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Insomnia, hypnotic use, and health-related quality of life in a nationally representative sample

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Abstract
Purpose To assess health-related quality of life (HRQoL) associated with insomnia and prescription hypnotic use.
Methods Primary outcomes were mental component summary (MCS) and physical component summary (PCS) scores from the 12-item Short-Form Health Survey. Using multiple regression, subjects in the 2005 through 2009 Medical Expenditure Panel Survey with diagnosed insomnia were compared against those without that diagnosis. Among subjects with diagnosed insomnia, users of prescription hypnotics were compared against nonusers.
Results Of 104,274 adults, 1.3 % ($n = 1{,}401$) had an insomnia diagnosis. Of those, 45.6 % ($n = 639$) used prescription hypnotics. For subjects with insomnia, mean PCS and MCS scores were 9.2 and 7.0 points lower ($p < 0.001$), respectively. After controlling for demographic and clinical covariates, differences remained significant (PCS:5.1; MCS:6.2; $p < 0.001$). Among subjects with insomnia, HRQoL scores were not different between prescription hypnotic users ($n = 639$) and nonusers ($n = 762$). Analysis by drug class revealed lower PCS scores (difference: 7.5, $p < 0.001$) with benzodiazepine use ($n = 129$) versus benzodiazepine receptor agonist use ($n = 493$), but the adjusted difference was not significant (difference: 3.8, $p = .018$).
Conclusions Diagnosed insomnia was associated with consistent decreases in both physical and mental HRQoL scores, regardless of whether prescription hypnotics were used. Benzodiazepine use may be associated with a further decrease in physical HRQoL scores. Although limited by its retrospective design, this study provides a first look at real-world hypnotic use outcomes at a national level. Important next steps include studies with patients serving as their own controls, and further evaluation of the sensitivity of HRQoL instruments to the effects of insomnia treatments.

Keywords Health-related quality of life · Insomnia · Sleep · Hypnotic · SF-12 · MEPS

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Introduction

Diminished health-related quality of life (HRQoL) is a significant predictor of medication use for insomnia [1]. Although insomnia is a disorder of sleep, symptoms that manifest during waking hours (e.g., fatigue, irritability, and decreased cognitive and psychomotor acuity) are what typically prompts insomnia sufferers to seek treatment [2, 3]. About one in five Americans (22 %) experience insomnia severe enough to cause daytime consequences [4], and it is well documented that insomnia sufferers experience reduced HRQoL [5–12]. It is reasonable to expect, therefore, that insomnia treatments improve not only sleep, but also HRQoL. Indeed, measuring daytime HRQoL is considered essential to evaluate insomnia therapies [13]. To date, however, there is limited evidence that medications approved for insomnia ('hypnotics') can improve HRQoL deficits associated with poor sleep.

In clinical trials, some medications show promise, but the literature as a whole remains equivocal, in part because HRQoL is not consistently included as an outcome [14–16]. Among trials that measure HRQoL, many observed no improvements. When improvements have been observed, they are often limited in effect size (small to moderate),

scope (one or a few domains), and/or duration (≤6 weeks). Study limitations also cloud the evidence: HRQoL is not typically a primary outcome, measures vary widely, instruments used are not always validated, and clinical trial conditions and populations may not reflect real-world hypnotic use. For example, a 4-week trial of doxepin ($n = 20$) versus placebo ($n = 20$) found improved visual analog scale ratings for 'working ability,' but no difference in 'energy' ratings [17]. A large trial of eszopiclone ($n = 593$) versus placebo ($n = 195$) over 6 months found sustained improvements in 'daytime ability to function,' 'daytime alertness,' and 'sense of physical well-being,' but these were not key measures for the study and the measurement instrument does not appear to have been validated [18]. A 4-week study of zolpidem ($n = 94$) versus placebo ($n = 96$) in subjects recently treated for major depressive disorder found significant improvement in the 'vitality' domain of the Short Form-36 Health Survey (SF-36, a validated HRQoL instrument comprising eight domains) [19], while an 8-week study of zolpidem ($n = 82$) versus placebo ($n = 81$) given intermittently (3–5 times/week) found no differences in any domain of the SF-36 [20]. For a more complete review of HRQoL measures in hypnotic trials, see the comprehensive reviews by Krystal [14], Kyle et al. [15], and Ishak et al. [16].

In contrast to these clinical trials, a survey of almost 3,000 subjects in Japan, which provided a snapshot of hypnotic use in 'usual' practice, found worsened physical HRQoL scores among hypnotic users [7]. The investigators proposed that adverse effects of benzodiazepines (BZDs; e.g., muscle weakness, next-day fatigue, and impaired cognition) may counteract benefits from prolonged sleep time, resulting in net worsened physical HRQoL [7, 21]. This is consistent with high reliance on BZDs (43 % of prescriptions for insomnia) in Japan in the early 2000s, when the study took place [1].

