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PRESS RELEASE

Hypnotics' association with mortality or cancer: a matched cohort study

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ABSTRACT

Objectives: An estimated 6%–10% of US adults took a hypnotic drug for poor sleep in 2010. This study extends previous reports associating hypnotics with excess mortality.

Setting: A large integrated health system in the USA.

Design: Longitudinal electronic medical records were extracted for a one-to-two matched cohort survival analysis.

Subjects: Subjects (mean age 54 years) were 10 529 patients who received hypnotic prescriptions and 23 676 matched controls with no hypnotic prescriptions, followed for an average of 2.5 years between January 2002 and January 2007.

Main outcome measures: Data were adjusted for age, gender, smoking, body mass index, ethnicity, marital status, alcohol use and prior cancer. Hazard ratios (HRs) for death were computed from Cox proportional hazards models controlled for risk factors and using up to 116 strata, which exactly matched cases and controls by 12 classes of comorbidity.

Results: As predicted, patients prescribed any hypnotic had substantially elevated hazards of dying compared to those prescribed no hypnotics. For groups prescribed 0.4–18, 18–132 and >132 doses/year, HRs (95% CIs) were 3.60 (2.92 to 4.44), 4.43 (3.67 to 5.36) and 5.32 (4.50 to 6.30), respectively, demonstrating a dose–response association. HRs were elevated in separate analyses for several common hypnotics, including zolpidem, temazepam, eszopiclone, zaleplon, other benzodiazepines, barbiturates and sedative antihistamines. Hypnotic use in the upper third was associated with a significant elevation of incident cancer; HR=1.35 (95% CI 1.18 to 1.55). Results were robust within groups suffering each comorbidity, indicating that the death and cancer hazards associated with hypnotic drugs were not attributable to pre-existing disease.

Conclusions: Receiving hypnotic prescriptions was associated with greater than threefold increased hazards of death even when prescribed <18 pills/year. This association held in separate analyses for several commonly used hypnotics and for newer shorter-acting drugs. Control of selective prescription of hypnotics for patients in poor health did not explain the observed excess mortality.

ARTICLE SUMMARY

Article focus

- Estimate the mortality risks associated with specific currently popular hypnotics in a matched cohort design, using proportional hazards regression models.
- Estimate the cancer risks associated with specific currently popular hypnotics.
- Explore what risk associated with hypnotics can be attributed to confounders and comorbidity.

Key messages

- Patients receiving prescriptions for zolpidem, temazepam and other hypnotics suffered over four times the mortality as the matched hypnotic-free control patients.
- Even patients prescribed fewer than 18 hypnotic doses per year experienced increased mortality, with greater mortality associated with greater dosage prescribed.
- Among patients prescribed hypnotics, cancer incidence was increased for several specific types of cancer, with an overall cancer increase of 35% among those prescribed high doses.

Strengths and limitations of this study

- Design strengths included matching patient and control cohorts by age, gender and smoking. Through stratified statistical analyses, patients using hypnotics were matched with controls diagnosed with the exactly the same combination of 12 categories of comorbidity in up to 116 strata.
- The major limitation was that residual confounding could not be fully excluded, due to possible biases affecting which patients were prescribed hypnotics and due to possible imbalances in surveillance.
- Cohort studies demonstrating association do not necessarily imply causality, but the preferable randomised controlled trial method for assessing hypnotic risks may be impractical due to ethical and funding limitations.

INTRODUCTION

Hypnotic drugs are among the most widely used treatments in adult medicine. We estimate that approximately 6%–10% of US adults used these drugs in 2010, and the percentages may be higher in parts of Europe.[1 2] By 1979, the Cancer Prevention

Study I of the American Cancer Society had found that both cigarette smoking and hypnotic consumption were associated with excessive deaths,[3 4] but the hypnotic findings were discounted since the Cancer Prevention Study I was not designed primarily to study these drugs.

At least 24 published studies have now examined mortality associated with hypnotic consumption (supplemental table 1). Of the 24 cited, 18 reported significant ($p<0.05$) associations of hypnotic usage with increased mortality. Lack of uniformity of measured elements makes it impossible to incorporate the majority of these studies into a meta-analysis. Nevertheless, of 22 reports from which a risk or hazard ratio (HR) for hypnotic-associated deaths could be estimated, 21 observed a risk exceeding 1.0 ($p<0.001$). One study observed a RR of 1.0 associating total mortality with hypnotics but found hypnotic use significantly associated with cancer mortality.[5] Three other studies have reported an association of hypnotics with cancer deaths.[6–8] These studies generally failed to report the specific hypnotic drugs used by the participants, often confounded hypnotics with tranquilisers not marketed for treatment of insomnia, and usually omitted monitoring of the quantities of hypnotic drugs provided participants during the follow-up intervals. Moreover, previous studies had insufficient data on the short-acting benzodiazepine agonists such as zolpidem, zaleplon, and eszopiclone that now dominate the US market because their shorter duration of action is believed to provide improved safety.

