: 3668117]
- Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol.* 2001;38:2101-13. [PMID: 11738322]

## Antral Injections of Botulinum A Toxin for the Treatment of Obesity

**TO THE EDITOR:** *Background:* In Germany, approximately 50% of the population are overweight and 20% are obese (1). Overweight and obesity increase the risk for metabolic complications, arterial hypertension, cardiovascular diseases, and cancer (1). Long-term reduction of excess weight may improve many of these health problems, but available treatments—diet, exercise, behavioral modification, and pharmacotherapy—achieve only short-term, limited weight loss in most patients (2). Botulinum A toxin is a powerful, long-acting inhibitor of muscular contractions in both voluntary and smooth muscles. It has been used to treat neurologic (3, 4) and gastroenterologic disorders, including achalasia and, most recently, idiopathic gastroparesis (5, 6). Moreover, results from animal experiments suggest that botulinum A toxin injected into the gastric wall may reduce body weight and food intake by inhibiting the antral pump, thereby inducing slowed gastric emptying and earlier satiety (6).

*Objective:* To present one of the first uses of antral botulinum A toxin injection for the treatment of obesity in humans.

*Case Report:* The patient was a 33-year-old man with obesity (weight, 100.6 kg; height, 179 cm; body mass index [BMI], 31.4 kg/m<sup>2</sup>), dyslipidemia, and borderline hypertension. He underwent several unsuccessful treatments for obesity, including diet and exer-

cise. After food intake was measured for 1 week with a patient diary, gastroscopy was performed and 500 MU of Dysport (Ipsen Pharma, Ettlingen, Germany) was injected circularly into the prepyloric antral gastric wall at 10 places. (Of note, the biological activity of 350 to 500 MU of Dysport compares with approximately 100 MU of Botox [botulinum toxin type A, Allergan, Irvine, California], which is available in the United States.) The Dysport injection was performed only once.

Four days after treatment, the patient reported feeling full even after intake of small food volumes. Daily food intake, assessed with the diary, was approximately 11,400 kJ before the injection and decreased to 3,700 kJ 1 month after the injection (−67.5%), 6,500 kJ 2 months after the injection (−43.0%), and 7,700 kJ 4 months after the injection (−32.5%). Similarly, weight decreased to 95.2 kg (BMI, 29.7 kg/m<sup>2</sup>), 93.2 kg (BMI, 29.1 kg/m<sup>2</sup>), and 91.6 kg (BMI, 28.6 kg/m<sup>2</sup>), respectively. No adverse events occurred.

*Discussion:* Botulinum A toxin has been used in the management of achalasia and gastroparesis (5, 6) because it blocks the release of the neurotransmitter acetylcholine at the neuromuscular junction of both voluntary and smooth muscles and leads to long-lasting muscle weakness. Animal experiments suggest that botulinum A toxin injected into the antral gastric wall has a weight-reducing effect (7).

We present one of the first uses of botulinum A toxin for the treatment of obesity in humans. Under gastroscopic control, 500 MU of Dysport was injected into the prepyloric antral gastric wall. The patient reported early satiety 4 days after injection and lost 9 kg of weight within 4 months (a decrease of 8.9%). Food intake decreased to 67.5% of baseline, which compares with the findings of animal studies (7).

Propulsive contractions of the antrum are necessary for gastric contents to pass into the duodenum. Botulinum A toxin appears to inhibit this mechanism. Thus, our patient's parallel reduction of body weight and food intake is consistent with slowed gastric emptying and early satiety caused by inhibition of the antral pump (7). The noticeable effect of botulinum A toxin approximately 1 week after injection is consistent with that seen in other studies (3). Furthermore, in a study by Kolbasnik and colleagues (5), 77% of patients with achalasia who received botulinum A toxin experienced symptomatic improvement for more than 3 months. This long-term efficacy was observed in our case as well.

*Conclusion:* Botulinum A toxin might be a promising alternative to surgery for obese persons. Our group is working on a double-blind, placebo-controlled pilot study to begin to evaluate its efficacy.

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#### References

- Heseker H, Schmid A. [Epidemiology of obesity]. *Ther Umsch.* 2000;57:478-81. [PMID: 11026082]
- Mun EC, Blackburn GL, Matthews JB. Current status of medical and surgical therapy for obesity. *Gastroenterology.* 2001;120:669-81. [PMID: 11179243]
- Rollnik JD, Matzke M, Wohlfarth K, Dengler R, Bigalke H. Low-dose treatment of cervical dystonia, blepharospasm and facial hemispasm with albumin-diluted botuli-

num toxin type A under EMG guidance. An open label study. *Eur Neurol.* 2000;43:9-12. [PMID: 10601802]

4. Rollnik JD, Hierner R, Schubert M, Shen ZL, Johannes S, Tröger M, et al. Botulinum toxin treatment of cocontractions after birth-related brachial plexus lesions. *Neurology.* 2000;55:112-4. [PMID: 10891916]

