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Sleep Disturbance Among HIV Infected and Uninfected Veterans

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To the Editors

Although sleep disturbance has been observed at all stages of HIV infection,^{1–4} the nature of the association between HIV and sleep disturbance has not been rigorously evaluated in the current treatment era. We explored the longitudinal associations between HIV status and self-reported occurrence or severity of sleep disturbance, with adjustment for demographics, comorbidities, and polypharmacy.

We used the Veterans Aging Cohort Study (VACS), a longitudinal, prospective observational study of HIV infected and uninfected Veterans enrolled at eight Veterans Health Administration (VHA) medical centers: Atlanta, Baltimore, Brooklyn and Manhattan, Bronx, Houston, Los Angeles, Pittsburgh, and Washington DC. HIV infected Veterans were matched one to one with uninfected Veterans by age, race/ethnicity, site of clinical care, and sex.⁵ Data for this analysis included electronic health-record (EHR) data and self-report questionnaires completed by participants at enrollment (baseline) (June 2002 through August 2012) and through six years of follow-up.

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We defined HIV infection as the presence of Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for HIV during least two outpatient visits or one inpatient event that were confirmed in the immunology case registry of the VHA.⁶

Our primary outcomes were sleep disturbance and its severity. Both were assessed on an annual basis using the self-completed HIV Symptom Index⁷ over a follow-up period of six years. The Index elicits the frequency and severity of discomfort for 20 symptoms commonly associated with HIV. If the symptom was present, participants were prompted to indicate the degree of severity, based on a five-point Likert scale (0=does not experience the symptom, 1=experiences the symptom but without bother, 2=bothered a little by this symptom, 3=bothered, and 4=experiences a lot of bother with the symptom). Sleep disturbance was dichotomized as occurrence (a non-zero response on the Likert scale), or non-occurrence (a zero response on the Likert scale). Severity was assessed using the ordinal range of responses. Sleep disturbance symptoms were elicited on the survey at baseline and at follow-up visits in years 1-4 and 6, facilitating the longitudinal modeling of sleep disturbance and its severity.

Covariates were selected *a priori* based on prior sleep disturbance research and data availability. Baseline demographic information included age, sex, and race/ethnicity. All other covariates were updated at each annual assessment. We identified ICD-9-CM codes one year before and six months after baseline for the following conditions: coronary artery disease, diabetes, liver disease (any of hepatitis B or C, cirrhosis, end stage liver disease), peripheral vascular disease, renal disease, cerebrovascular disease (including stroke), cancer, heart failure, COPD, other chronic lung diseases, obstructive sleep apnea, PTSD, and drug use or abuse.

Body mass index (BMI; weight in kilograms/height in meters²) and pain (pain level between 0 and 10) were identified using vital sign data. We categorized BMI according to WHO criteria: underweight (BMI<18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (BMI ≥ 30). Smoking status was categorized as current, former and never smoker. From survey data, we used the Patient Health Questionnaire PHQ-2 to assess depressive symptoms.⁸ Using the Alcohol Use Disorders Identification Test (AUDIT-C),^{9–11} we defined hazardous alcohol use as a score of ≥ 4 for men and ≥ 3 for women. For these time-updated variables, values within 90 days of each survey date were used. If multiple values occurred within this time period, the one closest to the survey date was used.

We included a count of unique medications (excluding antiretrovirals) prescribed within 90 days of each survey date over the six year follow-up period. Use of selective serotonin reuptake inhibitors (SSRIs), other antidepressants, benzodiazepines, and hazardous opiate use (≥ 120 morphine equivalents per day) were coded as dichotomous indicator variables. Among HIV infected individuals, we identified use of antiretroviral therapy (ART) within the same time window, as well as a separate marker of efavirenz use, given its historical association with sleep disturbance.¹² CD4 count and HIV-RNA were also time-updated, and the values closest to survey date were used. Time was quantified as a count variable ranging from 1 through 6 representing the baseline survey and the successive waves of follow-up that we included in the study.

Descriptive characteristics were calculated at baseline: continuous variables with means and standard deviations (SD) or with medians and interquartile ranges (IQR) and dichotomous variables with the percent of observations. Each characteristic was compared between Veterans with and without HIV infection.

