Over-the-counter and Prescription Sleep Medication and Incident Stroke: The REasons for Geographic And Racial Differences in Stroke Study

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Background: Preliminary evidence suggests sleep medications are associated with risk of vascular events; however, the long-term vascular consequences are understudied. This study investigated the relation between sleep medication use and incident stroke. *Methods:* Within the REasons for Geographic And Racial Differences in Stroke study, 21,678 black participants and white participants (≥45 years) with no history of stroke were studied. Participants were recruited from 2003 to 2007. From 2008 to 2010, participants self reported their prescription and over-the-counter sleep medication use over the past month. Suspected stroke events were identified by telephone contact at 6-month intervals and associated medical records were retrieved and physician-adjudicated. Proportional hazards analysis was used to estimate hazard ratios for incident stroke associated with sleep medication use (0, 1-14, and 15+ days per month) controlling for sociodemographics, stroke risk factors, mental health symptoms, and sleep apnea risk. *Results:* At the sleep assessment, 9.6% of the sample used prescription sleep medication and 11.1% used over-the-counter sleep aids. Over an average follow-up of 3.3 ± 1.0 years, 297 stroke events occurred. Over-the-counter sleep medication use was associated with increased risk of incident stroke in a frequency-response relationship (P = .014), with a 46% increased risk for 1-14 days of use per month (hazards ratio [HR] = 1.46; 95% confidence interval [CI], .99-2.15) and a 65% increased risk for 15+ days (HR = 1.65; 95% CI, .96-2.85). There was no significant association with prescription sleep medications (P = .80). *Conclusions:* Over-the-counter sleep medication use may independently increase the risk of stroke beyond other risk factors in middle-aged to older individuals with no history of stroke. **Key Words:** Sleep medication—sleeping pills—stroke—over-the-counter—REGARDS Study.

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Evidence suggests that poor or insufficient sleep is a risk factor for stroke.[1] Sleep problems and insomnia are commonly treated with prescription and/or over-the-counter (OTC) sleep medications.[2] Approximately 3.4% to 11.2% of the general population report taking sleeping medications to improve their sleep.[2-4] Prescription sleep medication is typically indicated for short-term treatment, although many people use these medications chronically. The long-term consequences of sleep medication use are mixed with recent placebo-controlled studies indicating sleep medication use is beneficial for treating insomnia,[5] whereas other studies report several associated adverse events including mortality.[6,7] Currently, the relationship between sleep medication and incident vascular outcomes is understudied. One reason for this maybe that there are multiple types of sleep medication, including benzodiazepines, sedating antidepressants, "non-benzodiazepines" (imidazopyridines, pyrazolopyrimidines, and cyclopyrrones), and antihistamines such as diphenhydramine, doxylamine, and hydroxyzine, that all vary in their vascular effects. For example, acute use of benzodiazepines is associated with increases in coronary flow rate,[8] whereas antidepressants are associated with altered cardiac electrophysiology, hence increasing risk for arrhythmias.[9] Zolpidem is associated with hypotension and tachycardia but only among a minority of people.[10] Lastly, tachycardia, hypertension, and echocardiogram disturbances have been associated with fatal and nonfatal cases of diphenhydramine intoxication of greater than .7 μg/mL.[11,12]

A few case–control and community-based longitudinal studies have found increased relative risk for cardiac events with benzodiazepine, tricyclic antidepressant use, and other nonspecified sleep medications.[13-15] Even fewer studies have examined associations between sleep medication and stroke risk. One cross-sectional study of a community-based cohort of middle-aged to older women found benzodiazepine use was related to a higher probability of stroke.[16] Most of these studies lacked sufficient adjustment for the participants' mental health status and vascular risk factors. Furthermore, the studies were mostly conducted in women, lacked diverse populations, and did not assess for relationships with OTC sleep aids.

In the present study, the longitudinal associations between the use of prescription and OTC sleep medication use at 1 timepoint and incident stroke at follow-up were examined, using data from a national cohort, the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods

Study Design

From 2003 to 2007, the REGARDS study recruited a nationwide cohort of adults 45 years of age or older to follow over time. The aim of the study was to determine the risk predictors for disparities in stroke mortality across racial (non-Hispanic whites and blacks) groups and regions. Participants residing in the "Stroke Belt" (including the following states: Alabama, Arkansas, Georgia, Louisiana, Minnesota, North Carolina, South Carolina, and Tennessee) were oversampled to better understand the causes for the greater incidence of stroke and stroke-related mortality in this region than for the rest of the United States. The study recruited 30,239 participants through mail and telephone methods. The total sample was composed of 42% non-Hispanic blacks, and 56% Stroke Belt residents. Baseline assessment was conducted with a telephone interview and an in-home visit by a health professional. Assessment consisted of demographic characteristics, history of stroke symptoms/stroke/transient ischemic attack and other medical conditions, anthropomorphic measurements, and an electrocardiogram. After baseline, participants are contacted by telephone at 6-month intervals for self-reported suspected stroke (or proxy-reported in case of death or small number of participants unable to respond), with retrieval of medical records and adjudication by physicians. The protocol was approved by all institutional review boards involved, and all participants provided written consent. The study methods have been described in detail previously.[17]

Sleep Measures

Sleep assessment was conducted during 1 of the 6-month telephone follow-up calls between 2008 and 2010. Self-reported sleeping pill usage was measured with the questions, "How many days/nights in the last month have you used prescription sleeping pills?" and "How many days/nights in the last month have you used nonprescription or over-the-counter sleeping pills?". Sleeping pill use was categorized in 2 ways: 1 or more day(s) per month vs. none; and no use versus 1-14 days per month, or 15+ days per month.

Stroke Events

Methods of stroke adjudication are reported elsewhere.[18] Briefly, during follow-up, a report of possible stroke, transient ischemic attack, death, hospitalization or emergency department visit for stroke symptoms, or unknown reason generated a request for medical records. Initial review of records was conducted by a stroke nurse to exclude obvious nonstroke, then records were centrally adjudicated by physicians. For deaths with no medical records, death certificates and/or proxy interviews were adjudicated. Stroke events were defined after the World Health Organization (WHO) definition.[19] Events not meeting the WHO definition but with symptoms lasting more than 24 hours with neuroimaging consistent with acute ischemia or hemorrhage were classified as "clinical strokes". When adjudicators agreed that the event was