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Over-the-Counter and Prescription Sleep Medication and Incident Stroke: The REGARDS Study

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Abstract

Purpose—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 and white participants (≥45yrs) with no history of stroke were studied. Participants were recruited from 2003−2007. From 2008−2010, 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

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Drs. Ruiter Petrov and Molano report no conflicts of interest. **Dr. Kleindorfer** reports a paid speaking engagement that had no conflict of interest with the content of the manuscript.

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All authors contributed to the interpretation of the data, revising the article, and giving final approval of the version to be published. **Drs. Ruiter Petrov, Howard, and Howard**, in addition, contributed to the conception, design, and analysis of the data.

and physician-adjudicated. Proportional hazards analysis was used to the estimate hazard ratios for incident stroke associated with sleeping 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 for incident stroke in a frequency-response relationship (p-trend = 0.014), with a 46% increased risk for 1–14 days of use per month (HR=1.46; 95%CI: 0.99–2.15) and a 65% increased risk for 15+ days (HR=1.65; 95%CI: 0.96–2.85). There was no significant association with prescription sleep medications (p = 0.80).

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.

Keywords

sleep medication; sleeping pills; stroke; over-the-counter; REGARDS Study

INTRODUCTION

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) sleeping 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, though 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 may be 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 persons (10). Lastly, tachycardia, hypertension, and echocardiogram disturbances have been associated with fatal and non-fatal cases of diphenhydramine intoxication of greater than 0.7 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 non-specified 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 one time-point 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 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: AL, AR, GA, LA, MS, NC, SC, and TN) 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 US. 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 (TIA) and other medical conditions, anthropomorphic measurements and an electrocardiogram (ECG). Following baseline, participants are contacted by telephone at six-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 one of the six-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 non-prescription, or over the counter sleeping pills?'. Sleeping pill use was categorized in two ways: one or more day(s) per month vs. none; and no use, 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 (TIA), 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 non-stroke, 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 following the World Health Organization (WHO) definition (19). Events not meeting the WHO definition but with symptoms lasting >24 hours with neuro-imaging consistent with acute ischemia or hemorrhage were classified as "clinical strokes". When adjudicators agreed that the event was likely a stroke but information was insufficient to meet other classifications, the event was classified as a "probable stroke." The analysis included WHO, clinical, and probable stroke cases, and both ischemic and hemorrhagic strokes.

Covariates

Demographic information included age, race/ethnicity (self-reported) and sex. Socioeconomic factors included income (<$20K, $20K–$34K, $35K–$74K, ≥ 75K) and education (< high school, high school graduate, some college, ≥ college graduate). Stroke risk factors consisted of systolic blood pressure, self-reported antihypertensive medication use, diabetes (fasting glucose ≥126mg/dL or non-fasting glucose ≥200mg/dL or self-report of pills or insulin), history of heart disease (i.e., self-reported myocardial infarction (MI), coronary artery bypass surgery, coronary angioplasty or stenting, or evidence of MI via ECG), atrial fibrillation, left ventricular hypertrophy, current smoking, and alcohol use. Depressive and anxiety symptoms were measured using the 4-item Center for Epidemiologic Studies Depression Scale (20), and the Perceived Stress Scale (21). Sleep apnea risk was measured two ways: self-reported diagnosis of sleep apnea by a physician and high risk status according to the Berlin Questionnaire (22). High risk for apnea was determined if the participant met two or more criteria from the Berlin Questionnaire (i.e., persistent snoring; frequent sleepiness; and high blood pressure or a body mass index greater than or equal to 30.0 kg/m^2). Systolic blood pressure and body mass index were determined from objectively-derived data from the baseline in-home visit.

Sampling frame

Exclusion criteria for the present analyses included self-reported stroke at baseline, missing data at baseline, stroke that occurred prior to the administration of the sleep assessment, and no follow-up data after the time of the sleep assessment. Of the active participants in the REGARDS cohort at the time of the sleep assessment, 23,919 participants completed the sleeping assessment module. A further 1,250 were excluded for a self-reported stroke at baseline, 10 for missing data at baseline, 315 for stroke events that occurred before the sleep assessment, and 666 participants with no follow-up information after the sleep assessment. The final sample size was 21,678 participants.

Statistical analysis

The descriptive characteristics among the prescription sleeping pill users, OTC sleeping pill users, and non-users were compared using χ^2 tests. For the main analyses, proportional hazards analysis was used to assess the relationship between sleeping pill use and stroke risk. The first analysis was used to estimate hazard ratios for stroke in prescription sleeping pill users compared to non-users, among OTC sleeping pill users compared to non-users, and among users of either prescription or OTC users compared to non-users. The second analysis of the dose-response relationship was conducted estimating the hazard ratios

comparing OTC and/or prescription sleeping pill users who reported using medication 1 to 14 days, and 15+ days, to non-users. Follow-up time was from the introduction of the sleeping pill assessment to the stroke event. The models were as follows: Model 1 = demographic factors; Model 2 = Model 1 + socioeconomic factors; Model 3 = Model 2 + stroke risk factors; Model 4 = Model 3 + mental health symptoms; and Model 5 = Model 4 + sleep apnea risk.