It is not clear whether similar results would be seen in a comparable study conducted in the USA, where BZD use for insomnia is less common. Between 1992 and 2005, four new drugs with improved side effect profiles over BZDs were approved for the treatment of insomnia; these were the so-called Z-meds (zolpidem, zaleplon, and eszopiclone) and a melatonin agonist (ramelteon). In 2003, BZDs represented only about 11 % of prescriptions for insomnia in the USA, while antidepressants and Z-meds accounted for about 22 and 18 %, respectively [1]. Through that decade, hypnotic use has increased overall, but Z-med use grew most dramatically, increasing nearly fourfold from 2000 to 2010 [22]. Z-meds are now the most commonly prescribed hypnotic for insomnia (about 38 % of prescriptions) in the USA, followed closely by the antidepressants trazodone and doxepin (36 %) [22]. Both classes outpace BZD use (17 %) by at least two to one [22]. Z-meds and antidepressants are considered safer than BZDs, whose diverse side effects include motor incoordination, cognitive impairment, and addictive potential [23, 24]. It is reasonable; therefore, to expect that US hypnotic users will have higher HRQoL scores than the hypnotic users in Japan studied by Sasai et al. [7].

As of today, we have still found no other publication assessing HRQoL associated with insomnia and hypnotic use in a real-world, nationally-representative population. Specifically, we compared HRQoL scores between (1) subjects with and without insomnia and (2) those with insomnia using, versus not using, hypnotic medications.

Methods

Data source

This study was a retrospective database analysis using data from 2005 to 2009 Medical Expenditure Panel Survey (MEPS). MEPS is conducted annually by the Agency for Healthcare Research and Quality (AHRQ) in a nationally representative sample of civilian Americans. Two strategies ensure that MEPS provides a nationally representative sample: Oversampling of Hispanics, Blacks, Asians, and low-income populations increases the precision of estimates for those subgroups, while sample weighting takes into account post-stratification, nonresponse, and oversampling [25]. Although MEPS is designed to capture the demographic diversity of the US population, it does not include enlisted personnel or institutionalized individuals, including those in hospitals, long-term care facilities, and prisons.

The MEPS dataset includes patient demographics, diagnostic codes, health care utilization data, prescribed medications, and health status indicators. Details collected during MEPS interviews are organized into topical data files (e.g., event files, medical condition files, and population characteristic files), and, for each year, data from different files can be linked to single respondents using unique person identifiers [26]. This study used the following component files: medical conditions files, prescribed medicines files, and full-year consolidated data files.

MEPS uses an overlapping panel design for sample selection. Each year, a new cohort is selected to remain in the survey for two and a half years. For any given calendar year, the subject pool comprises two cohorts, the one newly selected for that year and the one selected the preceding year and now in its second year. For each cohort, five rounds of interviews are conducted across two and a half years, but responses are pooled on a calendar year basis, rather than by individual cohort. Thus, in any given calendar year, one segment of the sample is completing the early interview rounds (one, two, and three for some) and

the other segment is completing the final interview rounds (three for some, and four and five). (The third round starts near the end of the year and is finished early in the following year; each round takes a few months to complete, given the large sample size.) With this design, patient samples are not completely independent from year to year, but pooling of data over years is considered valid because each single calendar year of MEPS is designed to be nationally representative [27].

The dependent variables of interest (HRQoL scores, see *Measures*, below) are assessed only during rounds two and four of MEPS. Because insomnia can be either transient or chronic, inclusion in the 'insomnia' cohort was restricted to subjects reporting a diagnosis of insomnia in round two or four for each year. This criterion ensured that subjects were classified as having or not having insomnia during the *same* round in which their HRQoL was assessed. For example, the insomnia group for 2005 included only subjects who reported insomnia in round two (subjects newly selected that year) or round four (subjects continuing from the previous year). An individual reporting insomnia in round two of 2005, but not in round four of 2006, would be classified accordingly each year.

The University of Texas at Austin Investigational Review Board reviewed and approved this project. Some analyses were conducted at the AHRQ Center for Financing, Access, and Cost Trends (CFACT) Data Center, and the support of AHRQ in accessing these data is acknowledged. The results and conclusions in this paper are those of the authors and do not indicate concurrence by AHRQ or the Department of Health and Human Services.

