ONLINE FIRST

Opioid Dose and Risk of Road Trauma in Canada

A Population-Based Study

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Background: Use of opioids may predispose drivers to road trauma, yet the effect of opioid dose on this association is unknown.

Methods: We conducted a population-based nested case-control study of patients aged 18 to 64 years who received at least 1 publicly funded prescription for an opioid from April 1, 2003, through March 31, 2011. Cases were defined as having an emergency department visit related to road trauma. Patients without road trauma served as a control group matched to cases by age, sex, index year, prior road trauma, and a disease risk index. We compared the risk of road trauma among patients treated with doses of opioids ranging from very low to very high (<20 to ≥200 morphine equivalents daily). In a subgroup analysis, we stratified our analysis by driver status.

Results: Among 549 878 eligible adults, we identified 5300 cases with road trauma and matched an equal number of controls. Multivariate adjustment yielded no significant association between escalating opioid dose and odds of road trauma (adjusted odds ratio ranged between 1.00 and 1.09). However, a significant association between opioid dose and road trauma was observed among drivers. Compared with very low opioid doses, drivers prescribed low doses had a 21% increased odds of road trauma (adjusted odds ratio, 1.21 [95% CI, 1.02-1.42]); those prescribed moderate doses, 29% increased odds (1.29 [1.06-1.57]); those prescribed high doses, 42% increased odds (1.42 [1.15-1.76]); and those prescribed very high doses, 23% increased odds (1.23 [1.02-1.49]).

Conclusions: Among drivers prescribed opioids, a significant relationship exists between drug dose and risk of road trauma. This association is distinct and does not appear with passengers, pedestrians, and others injured in road trauma.

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ROAD TRAUMA AND THE TOXIC effects of prescription drugs represent 2 leading causes of accidental death in North America,[1,2] resulting in substantial avoidable public health and economic losses. In 2009, 2.3 million adults in the United States attended the emergency department (ED) for a motor vehicle crash, and 475 000 visited the ED for reasons related to misuse and abuse of prescription painkillers.[3,4] During the past 2 decades, several studies investigating the effects of prescription medications on driving performance have highlighted how these drugs can influence reaction time, cognition, and concentration in simulated driving situations.[5-7] Although the potential effects of opioids on driving ability are of particular concern given their increasing use and misuse, major gaps persist in understanding the impact of opioid dose, concomitant medication use, and opioid formulation.[8]

Opioid-related drug overdoses are becoming increasingly prevalent, amounting to more than 40% of deaths due to drug overdoses in the United States.[1] Opioids can interfere with attention and impair reaction time,[9,10] leading to concerns regarding impaired driving performance. However, 2 small randomized controlled trials of driving simulations found no significant effect

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of opioids on driving performance, reaction time, or cognition,[5,6] although 1 study suggested that patients receiving opioids experienced reduced alertness and increased sedation while driving.[5] Furthermore, several small observational studies indicate a moderate but significant increased risk of road trauma among drivers prescribed opioids compared with controls,[11-13] whereas other studies show no such association.[14-16] How these divergent observa-

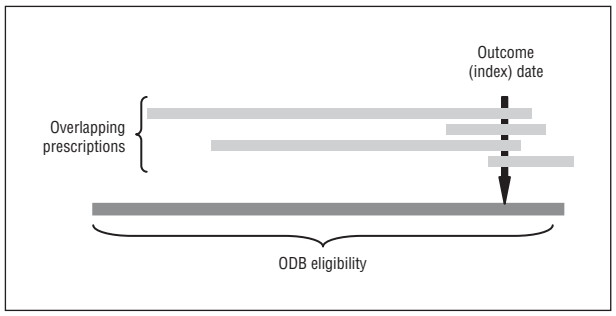

Figure 1. Study design. The definition of opioid dose was based on all prescriptions dispensed to cases and control subjects with a prescribed treatment duration that overlapped their index date. For each study subject, the total daily dose (converted into morphine equivalents) for each overlapping prescription was summed to generate a total prescribed daily dose. Eligibility in the Ontario Drug Benefit (ODB) database was defined as a minimum of 180 days before the index date.

tions translate to driver performance outside of a controlled experimental setting, at a population level, remains unknown.