RESULTS

Descriptive characteristics

Follow-up time from the sleep assessment to an independent stroke event or the most recent six-month phone call was 3.3 ± 1.0 years. OTC sleeping pill use was more common than prescription sleeping pill use in the total sample (11.1% vs. 9.6%). Table 1 displays the baseline characteristics of the sample by sleep medication status. Blacks, males, and those with left ventricular hypertrophy were less likely to take any type of sleep medication. Participants at high risk for sleep apnea were more likely to use any type of sleep medication. Participants with diagnosed sleep apnea were more likely to use prescription sleep medications. Participants who reported antihypertensive use, heart disease, atrial fibrillation, or higher CES-D-4 or Perceived Stress Scale scores were more likely to take prescription medications alone or both prescription and OTC medications. Current smokers were less likely to use OTC sleep medications. Participants with diabetes and those with the lowest education attainment were less likely to take OTC medications or both OTC and prescription sleep medications compared to the total sample.

Sleeping medication use and stroke

Of the 21,678 participants, 297 participants suffered a stroke during follow-up. Table 2 displays the adjusted models for the hazard of sleeping medication use on stroke by prescription, OTC or either sleeping medication status. There was an association between taking any form of sleeping medication at least once in the past month and risk for incident stroke in the demographic model, but it did not reach statistical significance. In separate analysis by medication type, OTC sleep medication use was found to be significantly associated with increased stroke risk in the demographic model and retained significance across all models. In the fully-adjusted model, OTC sleep medication users had a 52% increased risk of stroke compared to participants not taking any sleep medication. Prescription sleep medication use was not associated with risk for incident stroke in any of the models. When medication use was analyzed using frequency of use (i.e., none, 1–14 days/month, 15–30 days/month), a significant frequency/dose-response relationship was demonstrated for OTC sleep medication (see Table 3). The hazard estimates in the fully adjusted models increased with higher usage such that participants using OTC sleep medication 1–14 days/month had a 46% increased risk for stroke, and participants using 15–30 days/month had a 65% increased risk for stroke compared to non-users.

DISCUSSION

Reported use of OTC sleep medication in the past month was associated with an increased risk for stroke within four years among middle-aged to older men and women without a history of stroke. After adjusting for demographics, multiple stroke risk factors, mental health symptoms, and sleep apnea risk, any OTC sleep medication use increased risk for future stroke by 52%. There was also a significant frequency/dose-response relationship such that more frequent use of OTC sleep medications was related to a greater hazard for incident stroke. Prescription sleep medication use was not related to increased risk for stroke.

Our results suggest that OTC sleep medications are associated with a higher risk for stroke beyond other stroke risk factors and more than prescription sleep medications. This result is unexpected considering the increased side effects profile associated with prescription sleep medications including motor incoordination, lassitude, slowed reaction times, dysarthria, ataxia, nausea, headache, and drowsiness. Furthermore, prescription sleep medications have also been associated with mortality across multiple causes of death including stroke, ischemic heart disease, cancer, and accidents (14, 23, 24). However, many of these studies did not verify which medications were being taken and at what dosage and frequency, and the exact cause of death was often uncertain. A possible reason why prescription sleep medications were not associated with increased risk for stroke was these medications are more regulated and may be taken more appropriately (i.e., as prescribed) than OTC sleep medications. Individuals may not perceive that OTC sleep medications can also be harmful and may misuse them more often. For example, diphenhydramine poisonings are quite common (11).

OTC sleep medications, including diphenhydramine, doxylamine, valerian, and melatonin are not without their side effects such as headaches, memory problems, confusion, nervousness, and notably, cardiac and vascular disturbances (11, 12). They also have known problematic drug interactions with alcohol and other central nervous system depressants. Many of these medications have not been systematically scrutinized for their long-term consequences (25), so there may be direct relationships between their use and vascular dysfunction. Diphenhydramine and doxylamine are not recommended for persons with respiratory conditions such as asthma and chronic obstructive pulmonary disease, and those with cardiovascular disease or hypertension because it may induce atropine-related parasympathetic inhibition which may result in tachycardia (26). Furthermore, overdoses of diphenhydramine are associated with increased heart rate and prolongation of the heart-rate corrected QT interval (27). According to the US Food and Drug Administration, melatonin is classified as a dietary supplement (26). As a result, manufacture of melatonin is not regulated, side-effects do not need to be placed on product labels, and the long-term effects are unknown. One study found that melatonin reduces the sympathetic nervous system response during orthostatic stress, reducing blood flow to the brain, which suggests melatonin use by persons with orthostatic intolerance is contraindicated (28).

