

4. Tait RJ, Ngo HT, Hulse GK. Mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment. *J Subst Abuse Treat* 2008;35:116-24.
5. Kunøe N, Lobmaier P, Vederhus JK, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. *Br J Psychiatry* 2009;194:541-6.

THE AUTHORS REPLY: We agree with Saldaña and Hart that many trials investigating substitution treatment for opioid dependence have been conducted in the United States. However, there have been few studies of heroin substitution in the United States, particularly phase 3 studies with a large outpatient population. Of the four trials analyzed in the most recent Cochrane review of heroin-assisted therapy,¹ not one was conducted in the United States. Our American collaborators in the NAOMI study group concluded, after several years of work, that they were unable to overcome regulatory barriers or to secure the funding necessary for a large-scale effectiveness trial.

Although many physicians may not use proper doses of methadone, this was not the case in the NAOMI trial. The mean of 12 days of illicit heroin use in the methadone group to which Kahan refers was calculated on an intention-to-treat basis; for patients who remained in the study the mean was 6 days. Study physicians followed best practices and titrated doses to the clinical needs of each patient. Doses in the range of 120 to 140 mg are recommended but only if tolerated. Low dosages were clearly not an issue in our trial, since the response rates of patients in the methadone group who received daily doses above or below 100 mg were similar (68% vs. 62%, $P=0.63$). Our findings mirrored those of a German heroin trial in which the overall average dose of methadone was 99 mg and did not differ significantly between those who did and those who did not respond to treatment (97 mg and 104 mg, respectively).² We too await publication of the full results of the RIOTT study. However, the investigators have recently announced a positive result consistent with our findings — that is, three

quarters of the participants for whom heroin was prescribed made substantial reductions in their use of street heroin, as compared with about a third of the participants in the groups receiving injectable methadone or optimized oral methadone.³

Reece is right to point out the important issue of cost. In a Dutch trial of heroin-assisted therapy, it was estimated that treatment, even though more expensive than methadone maintenance, led to an overall annual savings of approximately \$18,900 in U.S. dollars.⁴ A formal pharmacoeconomic evaluation of our trial is under way. Meanwhile, it is noteworthy that the annual societal cost of each untreated heroin user in Canada in 1996 was estimated at approximately \$41,700 in U.S. dollars.⁵ Optimized methadone maintenance, provided with adjunctive diacetylmorphine treatment when necessary, can be offered for less than a quarter of this amount.

Eugenia Oviedo-Joekes, Ph.D.

University of British Columbia School of Population and Public Health
Vancouver, BC, Canada

David Marsh, M.D.

Vancouver Coastal Health
Vancouver, BC, Canada

Martin T. Schechter, M.D., Ph.D.

University of British Columbia School of Population and Public Health
Vancouver, BC, Canada
martin.schechter@ubc.ca

1. Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin dependents. *Cochrane Database Syst Rev* 2005; 2:CD003410.
2. Haasen C, Vertheim U, Degkwitz P, et al. The German model project for heroin assisted treatment of opioid dependent patients: a multicentric, randomized, controlled treatment study. Hamburg, Germany: Centre for Interdisciplinary Addiction Research of Hamburg University (ZIS), 2006.
3. Siva N. Heroin clinics reduce street drug use and crime, shows study. *BMJ* 2009;339:b3845.
4. Dijkgraaf MG, van der Zanden BP, de Borgie CA, Blanken P, van Ree JM, van den Brink W. Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials. *BMJ* 2005; 330:1297.
5. Wall R, Rehm J, Fischer B, et al. Social costs of untreated opioid dependence. *J Urban Health* 2000;77:688-722.

