ONLINE FIRST

Nocturnal Leg Cramps and Prescription Use That Precedes Them

A Sequence Symmetry Analysis

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Background: The use of diuretics, statins, and inhaled long-acting β2-agonists (LABAs) is linked to muscle cramps but largely by anecdotal evidence. This study sought population-level data to better evaluate these associations.

Methods: Linked health care databases containing prescribing information (December 1, 2000, to November 30, 2008) about 4.2 million residents of British Columbia, Canada, were evaluated using sequence symmetry analysis to determine in adults 50 years or older whether new quinine prescriptions (initiations of cramp treatment) increase in the year following diuretic, statin, or LABA starts. The statistic of interest was the sequence ratio: the number of quinine starts in the year following index drug introduction compared with the number of quinine starts in the preceding year (adjusted for age and time trends in population prescribing).

Results: Adjusted sequence ratios (95% CIs) for the 3 drug classes were 1.47 (1.33-1.63 [$P<.001$]) for diuretics, 1.16 (1.04-1.29 [$P=.004$]) for statins, and 2.42 (2.02-2.89 [$P<.001$]) for LABAs. For diuretic subclasses, adjusted sequence ratios (95% CIs) were 2.12 (1.61-2.78 [$P<.001$]) for potassium sparing, 1.48 (1.29-1.68 [$P<.001$]) for thiazidelike, and 1.20 (1.00-1.44 [$P=.07$]) for loop. For LABA subclasses, adjusted sequence ratios (95% CIs) were 2.17 (1.56-3.02) for LABAs alone and 2.55 (2.06-3.12) for LABAs-corticosteroids ($P<.001$ for both).

Conclusions: Cramp treatment was substantially more likely in the year following introduction of LABAs, potassium-sparing diuretics, or thiazidelike diuretics, and 60.3% of quinine users (individuals experiencing cramp) received at least 1 of these medications during a 13-year period. In contrast, statin and loop diuretic associations were small. Physicians should be mindful that the use of these medications may worsen symptoms in patients experiencing nocturnal leg cramps.

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NOCTURNAL LEG CRAMPS (also called *rest cramps*) are painful involuntary muscle contractions, typically in the legs or feet, that occur during prolonged rest and often disrupt sleep. They are common among older persons (37%-50% prevalence), and some individuals experience multiple such painful wakenings nightly.[1,2] Despite the high prevalence of the condition, common treatments are discouraged by multiple governmental drug regulatory bodies based on safety concerns (in the case of quinine)[3-5] or have been proven ineffective (prophylactic stretching and the use of magnesium supplements).[6,7]

Adverse drug effects often go unrecognized[8] and can result in additional prescribing (the prescribing cascade) intended to deal with adverse effects that might be better addressed by reduction, substitution, or discontinuation of the offending agent. Muscle cramping has been linked to the use of various common medications, but evidence supporting these associations is weak.[9-14] More reliable information and better awareness of which drugs might promote muscle cramping would be useful when individualizing the therapy of older persons, who are prone to both polypharmacy use and rest cramps.

The 3 most commonly prescribed medication classes with a potential link to cramping are diuretics, statins, and inhaled long-acting β2-agonists (LABAs). Our primary objective was to determine whether treatment for muscle cramps increased in the year following introduction of 1 of these common drug classes. Because quinine is commonly prescribed in Canada and used almost exclusively to treat rest cramps, we were able to apply the novel method of prescription sequence symmetry analysis to detect any changes in cramp treatment associated with the use of these drugs. Our secondary objectives were to explore for heterogeneity of effect across the 3 main di-

uretic subclasses (potassium sparing, thiazidelike, and loop) and the 2 main LABA subclasses (LABAs alone and LABAs-corticosteroids).

METHODS

DESIGN

An innovation of this study was the use of sequence symmetry analysis[15] to evaluate individuals starting, within a year of each other (in either order), prescriptions for both quinine and 1 of 3 index drug classes being investigated for cramp association (index drugs). Sequence symmetry analysis exploits the fact that, if no relationship exists between 2 drugs, recipients of both should be equally likely to receive them in either order. In contrast, if one drug causes a symptom that the other treats, the causal drug will more often be prescribed first. Sequence order is largely independent of time-invariant patient characteristics; hence, sequence symmetry analysis helps control for many potential confounders (eg, age, sex, comorbidity, and polypharmacy use). Most important, this technique helps control for unrecognized but important patient characteristics that might unknowingly unbalance cohorts constructed to answer the same question.