Although the association between opioid use and risk of road trauma is disputed, no studies have investigated whether the opioid dose may explain these inconsistencies. This distinction is particularly timely given recent evidence indicating that opioids are being prescribed at increasingly high doses.[17] For example, more than one-quarter of patients prescribed publicly funded long-acting opioids in Ontario in 2008 received doses exceeding 200 mg of morphine (or the equivalent),[17] a threshold identified as important in clinical guidelines.[18,19] Therefore, we sought to characterize the relationship between opioid dose and risk of road trauma among patients receiving public drug coverage in Ontario, Canada.

METHODS

SETTING

We conducted a population-based nested case-control study of Ontario adults aged 18 to 64 years who were eligible for prescription drug coverage under the Ontario Provincial Public Drug Program and who were prescribed opioid analgesics from April 1, 2003, through March 31, 2011. All residents of Ontario receive publicly funded physician and hospital care. The study protocol was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

DATA SOURCES

We used the Ontario Drug Benefit database to identify all prescription medications dispensed to eligible residents of Ontario. Eligibility criteria for drug coverage among adults aged 18 to 64 years included unemployment, disability, high prescription drug costs relative to net household income, or receipt of home care services. We used the Discharge Abstract Database of the Canadian Institute for Health Information to identify inpatient hospitalizations and the National Ambulatory Care Reporting System to identify ED visits. Claims for physicians' services (including palliative care services) were obtained from the Ontario Health Insurance Plan database. Finally, we used the Institute for Clinical Evaluative Sciences Physician Database to determine physician specialty and the Registered Persons Database to define patient demographic information.

IDENTIFICATION OF PATIENTS AND OUTCOMES

Opioids included in the exposure definition in this study were oral formulations of codeine, morphine sulfate, oxycodone or hydromorphone hydrochloride, and transdermal fentanyl patches. We did not include prescriptions for injectable opioids and rarely used drugs such as anileridine, levorphanol tartrate, meperidine hydrochloride, oxymorphone hydrochloride, pentazocine, propoxyphene, or methadone in our calculation of opioid dose. Methadone was not included because it is most often prescribed in Ontario for opioid addiction rather than pain, and hydrocodone was not included because its oral formulation is not covered by the public drug plan in Ontario.

Cases were defined as patients who visited an ED with an external cause of injury related to road trauma (codes V00 to V89 from the *International Statistical Classification of Diseases, 10th Revision*) during the study period. This definition includes drivers, passengers, pedestrians, and patients in miscellaneous positions (eg, bicyclists or unknown location). Details of these codes and the stratification by patient position can be found in eTable 1 (http://www.jamainternalmed.com). The date of the ED visit served as the index date for cases. If these patients had multiple incidents of road trauma during the study period, only the first event was considered in the analyses. Potential controls were selected as those individuals who did not attend an ED with road trauma during our study period. The temporal distribution of the index dates for all cases was determined. To ensure that cases and controls were similarly dispersed over time, each potential control was assigned an index date at random such that the temporal distribution of index dates among controls mirrored that of the cases.

Cases and controls were eligible for inclusion only if they had at least 6 months of continuous eligibility for public drug coverage before their index date and at least 1 opioid prescription with a duration that overlapped their index date. Cases and controls were excluded if they had invalid patient identifiers, had missing information about age or sex, received palliative care services in the 6 months before their index date, lived in a long-term care home at the index date, or had a prescription for a nonstudy opioid with a duration that overlapped the index date.

We developed a disease risk index for all cases and potential controls to generate predicted probabilities of road trauma. This index was based on measured demographic characteristics, medical disorders, and psychiatric conditions (eTable 2). The components of this risk score have been published previously.[20] We selected 1 control for each case using incidence density sampling.[21] Cases were matched to controls by sex, age (within 3 years), index year (within 1 year), ED visit for road trauma in the past year, and disease risk index (within 0.2 SD). Cases with no matched controls were excluded from analyses.