Using data from longitudinal electronic medical records maintained by a large integrated US health system, the authors planned a matched cohort study to contrast mortality and cancer associations of zolpidem and other new short-acting hypnotics with controls and with older hypnotics.

METHODS

This study was conducted in the population served by the Geisinger Health System (GHS), the largest rural integrated health system in the USA. GHS serves a 41 county area of Pennsylvania with approximately 2.5 million people. The population is mostly of low socio-economic status, having less than high school education and less than one-third are insured under the Geisinger Health Plan. During the study period, the Geisinger Clinic provided primary care to approximately 250 000 unique outpatients annually, whose average duration of care in the system exceeds 10 years. Geisinger implemented an electronic health record (EHR) in 1996; it has been the sole-source ambulatory record since 2001. All outpatient encounters and related prescriptions are captured in the EHR, and Geisinger's implementation requires that both these elements be linked to an ICD-9 diagnosis code. Mortality ascertainment is updated monthly using the Social Security Death Index, thought to be accurate, but reliable cause-of-death data are not available.

Using a query into the EHR, we selected all 224 757 primary care patients ≥18 years of age with outpatient visits between 1 January 2002 and 30 September 2006. A further query of this subset identified 12 465 unique patients who had at least one order for a hypnotic medication and were followed-up and survived ≥3 months subsequent to that order. For each hypnotic user, we attempted to identify two controls with no record of a hypnotic prescription in the EHR at any time from among the 212 292 remaining non-users. Non-user controls were matched to the user cohort by: sex, age ±5 years, smoking status and start of period of observation either by calendar date ±1 year (preferred) or by length of observation. A control likewise could not have <3 months of observation in the EHR. We identified 24 793 controls, there being fewer than 200 hypnotic users for whom only one control could be matched. We extracted demographic data, height and weight measurements, diagnoses recorded in outpatient visit records, problem lists and the cancer registry, and orders for all medications, including the indication associated with that order. Only hypnotics frequently prescribed in the EHR and FDA-indicated by the US Food and Drug Administration for insomnia were included in these analyses and then only if it appeared that bedtime dosage was intended (see supplemental files). Roughly three of four (76.3%) of prescribed hypnotics had an explicitly sleep-related indication since physicians often use another diagnosis when they believe that insomnia is secondary to other conditions.[9] Medication orders were further reviewed by a physician (DFK) to exclude initially identified patients who did not fully meet criteria for users and matched non-users of hypnotics. Two per cent of patients were excluded for these reasons. Patients diagnosed with major cancer (apart from non-melanoma skin cancers) before the period of observation or within the first 0.05 years of follow-up were also excluded, reducing the numbers to 10 531 users and 23 674 matched non-user controls.

As prospectively planned, we examined the associations of hypnotic prescriptions with deaths, using Cox proportional hazards models in SPSS V.12.0.0 (SPSS, Inc.). Backwards stepwise models were calculated, with likelihood ratio criteria of $p<0.10$ to retain a variable and $p<0.05$ to re-enter. To control for potential confounders, model covariates included age, sex, ethnicity, marital status, body mass index (BMI) and self-reported alcohol use and smoking status. To minimise confounding by indication (eg, a physician might have prescribed a hypnotic to treat a non-sleep condition associated with disturbed sleep), comorbid diagnoses were entered as strata in the primary models as described in the following paragraph, and other models were constructed limited to users and controls with specific categories of comorbidity. To address the possibility that hypnotics were prescribed for an emerging condition that was not yet recorded as a diagnosis, comorbid conditions were controlled whether first diagnosed before or during the period of observation.

To control for different classes of comorbidity and each patient's overall burden of comorbidities, the primary

proportional hazards models were constructed incorporating stratification on up to 116 comorbidity combinations. The 116 strata compared almost all hypnotic users with non-users having exactly the same combinations of 12 classes of comorbidity. Two sets of additional models were constructed for confirmation of effects. One used strata constructed using the numbers of comorbidities comparing hazards in hypnotic users and non-users with equivalent numbers of major comorbid conditions. Another set of models restricted the population in each model to users and controls having a specific class of major chronic disease. Additional methods are described in the online supplemental files.

This study followed the guidelines of the 2008 Declaration of Helsinki and was approved and overseen by the Geisinger Institutional Review Board (IRB). Secondary approval was obtained from IRBs at the Scripps Clinic and the University of California, San Diego. The data were obtained under a data use agreement between the lead authors (RDL and DFK) and the GHS. No personally identifying data were included in the data distributed to the authors, the use of which the IRBs approved without patient consent.

