

Therefore, the results seem consistent with our finding that diabetes risk decreases to the background rate during this time. Second, he suggests that the common practice of introducing BMI into multivariate models that relate smoking to diabetes risk might constitute inappropriate overadjustment for a risk mediator (insofar as smoking-related weight loss might contribute to reduced diabetes risk) that would bias risk estimates upward. We therefore did an additional analysis excluding BMI and waist circumference from the fully adjusted model. This led to a small attenuation in the risk estimates, but the relationship remained graded and statistically significant. Finally, Dr. Onat questions the appropriateness of pooling men and women into a single analysis, because the effects of smoking on weight might differ by sex. We therefore assessed for possible interactions in models with and without BMI and waist circumference. There was no evidence of effect modification by sex in either model. We therefore stand by our pooled approach.

Finally, the comments by Dr. Shriner and colleagues regarding potential changes in eating habits after quitting are well taken. Unfortunately, we cannot test their hypothesis in the ARIC cohort. The ARIC study used a food-frequency questionnaire to collect usual dietary intake, which does not reflect daily eating behavior, but rather long-term dietary patterns. Dr. Shriner and colleagues also recommend checking fasting insulin and CRP levels as part of a postcessation monitoring plan. Although additional assays would provide further information, demographic and clinical factors readily available in the primary care setting without extra cost seem to carry a great deal of predictive information: Older men who were heavy smokers and who gained more weight after quitting have by far the highest risk for diabetes. Physicians and patients should be aware of those risk factors even without additional blood assays.

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Potential Conflicts of Interest: None disclosed.

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Opioids in Management of Chronic Noncancer Pain

This conversation continues on the Web. To read more, go to http://annals.org/content/152/2/123.full/reply#annintmed_el_124279.

TO THE EDITOR: In addition to the overdose and mortality risks from prescription opioids discussed by McLellan and Turner (1), 3 additional opioid-related issues require attention: the possibility that many persons who have overdosed or died of illegally diverted prescription opioids (or heroin) initially became addicted through the use of a legitimate prescription; the prominent role of psychological disorders, which have substantially contributed to the overprescription of opioid analgesics; and the likelihood that extended-release and long-acting opioids carry greater risks for addiction, overdose, and death than shorter-acting agents.

Many persons who overdosed or died of diverted prescription opioids or heroin (obtained either from the street or from friends or

relatives) may have initially been prescribed an opioid for some type of pain, which led to addiction and then to the drug-seeking behaviors associated with this disease. Likewise, many addicted persons who obtain most of their opioids through illegal “doctor shopping” may have developed their addiction through an initial or continued legal prescription for pain medicines. These common situations underscore the importance of prudent, selective prescribing of opioids for specific clinical indications for chronic noncancer pain, with close attention to the risk–benefit ratio and to recently established guidelines, as well as to careful monitoring and knowing when to discontinue or taper these potent brain-active drugs.

As stated by McLellan and Turner, opioid overdose and death were associated with depression, benzodiazepine use, and history of substance abuse. This suggests that many opioid prescriptions are written for chronic noncancer pain in which psychological disorders, such as anxiety syndromes and depressive disorders, are present but often missed. Because psychological comorbid conditions are common in chronic noncancer pain disorders, particularly fibromyalgia (2, 3), treatment with nonopioid agents and nonpharmacologic approaches is indicated, possibly including referral for psychological or behavioral therapies (4).

My observation from clinical practice and as a national disability peer-reviewer in rheumatology is that many patients have undiagnosed or underdiagnosed psychological disorders that have been inadequately addressed by focusing mainly on chronic pain misattributed solely to a somatic structure, such as degenerative discs, arthritis, or muscle tissue (such as in fibromyalgia). These somatic labels then become the indication to prescribe opioids for presumed tissue pain, while the psychological disorders underlying the pain go unrecognized. This predisposes to persistence of symptoms, drug dependence, and continued dysfunction and increases claims for long-term disability. These factors have become a major contributor to the rising health care costs affecting our nation and, unless recognized, will continue to fuel the prescription opioid epidemic and its adverse consequences, including addiction, overdose, and death.

Finally, as noted by the authors, the study by Dunn and colleagues (5) focused on short-acting opioids used by more than 90% of the cohort, but if extended-release and long-acting opioids, such as oxycontin and methadone, had been the main drugs studied, the outcomes would most likely have been worse, especially because oxycodone and methadone have resulted in the highest reported mortality rates (6). We hope to see further studies and discussions about the problems of prescription opioids, which continue to take a large toll on the public health and social systems of our nation.