EXPOSURE DEFINITION

Computerized medication records were used to identify all prescriptions for study opioids with a duration that overlapped the patient's index date (**Figure 1**). The daily dose for each prescription was defined as the total number of pills dispensed multiplied by the strength of the pill in milligrams and divided by the total days' supply of the prescription. The daily dose was converted to morphine equivalents (MEQ) using the morphine equivalence ratios defined by the Canadian National Opioid Use Guideline Group,[19] and each patient's total opioid exposure was defined as the sum of all opioid prescriptions overlapping the index date. The primary analysis stratified the

average daily dose at the index date into the following 5 categories: very low (<20 MEQ), low (20-49 MEQ), moderate (50-99 MEQ), high (100-199 MEQ), and very high (≥200 MEQ). In a secondary analysis, we defined new users of opioids as those whose first prescription for an opioid during the study period occurred in the 14 days before their index date.

STATISTICAL ANALYSIS

We summarized patient characteristics using descriptive statistics and compared cases and controls using standardized differences. A standardized difference greater than 0.10 was defined as a meaningful difference.[22] We used conditional logistic regression to examine the relationship between opioid dose and the odds of an ED visit for road trauma. The category of very low dose was used as the reference group. In a subgroup analysis, we stratified cases into drivers and nondrivers visiting the ED for road trauma, assuming that drivers might have the strongest association with road trauma risk. In a sensitivity analysis to test the robustness of our findings, we used logistic regression to examine the relationship between dose and road trauma in our entire cohort of cases and controls before matching.

We adjusted all models for a variety of potential confounders, including age, past hospitalization or physician visit for alcoholism, past ED visits for alcoholism, past medication use (selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines, and other depressants of the central nervous system, separately), total number of drugs dispensed in the past 180 days, and numbers of physician and ED visits in the past year. Furthermore, duration of publicly funded opioid use was included in all models and was defined as the period from the patient's first opioid prescription in our records (starting April 1, 1990) and the index date. This duration does not include any prior use of opioids that was not covered by the provincial public drug program. All analyses were performed using commercially available statistical software (SAS, version 9.2; SAS Institute Inc) and used a type I error rate of .05 as the threshold for statistical significance.

RESULTS

A total of 549 878 patients aged 18 to 64 years were dispensed at least 1 opioid during the 8-year study period. Among these patients, we identified 85 441 ED visits for road trauma. After applying exclusion criteria, 6006 cases were eligible for our study (**Figure 2**); of these, 5300 (88.25%) were matched with a control. Among eligible cases, 2428 (45.81%) were drivers, 840 (15.85%) were passengers, 579 (10.92%) were pedestrians, and 1453 (27.42%) were in unknown or miscellaneous positions.

Overall, cases were similar to controls with respect to several important demographic and comorbid characteristics (**Table**). However, cases included patients who, in the preceding year, visited the ED more frequently and were more likely to have visited an ED for alcohol-related reasons. Furthermore, most of the patients in each group had averaged at least 1 visit to a physician monthly during the year before the index date.

In our primary analysis, we found no association between escalating opioid dose and odds of road trauma (**Figure 3**), with adjusted odds ratios ranging from 1.00 to 1.09 for each dose category compared with patients prescribed very low doses of opioids. However, in a subgroup analysis of drivers, we found significantly increased odds of road trauma among patients prescribed low, moderate, high, and very high opioid doses. Compared with patients prescribed very low opioid doses, those prescribed low and moderate doses had a 21% and 29% increased odds of road trauma, respectively (adjusted odds ratios, 1.21 [95% CI, 1.02-1.42] and 1.29 [1.06-1.57], respectively). Similarly, patients prescribed high and very high doses of opioids had a 42% and 23% increased odds of road trauma, respectively, when compared with patients prescribed very low doses (adjusted odds ratios, 1.42 [95% CI, 1.15-1.76] and 1.23 [1.02-1.49], respectively). As expected, we found no association between opioid dose and risk of road trauma among nondrivers. The results of our sensitivity analysis were consistent with those of our primary matched analysis (eTable 3 and eFigure for full results).

An analysis of new opioid users found no significant difference in risk of road trauma between individuals who initiated opioid therapy in the prior 2 weeks compared with longer-term users of opioids (adjusted odds ratio, 1.33 [95% CI, 0.84-2.12]).