Study population

In MEPS, patient-reported medical conditions are assigned diagnostic codes by trained medical coders. Subjects in the insomnia group were identified using the following International Classification of Diseases, Ninth Revision (ICD-9) codes: 307.41 (adjustment), 307.42 (psychophysiological), 327.00 (organic), 327.01 (due to medical condition), and 780.52 (unspecified). The prescribed medication files provided information to identify respondents who used any approved insomnia medications from 2005 through 2009: zolpidem, eszopicplone, zaleplon, estazolam, flurazepam, quazepam, temazepam, triazolam, and ramelteon. Drugs were identified via hand search by name (brand and generic), including all formulations, abbreviations, spellings, and misspellings.

Measures

The primary dependent variables were the mental component (MCS) and physical component (PCS) summary scores from the Short Form-12 (SF-12) survey. The SF-12 is derived from the Short Form-36 Health Survey (SF-36), which assesses patient health with 36 questions across eight domains: physical function, social function, physical role limitations, emotional role limitations, bodily pain, vitality, general mental health, and general health [28]. SF-36 scores can be summarized into two general indicators of patient status, MCS and PCS scores, which are reported as norm-based scores standardized to 1998 population norms (mean = 50, SD = 10). A score of 50 represents the 'norm' or average score for the general population, with higher and lower scores indicating better or worse HRQoL, respectively. From the SF-36, twelve questions addressing all eight domains were selected to create the SF-12, a shorter survey instrument that yields MCS and PCS scores consistent with the SF-36 [29].

Although neither the SF-36 nor the SF-12 includes items specific to sleep, both instruments have been used to assess HRQoL in insomnia sufferers. Poor SF-36 and SF-12 scores are significantly correlated with poor sleep, and the severity of sleep disturbance is reflected in the degree of reduction in HRQoL scores [4, 10, 30–33]. A recent evaluation confirmed the reliability and validity of SF-12 PCS and MCS scores as reported in MEPS [34]. To date, a minimally important difference (MID) in SF-36 or SF-12 component summary scores has not been established for insomnia. Given the population standard deviation of ten points, however, it is reasonable to consider a five-point change to be meaningful. A difference of five points represents one-half standard deviation, which is a common MID threshold [35], and an effect size of moderate magnitude ($d = 0.5$) according to Cohen's formulation of effect size for a t test (Cohen's d = difference between means/standard deviation) [36].

Covariates controlled for in this study included both demographic and clinical characteristics. Demographic variables were age, race, marital status, education, family income, health insurance status, and region (Tables 2, 3). Clinical characteristics were represented by Charlson Comorbidity Index (CCI) scores, calculated using data available in MEPS [37]. CCI scores are estimates of life-year expectancy that reflect the presence (and, in some cases, the severity) of any of 16 major comorbidities (e.g., myocardial infarction, congestive heart failure, kidney disease, cancer, and AIDS) [38].

Statistical analysis

All statistical analyses were performed with SAS® 9.3 (SAS Institute Inc., Cary, NC, USA). The 'survey' procedure was used to account for the complex sampling design of MEPS and to ensure accurate estimates of standard errors. In consideration of the large weighted sample size from MEPS estimates and the multiple analyses performed,

an alpha of 0.01 was considered statistically significant. Descriptive statistics were calculated for two pairs of groups: (1) subjects with and without insomnia and (2) among subjects with insomnia, hypnotic users and nonusers. Comparisons were made using *t* tests (continuous variables) and Rao-Scott Chi-square tests (categorical variables). *T* tests were used to examine differences in HRQoL scores between groups: (1) with versus without insomnia and (2) with insomnia who used versus did not use hypnotics. Adjusted differences in HRQoL were estimated using multiple regression to control for demographic and clinical characteristics.

Results

Rates of insomnia and hypnotic use

From 2005 through 2009, there were 104,274 adults in MEPS, of which 1.3 % ($n = 1{,}401$) reported a diagnosis of insomnia (Table 1). Insomnia was reported with higher frequency by females, Whites, non-married, older respondents, and those with lower income, public health insurance, and a higher CCI (Table 2). Among subjects reporting insomnia, 45.6 % ($n = 639$) used a hypnotic. The only variable significantly related to hypnotic use was insurance status; a greater percent of those with private health insurance used a hypnotic, compared to those with public or no insurance (Table 3). Use of hypnotics was also more common among subjects with higher family income, but this trend ($p = .029$) did not meet our alpha-level (0.01) for statistical significance.

Quality of life measures

For subjects with an insomnia diagnosis, PCS scores were significantly lower than for those without diagnosed insomnia (Table 4a; Fig. 1). The adjusted difference, controlling for demographic and clinical characteristics, remained significant. Similarly, MCS scores were significantly lower in the group with diagnosed insomnia, and the adjusted difference remained significant.