We compared the number of individuals in whom quinine use followed their use of the index drug (ie, the potentially causal sequence) with the number of individuals in whom quinine use preceded it (the noncausal sequence). This was done by dividing the number of pairs with "quinine following" by the number of pairs with "quinine preceding" to create the crude sequence ratio. If prescribing rates are constant and if there is no relationship between the drugs, we expect a crude sequence ratio of 1; if there is a causal relationship, we expect a crude sequence ratio exceeding 1.

Because prescribing rates can vary with time, fluctuations in population prescribing also need consideration. For instance, a drug increasing in use would be expected to occur second more often simply because prescriptions for it are more frequent in the later period. Sequence symmetry analysis accounts for this by calculating the null ratio, the expected crude sequence ratio if there is no relationship, based on the overall prescribing of both drugs in the population at large. The crude sequence ratio is then divided by the null ratio to create the adjusted sequence ratio (ASR), which accounts for fluctuations in population prescribing. Although the null ratio usually uses all prescriptions in the database, we stratified it by year of birth; that is, the index first probability of each participant was calculated using only persons in the population at large who were the same age. Details about construction of the null ratio are given online in eAppendix A (http://www.archinternmed.com).

The sequence ratio is best conceptualized as the rate of events in exposed individuals compared with what would be expected for a similar unexposed population (ie, the same individuals in the year before the exposure). This is essentially a relative risk, and the 2 measures can be shown to approximate each other under certain conditions (eAppendix B).

SETTING

Pharmacists in British Columbia, Canada, are required to enter all prescriptions dispensed, independent of payer, into the provincewide PharmaNet database, providing drug use data with minimal underreporting or misclassification.[16,17] The British Columbia Ministry of Health also maintains linkable data on all physician services and hospitalizations for all individuals in its publicly funded health care system. These 2 databases, along with Medical Services Plan registration data and vital statistics data on the date of death, were linked for the period January 1, 1996, to June 23, 2009, and comprised our source data. We did not have permission to use data from the 4% of the population who are federally insured (military personnel, aboriginals, and prisoners). The source population consisted of 4.2 million residents of British Columbia.

On November 30, 2000, quinine ceased to be available without a physician's prescription in British Columbia. To ensure that new PharmaNet prescriptions were true starts and not renewals of over-the-counter (previously unrecorded) quinine use, we limited our analysis to new quinine prescriptions dispensed at least 1 year after the date of the mandatory prescription status of quinine. Therefore, the earliest eligible quinine prescription was on December 1, 2001.

To avoid the possibility of seasonal bias, we analyzed data in multiples of 1 year so that all months of the year were equally represented. Because we required 2 years of index data following the last eligible quinine start (1 year to see if the index drug was prescribed and another year to see if it was renewed), the last date for eligible quinine starts was November 30, 2006.

POPULATION

Study Size

Study size was based on the number of eligible cases. This number was obtained from the PharmaNet database.

Inclusion Criteria

Inclusion criteria were the following: (1) age 50 years or older (nocturnal leg cramps are uncommon in younger adults, and young persons with nocturnal leg cramps may have a higher proportion of neurodegenerative disorders); (2) receipt of a first-ever prescription for quinine between December 1, 2001, and November 30, 2006, inclusive; (3) receipt of a first-ever prescription of 1 of 3 classes of index drugs within 1 year of (before or after) the start of quinine; (4) renewal of the index drug within 1 year of its start date (to help ensure that the prescription was used); and (5) evidence within the Ministry of Health databases that the patient received medical services over a period at least 2 years before and at least 2 years after the quinine start date.

Evidence of at least 2 years of medical services before the quinine start date was required to ensure that new residents or transients through the province were not filling renewal prescriptions that falsely seemed to be new starts (because they were new to the province). The 2-year data period after the quinine start date ensured full opportunity for index drug prescription and renewal. We used services rendered, rather than registration data, to determine whether patients were resident in the province, as individuals beginning to live abroad might not immediately cancel their provincewide medical plan coverage.