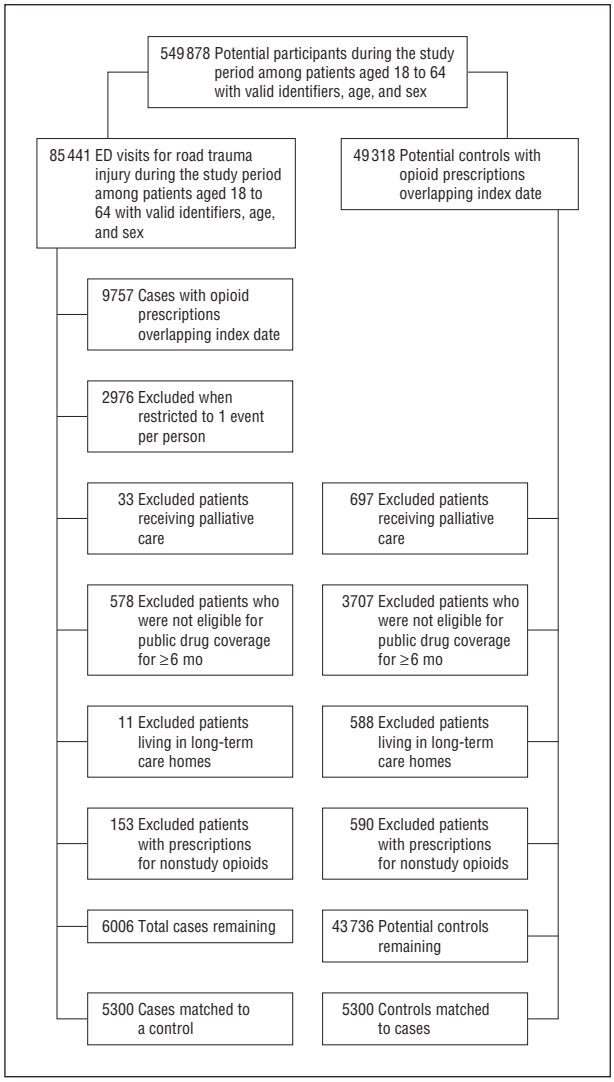

Figure 2. Exclusion criteria applied to cases and potential control subjects. ED indicates emergency department.

Table. Characteristics of Cases and Matched Control Subjects[a]

Characteristic	Cases (n = 5300)	Controls (n = 5300)	Standard Difference
Demographics			
Age, mean (SD), y	45.76 (9.86)	45.75 (9.85)	0
Male sex	2725 (51.42)	2725 (51.42)	0
Income quintile			
1	2280 (43.02)	2292 (43.25)	0.01
2	1286 (24.26)	1305 (24.62)	0.01
3	737 (13.91)	720 (13.58)	0.01
4	560 (10.57)	552 (10.42)	0.01
5	404 (7.62)	399 (7.53)	<0.01
Missing	33 (0.62)	32 (0.60)	<0.01
Urban residence	4439 (83.75)	4451 (83.98)	0.01
ODB plan coverage			
Social assistance	1169 (22.06)	1113 (21.00)	0.03
Disability support	3601 (67.94)	3528 (66.57)	0.03
Other	530 (10.00)	659 (12.43)	0.08
Charlson Comorbidity Index			
No hospitalization	3273 (61.75)	3328 (62.79)	0.02
0	1242 (23.43)	1187 (22.40)	0.03
1	363 (6.85)	335 (6.32)	0.02
≥2	422 (7.96)	450 (8.49)	0.02
Duration of opioid use, mean (SD), y	7.09 (3.67)	6.84 (3.72)	0.07
Comorbidity measures in past 1 y			
ED visit for alcohol abuse	287 (5.42)	147 (2.77)	0.13
ED visit for road trauma	332 (6.26)	332 (6.26)	0
ED visit for drug toxicity	212 (4.00)	155 (2.92)	0.06
Total No. of ED visits, mean (SD)	3.93 (5.40)	2.07 (4.48)	0.38
Total No. of physician visits, median (IQR)	21 (12-36)	21 (12-36)	0.01
Total No. of visits to a family physician, median (IQR)	13 (7-20)	12 (6-19)	0.04
Visit to a psychiatrist	1021 (19.26)	1030 (19.43)	<0.01
Medication use in past 180 d			
No. of drugs dispensed, median (IQR)	11 (7-16)	11 (7-16)	0.07
SSRIs	1959 (36.96)	1963 (37.04)	<0.01
Other antidepressants	1783 (33.64)	1842 (34.75)	0.02
Antipsychotics	898 (16.94)	886 (16.72)	0.01
Benzodiazepines	2764 (52.15)	2649 (49.98)	0.04
Other CNS depressants	344 (6.49)	381 (7.19)	0.03
Comorbidity measures in past 3 y			
Hospitalization for poisoning or drug toxicity	991 (18.70)	971 (18.32)	0.01
Alcohol abuse	646 (12.19)	661 (12.47)	0.01
Affective disorder	590 (11.13)	541 (10.21)	0.03
Anxiety or sleep disorder	3694 (69.70)	3700 (69.81)	<0.01
Psychosis	406 (7.66)	404 (7.62)	<0.01
Other mental disorder	3026 (57.09)	2986 (56.34)	0.02
Injury	291 (5.49)	324 (6.11)	0.03
Osteoarthritis	1951 (36.81)	1912 (36.08)	0.02
Rheumatoid arthritis	334 (6.30)	356 (6.72)	0.02