Among subjects with diagnosed insomnia, there was no difference in PCS scores or in MCS scores between users and nonusers of hypnotics (Table 4a; Fig. 2).

To assess possible differences in outcomes between different types of medications, users of hypnotics with insomnia were grouped by medication class: BZD, Z-med, and melatonin agonist. The melatonin agonist group was excluded from further analysis, as the sample size was too small to make national estimates using MEPS. PCS scores were significantly lower in the BZD group compared with the Z-med group (Table 4c; Fig. 3). After adjusting for covariates, however, this difference did not meet our threshold for significance ($p = 0.018$, alpha = 0.01). No difference was detected in MCS scores between the BZD and Z-med groups.

Table 1 Yearly breakdown of subjects with insomnia diagnosis, without and with hypnotic use

	Insomnia diagnosis		Insomnia and hypnotic use	
	n	*N*	*n*	*N*
2005	244	2,574,354	106	1,195,770
2006	308	3,288,334	127	1,487,719
2007	270	3,275,697	139	1,868,380
2008	247	3,220,177	106	1,412,915
2009	332	3,630,789	161	1,790,148
Total	1,401	15,989,351	639	7,754,932

n = number sampled from MEPS, per person-year from 2005 through 2009, N = weighted n, per person-year from 2005 through 2009

Discussion

In summary, four key findings emerged from this study. (1) Rates of reported insomnia diagnosis were substantially lower than the estimated prevalence of insomnia. (2) Insomnia diagnosis was associated with lower socioeconomic status, but hypnotic use appeared to be associated with higher socioeconomic status. (3) Insomnia was associated with reduced HRQoL, even after adjusting for possible correlates of insomnia such as comorbidities and demographic characteristics. (4) For subjects with insomnia, no difference in HRQoL was observed between users and nonusers of hypnotics. Notably, however, comparison by drug class found a possible trend of reduced physical HRQoL with BZD use, relative to Z-med use. A more detailed discussion of each finding follows.

Our first finding, that only 1.3 % of MEPS respondents reported an insomnia diagnosis, while an estimated 22 % of the US population meet the diagnostic criteria for insomnia [4], is not surprising. Studies in both inpatient and outpatient settings have found that physicians often fail to screen for sleep disturbances, resulting in prevalence estimates as low as 0.1 % for *all* sleep disorders [39–43]. Patients, too, often fail to regard poor sleep patterns as a medical issue. Léger and Poursain [1] found that only 14.7 % of Americans experiencing insomnia presented their symptoms to a physician. Even when physicians are made aware of a patient's trouble sleeping, rates of diagnosis are low. Morlock et al. [44] found that physicians assigned an insomnia diagnosis to only 9.8 % of patients complaining of symptoms.

Table 2 Sociodemographic and clinical characteristics of total study population, comparing those with and without insomnia

	No insomnia		Insomnia		χ^2 test	*p* value
	n	*N* (%)	*n*	*N* (%)		
Total	102,873	1,102.0 M (98.7)	1,401	16.0 M (1.3)		
Sex						
Male	46,862	534.0 M (48.5)	470	5.7 M (35.6)	51.42	<.001
Female	56,011	568.0 M (51.5)	931	10.3 M (64.4)		
Race						
White	76,654	896.8 M (81.4)	1,143	13.9 M (86.9)	18.16	<.001
Black	17,971	128.2 M (11.6)	155	1.1 M (7.0)		
Other	8,248	77.0 M (7.0)	103	1.0 M (6.1)		
Marital status						
Married	55,806	607.7 M (55.1)	649	7.8 M (48.6)	11.09	<.001
Single	47,064	494.3 M (44.9)	752	8.2 M (51.4)		
Education						
<High school	26,075	194.1 M (17.7)	349	2.9 M (18.4)	2.74	.602
High school	31,992	344.0 M (31.4)	425	5.0 M (31.2)		
2-year college	18,230	214.1 M (19.6)	289	3.4 M (21.2)		
College	17,336	227.3 M (20.8)	216	3.0 M (18.6)		
Advanced degree	8,435	114.8 M (10.5)	116	1.7 M (10.7)		
Family income						
Poor/negative	17,352	121.2 M (11.0)	275	2.0 M (12.6)	17.21	.002
Near poor	6,122	44.8 M (4.1)	113	1.0 M (6.4)		
Low income	16,772	143.9 M (13.1)	210	2.3 M (14.3)		
Middle income	30,669	341.8 M (31.0)	381	4.5 M (28.2)		
High income	31,958	450.2 M (40.9)	422	6.2 M (38.5)		
Health insurance						
Private	62,273	768.8 M (69.8)	804	10.7 M (67.1)	106.24	<.001
Public	20,536	168.0 M (15.2)	497	4.3 M (26.7)		
No insurance	20,064	165.2 M (15.0)	100	1.0 M (6.3)		
Region						
Northeast	15,446	204.2 M (18.5)	201	2.7 M (17.0)	5.65	.13
Midwest	20,666	242.6 M (22.0)	299	3.5 M (22.0)		
South	39,698	402.1 M (36.5)	490	5.4 M (33.9)		
West	27,063	253.1 M (23.0)	411	4.3 M (27.2)		
	Mean ± SE		Mean ± SE		*t* test	*p* value
Age	46.18 ± 0.15		55.32 ± 0.54		−17.03	<.001
CCI score	0.36 ± 0.01		0.94 ± 0.05		−11.41	<.001