Exclusion Criteria

Exclusion criteria were physician diagnostic coding or procedural billing indicating malaria, dialysis, or amyotrophic lateral sclerosis at any point in the data record. This eliminated potential quinine users who did not have nocturnal leg cramps.

Switching Within a Drug Class

Patients at times switch between different drugs within a class (eg, switching between statins if there were adverse effects). We counted only the first renewed prescription within a class for the purpose of our analysis. Hence, if an individual started taking

Table 1. Breakdown of Index Drugs Used in Sequence Symmetry Analysis

Index Drug	No. (%)
Diuretics (n=1590)	
Loop	**407** (25.6)
Furosemide	406 (99.8)
Ethacrynate sodium	1 (0.2)
Thiazidelike	**977** (61.5)
Hydrochlorothiazide	971 (99.4)
Indapamide	6 (0.6)
Potassium sparing	**206** (13.0)
Triamterene-hydrochlorothiazide	119 (57.8)
Spironolactone	46 (22.3)
Amiloride hydrochloride–hydrochlorothiazide	34 (16.5)
Spironolactone-hydrochlorothiazide	7 (3.4)
LABAs (n=576)	
LABA alone	**137** (23.8)
Salmeterol	65 (47.4)
Terbutaline sulfate	39 (28.5)
Formoterol fumarate	32 (23.4)
Fenoterol	1 (0.7)
LABA-corticosteroid	**439** (76.2)
Salmeterol–fluticasone propionate	291 (66.3)
Formoterol fumarate–budesonide	148 (33.7)
Statins (n=1326)	
Atorvastatin calcium	876 (66.1)
Simvastatin	258 (19.5)
Rosuvastatin calcium	142 (10.7)
Pravastatin sodium	38 (2.9)
Lovastatin	6 (0.5)
Fluvastatin sodium	6 (0.5)

Abbreviation: LABA, inhaled long-acting β2-agonist.

pravastatin sodium (with renewal) and then changed to atorvastatin calcium, the atorvastatin prescription was not considered a new start and was excluded from our analysis. Similarly, any loop diuretic prescription after a renewed thiazide prescription was excluded. Only the first renewed diuretic start was eligible. We did not consider salbutamol (albuterol) to be a LABA, and preceding prescriptions for salbutamol did not exclude subsequent LABA starts. Cerivastatin sodium was withdrawn from the Canadian market in August 2001 because of an association with rhabdomyolysis. Because the first eligible quinine prescription was December 1, 2001, we excluded anyone from the statin analysis if his or her first renewed statin was cerivastatin.

Combination Products

Many drugs are available as combination products. For each analysis, we excluded all combination products and combination first users. The exception to this was potassium-sparing diuretics, most of which are prescribed in Canada in combination with a thiazide. Therefore, the subclass of potassium-sparing diuretics in our analysis includes potassium-sparing diuretics with or without a combined thiazide. The breakdown of specific index drugs included in the analysis is given in **Table 1**.

BIAS

Confounders in sequence symmetry analysis are prescribing influences that vary over time or link prescribing order in ways other than those hypothesized.[15] We corrected for trends in prescribing that vary with time, age, and aging (during the 2-year window of observation surrounding the quinine start date) using the birth year–stratified null ratio. In addition, quinine shares no common indications or contraindications with the index drugs that should affect prescribing order (ie, no first-line drugs preceding second-line drugs or avoidance of one drug because another is in use).

However, it is conceivable that the indication for an index drug (eg, leg edema as an indication for diuretics) might also be an unrecognized trigger for cramps. If patients are consistently quicker to seek treatment for 1 of these indications (eg, faster to treat edema than cramps), then an association (in either direction) could be produced. As well, if 1 of 2 drugs is more likely to lead to follow-up visits, then increased physician contact following initiation of that drug could give greater opportunity for discussion and prescription of the other study drug. Although this could occur in either direction, drugs with a greater expectation of planned follow-up visits, such as statins and antihypertensives (eg, diuretics), might be expected to have an increase in subsequent quinine prescribing because of greater prescriber contact.