Clinical and demographic characteristics plausibly associated with the presence or severity of sleep disturbance were tested in multivariable longitudinal models that employed generalized estimating equations with an autoregressive correlation structure. Approximately 7% of observations were missing. Because we believed the missing-ness to be at random, ten imputations of the entire longitudinal dataset were created with a full conditional specification. The associations of clinical and demographic factors with occurrence of sleep disturbance were modeled using logistic regression. We assessed model fit using discrimination (C-statistic) and calibration (Hosmer-Lemeshow chi-square statistic). Severity of sleep disturbance was modeled with a negative binomial distribution. Separate models of each outcome were fit to the combined sample and to the subgroup of HIV infected individuals. To discern whether the effect of polypharmacy was due to the number of medications taken or to the inclusion of certain classes of medications that might be particularly associated with sleep disturbance, we also included indicators of use of the following medication classes: benzodiazepines, Z-drugs (non-benzodiazepine sleep medications), hazardous opiate use, SSRIs, and other antidepressants. All analyses were performed using SAS version 9.4. Because of the large number of analyses, p-values from multivariable models were adjusted for multiple comparisons using the Hochberg method.¹³

We included all VACS participants (N=7,515). The sample was composed predominantly of Black (65%) and non-Hispanic (90%) men (95%) of whom 50% were HIV infected. Relative to their uninfected counterparts, HIV infected individuals were younger (49 ± 9 years vs 50 ± 10 years, $p < 0.0001$), had a lower BMI (26 ± 4 kg/m² vs 30 ± 6 kg/m², $p < 0.0001$), were more likely to have liver (54% vs 30%, $p < 0.0001$) or renal disease (5% vs 3%, $p = 0.0003$), and less likely to have heart failure (2% vs 3%, $p = 0.003$), sleep apnea (1% vs 3%, $p < 0.0001$), PTSD (8% vs 12%, $p < 0.0001$), drug use/abuse (24% vs 27%, $p = 0.006$), coronary artery disease (8% vs 12%, $p < 0.0001$), diabetes (12% vs 22%, $p < 0.0001$), or peripheral vascular disease (2% vs 3%, $P = 0.0002$). There were no differences between HIV infected and uninfected individuals in terms of COPD (5% vs 5%, $p = 0.27$), other chronic lung conditions (8% vs 9%, $p = 0.05$), cerebrovascular disease or stroke (0.8% vs 1%, $p = 0.05$), and cancer (5% vs 5%, $p = 0.83$). HIV infected Veterans had lower AUDIT C scores (median [IQR]: 2[1, 5] vs 3[1, 5], $p = 0.001$) and fewer prescriptions for benzodiazepines (8% vs 10%, $p = 0.003$) and other antidepressants (16% vs 18%, $p = 0.03$). Prescriptions for opiates (HIV infected: 21% vs uninfected: 22%, $p = 0.88$), SSRIs (19% for both, $p = 0.58$) and Z-drugs (2%, and 3%, respectively; $p = 0.79$) did not differ by HIV status. Depressive symptom scores were similar in both groups (HIV infected median 4 [IQR: 1, 9] and HIV uninfected median 3 [IQR 1, 5]) Among HIV infected Veterans, the mean CD4 count was 410 ± 287 (cells/mm³) and mean HIV-RNA was $37,013 \pm 170,242$ (copies/mL). Eighty percent were on ART within 90 days of the baseline survey, and 28% were on efavirenz.

Among HIV infected individuals, 61% experienced sleep disturbance, compared with 58% of uninfected ($p=0.01$). The full range of severity scores was observed in both groups, who shared a common median of two (bothered a little by this symptom).

In unadjusted models, HIV infection was associated with sleep disturbance (odds ratio (OR)= 1.13; 95% CI: 1.03, 1.24, $p=0.01$) but not its severity (relative risk (RR) =1.03; 95% CI: 0.98, 1.08, $p=0.32$). In multivariable models with adjustment for multiple comparisons, HIV was associated with neither outcome (sleep disturbance OR: 1.08; 1.01, 1.15, $p=0.39$; severity: RR: 1.02; 95% CI: 0.99, 1.04, $p=0.98$).