n = number sampled from MEPS, total person-years from 2005 through 2009, *N* = weighted *n* in millions, total person-years from 2005 through 2009, M = million, Health insurance = any private during the year, public only during the year, uninsured for the entire year, CCI = Charlson Comorbidity Index computed after identification of chronic conditions via ICD-9 codes

Complicating this issue is the diversity of diagnostic criteria and assessment instruments for insomnia as well as the question of whether insomnia is a primary or secondary condition. Furthermore, a diagnosis of insomnia may not be necessary for a patient to receive adequate treatment. For example, patients reporting insomnia symptoms often receive diagnoses for depression and/or anxiety [44, 45]. Such a diagnosis may be sufficient to address insomnia, as many therapies for anxiety and depression have beneficial effects on sleep [39, 41]. Alternatively, there is evidence that some patients are prescribed insomnia treatments without receiving an insomnia diagnosis [44–47]. Although an insomnia diagnosis is not necessary to receive treatment, low rates of diagnosis could signify under-treatment. It may, therefore, be useful to investigate whether formal insomnia diagnosis is related to any differences in clinical outcomes.

Our second key finding concerns the distribution of insomnia and insomnia treatments throughout the USA. Similar to prior studies, we found associations between insomnia and female sex, low income, and comorbidity [4,

Table 3 Sociodemographic and clinical characteristics of subjects with insomnia, comparing those without and with hypnotic use

	Insomnia and no hypnotic use		Insomnia and hypnotic use		χ^2 test	*p* value
	n	*N* (%)	*n*	*N* (%)		
Total	762	8.2 M (54.4)	639	7.8 M (45.6)		
Sex						
Male	278	3.1 M (37.9)	192	2.6 M (33.1)	1.98	.159
Female	484	5.1 M (62.1)	447	5.2 M (66.9)		
Race						
White	616	7.1 M (86.0)	527	6.8 M (87.8)	1.32	.517
Black	89	.6 M (7.0)	66	.5 M (7.0)		
Other	57	.6 M (7.0)	46	.4 M (5.2)		
Marital status						
Married	331	3.7 M (45.3)	318	4.0 M (52.2)	3.36	.067
Single	431	4.5 M (54.7)	321	3.7 M (47.8)		
Education						
<High school	210	1.7 M (20.8)	139	1.2 M (15.9)	8.09	.088
High school	231	2.6 M (32.0)	194	2.3 M (30.2)		
2-year college	159	1.8 M (21.3)	130	1.6 M (21.0)		
College	97	1.2 M (15.0)	119	1.7 M (22.3)		
Advanced degree	60	.9 M (10.8)	56	.8 M (10.6)		
Family income						
Poor/negative	168	1.2 M (14.8)	107	.8 M (10.3)	10.81	.029
Near poor	74	.6 M (7.8)	39	.3 M (4.8)		
Low income	119	1.2 M (15.1)	91	1.0 M (13.5)		
Middle income	199	2.3 M (27.8)	182	2.2 M (28.7)		
High income	202	2.8 M (34.5)	220	3.3 M (42.7)		
Health insurance						
Private	385	5.0 M (60.7)	419	5.7 M (73.9)	19.11	<.001
Public	302	2.5 M (30.8)	195	1.7 M (22.3)		
No insurance	75	.7 M (8.6)	25	.3 M (3.8)		
Region						
Northeast	107	1.3 M (16.0)	94	1.34 M (18.0)	3.72	.294
Midwest	169	2.1 M (25.0)	130	1.5 M (18.9)		
South	251	2.6 M (31.3)	239	2.8 M (36.6)		
West	235	2.3 M (27.8)	176	2.1 M (26.6)		
	Mean ± SE		Mean ± SE		*t* test	*p* value
Age	55.8 ± 0.80		54.8 ± 0.77		0.93	.352
CCI score	0.87 ± 0.06		1.00 ± 0.08		−1.26	.209

n = number sampled from MEPS, person-years from 2005 through 2009, *N* = weighted *n* in millions, person-years from 2005 through 2009, M = million, Health insurance = any private during the year, public only during the year, uninsured for the entire year, CCI = Charlson Comorbidity Index computed after identification of chronic conditions via ICD-9 codes