STATISTICAL ANALYSIS

The primary outcome measure of this study was the sequence order of index quinine starts, and the primary statistic of interest was the ASR. We calculated sequence ratios for the 3 main index drug classes (diuretics, statins, and LABAs), the 3 main diuretic subclasses (potassium sparing, thiazidelike, and loop), and the 2 main LABA subclasses (LABAs alone and LABAs-corticosteroids).

The CIs were created using bootstrap resampling methods.[18] Specifically, 10 000 bootstrap samples of the ASR were created by (1) bootstrapping (resampling with replacement) all observed index quinine pairs to produce 10 000 crude sequence ratios and (2) bootstrapping all in-range (ie, within 1 year of the quinine prescription being matched), same-age population index starts to produce 10 000 null ratios. Each bootstrapped iteration of the crude sequence ratio and null ratio was then divided to produce each iterative ASR value. For all drug classes and subclasses, the distribution of ASR iterations was smooth, approximately symmetric, and centered on the observed values for ASR. As such, percentile-based bootstrap CIs were appropriate,[19] and 95% CIs for the ASR were determined from the 2.5 and 97.5 percentiles of the ASR bootstrap distribution.

Approximate *P* values for each drug class and subclass were estimated. We used the normal approximation to the binomial distribution to determine the probability of observing a number of index first prescriptions as extreme as that observed if the true probability was the null probability.

SECONDARY ANALYSIS

To confirm our findings, we performed sequence symmetry analysis on medications for which a null effect was postulated (negative controls), these being β-blockers and the inhaled anticholinergics ipratropium bromide and tiotropium bromide (which share a first-line indication with LABAs for the treatment of chronic obstructive pulmonary disorder). β-Blockers were chosen because their mechanism of action is opposite to that of LABAs and because they are often prescribed in settings similar to those of diuretic and statin use (ie, hypertension, congestive heart failure, and after myocardial infarction).

As a further check, we performed a Cox proportional hazards regression model analysis comparing time to quinine start. This was performed among new users of LABAs (cases) or inhaled anticholinergics (controls) who first filled (and renewed within 1 year) their medication between December 1, 2001, and November 30, 2006 (eAppendix C).