Variables associated with increased risk of sleep disturbance included (Table 1) depressive symptom score (OR: 3.56; 95% CI: 3.14, 4.04, $p<0.0001$), female sex (1.75; 1.47, 2.08, $p<0.0001$), pain (1.06; 1.03, 1.08, 0.0006); liver disease (1.13; 1.06, 1.20, $p=0.0068$), PTSD (1.81; 1.60, 2.04, $p<0.0001$), hazardous alcohol use (1.15; 1.07, 1.23, $p=0.0014$), current smoking (1.20; 1.10, 1.30, $p=0.0007$); and higher medication count (1.06; 1.05; 1.08, $p<0.0001$). Variables protective against sleep disturbance included age over 65 years (0.78; 0.69, 0.87, $p=0.0007$), Black race (0.64; 0.60, 0.69, $p<0.0001$), and Hispanic ethnicity (0.76; 0.68, 0.85, $p<0.0001$). When the five indicators for specific medication classes were included in the model, only hazardous opiate use was not associated with sleep disturbance. After controlling for these specific medication classes, medication count retained the significance of its association (1.04; 1.03, 1.06, $p=0.003$).

Results for sleep disturbance were similar in the analyses restricted to HIV infected Veterans. Of note, none of the HIV-specific variables (CD4 count (1.00; 1.00, 1.00, $p=0.95$), HIV-RNA (1.00; 1.00, 1.00, $p=0.90$), ART use (1.02; 0.92, 1.14, $p=0.95$), and efavirenz use (0.96; 0.88, 1.05, $p=0.94$)) were associated with occurrence of sleep disturbance.

The C-statistics for the combined and HIV-only samples were 0.78 and 0.77 and both exhibited good calibration per the Hosmer and Lemeshow Goodness-of-Fit statistic.¹⁴

The explanatory variables used to model the association between HIV infection and sleep disturbance severity were virtually identical to those utilized for the dichotomized outcome. Severity was also modeled in combined and HIV infected only samples.

Strengths

This longitudinal study explored self-reported sleep disturbance and severity in a large matched cohort of HIV infected and uninfected Veterans. Adjustment for comorbid conditions and medication counts helped differentiate the relative contributions of chronic disease and polypharmacy. It is notable that the HIV infected individuals included in this analysis had a high CD4 count at baseline, accurately reflecting the relatively good health of persons comprising the current epidemic.

The question of the generalizability of our results to populations outside of the VA is pertinent. A recent study explored the overlap between Veterans receiving care in the Veterans Health Administration and civilian cohorts found that VHA enrollees had similar demographic and health characteristics as individuals with Medicaid, Medicare, or private

insurance coverage. These results suggest that research done within the VHA may be generalizable to other clinical populations.¹⁵

Limitations

The primary limitation of this study was its reliance on a single question from the HIV Symptom Index to assess sleep disturbance. The self-reported outcome essentially reflected degree of severity rather than its true occurrence. Any non-reporting of sleep disturbance might therefore reflect patients' focus on other issues that were of greater concern at that moment. Future studies will include the use of validated sleep questionnaires and physiologic measures of sleep (actigraphy or polysomnography) for a more in-depth understanding of the nature and severity of the sleep disturbance. The dichotomization of the outcome may have decreased our power to detect sleep disturbance, but this limitation is attenuated by the large sample size and the fact that results from the full range of outcome values from the Symptom Index scale did not differ substantively from those of the dichotomized outcome. While selection bias is always a concern in any observational study, the matching of HIV infected and uninfected participants by age, race, and gender does address potential imbalance in those important confounders. Lastly, because this study was observational, we make no claims of causality.