48]. We also found insomnia reported more frequently by subjects with public health insurance (vs. private or no insurance). Notably, however, hypnotic use was associated only with health insurance status; in particular, hypnotic use was more prevalent among subjects with private insurance. We also found a trend (not significant at $p < 0.01$) of higher reported hypnotic use among subjects with higher family incomes; this is consistent with a recent evaluation of use patterns for prescription insomnia medications [22].

These results suggest that lower socioeconomic classes may be under-treated for insomnia, which is troubling in light of evidence that insomnia is more common in this population segment [4, 12, 48, 49]. Furthermore, detrimental effects of insomnia on physical and psychological health are likely to take a greater toll on those with limited access to health care. Notably, insomnia may itself be a risk factor for poor economic status; workers with insomnia experience increased odds of negative work outcomes, including decreased concentration and productivity and increased absenteeism and accidents [50]. Untreated insomnia can also increase patients' healthcare-related costs by an estimated $1200 yearly (US$2003) [51]. With new treatments entering the market over the last

Table 4 Group comparisons of health-related quality of life scores

(a) Analysis of all subjects in MEPS, 2005–2009 (n = 104,274)

	No insomnia n = 102,873 Mean (SD)	Insomnia n = 1,401 Mean (SD)	Unadjusted		Adjusted[a]	
			Difference	p	Difference	p
PCS	49.8 (.1)	40.6 (.5)	9.2 (.5)	<.001	5.1 (.4)	<.001
MCS	51.1 (.0)	44.1 (.4)	7.0 (.4)	<.001	6.2 (.4)	<.001

(b) Analysis of all subjects with insomnia diagnosis (n = 1,401)

	Hypnotic n = 639 Mean (SD)	No hypnotic n = 762 Mean (SD)	Unadjusted		Adjusted[a]	
			Difference	p	Difference	p
PCS	40.6 (.8)	40.6 (.7)	.0 (1.0)	.991	1.0 (.8)	.223
MCS	44.3 (.6)	43.9 (.5)	.4 (.8)	.586	.0 (.8)	1.000

(c) Analysis of all subjects with insomnia diagnosis and using prescription hypnotics (n = 762)[b]

	Z-Meds n = 493 Mean (SD)	BZDs n = 129 Mean (SD)	Unadjusted		Adjusted[a]	
			Difference	p	Difference	p
PCS	41.8 (.9)	34.7 (1.5)	7.5 (1.6)	<.001	3.8 (1.6)	.018
MCS	44.5 (.7)	43.4 (1.6)	1.0 (1.8)	.570	1.5 (1.5)	.307

MEPS: Medical Expenditure Panel Survey. PCS: SF-12 physical composite score. MCS: SF-12 mental composite score. Z-meds: zolpidem, zaleplon, and eszopiclone. BZDs: estazolam, flurazepam, quazepam, temazepam, and triazolam

[a] Adjusted using the following covariates: age, race, marital status, education, family income, health insurance status, region, and Charlson Comorbidity Index

[b] Subjects using ramelteon were excluded from analysis; sample size (n = 17) was too small

decade, many still under patent-protected pricing, more contemporary analyses of the pharmacoeconomic and clinical impacts of hypnotics are needed, especially for patients with limited economic resources.

Our third key finding confirmed, as other studies have shown, an association between insomnia and significantly reduced HRQoL. A strength of this study, however, was the large, nationally representative sample population, which provides a more comprehensive epidemiologic picture along with the ability to control for several demographic and clinical covariates. It is well established that there is a strong relationship between insomnia and demographic or clinical hardships that can be detrimental to HRQoL (e.g., divorce, low income, unemployment, and comorbidities) [4, 48]. Even after adjusting for these conditions, however, we found significant reductions in both physical and mental HRQoL among patients with diagnosed insomnia. This finding underscores the importance of effectively treating insomnia as a distinct medical condition, regardless of whether it is coincident with other diagnoses.