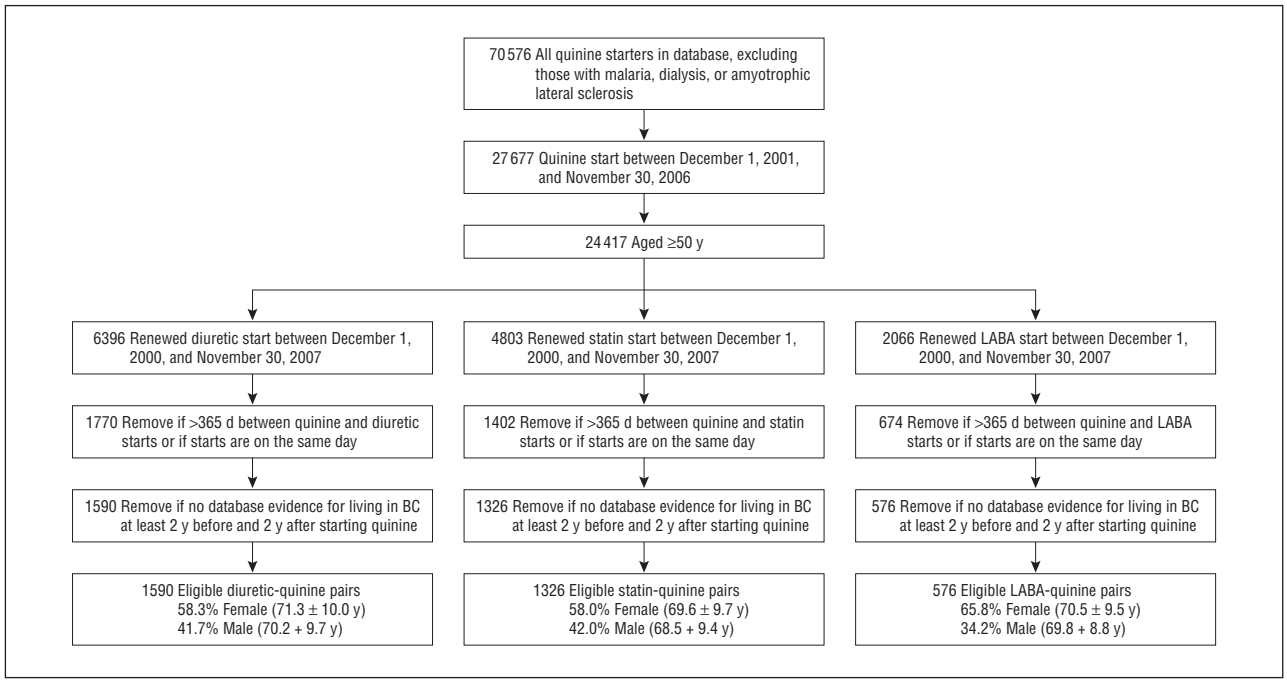

Figure 1. Flow diagram for selecting sequence symmetry analysis populations. BC indicates British Columbia; LABA, inhaled long-acting β2-agonist.

Table 2. Prescribing Order in Recipients of Both Quinine and Select Index Drugs

Index Drug Class	No. of Pairs: Index Preceding[a]	No. of Pairs: Index Following[b]	Null Probability[c]	Adjusted Sequence Ratio (95% CI)[d]	*P* Value
All statins	716	610	.50	1.16 (1.04-1.29)	.004
All LABAs	**397**	**179**	.48	2.42 (2.02-2.89)	<.001
LABA alone	100	37	.56	2.17 (1.56-3.02)	<.001
LABA-corticosteroid	297	142	.45	2.55 (2.06-3.12)	<.001
All diuretics	**956**	**634**	.51	1.47 (1.33-1.63)	<.001
Loop	226	181	.51	1.20 (1.00-1.44)	.07[e]
Thiazidelike	586	391	.50	1.48 (1.29-1.68)	<.001
Potassium sparing	144	62	.53	2.12 (1.61-2.78)	<.001
Negative controls					
All β-blockers	450	447	.51	0.97 (0.85-1.11)	.62
All inhaled anticholinergics	170	166	.49	1.07 (0.84-1.36)	.56

Abbreviation: LABA, inhaled long-acting β2-agonist.
[a] Potentially causal sequence: the index drug precedes cramp treatment.
[b] Noncausal sequence: the index drug follows cramp treatment.
[c] Probability of the index drug coming first based on age-matched population index prescribing.
[d] Ratio of the crude sequence ratio (number of potentially causal sequences divided by the number of noncausal sequences) to the null ratio (expected crude sequence ratio based on age-matched population prescribing).
[e] The CI and *P* value are estimated using different methods. Hence, the loop diuretic CI can sit on the border of significance when the approximated *P* value is not exactly .05. The CI determined significance.

RESULTS

DESCRIPTIVE DATA

Excluding individuals undergoing dialysis or those having malaria or amyotrophic lateral sclerosis but before applying any age or index drug exclusions, the cohort of all provincewide quinine starters (which we assume to be individuals with rest cramps) between December 1, 2001, and November 30, 2006, was 62.5% female, with a median age of 69 years (interquartile range, 58-80 years; mode, 73 years). Family physicians provided 87.1% of these quinine prescriptions, and during a 5-year period, 48.5% of recipients renewed their quinine prescriptions. Subgroup demographics and a breakdown of exclusions are shown in **Figure 1**. Of 24 417 eligible quinine starters, there were 1590 diuretic, 1326 statin, and 576 LABA starters on which sequence symmetry analysis could be performed.