Abbreviations: CNS, central nervous system; ED, emergency department; IQR, interquartile range; ODB, Ontario Drug Benefit; SSRIs, selective serotonin reuptake inhibitors.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

COMMENT

In this population-based study spanning 8 years, we did not find an association between opioid dose and the risk of road trauma among adults younger than 65 years and eligible for public drug coverage. However, after restricting our analysis to drivers, we found that prescribed daily doses exceeding 20 MEQ were associated with a 21% to 42% increased odds of road trauma. Together, these findings agree with past studies suggesting that increasing opioid doses can impair drivers and contribute to risk of road trauma.[5,10-13]

We found that, compared with patients receiving very low opioid doses, the odds of road trauma among drivers in the highest dose category were slightly more attenuated than in the high-dose category. Although this finding is difficult to explain, risks might be attenuated at the extremes for several reasons, such as an increased likelihood of medication diversion in this subgroup or physiologic opioid tolerance among patients who undergo long-term treatment at a fixed dose that may offset the detrimental effects of these drugs on driver performance.[10] Therefore, our observed attenuation of risk at the extremes may reflect behavioral or biological explanations.

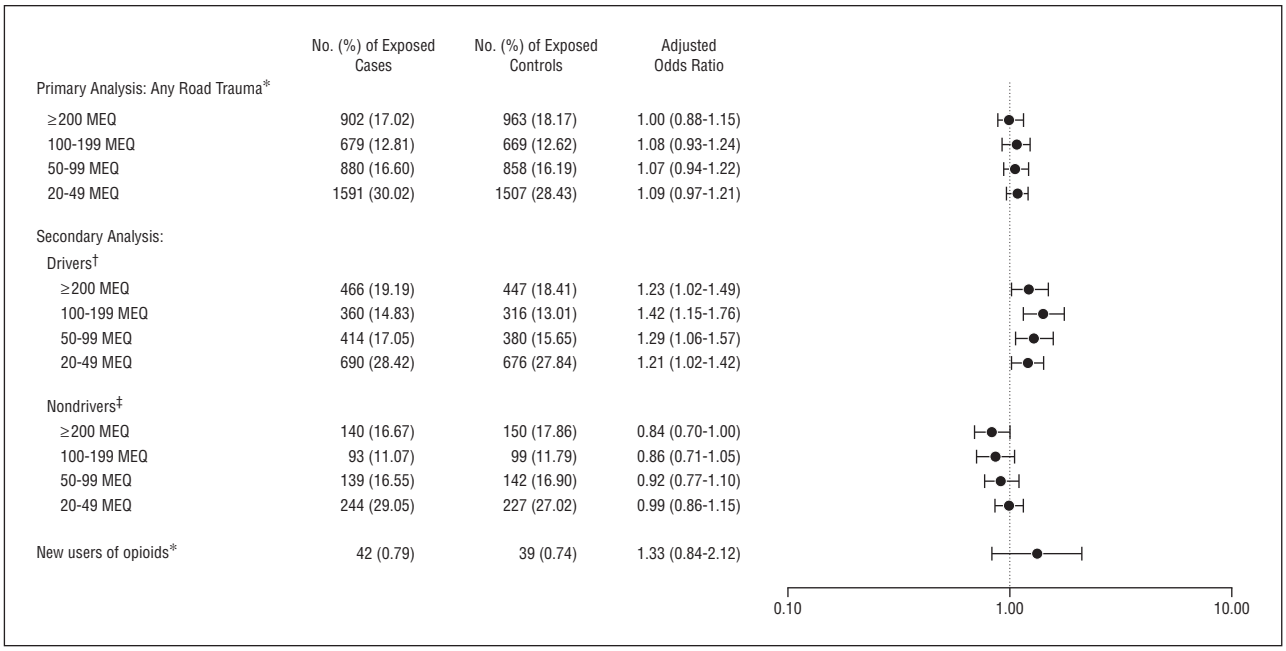

Figure 3. Association between opioid dose and road trauma, adjusted for age, past (3 years) hospitalization for alcoholism, past (1 year) emergency department (ED) visit for alcoholism, duration of opioid treatment, medication use in past 180 days (ie, selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines and other depressants of the central nervous system, separately), number of drugs dispensed in the past 180 days, and numbers of physician and ED visits in the past 1 year. For all comparisons, the reference group includes those who received an opioid dose of 1 to 19 mg of morphine or equivalent (MEQ). *Includes 5300 cases and controls. †Includes 2428 cases and controls. ‡Includes 840 cases and controls.

Several limitations of our study merit discussion. First, our population was restricted to younger adults eligible for public drug coverage in Ontario. This constitutes a socioeconomically disadvantaged population, and our findings may not be generalizable to individuals with higher socioeconomic status, older adults, and other jurisdictions. Second, we cannot determine the indication for opioid therapy and thus cannot elucidate how pain severity influenced our findings. Third, we have no information regarding