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Potential Conflicts of Interest: None disclosed.

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TO THE EDITOR: While preparing some reading material for the trainees in pain medicine to whom I give a seminar as part of my clinical faculty teaching, I reviewed the recent editorial by McLellan and Turner (1), written in response to the study by Dunn and colleagues (2). As an addiction medicine specialist and an American Board of Medical Specialties–certified pain specialist, my teaching often focuses on the substance abuse and psychosocial aspects of the therapeutic use of controlled substances.

I will not comment on the cohort study on opioid overdose or the general details of the editorial itself. Both publications make important contributions to the field of pain medicine and public health, and I predict that the issues raised will stimulate thinking and responses that will lead to important academic and policy dialogue. However, the authors should consider modifying the statement that “[p]rescribing opioids at high doses is both dangerous and questionable for indications other than methadone treatment of opioid dependence,” by substituting “can be” for “is.”

Those familiar with the literature on pain medicine (3–6) and the standards of care across the United States (7) know that the statement overreaches and seems to overlook the ostensibly few cases of both malignant and nonmalignant pain in which the appropriate use of high-dose opioids has been both successful and accepted by the medical community and has become an essential part of the practice of medicine for a particular patient. Both the literature and the medical board guidelines emphasize diligent selectivity and continuous and careful monitoring, particularly when the opioid dose is substantial and long-term, but wisely avoid absolute statements that question or label as dangerous a particular clinical practice.

Because this statement has the imprimatur of both the White House Office of National Drug Control Policy and *Annals*, and because adverse consequences may occur both therapeutically and in medicolegal contexts as a result of this statement, I believe it is important to correct it.

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Potential Conflicts of Interest: None disclosed.

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TO THE EDITOR: The editorial by McLellan and Turner (1) states that “Opioid overdose is among the most common causes of death nationwide.” Reference 3 gave a total of 9798 deaths from opioids plus cocaine in 2004. Because some deaths were due to cocaine, the number of opioid deaths was less than 9798. They may have meant the most common cause of accidental deaths or poisoning deaths, but deaths from opioid overdose are certainly not more common than deaths from cancer, heart disease, or stroke.

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Potential Conflicts of Interest: None disclosed.

Reference

1. McLellan AT, Turner BJ. Chronic noncancer pain management and opioid overdose: time to change prescribing practices [Editorial]. *Ann Intern Med.* 2010;152:123-4. [PMID: 20083830]

IN RESPONSE: The remarks from Dr. Gelfand and Dr. Kornfeld exemplify the wide spectrum of opinions about the use of opioids for chronic noncancer pain. Dr. Gelfand questions the use of these drugs in persons with mental health disorders, and Dr. Kornfeld takes issue with our suggestion that high-dose opioids should be avoided. However, Dr. Gelfand accurately emphasizes the high prevalence of comorbid mental health disorders in persons prescribed opioids. In a national population-based community survey (1), persons with a history of mood disorder (such as depression and anxiety disorder) were more than 4 times more likely than persons without such a history to report subsequent opioid treatment. We agree that physicians need to address mental health disorders when treating pain, but we would not deny a potentially beneficial therapy to patients just because they have such a disorder.

In his remarks supporting the use of high-dose opioids, Dr. Kornfeld does not distinguish whether this treatment is for cancer or noncancer pain, but our editorial and the article by Dunn and colleagues (2) concern only noncancer pain. The American Pain Society–American Academy of Pain Medicine Opioids Guidelines Panel stated that “. . . there is little evidence to guide safe and effective prescribing at higher [opioid] doses and there is no standardized definition for what constitutes a ‘high’ dose” (3). The Panel raises serious concerns, as do we, about high-dose opioid therapy (which they define as oral morphine or equivalent, >200 mg/d) because of the risks for diversion, opioid-related adverse effects, changes in health status, and poor adherence to the opioid treatment plan.

If patients require high-dose therapy, the panel recommends using complementary nonopioid therapies to help reduce reliance on opioids and possibly rotating opioids along with dose reductions (3). An American Pain Society–American Academy of Pain Medicine panel identified related research gaps, including, “What are the benefits and harms of high (>200 mg/d of morphine or equivalent) versus lower doses of opioids for chronic noncancer pain?” and “Are high doses of opioids associated with different or unique harms compared with lower doses?” (4). Such fundamental gaps in our knowledge, along with worrisome evidence of serious risks, raise serious questions about the use of high-dose opioids to manage noncancer pain.