MAIN FINDINGS

Quinine prescriptions were significantly more likely to follow, rather than precede, prescriptions from all 3 main index classes (**Table 2**). The association was greater for LABAs than for statins and did not differ whether LABAs

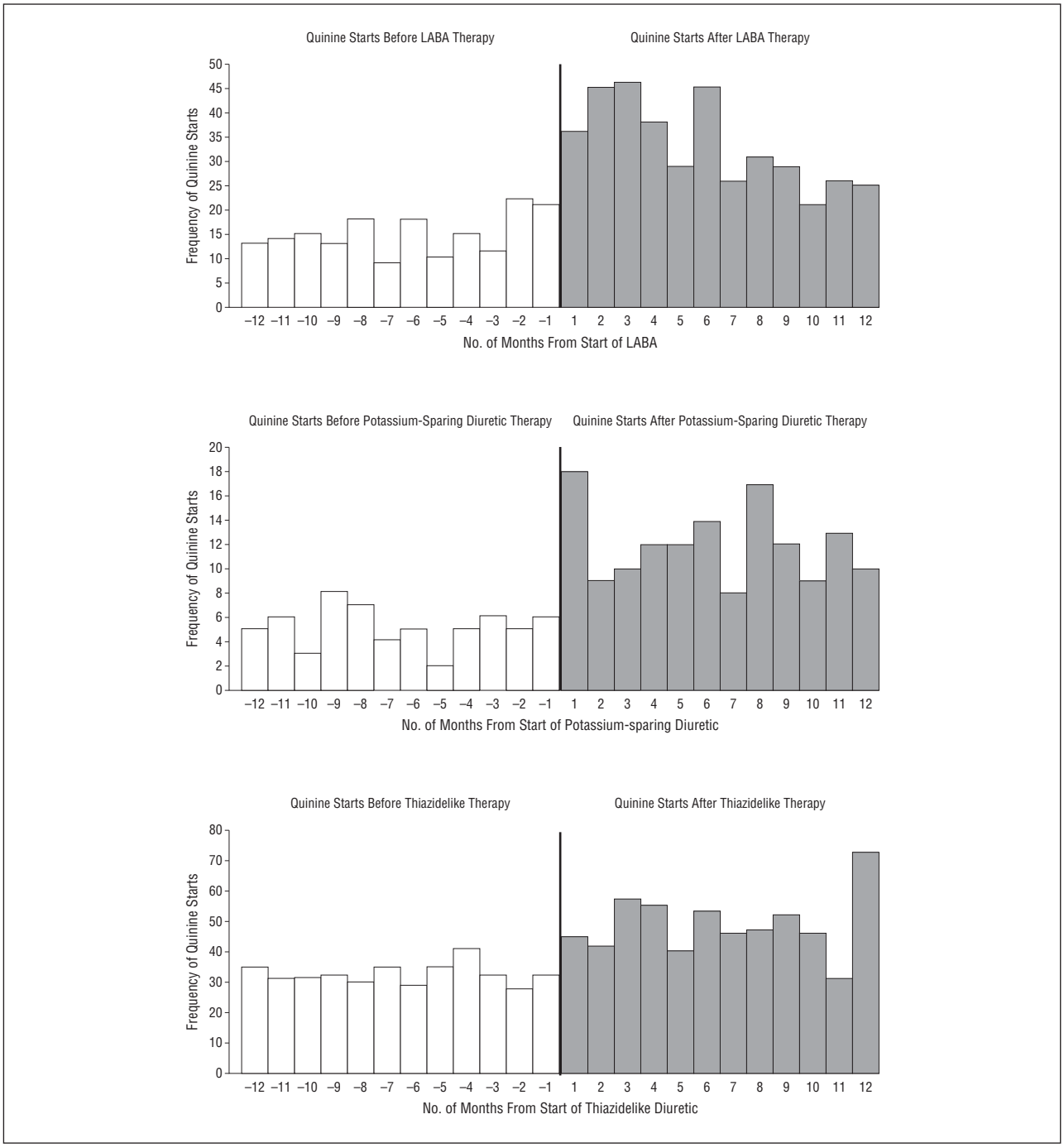

Figure 2. Frequency of quinine starts in the months preceding and following initiation of an index drug (shows the drugs having the greatest association with cramp treatment). LABA indicates inhaled long-acting β2-agonist.

were combined with corticosteroids or were used alone. The use of thiazidelike diuretics and, particularly, potassium-sparing diuretics was more strongly associated with cramp treatment than was the use of statins. Loop diuretics and statins had small magnitudes of association. Neither of the negative control drug classes (β-blockers and inhaled anticholinergics) was associated with cramp treatment.