Our fourth, and most important, key finding pertains to the relationship between hypnotic use and HRQoL. Shortened sleep time, as experienced with insomnia, has numerous undesirable effects on both physical and mental health during waking hours [1, 44, 46, 47, 52]. Ideally, insomnia medications should improve sleep sufficiently to reverse these HRQoL deficits. We found no difference, however, in HRQoL between users and nonusers of hypnotics in the insomnia group.

It is possible that the magnitude of HRQoL change associated with hypnotic use was below the sensitivity threshold of the SF-12. If so, better sensitivity may require a disease-specific instrument. Three such instruments have been developed (the quality of life of insomniacs questionnaire (QOLI) [53], the Hotel Dieu 16 (HD-16) [54], and the Glasgow Sleep Impact Index (GSII) [55]), but none has gained widespread use, to date. Moreover, the sensitivity of these instruments for evaluating insomnia and insomnia treatments should be evaluated against the more widely used SF-12 and SF-36, both of which have demonstrated sensitivity to the effects of insomnia on HRQoL, even distinguishing between levels of severity [4, 10, 30–33]. Notably, the SF-36 has detected small to moderate (<5 points), and significant, improvements in HRQoL in response to insomnia treatments, including cognitive behavioral therapies [56, 57], valerian and hops [58, 59], zolpidem [19], and eszopiclone [60]. Given this degree of sensitivity, it may not be necessary—or even meaningful—to detect changes that fall below the detection threshold of the SF-36. The sensitivity of the SF-12 in assessing insomnia-related HRQoL is comparable to the SF-36, but it may be inadequate to assess treatment effects. In hypnotic drug trials that include HRQoL assessments, observed improvements are often limited to only one or a few domains [14, 15]. Thus, effects might not be captured by the SF-12, which collapses eight domains into two composites. Further research is needed to identify and validate instruments with sufficient sensitivity to the effects of insomnia treatments on HRQoL.

In a sub-analysis, BZDs and Z-meds were evaluated separately. In neither group did mean HRQoL scores exceed those of the untreated insomnia group. The shared mechanism of action of Z-meds and BZDs may help to explain why neither group demonstrated superior results, but this

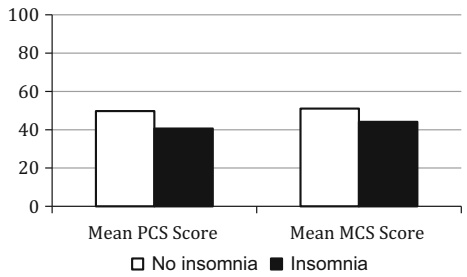

Fig. 1 Unadjusted SF-12 composite scores for all subjects, no insomnia versus insomnia. SF-12 scores are summarized into two composites: the mental component summary (MCS) and physical component summary (PCS). Both are reported as norm-based scores (mean = 50, SD = 10), with a score of 50 representing the 'norm' or average score for the general population, and higher or lower scores indicating better or worse HRQoL, respectively

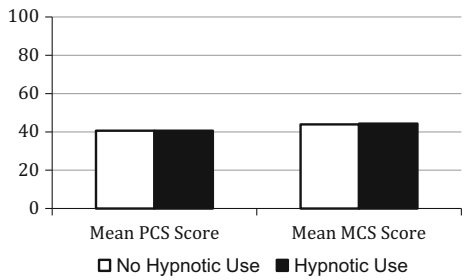

Fig. 2 Unadjusted SF-12 composite scores for subjects with insomnia, hypnotic use versus no hypnotic use. Hypnotics used were: zolpidem, zaleplon, eszopiclone, estazolam, flurazepam, quazepam, temazepam, and triazolam

should be confirmed in studies designed specifically to assess comparative effectiveness. Where differences between Z-meds and BZDs might be expected is in relative safety. Although they have the same action as BZDs, Z-meds have fewer side effects due to their selectivity for a subset of receptors [61]. Analyzed separately (and before adjusting for covariates), BZD users had significantly reduced physical HRQoL (PCS scores) relative to Z-med users. Although this result was not significant (at $p < 0.01$) after adjusting for covariates, it may warrant further investigation, especially since it is consistent with earlier findings. Sasai et al. [7] found decreased physical HRQoL with hypnotic use in Japan, where BZDs were used widely for insomnia, and hypothesized that this reflected BZD side effects, such as daytime sedation and myorelaxation. If confirmed, such a result would argue in favor of Z-meds over BZDs for insomnia, as well as raise the concern that BZD use for insomnia may produce more harm than good.