There are several other mechanisms that may explain the relationship between OTC sleeping pill use and incident stroke. Confounding variables related to stroke may be present such as

poor health, and confounders of indication such as sleep disturbances and psychopathology. With the exception of sleep disturbances, these possibilities are less likely in the present study because many stroke risk factors and other confounders were adjusted for in the analyses. Sleep disturbances is an important confounder of indication that should be controlled for in future studies, especially considering its association with stroke (29). Another possibility is there is an indirect relationship between the pharmacological toxicity and side effects of sleeping pills that are hazardous to blood vessel endothelium. For example, some sleeping pills can increase snoring and respiratory effort during sleep, particularly when combined with alcohol or other central nervous system depressants, hence creating sleep-disordered breathing. Sleep-disordered breathing is a significant independent risk factor for hypertension and stroke (30). While we controlled for the presence of a reported diagnosis of sleep apnea and high risk status for sleep apnea, nonetheless, the presence of sleep-disordered breathing in the sample may be underestimated because witnessed apneas often require a bed partner which not all participants had. There could also be multiple mediators in the pathway between OTC sleeping medication use and future stroke. For example, the somnolence and sedation associated with these medications may cause decrements in physical activity and contribute to a more sedentary lifestyle, which may lead to a cascade of pathological cardiovascular developments leading to stroke. Future studies should adjust for objective physical activity in the association between sleeping pill use and stroke.

Although the results represent a nationally-based socially, ethnically, and regionally diverse sample, there were limitations to this study. First, self-report data for the exposure variable (frequency of sleep medication use) are prone to recall bias. Second, we did not determine the classes and dosages of the sleep medications used nor how long prior to the two-week period these medications were used. Third, there is also the unavoidable possibility of unmeasured confounding that may have influenced sleeping pill use and stroke occurrence. Sleep disturbance, in particular, could be a confounder because it is an indication for sleeping pill use, and insufficient sleep has been associated with stroke (1).However, to mitigate this possibility we controlled for reported physician-diagnosed sleep apnea and apnea risk which may have been able to partially control for sleep disturbances due to this disorder. Fourth, exposure to sleep medication was not assessed during further follow-ups, so the exposure status is based on one time-point. Lastly, the time period between baseline covariate assessment (2003–2007) and reported sleeping pill use was disparate (2008–2010).

In conclusion, OTC sleeping pill use may be an independent risk factor for incident stroke, beyond other stroke risk factors, among middle-aged to older persons. Further study of the long-term risk-benefits ratios of OTC sleep medication is needed to verify these findings. Our results suggest that individuals may want to exercise greater caution and consult with their doctor when choosing to use OTC sleep medications. If they do choose to use these medications, then they should not take these medications any longer thanp suggested on package labels.

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Table 1

Baseline Characteristics of the Total Sample (2003–2007) and by Sleep Medication Status (2008–2010) in the REGARDS Study.

Variable	Total Sample	Non-User	Prescription only	OTC only	Both
	n = 21,678	n = 17,388	n = 1,753	n = 2,079	n = 302
Age (years; *M* ± *SD*)	64.2 ± 9.1	64.3 ± 9.0	64.1 ± 9.3	63.9 ± 9.0	64.6 ± 9.9
Black (%)	37.7	40.6	27.7	24.1	25.5
Male (%)	43.8	45.5	37.0	37.4	29.1
Education (%)					
Less than high school	9.8	10.0	10.8	7.2	9.3
High school graduate	25.2	24.7	26.5	25.4	29.8
Some college	26.8	26.8	26.6	27.7	22.2
College graduate and above	38.3	38.4	36.1	39.6	38.7
Income (%)					
less than $20k	14.8	14.7	17.6	12.3	15.6
$20k–$34k	23.1	23.1	24.0	23.6	19.9
$35k–$74k	32.1	32.3	29.4	33.2	30.8
$75k and above	18.3	18.2	16.9	19.9	20.9
Refused	11.7	11.6	12.2	11.0	12.9
Systolic Blood Pressure (mmHg; *M* ± *SD*)	126.5 ± 16.1	126.8 ± 16.1	125.3 ± 17.0	124.9 ± 15.4	124.7 ± 16.2
Heart Disease (%)	15.1	14.6	18.8	15.0	18.2
Antihypertensive use (%)	48.6	48.1	53.2	48.1	52.0
Diabetes (%)	18.9	19.4	19.4	14.8	15.1
Left Ventricular Hypertrophy (%)	9.0	9.5	7.4	6.7	5.7
Atrial Fibrillation (%)	7.6	7.0	12.1	8.3	9.7
Current Smoking (%)	12.6	12.4	14.4	1.2	14.0
CESD-4 (*M* ± *SD*)	1.01 ± 1.91	0.92 ± 1.80	1.75 ± 2.55	1.07 ± 1.96	1.45 ± 2.30
Perceived Stress Scale (*M* ± *SD*)	3.03 ± 2.83	2.92 ± 2.77	3.88 ± 3.23	3.15 ± 2.81	3.49 ± 2.95
Diagnosed sleep apnea (%)	10.9	10.4	16.7	10.7	11.6
High risk of sleep apnea on Berlin Questionnaire (%)	17.4	16.6	21.5	19.1	24.8