RESULTS

Zolpidem was the most frequently prescribed hypnotic drug during the study interval from 2002 to 2006, and temazepam was the next most common. Table 1 describes the characteristics of the study sample, including details by categories of hypnotic used. The hypnotic user and control cohorts were well matched in age, gender, period of observation and BMI, and did not

Table 1 Characteristics of study participants

	Non-users	Any hypnotic users	Zolpidem	Temazepam
N	23 674	10 531	4338	2076
% Female*	62.7	63.9	64.8	60.0
Age (years, mean±SD)*	53.6 ±16.6	54.0±16.9	54.0±17.1	53.7±17.2
Years of observation (mean±SD)	2.50±1.43	2.49±1.39	2.34±1.33	2.51±1.37
Comorbidity classes (mean ±SD)***	1.06±1.27	1.53±1.55	1.49±1.54	1.53±1.52
Died during observation (% deceased)***	295 (1.2)	638 (6.1)	265 (6.1)	143 (6.9)
BMI (%)***				
<18.5	1.1	1.5	1.3	1.7
18.5–24.9	18.7	19.3	19.5	18.4
25–29.9	24.6	23.6	23.4	23.7
30–34.9	15.8	16.0	15.8	16.1
>35	13.1	14.4	13.7	14.2
Unknown	26.8	25.3	26.3	26.0
Marital status (%)***				
Married	62.7	56.1	56.6	57.7
Divorced	7.9	12.0	11.4	11.9
Single	15.1	14.7	14.3	13.8
Separated	1.8	2.3	2.4	2.0
Widowed	12.5	14.8	15.3	14.4
Unknown	0.0	0.1	0.0	0.1
Ethnicity (%)***				
White	93.5	97.0	97.2	96.8
Asian, Black, Hispanics	5.6	2.6	2.4	2.8
Native or other	0.9	0.4	0.4	0.3
Smoking status (%)***				
Never	42.7	42.8	44.1	41.0
Unknown	3.1	3.2	3.6	3.5
Passive	0.7	0.5	0.5	0.3
Quit	32.6	29.9	29.3	30.6
Yes, now	21.0	23.5	22.5	24.5
Alcohol use (%)***				
Yes	42.0	38.5	39.4	37.0
No	46.3	51.7	49.7	53.2
Unknown	11.7	9.7	10.9	9.8

Non-users: controls with no record of hypnotic prescription. Any hypnotic users: receiving any hypnotic prescription during the period of observation. Zolpidem: users receiving prescriptions for zolpidem only. Temazepam: users receiving prescriptions for temazepam only. Years of observation: the period of observation for users and non-users in years. Comorbidity classes: the number of disease classes diagnosed both before and during the period of observation (see supplemental files for definitions of comorbidity classes). BMI (%): the percentage of the total group within the BMI range defined (kg/m^2). Ethnicity (%): the percentage in each self-reported ethnicity (Asians, Blacks and Hispanics were combined because of small numbers). Alcohol use (%): a simple yes/no self-report. See supplemental table 3 for data concerning the less commonly prescribed hypnotics. * indicates $p<0.05$ and *** indicates $p<0.001$, contrasting non-users versus all hypnotic users.
BMI, body mass index.

differ importantly in ethnicity, marital status or smoking status.

Table 2 presents the rates of comorbidities, including incident diagnoses. These data indicated greater comorbidity among hypnotic users for each class of diagnoses, except for dementias. For most diagnoses, there was greater comorbidity among hypnotic users before the period of observation, and greater new comorbidity incidence during the period of observation (supplemental tables 4–6.)

Associations between hypnotic use and death

Associations between hypnotic prescriptions and deaths from Cox proportional hazards models stratified by comorbidity classes are presented in table 3. Patients prescribed any hypnotic had substantially elevated hazards of dying compared to those with equivalent comorbidity who took no hypnotics. Importantly, the death hazard was evident even in the lowest tertile of use. Compared with non-users, patients prescribed 1–18 pills of any hypnotic per year had a HR for death of 3.60 (95% CI 2.92 to 4.44). HRs increased further in the second and third tertiles of estimated pills consumed at 4.43 (95% CI 3.67 to 5.36) and 5.32 (95% CI 4.50 to 6.30). For use of zolpidem, the HR in the lowest tertile (5–130 mg/year) was similar, 3.93 (95% CI 2.98 to 5.17), and not significantly different from the HR for the lowest tertile of temazepam, 3.71 (95% CI 2.55 to 5.38), with exposure to 10–240 mg/year. For any hypnotic, or for zolpidem or temazepam specifically, the hazards of death in the middle tertiles of use were four to five times higher in users compared to non-users, and the hazards in the highest tertiles were five- or sixfold greater than those in non-users, indicating dose–response relationships for zolpidem and temazepam specifically and for any hypnotic.