The Hypertension Paradox

TO THE EDITOR: In the Shattuck Lecture on the hypertension paradox (Aug. 27 issue),¹ Chobanian points out that the number of people with uncontrolled hypertension is increasing. Nonadherence to treatment is a possible explanation for

this finding, since estimated adherence rates are 51 to 79%, depending on the number of daily doses prescribed.² Nonadherence is a recognized cause of adverse outcomes, particularly among patients with cardiovascular disease.³ In a recent

editorial on osteoporosis in the *Journal*,⁴ Khosla wrote that treatment success increasingly depends not so much on the drugs available to us but rather on our ability to engage our patients and ensure that they take the medications we prescribe. In my opinion, his statement is perfectly well suited to describe the situation concerning the treatment of hypertension.

Urs Schwarz, M.D.

Via Leoni 5
Breganzona, Switzerland
dottori.schwarz.hoey@bluewin.ch

1. Chobanian AV. Shattuck Lecture: the hypertension paradox — more uncontrolled disease despite improved therapy. *N Engl J Med* 2009;361:878-87.
2. Claxton AJ, Cramer J, Pierce CA. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23:1296-310.
3. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-97.
4. Khosla S. Increasing options for the treatment of osteoporosis. *N Engl J Med* 2009;361:818-20.

TO THE EDITOR: In his article, Chobanian did not address the complexity of the management of hypertension in the geriatric population, although the majority of patients with hypertension are elderly. The low control rates of hypertension are largely attributable to inadequate treatment of systolic hypertension.¹ Earlier research² showed that treatment of systolic hypertension in the elderly resulted in impressive reductions in the incidence of stroke, coronary heart disease, and congestive heart failure. Study data³ also indicate that treatment of systolic hypertension (systolic blood pressure ≥ 160 mm Hg) in older patients is strongly recommended, whereas recommendations for treatment when systolic blood pressure is 140 to 159 mm Hg are less strong. More recent studies^{4,5} suggest that reaching a goal for systolic blood pressure at the expense of a reduction in excessive diastolic blood pressure may increase morbidity and mortality, particularly in cases of isolated systolic hypertension. It would be important to take these compelling study outcomes into account when developing treatment strategies for elderly patients with hypertension, particularly systolic hypertension.

Asit Baran Shil, M.D.

University of Southern California Keck School of Medicine
Los Angeles, CA
shil@usc.edu

1. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Re-

port of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA* 2003;289:2560-72.

2. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255-64.
3. Chaudhry SI, Krumholz H, Foody JM. Systolic hypertension in older persons. *JAMA* 2004;292:1074-80.
4. Ungar A, Pepe G, Lambertucci L, et al. Low diastolic ambulatory blood pressure is associated with greater all-cause mortality in older patients with hypertension. *J Am Geriatr Soc* 2009;57:291-6.
5. Oates DJ, Berlowitz DR, Glickman ME, Silliman RA, Borzecki AM. Blood pressure and survival in the oldest old. *J Am Geriatr Soc* 2007;55:383-8.

TO THE EDITOR: In his recent Shattuck Lecture on hypertension, Chobanian states, “From the prehypertensive range upward, the effect of blood pressure on cardiovascular risk is progressive and continuous. . . . Thus, patients with prehypertension should be targeted for lifestyle interventions that reduce blood pressure. . . .” Other investigators have even begun to explore the value of treating such patients pharmacologically.¹ Given these characteristics of prehypertension (i.e., increased risk, leading to recommendations for blood-pressure reduction), it is hard to understand what is “pre” about it. I believe that the term is misleading, because it implies that it is solely a precursor of hypertension, but the epidemiologic evidence of added risk shows that it is much more than that. On the basis of these considerations, I suggest that the term “prehypertension” be eliminated and replaced with “stage 1 hypertension,” while bumping up the current stages 1 and 2 to stages 2 and 3.

Aaron Spital, M.D.