CES-D = Center for Epidemiological Studies – Depression Scale; M = mean; REGARDS = REasons for Geographic and Racial Differences in Stroke; SD = standard deviation

Table 2

Estimated Hazard Ratios and 95% Confidence Intervals for the Association between Sleep Medication Use and Stroke Risk

	Models				
Medication Type	**1 Demographic**	**2 + SES**	**3 + Risk Factor**	**4 + Mental Health**	**5 + Apnea**
OTC	1.52** (1.11 – 2.09)	1.52** (1.11 – 2.09)	1.52* (1.09 – 2.12)	1.52* (1.09 – 2.12)	1.52* (1.09 – 2.11)
Prescription	1.11 (0.76 – 1.62)	1.10 (0.75 – 1.60)	0.89 (0.59 – 1.36)	0.88 (0.57 – 1.34)	0.89 (0.58 – 1.35)
Either	1.31 ≠ (1.00 – 1.73)	1.31 ≠ (0.99 – 1.72)	1.22 (0.91 – 1.63)	1.21 (0.90 – 1.62)	1.21 (0.90 – 162)

Demographic = age, race, sex; + SES = income, education; + Risk Factors = systolic blood pressure, antihypertensive use, diabetes, current smoking, left ventricular hypertrophy, atrial fibrillation, heart disease; + Mental Health = Center for Epidemiological Studies – Depression 4-item form, Perceived Stress Scale score; + Apnea = diagnosed sleep apnea, apnea risk on the Berlin Questionnaire; OTC = over-the-counter sleeping pills; REGARDS = REasons for Geographic and Racial Differences in Stroke

** $p < 0.01$;

* $p < 0.05$;

≠ $p < 0.06$

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Table 3

Estimated Hazard Ratios and 95% Confidence Intervals for the Dose-Response Relations between Sleep Medication Use Frequency and Stroke Risk

			Models				
Medication Type	**Days of Use**	**Dose-response *p*-trend**	**1 Demographic**	**2 + SES**	**3 + Risk Factor**	**4 + Mental Health**	**5 + Apnea**
OTC	Reference: 0 (n = 19,181)		--	--	--	--	--
	1–14 (n = 1,731)		1.45 $^{\neq}$ (1.00 – 2.11)	1.46 * (1.00 – 2.12)	1.46 $^{\neq}$ (0.99 – 2.16)	1.46 $^{\neq}$ (0.99 – 2.16)	1.46 $^{\neq}$ (0.99 – 2.15)
	15+ (n = 665)		1.70 * (1.01 – 2.87)	1.67 $^{\neq}$ (0.99 – 2.83)	1.67 $^{\neq}$ (0.97 – 2.87)	1.66 $^{\neq}$ (0.96 – 2.86)	1.65 $^{\neq}$ (0.96 – 2.85)
		p-trend	0.009	0.009	0.013	0.013	0.014
Prescription	Reference: 0 (n = 19,507)		--	--	--	--	--
	1–14 (n = 1,023)		0.82 (0.45 – 1.51)	0.84 (0.46 – 1.54)	0.71 (0.37 – 1.39)	0.71 (0.36 – 1.38)	0.71 (0.36 – 1.38)
	15+ (n = 1,045)		1.38 (0.87 – 2.21)	1.34 (0.84 – 2.13)	1.05 (0.62 – 1.78)	1.04 (0.61 – 1.76)	1.04 (0.62 – 1.77)
		p-trend	0.33	0.38	0.83	0.80	0.80

Demographic = age, race, sex; + SES = income, education; + Risk Factors = systolic blood pressure, antihypertensive use, diabetes, current smoking, left ventricular hypertrophy, atrial fibrillation, heart disease; + Mental Health = Center for Epidemiological Studies – Depression 4-item form, Perceived Stress Scale score; + Apnea = diagnosed sleep apnea, apnea risk on the Berlin Questionnaire; OTC = over-the-counter sleeping pills; REGARDS = REasons for Geographic and Racial Differences in Stroke

$^{*}p < 0.05$;

$^{\neq}p < 0.07$

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