access to motor vehicles or the frequency of driving among patients in our cohort. Fourth, our definition of road trauma has not been validated; therefore, we may not have identified all ED visits related to road trauma during our study period. Fifth, we defined opioid dose on the basis of publicly funded prescriptions, and we do not know how unused prescription drugs, drugs prescribed to be used as needed, illegal drug diversion, quantities obtained illicitly, or drugs paid for privately would influence our calculations. All of these limitations likely serve to attenuate our findings, particularly among patients receiving the highest doses. Finally, it is possible that adverse selection, that is, the tendency for patients with substance abuse disorders and mental health conditions to receive long-term opioid therapy, might have influenced our findings.[23] Although we attempted to address this by adjusting for various factors in our models, this selection among users of high-dose opioids may contribute to the dose-response relationship observed in this study.

In summary, although the relationship between the use of opioids and risk of road trauma has been described frequently in small samples, this study is the first, to our knowledge, to demonstrate the relationship between opioid dose and this risk among drivers in a population-based setting. Our findings have important implications in clinical practice and suggest that physicians may want to warn patients about potentially decreased driving ability when escalating to high opioid doses, particularly before acclimation to a fixed dose develops. Furthermore, policy makers could improve public education surrounding the potential risks of opioid medications and could consider restricted drivers' licenses for patients treated with high-dose opioids.

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Author Contributions: Ms Gomes had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Gomes, Redelmeier, Juurlink, Dhalla, Camacho, and Mamdani. *Acquisition of data:* Gomes. *Analysis and interpretation of data:* Gomes, Redelmeier, Juurlink, Dhalla, Camacho, and Mamdani. *Drafting of the manuscript:* Gomes. *Critical revision of the manuscript for important intellectual content:* Redelmeier, Juurlink, Dhalla, Camacho, and Mamdani. *Statistical analysis:* Gomes and Redelmeier. *Obtained funding:* Gomes, Juurlink, and Mamdani. *Administrative, technical, and material support:* Mamdani. *Study supervision:* Redelmeier.
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Online-Only Material: The eTables and eFigure are available at http://www.jamainternalmed.com.
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