5. Kolbasnik J, Waterfall WE, Fachnie B, Chen Y, Tougas G. Long-term efficacy of Botulinum toxin in classical achalasia: a prospective study. *Am J Gastroenterol.* 1999;94:3434-9. [PMID: 10606299]

6. Miller LS, Szych GA, Kantor SB, Bromer MQ, Knight LC, Maurer AH, et al. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. *Am J Gastroenterol.* 2002;97:1653-60. [PMID: 12135014]

7. Gui D, De Gaetano A, Spada PL, Viggiano A, Cassetta E, Albanese A. Botulinum toxin injected in the gastric wall reduces body weight and food intake in rats. *Aliment Pharmacol Ther.* 2000;14:829-34. [PMID: 10848669]

## GENERAL COMMENTARY

### Food and Drug Administration Approval of Buprenorphine–Naloxone for Office Treatment of Addiction

**TO THE EDITOR:** Many persons addicted to opium decline available treatment methods but accept buprenorphine, particularly when it is offered in a private office (1). On 8 October 2002, the U.S. Food and Drug Administration approved buprenorphine, a schedule III partial morphine agonist, for treatment of opioid dependence. This approval, together with provisions in the Drug Addiction Treatment Act of 2000, expands the venues for the treatment of opioid dependence from specially licensed methadone facilities to physicians' private offices, where schedule III to schedule V drugs can be prescribed. Expansion of treatment to private practice creates opportunities to provide holistic care for addicted patients with AIDS, hepatitis, or other conditions that are complicated by opioid dependence. In addition, this expansion could have substantial public health benefits by reducing heroin demand.

Buprenorphine has a wide safety margin and is as efficacious as methadone but safer in overdose (2). For addiction treatment, buprenorphine is approved as a sublingual tablet (2 mg and 8 mg) containing a small amount of naloxone that is marketed under the brand name Suboxone (Reckitt Benckiser, Berkshire, United Kingdom). Naloxone has no effect sublingually but precipitates abstinence if administered parenterally by an opioid-dependent person, thereby limiting diversion and providing the rationale for permitting take-home doses (3).

To treat addiction with buprenorphine, a physician must notify the U.S. Secretary of Health and Human Services that he or she has completed an 8-hour training course (offered by many medical societies), that a maximum of 30 patients will be treated in each office location, and that appropriate patients are being referred for psychosocial therapy. Previous experience with addiction treatment may substitute for the course. The notification form is obtainable from the Center for Substance Abuse Treatment (telephone, 301-443-7745).

Physicians must be aware, however, of clinical complexities.

Unless an adequate opioid-free period has elapsed, initial doses of buprenorphine may precipitate abstinence. Discontinuation may produce anergia, often leading to relapse (4). Increasing maintenance doses can reduce administration to 3 to 4 days per week (5).

Private treatment reduces the stigma associated with use of opioid drugs and brings addiction treatment into the mainstream of health care. It is to be hoped that treatment of persons with addiction will become similar to that of other chronically ill patients.

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## References

1. Resnick RB, Galanter M, Resnick E, Pycha C. Buprenorphine treatment of heroin dependence (detoxification and maintenance) in a private practice setting. *J Addict Dis.* 2001;20:75-83. [PMID: 11318399]
2. Raisch DW, Fye CL, Boardman KD, Sather MR. Opioid dependence treatment, including buprenorphine/naloxone. *Ann Pharmacother.* 2002;36:312-21. [PMID: 11847954]
3. Fudala PJ, Yu E, Macfadden W, Boardman C, Chiang CN. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. *Drug Alcohol Depend.* 1998;50:1-8. [PMID: 9589267]
4. Resnick RB, Galanter M, Pycha C, Cohen A, Grandison P, Flood N. Buprenorphine: an alternative to methadone for heroin dependence treatment. *Psychopharmacol Bull.* 1992;28:109-13. [PMID: 1609035]
5. Amass L, Kamien JB, Mikulich SK. Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. *Drug Alcohol Depend.* 2000;58:143-52. [PMID: 10669065]

## CORRECTION

### Correction: Postmenopausal Estrogen Replacement and Risk for Venous Thromboembolism

The first paragraph of an article on postmenopausal estrogen replacement and risk for venous thromboembolism (1) states that the most recent systematic review on this topic (2) did not include a meta-analysis. The review referred to, however, was a meta-analysis of studies published from 1966 to 1996.

## References

1. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;136:680-90. [PMID: 11992304]
2. Douketis JD, Ginsberg JS, Holbrook A, Crowther M, Duku EK, Burrows RF. A reevaluation of the risk for venous thromboembolism with the use of oral contraceptives and hormone replacement therapy. *Arch Intern Med.* 1997;157:1522-30. [PMID: 9236553]