The death HR associated with prescriptions for less commonly prescribed hypnotic drugs were likewise elevated, and the confidence limits of death hazards for each other hypnotic overlapped that for zolpidem, with the exception of eszopiclone, which was associated with higher mortality (see supplemental files).

Figure 1 shows that the hazards of hypnotics were seen in every age group. Whereas the absolute magnitude of the added hazards associated with hypnotics increased with age, as did the survival risks of hypnotic-free controls, the ratio of death hazards of hypnotic users compared to non-users was greater in users aged 18–55 years than in older groups (supplemental files).

Models addressing potential confounding of mortality association by health status

To further address the possibility that hypnotic-associated hazards were due to use of hypnotic drugs by patients with a greater burden of disease, so that elevated risks of death might be attributable to comorbidities rather than to hypnotic medications, we conducted analyses within subgroups of hypnotic non-users and users defined by diagnoses in specific disease classes (supplemental table 7). Allowing for differences in sample size, hazards in subgroups restricted to patients with specific diseases were generally consistent with the overall findings. We also observed no statistically reliable differences in death HR in subgroups constructed to assess the overall burden of disease by stratifying on the total number of comorbidities diagnosed for each patient, and no reliable differences in death HR comparing groups diagnosed with different numbers of comorbidity classes. Whereas the raw death rate of the user cohort was 4.86 times that of non-user controls (table 1), adjustment for all covariates (eg, age, gender, BMI, smoking) with stratification by comorbidities only reduced the overall HR to 4.56 (95% CI 3.95 to 5.26).

Associations between hypnotic use and incident major cancer

Since prior studies suggested an association between hypnotics and deaths from major cancers, we

Table 2 Comorbid diagnoses of non-users and users of hypnotics (percentages of total group)

Comorbidity	Non-users	Any hypnotic users	Zolpidem	Temazepam
Asthma***	6.6	11.3	10.9	11.3
Cerebrovascular disease***	3.8	6.2	5.9	6.1
Coronary heart disease***	9.4	14.5	14.1	15.8
Chronic kidney disease***	0.9	1.7	1.5	1.9
COPD***	5.5	9.1	8.8	8.8
Cardiovascular disease, all***	14.1	21.4	21.1	22.3
Dementia	0.6	0.6	0.7	0.2
Diabetes***	14.6	17.9	17.8	18.5
Heart failure***	3.2	6.6	6.6	6.6
Hypertension***	37.5	42.8	41.9	43.9
Obesity***	6.7	10.5	9.6	10.0
Reflux and peptic disease***	15.0	27.9	26.9	26.3
Peripheral vascular disease***	2.1	3.9	4.0	3.7

The percentages with each class of comorbidity diagnoses are shown for non-users and users of hypnotics. Among users, specific comorbidity percentages are shown for those prescribed only zolpidem or only temazepam. Comorbidity classes are further defined in supplemental table 2.
***Indicates $p<0.001$, contrasting non-users versus all hypnotic users.

Table 3 HRs for deaths and for cancers with dose–response analyses

	Deaths		Cancers	
Hypnotic	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**
Any hypnotic: doses/year	<0.001		<0.001	
No hypnotics, N=23 676	Reference		Reference	
0.4–18 pills/year, mean 8, N=3491	<0.001	3.60 (2.92 to 4.44)	0.086	0.86 (0.72 to 1.02)
18–132 pills/year, mean 57, N=3548	<0.001	4.43 (3.67 to 5.36)	0.022	1.20 (1.03 to 1.40)
>132 pills/year, mean 469, N=3490	<0.001	5.32 (4.50 to 6.30)	<0.001	1.35 (1.18 to 1.55)
Zolpidem only: mg/year	<0.001		0.035	
No zolpidem or other hypnotics, N=23 671	Reference		Reference	
Zolpidem 5–130 mg/year, mean 60, N=1453	<0.001	3.93 (2.98 to 5.17)	0.095	0.79 (0.60 to 1.04)
Zolpidem 130–800 mg/year, mean 360, N=1456	<0.001	4.54 (3.46 to 5.95)	0.585	1.07 (0.83 to 1.39)
Zolpidem >800 mg/year, mean 3600, N=1427	<0.001	5.69 (4.58 to 7.07)	0.023	1.28 (1.03 to 1.59)
Temazepam only: mg/year	<0.001		<0.001	
NO temazepam or other hypnotics, N=23 674	Reference		Reference	
Temazepam 1–240 mg/year, mean 98, N=798	<0.001	3.71 (2.55 to 5.38)	0.003	0.48 (0.30 to 0.77)
Temazepam 240–1640 mg/year, mean 683, N=613	<0.001	4.15 (2.88 to 5.99)	0.024	1.44 (1.05 to 1.98)
Temazepam >1640 mg/year, mean 7777, N=665	<0.001	6.56 (5.03 to 8.55)	<0.001	1.99 (1.57 to 2.52)