It should be noted, however, that Z-med use is not without problems, especially at higher doses [62]. Residual next-day sedation and impaired cognition have been reported commonly, prompting the Food & Drug Administration (FDA) in 2013 to require lower recommended

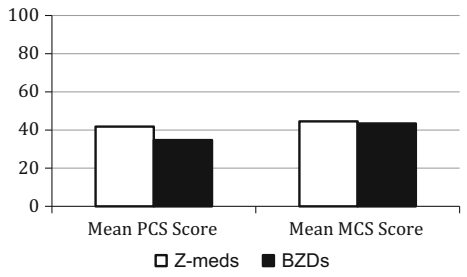

Fig. 3 Unadjusted SF-12 composite scores for subjects with insomnia who used hypnotics, benzodiazepine receptor agonist (Z-med) use versus benzodiazepine (BZD) use. Z-meds were: zolpidem, zaleplon, and eszopiclone. BZDs were: estazolam, flurazepam, quazepam, temazepam, and triazolam

doses for certain formulations of zolpidem [63, 64]. For some patients, at least, residual effects of Z-meds may negatively affect HRQoL. In addition, both BZDs and Z-meds are associated with abnormal sleep architecture, including decreased time spent in slow wave and rapid eye movement sleep [65–67]. Reversing the effects of insomnia on HRQoL may require treatments that address not only sleep duration, but also sleep architecture [68]. Our study evaluated only drugs with FDA approval for the treatment of insomnia, but several other medications are used 'off-label,' including tricyclic antidepressants, anticonvulsants, and atypical antipsychotics [22]. Because some of these drugs have demonstrated beneficial effects on sleep architecture [24, 41], it may be worthwhile to evaluate HRQoL in patients using them for insomnia.

Although our study design does not permit drawing conclusions about cause and effect, our results suggest the need to investigate further the clinical outcomes of hypnotics, especially in real-world settings with HRQoL measures included as primary end points. Using a 'before and after therapy' design, with patients serving as their own controls, could provide additional insight. It may also be necessary to identify and adopt a standardized, disease-specific measure of HRQoL in patients with insomnia.

Limitations

MEPS provides a large, nationally representative study population, but does not include enlisted military personnel or institutionalized individuals. This limits the generalizability of our results, as does restricting our study to adults only. Reliance on diagnostic codes to identify patients with insomnia (along with low rates of diagnosis as reported in the literature) may have artificially reduced the insomnia sample group. Thus, our results may not be generalizable to the larger population of insomnia sufferers with no recorded diagnosis. Reporting bias may have also reduced the insomnia group, as there is some evidence that MEPS

participants tend to underreport their medical conditions [69, 70]. Our study results may have been confounded by use of alternative treatments for insomnia, including cognitive behavioral therapy, off-label drugs, and over-the-counter medications, which were not evaluated. It is also not possible to determine whether the severity of insomnia was comparable between the groups using and not using hypnotics. A further limitation was our inability to determine the duration of insomnia or the persistence of hypnotic use for our patient population; it is possible that short disease courses, short treatment durations, or poor adherence affected the outcomes. Protopathic bias may be a concern because subjects were not excluded on the basis of comorbid conditions. A subject in the diagnosed insomnia group may, therefore, have also had one or more comorbid conditions known to be associated with and/or treated similarly to insomnia (e.g., depression, anxiety, and pain). To ensure that the insomnia group comprised subjects for whom insomnia was a disorder in its own right (rather than a secondary symptom or a medication side effect) and to reduce the likelihood of misattribution of main effects, we studied only patients reporting diagnosed insomnia and only medications specifically indicated for insomnia. Other than including the Charlson Comorbidity Index as a covariate, measures were not taken to mitigate more subtle interactions among comorbid diseases and concomitant drugs, but this may be considered reasonable for a study in a 'real-world' setting. Finally, although regression was used to control for demographic and clinical differences in cohorts, selection bias cannot be ruled out.

Conclusion

This study characterized HRQoL associated with insomnia and use of prescription hypnotics in a large, nationally representative sample reflecting real-world conditions. Although reported rates of insomnia diagnosis were quite low in this population, about half of patients diagnosed with insomnia were prescribed a hypnotic. There was an association between insurance coverage (and possibly economic status) and use of prescription hypnotics for insomnia that should be studied further. Independent of demographic and clinical characteristics, insomnia was associated with lower mental and physical HRQoL scores compared to patients without this diagnosis. It appears, however, that among persons diagnosed with insomnia, quality of life for those using prescription hypnotics is no different than for those not using prescription hypnotics. More research is needed to assess the effects of prescription hypnotics on sleep patterns as well as effects during waking hours. In particular, HRQoL measures should be included as primary end points in future clinical trials of hypnotics, and more specific insomnia-related HRQoL measures may be needed to quantify treatment effects.

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