Finally, we thank Dr. Reidenberg for his correction. The sentence in our editorial to which he refers should have read, “Opioid overdose is among the most common causes of accidental death nationwide.” This has been corrected in the online version.

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Note: The opinions expressed here do not necessarily represent those of the White House Office of National Drug Control Policy.

Potential Conflicts of Interest: None disclosed.

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CLINICAL OBSERVATION

Bilateral Necrosis of Earlobes and Cheeks: Another Complication of Cocaine Contaminated With Levamisole

Background: Levamisole is a veterinary antihelminthic agent that has also been used as an immunomodulating agent to treat cancer, autoimmune diseases, and the nephrotic syndrome. It has been shown to cause neutropenia and vasculitis (1–3). The practice of cutting cocaine with levamisole has been increasing since 2005, and in 2009, 70% of cocaine seized at U.S. borders contained levamisole (4). Recent reports (4, 5) have implicated levamisole as a cause of

neutropenia in cocaine abusers. Two cocaine abusers with similar cases of neutropenia and vasculitis presented to the University of Rochester Medical Center, New York, within 8 days of each other. We hypothesize that cocaine contaminated with levamisole may cause not only neutropenia but also vasculitis.

Case Report: The first patient was a 57-year-old woman who presented with 2 days of worsening cutaneous lesions, fevers, chills, arthralgias, and flare-ups of recurrent *Staphylococcus aureus* boils. She had no significant medical history except for smoking cocaine, with her last use 4 days before presentation. On examination, she had tender palpable purpuric plaques on both cheeks and ear lobes with central areas of necrosis (Figure).

On the day of admission, the patient’s absolute neutrophil count was 2.3×10^9 cells/L; within 48 hours, it dropped to 0.5×10^9 cells/L. Anticardiolipin IgM levels were low- to medium-positive. Perinuclear antineutrophil cytoplasmic antibody (P-ANCA) was positive (titer > 1:2560). Further work-up for hematologic and rheumatologic disorders was negative. Histopathologic examination of her right cheek lesion showed organizing thrombi in small-caliber vessels associated with perivascular lymphocytic inflammatory cell infiltrates; these findings were consistent with a thrombotic disorder and would be less likely with small-vessel vasculitis. The skin lesions resolved spontaneously, and neutropenia was corrected by treatment with filgrastim.

The second patient was a 22-year-old woman who presented with 2 weeks of a painful rash on her face, ears, legs, thighs, and buttocks. Her medical history was significant for cocaine abuse. Examination revealed many exquisitely tender erythematous plaques with central necrosis on her thighs, lower extremities, and buttocks. Her cheeks had erythematous plaques, and her nose had a prominent necrotic lesion on an erythematous base.

Laboratory data showed an absolute neutrophil count less than 1.0×10^9 cells/L. Her P-ANCA results were positive (titer, 1:2560). Anticardiolipin IgM antibody and plasma serine IgM levels were elevated. Complement and protein C and S levels were moderately low. Results of further work-up for hematologic and rheumatologic disorders were negative. Toxicology screening was positive for cocaine.

A skin biopsy showed small-vessel vasculitis with associated multiple intravascular thrombi consistent with leukocytoclastic vasculitis. The patient was treated with steroids, and her lesions and neutropenia improved rapidly.

Discussion: Both patients presented with a clinical, histologic, and immunologic profile typical of levamisole toxicity. Although levamisole levels were not obtained, exposure is very likely because 70% of cocaine is contaminated by levamisole (4). Levamisole has serious side effects, such as bone-marrow suppression; skin reactions, including cutaneous vasculitis, are less frequent. Vasculitis has a very distinct presentation, with purpuric lesions preferentially involving the ear lobes and an association with anticardiolipin and P-ANCA levels similar to the presentation of our patients. Histologic examination of the skin lesions shows a vasculopathic reaction pattern ranging from leukocytoclastic and thrombotic vasculitis to vascular occlusive disease without true vasculitis (2, 3). Spontaneous resolution occurs by discontinuing levamisole use.

Conclusion: Clinicians should suspect exposure to cocaine contaminated with levamisole in patients presenting with both neutropenia and necrotic skin lesions. Testing for levamisole in urine and