HRs associated with levels of hypnotic consumption from Cox proportional hazards survival analyses, controlled for age, gender, ethnicity, smoking status, body mass index, marital status and alcohol use and stratified by diagnoses in 12 classes of comorbidity. N: number of patients in each dose group for deaths. Restrictions of stratification produced small differences in N for the cancer analyses. p: probability that HR=1 from Cox proportional hazards models. For each drug, the top p level is for the overall contrast among dosage categories (including the no medication or reference category), and the lower p values are for the significance of each HR referenced to no hypnotic use. HR: hazard ratio for death or cancer (95% CI). Models for zolpidem and temazepam excluded patients receiving other hypnotics. See the supplemental files for additional HRs.

constructed Cox models for major cancer incidence (ie, excluding non-melanoma skin cancer incidence) and excluding all patients who had major cancers diagnosed before the period of observation. As shown in table 3, there were modestly increased statistically significant cancer HRs for those prescribed any hypnotic compared to non-users, with the middle and highest tertiles having cancer HRs of 1.20 (95% CI 1.03 to 1.40) and 1.35 (95% CI 1.18 to 1.55), respectively. The association with zolpidem was significant for the highest tertile. The HRs for temazepam were significant for the middle tertile and the highest tertile. The cancer HR of 1.99 (95% CI 1.75 to 2.52) for the highest tertile of temazepam was significantly greater than the corresponding HRs for zolpidem or for all hypnotics combined.

DISCUSSION

Patients with prescriptions for hypnotics had approximately 4.6 times the hazard of dying over an average observation period of 2.5 years as compared to non-users. These findings were robust with adjustment for multiple potential confounders and consistent using multiple strategies to address confounding by health status. A dose–response effect was seen. Among users in the highest tertiles of annualised dosages, the HRs for death were 5.3, 5.7 and 6.6, respectively, for all hypnotics, zolpidem alone and temazepam alone. This top third of users were prescribed 92.8% of all the prescription doses of hypnotics (supplemental figure 2). Those in the top third were also 35% more likely to develop a new major cancer.

Perhaps the most striking finding was that an increased hazard for death was present even in the lowest tertile of hypnotic use, such that hypnotic drugs were associated with a 3.6-fold increased risk of dying for patients using <18 hypnotic pills per year. Several strategies to discover biases that could account for this hazard, even at low levels of use, revealed none. Nonetheless, some residual confounding is inevitable in our results as a consequence of factors that were inadequately assessed. However, considering the minimal impact of the major confounders for which we did control upon the HRs, we think it unlikely that confounding explains the high mortality that we found associated with hypnotics.

Multiple causal pathways by which hypnotics might lead to mortality have been demonstrated. Though the acute lethality of benzodiazepine agonists seems less than that of barbiturates, it has been demonstrated in animals given high doses of benzodiazepine agonists, especially in combination with alcohol. Moreover, benzodiazepines and agonists are often present in mixed-drug overdoses.[10 11] Compilation of randomised controlled trials has shown that hypnotics increase incident depression.[12] Several non-randomised studies have reported an increase in suicide associated with hypnotics use,[8 13–15] and depression may increase mortality through other mechanisms besides suicide.[16 17]

Controlled trials show that hypnotics impair motor and cognitive skills, such as driving.[18] Hypnotics have been associated with increased automobile crashes and an increase in falls, due to hangover sedation.[19–22] In some patients, hypnotics increase sleep apnoea, prolong apnoeas or suppress respiratory drive, though among other patients, there may be mild improvement.[23–25] Sleep apnoeas, in turn, may lead to motor vehicle