Conclusion

Our results demonstrate that while sleep disturbance is more common among HIV infected individuals, its higher incidence may be driven by numerous factors known to cause sleep disturbance in the general population, rather than from HIV-specific factors. Until we have guidelines for treatment of sleep disturbance among HIV infected individuals, we recommend avoiding the use of sleep medications and routine use of CBT-I¹⁶ and/or CAM therapies. Patients may benefit from a provider's review of their medications and subsequent elimination of those not central to their goals of care. Future studies should include physiologic measures of sleep, such as those measured with actigraphy and polysomnography. Those techniques will more clearly characterize sleep patterns in this population and enhance evaluation of the association between HIV infection and sleep disturbance.

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Table

HIV and self-reported sleep disturbance: unadjusted and adjusted models.*

	Unadjusted		Adjusted Polypharmacy only		Adjusted Polypharmacy and specific sleep-related medications
	Odds Ratio (95% CI)**	p [‡]	Odds Ratio (95% CI)**	p [‡]	p [‡]
HIV	1.13 (1.03, 1.24)	0.01	1.08 (1.01, 1.15)	0.39	1.08 (1.01, 1.05)
Age		--			
< 50 years of age			REF	REF	REF
50 – 65 years of age			0.93 (0.87, 1.00)	0.65	0.94 (0.88, 1.01)
> 65 years of age			0.78 (0.69, 0.87)	0.0007	0.80 (0.72, 0.90)
Race		--			
White			REF	REF	REF
Black			0.64 (0.60, 0.69)	<0.0001	0.69 (0.64, 0.75)
Hispanic			0.76 (0.68, 0.85)	<0.0001	0.79 (0.71, 0.89)
Other			0.84 (0.72, 0.99)	0.69	0.90 (0.77, 1.06)
Female	--	--	1.75 (1.47, 2.08)	<0.0001	1.74 (1.46, 2.07)
Pain Score	--	--	1.06 (1.03, 1.08)	0.0006	1.06 (1.03, 1.08)
Depression [§]	--	--	3.56 (3.14, 4.04)	<0.0001	3.49 (3.08, 3.97)
Liver disease	--	--	1.13 (1.06, 1.20)	0.0068	1.11 (1.04, 1.18)
PTSD	--	--	1.81 (1.60, 2.04)	<0.0001	1.55 (1.37, 1.75)
Hazardous alcohol use	--	--	1.15 (1.07, 1.23)	0.0014	1.14 (1.07, 1.22)
Smoker	--	---			
Never			REF	REF	REF
Former			1.05 (0.96, 1.14)	0.86	1.05 (0.97, 1.14)
Current			1.20 (1.10, 1.30)	0.0007	1.20 (1.10, 1.31)
Medication count	--	--	1.06 (1.05, 1.08)	<0.0001	1.04 (1.03, 1.06)

	Unadjusted		Adjusted Polypharmacy only		Adjusted Polypharmacy and specific sleep-related medications	
	Odds Ratio (95% CI)**	p [‡]	Odds Ratio (95% CI)**	p [‡]		p [‡]
Benzodiazepine use	--	--	--	--	1.60 (1.42, 1.80)	0.003
Z-drug use	--	--	--	--	2.15 (1.74, 2.66)	0.003
Hazardous opiate use	--	--	--	--	1.05 (0.92, 1.18)	0.832
SSRI use	--	--	--	--	1.20 (1.10, 1.32)	0.003
Other antidepressant use	--	--	--	--	1.60 (1.46, 1.76)	0.003

* Variables included in the model but not significantly associated with self-reported sleep disturbance: underweight (body mass index < 18.5), normal weight (BMI between 18.5 and 25), overweight (BMI between 25 and 30), obesity (BMI ≥ 30), heart failure, COPD, other lung disease, drug use or abuse, coronary artery disease, diabetes, peripheral vascular disease, renal disease, cerebrovascular disease/stroke, cancer, sleep apnea, female × depression^{1/2}, female × depression, medication count × pain score, (medication count)² × pain score, depression (PHQ-2), survey wave. (baseline, follow-up 1-6)

** Model fit: C statistic: 0.78; Hosmer and Lemeshow Goodness-of-Fit> 0.05

[‡] Model fit: C statistic: 0.77; Hosmer and Lemeshow Goodness of Fit >0.05

[‡] p values calculated by Hochberg to control for multiple comparisons

[§] square root of PHQ-2 score.