Of all quinine recipients, 77.5% filled a prescription for diuretics or statins or LABAs during 13 years of available data. Medications that are most associated with cramp treatment (LABAs, potassium-sparing diuretics, and thiazidelike diuretics) were filled by 60.3% of quinine users. If we assume that the potential cramp-promoting effects of these drugs extends to renewals, up to 13.6% of quinine starts could be attributable to their use (eAppendix D). Unfortunately, our data cannot produce a meaningful estimate of absolute risk increase because only a small fraction of those with a greater cramp burden can be detected using new quinine starts (ie, our analysis excludes anyone with prior quinine use and cannot detect altered cramp rate in non–quinine users).

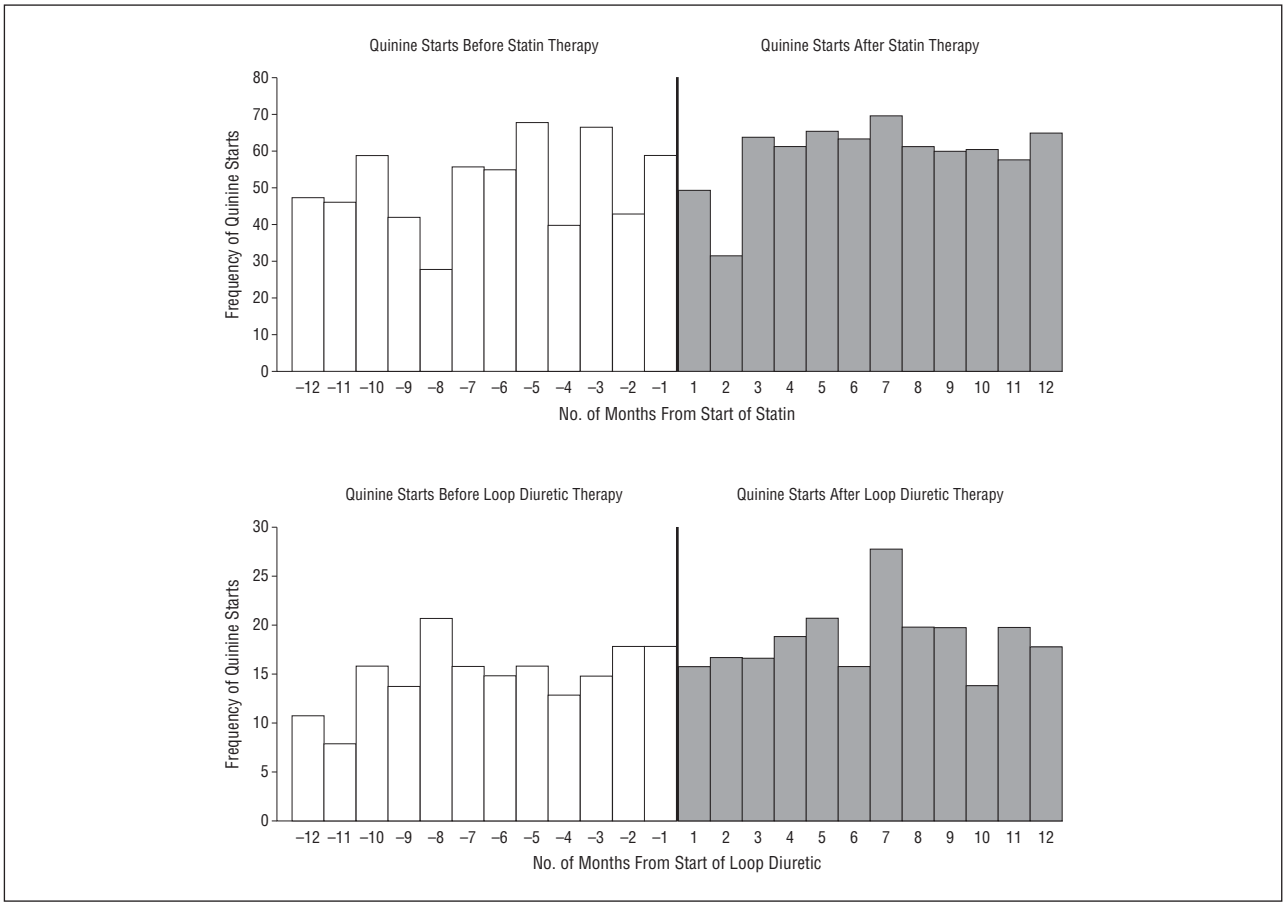

Figure 3. Frequency of quinine starts in the months preceding and following initiation of an index drug (shows the drugs having the least association with cramp treatment).