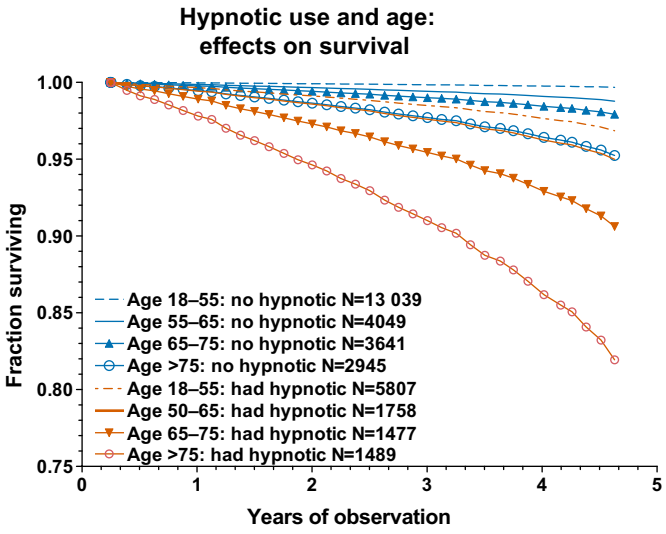

Figure 1 Survival curves for patients prescribed no hypnotic are compared with survival curves for patients prescribed hypnotics, divided into four age groups (age at commencement of period of observation). These curves were derived from a special Cox proportional hazards model in which those taking and not taking hypnotics in the four age groups were coded as eight categories of an independent predictor variable. The curves represent the fraction of patients surviving over the increasing years of observation until censored (died, lost to follow-up or end of observation). Those censored <0.23 year of observation were excluded. The red curves represent the fact that a higher percentage of hypnotic users died during the observation periods and fewer survived. Each curve was adjusted for covariates except age (which shared excessive colinearity with the age-based categories) and was adjusted for comorbidity strata.

crashes, hypertension, heart failure, arrhythmias, cardiovascular diseases and death.[26] Hypnotics may cause somnambulistic night-eating syndromes resulting in poor diet and obesity[27] as well as other automaton-like behaviours, which can be dangerous.[28 29] Indeed, in controlled trials, participants randomised to hypnotics experience more adverse medical events overall than those randomised to placebo.[21 30]

Zolpidem has been shown to increase gastroesophageal regurgitation.[31] In our sample, hypnotic prescriptions were associated with increased diagnoses of oesophageal regurgitation and peptic ulcer disease (supplemental files). Increased regurgitation could cause oesophageal damage and cancer. In randomised controlled trials, patients receiving hypnotics reported significantly more infections.[32] Joya *et al*[32] inferred that increased upper respiratory irritation and infection might result from the increased gastroesophageal regurgitation caused by hypnotics. Infections, in turn, are major causes of mortality and cancer.[33]

Sparse data from randomised controlled trials of hypnotics suggested increased rates of cancer,[34] and those findings are supported by studies demonstrating carcinogenic effects of hypnotics in laboratory rodents and by evidence that hypnotics can cause chromosomal damage.[34] Our finding that for lymphomas, lung, colon and prostate cancers, the HR for hypnotic usage was even greater than the HR for current smoking (supplemental table 11) argues for specific biologic mechanisms. It is possible that patients receiving hypnotics experienced more medical care than non-users, providing greater surveillance and potential cancer detection as contrasted to non-users, even though the Cox models matched users and non-users by numbers of comorbidities. However, it would be hard to imagine how greater surveillance of hypnotic users could explain two- to threefold higher HR for some cancers with no excess mortality for other cancers (see supplemental table 11), whereas specific biological effects of hypnotics would more plausibly explain the differences in HR between cancers.

In addition to the residual confounding discussed above, the data available for this study had further limitations, which should be noted. Importantly, the EHR provided information on medication orders but not on dispensing. Accordingly, we were unable to verify that the medications ordered were dispensed by a pharmacy, and, if dispensed, whether the patient ingested the prescribed hypnotic. Moreover, controls not receiving hypnotic prescriptions might have taken hypnotics prescribed for others or over-the-counter antihistamine sleep drugs equivalent to prescribed antihistamines. Such errors of overestimation of hypnotic consumption among users or underestimation among controls would lead to underestimation of the true hypnotic hazards.

We were unable to control for depression, anxiety and other emotional factors because of Pennsylvania laws protecting the confidentiality of these diagnoses. However, several previous studies reporting hypnotic risks have controlled for these confounders.[7 35] Mallon *et al* found that when depression, hypnotic use and other risk factors were entered into a multivariate model for all-cause mortality, hypnotic use was the strongest risk factor among men (stronger than cigarette smoking). In that analysis, depression was not an independent risk factor for death in either men or women.[7] Moreover, one might expect an emotional confounder to cause insomnia, leading, in turn, to use of hypnotics, but several large studies have reported that insomnia is not a significant mortality risk factor, especially when hypnotic usage is controlled.[7 35–37] Nevertheless, to the extent that social and psychological problems lead patients to receive hypnotics, and to the extent that these problems cause death through pathways independent of hypnotics, our findings might reflect some confounding by those conditions.

CONCLUSIONS

Rough order-of-magnitude estimates at the end of the supplemental files suggest that in 2010, hypnotics may have been associated with 320 000 to 507 000 excess deaths in the USA alone. From this non-randomised study, we cannot be certain what portion of the mortality associated with hypnotics may have been attributable to

these drugs, but the consistency of our estimates across a spectrum of health and disease suggests that the mortality effect of hypnotics was substantial. Even 10 000 yearly excess deaths caused by hypnotics would be too many.