Elmhurst Hospital Center
Elmhurst, NY
aspital@att.net

1. Kaplan NM. Prehypertension: is it relevant for nephrologists? *Clin J Am Soc Nephrol* 2009;4:1381-2.

THE AUTHOR REPLIES: As Schwarz indicates, non-adherence to medications is a problem for the control of hypertension and cardiovascular diseases. Approximately half of hypertensive patients discontinue medications in the first 6 to 12 months of therapy; treatment adherence involves not only patients but also clinicians and the quality of their interactions.¹ However, this does not negate

the importance of unhealthy lifestyles in promoting population-wide rises in blood pressure, leading to an increase in the prevalence of hypertension in the United States and most other parts of the world.

Shil raises issues regarding the management of systolic hypertension in elderly patients. Although the control of hypertension in the geriatric population is admittedly an important and complex problem, it was not the focus of the lecture, and space considerations precluded a full discussion of the topic. However, my views on the subject have been summarized in another publication.²

Spital disagrees with the designation of “prehypertension” for persons with blood pressures in the 120–139/80–89 mm Hg range and instead would replace the term with “stage 1 hypertension.” The prehypertension terminology has been the subject of considerable discussion and debate since its introduction in 2003.¹ It identifies persons

who are at greater risk of cardiovascular disease than those who have lower blood pressures.¹ Other than for patients with chronic renal diseases, diabetes, or certain cardiac conditions, no data are yet available for this group regarding the benefits or risks of therapy with antihypertensive drugs. Until such evidence becomes available, it is appropriate to classify such persons as prehypertensive and restrict therapy to appropriate healthy lifestyles that reduce blood pressure and minimize age-related increases.

Aram V. Chobanian, M.D.

Boston University Medical Center
Boston, MA
achob@bu.edu

1. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.

2. Chobanian AV. Isolated systolic hypertension in the elderly. *N Engl J Med* 2007;357:789-96.

COX-2 Inhibitors in Patients with Sensitivity to Nonselective NSAIDs

TO THE EDITOR: Controlled oral challenge is the only definitive way to detect sensitivity to nonsteroidal antiinflammatory drugs (NSAIDs) in patients with adverse reactions to these agents.¹ Patients who have adverse reactions to nonselective NSAIDs have very limited analgesic and antiinflammatory therapeutic options, but several studies have shown that highly selective cyclooxygenase-2 (COX-2) inhibitors can be safely used.²⁻⁴ However, in a small percentage of cases, adverse reactions (respiratory or cutaneous) have been observed during challenge with a COX-2 inhibitor.⁵ When these occur, the next step to be taken is not clear. Can we use another highly selective COX-2 inhibitor as a safe alternative? We present two patients with skin reactions to highly selective COX-2 inhibitors (confirmed by oral challenge) who had no adverse reactions to another COX-2 inhibitor.

The first patient was a 69-year-old man with no history of asthma or atopic disorders who had several episodes of exanthema during treatment with nonselective NSAIDs (ibuprofen, aspirin, diclofenac, and dipyron). A single-blind, placebo-controlled oral challenge with the highly selec-

tive COX-2 inhibitor etoricoxib was carried out in a supervised hospital setting. A nonpruritic exanthem limited to the patient's arms and internal thighs developed 145 minutes after he reached the 60-mg dose. Diphenhydramine and deflazacort were administered orally, with rapid clinical resolution. One week later, a similar oral challenge was performed with 200 mg of celecoxib; no adverse reaction occurred.

The second patient was a 32-year-old woman without asthma in whom a generalized cutaneous rash had previously developed when ibuprofen and dipyron were administered. She underwent a single-blind, placebo-controlled oral challenge with celecoxib, and a non-itching exanthem on her upper limbs developed 60 minutes after she reached the 200-mg dose. A similar oral challenge confirmed that there were no adverse reactions to 60 mg of etoricoxib. Neither patient had an adverse reaction to acetaminophen.

These cases show that choosing another highly selective COX-2 inhibitor may be a safe alternative in patients who have adverse reactions to nonselective NSAIDs and who have previously had an adverse reaction to a first COX-2 inhibitor. They