Histograms of the distribution of intervals between index prescribing and quinine receipt are shown in **Figure 2** and **Figure 3**. Quinine prescriptions rose sharply within a month of introducing diuretics or LABAs. The small rise in quinine prescribing following statin starts took 3 months to manifest.

SECONDARY ANALYSIS

Consistent with the LABA sequence symmetry analysis results, Cox proportional hazards regression model analysis comparing LABA starters with inhaled anticholinergic starters yielded a hazard ratio of 2.37 (95% CI, 1.73-3.23 [$P < .001$]) for a quinine start in the following year. Details are given in eAppendix C.

COMMENT

These populationwide observational data suggest that the use of diuretics, statins, and LABAs promotes muscle cramping in older adults. The association is particularly strong for LABAs (ASR, 2.42) and potassium-sparing diuretics (ASR, 2.12), is moderate for thiazidelike diuretics (ASR, 1.48), and is weak for loop diuretics (ASR, 1.20) and statins (ASR, 1.16). Except for aboriginals, whose prescription use was unavailable to us, our results are drawn from the large multiethnic population of British Columbia and should generalize well to similar populations.

Our analytic design controls for patient attributes (including polypharmacy use and comorbidity) and corrects for trends in prescribing that vary with time, age, and aging using the birth year–stratified null ratio. Although the sudden change in quinine starts following LABA, potassium-sparing diuretic, or thiazidelike diuretic starts (Figures 2 and 3) supports the hypothesized effect of cramp promotion, the same observation could also be explained by the use of quinine lessening the likelihood of a subsequent index prescription. This could occur if quinine had a biologic effect (eg, blood pressure lowering) that lessened the indication for index drug use or if physicians already avoid these index drugs among individuals with cramp. In addition, if follow-up care is more frequent following prescription of index drugs than quinine, then greater opportunity for cramp discussion and prescription could arise. Conceivably, the small statin and loop diuretic associations might be explained by greater physician contact and prescription in the follow-up period or by avoidance of these drugs among individuals with cramp.

Using provincewide administrative pharmacoepidemiological data, our results substantially extend and support the limited evidence linking the use of LABAs and diuretics to muscle cramping.[9-13] We found the statin associa-

tion to be minor. Although statins are widely known to cause muscle symptoms, the description of statin myopathy does not include muscle cramps.[20] The sole literature linking the use of statins to cramping is a single study[14] of patients with amyotrophic lateral sclerosis. Randomized controlled trials have not implicated any of the medications we studied as causing cramp (possibly because older persons are poorly represented in most clinical trials).

Our sequence ratios represent the rate of cramp treatment in the year following index drug introduction compared with the expected rate in the same population. Viewed in this way, LABAs, potassium-sparing diuretics, and thiazidelike diuretics (prescribed to 60.3% of quinine recipients during a 13-year span) have sequence ratios that suggest a 47.7% (for thiazides) to 142.0% (for LABAs) increase in the indication for cramp treatment. If discontinuing these drugs or switching to other therapeutic options were to provide an equivalent reduction in the need for cramp treatment, such a maneuver would result in numbers needed to treat of 1.7 (for LABAs) to 3.1 (for thiazides).

Physicians may be surprised that potassium-sparing diuretics have a stronger link to cramp treatment than loop diuretics. Yet, hyperkalemia facilitates neuronal excitation, and hypokalemia suppresses motor neuron activity.[21,22] β2-Agonists are known to have a stimulatory effect on motoneurons, and β2-adrenergic receptors are found on peripheral nerves.[23-25] Irrespective of the mechanisms explaining the phenomenon, physicians should be aware of the epidemiological association between cramp treatment and the use of LABAs, potassium-sparing diuretics, and thiazidelike diuretics.

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Online-Only Material: eAppendixes A through D are available at http://www.archinternmed.com.

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