A randomised clinical trial of sufficient duration and size could provide definitive evidence for or against the disturbing mortality hazards suggested by our study. Some American NIH reviewers have opined that a randomised trial of hypnotic lethality would be unethical. No such trial has ever been mounted, perhaps for reasons similar to the absence of randomised trials of cigarettes and of skydiving without parachutes.[38] Absent randomised trials of sufficient dimensions, we must be guided by observational data for hypnotics, as we have been guided by similar data for cigarettes.

Excess mortality is associated with hypnotic use. Hypnotic users had more prevalent disease of many sorts than non-users before hypnotics were ordered. However, the consistent results across varying levels of comorbidity and the persistent elevated hazards within strata of users and non-users matched for comorbid diagnoses strongly suggest that neither the level of individual health nor the presence of particular categories of comorbidity explains the bulk of the hazard associated with the use of hypnotic medications.

The meagre benefits of hypnotics, as critically reviewed by groups without financial interest,[21 30 39] would not justify substantial risks. A consensus is developing that cognitive-behavioural therapy of chronic insomnia may be more successful than hypnotics.[40 41] Against meagre benefits, it is prudent to weigh the evidence of mortality risks from the current study and 24 previous reports, in order to reconsider whether even short-term use of hypnotics, as given qualified approval in National Institute for Clinical Excellence guidance,[39] is sufficiently safe.

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Contributors DFK contributed to study concept and design, performed statistical analyses and drafted and revised the manuscript. RDL contributed to study concept and design, supervised the queries of electronic records, transformed the data files, performed statistical analyses and revised the manuscript. LEK obtained funding and administrative support, contributed public health perspectives and revised the manuscript. All authors approved the final manuscript. DFK is the guarantor of the manuscript.

Competing interests All authors have completed the Unified Competing Interest form. DFK reports long-term criticism of hypnotic drugs at his non-profit web site, http://www.DarkSideOfSleepingPills.com. DFK reports a family interest in an investment corporation, which has a small percentage of its assets in stock of Sanofi-Aventis and Johnson & Johnson. RDL and LEK report no competing interests.

Provenance and peer review Not commissioned; externally peer reviewed

Data sharing statement No additional data available.

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Page numbers for "Increased Mortality with Sedative-Hypnotics: Unsafe At Any Dose?" BMJ.2011.001445, refer to the pages of the 53-page *.PDF file uploaded on October 8, 2011.

STROBE statement checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract		
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 3, line 15
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 3, but note that the web site restricted abstracts to 250 words, when BMJ instructions elsewhere allow a longer abstract for research reports.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5-6, the hypotheses that deaths and cancers would be associated with hypnotic use was being replicated, but no superiority of zolpidem to other hypnotics was hypothesized.
Methods		
Study design	4	Present key elements of study design early in the paper pages 6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 6
Participants	6	(*a*) *Cohort study*?Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6 *Case-control study*? Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls*Cross sectional study*?Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*?For matched studies, give matching criteria and number of exposed and unexposed Pages 6-7 *Case-control study*?For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Covariate categories are in Table 1, pages 22-23. Confounders are defined in Supplementary Table 2, page 37-38.

	Item No	Recommendation
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6 and Page 36.
Bias	9	Describe any efforts to address potential sources of bias Page 6-7, 9, 37-38, table 7 page 41.
Study size	10	Explain how the study size was arrived at Page 6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding page 7-8, pages 37-8 (*b*) Describe any methods used to examine subgroups and interactions 13 tables and 3 figures describe subgroups and interactions (*c*) Explain how missing data were addressed Table 1, pages 22-23, shows that data-missing were entered as a separate category in Cox Models. (*d*) *Cohort study*?If applicable, explain how loss to follow-up was addressed page 35 *Case-control study*?If applicable, explain how matching of cases and controls was addressed*Cross sectional study*?If applicable, describe analytical methods taking account of sampling strategy (*e*) Describe any sensitivity analyses page 43 and numerous tables
Results		
Participants	13*	(*a*) Report numbers of individuals at each stage of study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Pages 6-7 (*b*) Give reasons for non-participation at each stage Pages 6-7 (*c*) Consider use of a flow diagram
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders pages 23-27 (*b*) Indicate number of participants with missing data for each variable of interest pages 23-25 (*c*) *Cohort study*?Summarise follow-up time (eg average and total amount) page 23
Outcome data	15*	*Cohort study*?Report numbers of outcome events or summary

	Item No	Recommendation
		measures over time page 23, 30, 39, 43, 45, 47
		*Case-control study?*Report numbers in each exposure category, or summary measures of exposure
		*Cross sectional study?*Report numbers of outcome events or summary measures
Main results	16	(*a*) Report the numbers of individuals at each stage of the study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 6-7
		(*b*) Give reasons for non-participation at each stage
		(*c*) Consider use of a flow diagram
Other analyses	17	Report other analyses done?eg analyses of subgroups and interactions, and sensitivity analyses throughout
Discussion		
Key results	18	Summarise key results with reference to study objectives pages pages 10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 11, 13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence pages 14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results pages 33-34
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 15, lines 9-10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross sectional studies.

The STROBE checklist is best used in conjunction with the explanation and elaboration article.[18-20] This article and separate versions of the checklist for cohort, case-control, and cross sectional studies are available at www.strobe-statement.org

Web Extra

Extra material supplied by the authors

Files in this Data Supplement:

- Data Supplement - Appendix 1: additional introduction, methods, results, and discussion.

Contents

Additional Introduction

U.S. hypnotic consumption estimates of the International Narcotics Control Board

According to the *Psychotropic Substances: Statistics for 2008* report of the International Narcotics Control Board,[1] U.S. consumption of all sedative hypnotics, averaged for 2006-2008, was 23.20 statistically defined daily doses (DDD) per thousand of the population. Assuming that almost all hypnotic doses are taken by those 18 years of age and older, and employing the U.S. census 2010 projection of a U.S. population of 310,233,000 of whom 235,016,000 were over 18, the defined daily doses per adult would be about 23.20 * (310,233,000 / 235,016,000) = 30.625. This would potentially provide a daily dose to 30.625 adults per thousand or 3.0625% of adults. Benzodiazepines made up only 36.7% of total hypnotic doses, and zolpidem (a benzodiazepine agonist) apparently accounted for much of the rest, enough to supply 1-2% of U.S. adults with a daily zolpidem dose.

The International Narcotics Control Board's estimated U.S. 2010 annual requirement for zolpidem was 122,542,430 grams, which would be 12,254,243,000 defined daily doses (their Table 5).[1] Twelve billion doses would be sufficient to supply 53 defined daily doses per year to each U.S. adult, or nightly doses to approximately 14.5% of adults, but the Chief of the Psychotropics Control Section of the International Narcotics Control Board Secretariat advised that this estimated "requirement" is likely to be a great exaggeration (personal communication), since it is thought to be more than 8 times the 2008 U.S. consumption. Indeed, 122,542,430 grams of zolpidem would be more than 4 times the total global manufacture of zolpidem for 2008. Probably, actual 2010 U.S. zolpidem consumption was somewhere between the 2006-2008 consumption and the 2010 estimated "requirement". The estimated 2011 "requirement" was 19,572,900 grams.[2]

There are several reasons to suspect that an estimate of 3.0625% of U.S. adults using hypnotics nightly is likely to be an underestimate for 2010.[2] The International Narcotics Control Board estimate for 2007-2009 U.S. consumption was about 9% higher than the estimate for the interval 1 year earlier.[2] Consumption has apparently increased since mid 2007, when lower-priced generic zolpidem became available, according to newspaper summaries of data collected by IMS Health.[3] Also, the International Narcotics Control Board did not include zaleplon or eszopiclone in its estimates of hypnotic consumption. Further, the International Narcotics Control Board does not include sedative antihistamines such as diphenhydramine in its compilations, though it is recognized that these drugs constitute a substantial portion of the drugs prescribed for treatment of insomnia.[1] Sedative antidepressants such as trazodone or doxepin are also commonly used as hypnotics, but these were not included either in the International Narcotics Control Board study or in the present research.

Review of epidemiologic studies of hypnotics

Prior to this report, 24 published studies have examined mortality related to sleeping pill use, as shown in Supplementary Table 1.

Supplementary Table 1. Previous studies of mortality associated with sleeping pills consumption.

Report	N subjects	Years	Risk Ratio	Significance
Ahmad & Bath, 2005[4]	1,042	15 yr	1.013	NS
Allgulander et al., 1987[5]	unclear	30 yr	2.1-5.0	P=0.005 to <0.001
Belleville, 2010[6]	14,117	12 yr	1.36	P<0.05
Brabbins et al., 1993[7]	1,063	3 yr	not given	NS
Fukuhara et al., 2006[8]	5,041	5 yr	1.27	P=0.04
Hausken et al., 2007[9]	14,951	18 yr	1.6	<0.05 women
Hays, Blazer & Foley, 1996[10]	3,962	4 yr	1.03	NS
Hedner et al., 2002[11]	1,211	5 yr	1.65	P=0.01
Hoffmann et al., 2007[12]	7,658	3 yr	~1.5	P=0.002
Hublin et al, 2007[13]	21,268	22 yr	1.7	P<<0.05
Isacson et al., 1992[14]	19,926	8 yr	>1	Mostly significant
Kojima et al., 2000[15]	5,322	12 yr	1.62	NS
Kripke et al., 1979[16]	823,065	6 yr	1.13-1.57	P<0.001
Kripke et al., 1998 & 2002[17 18]	1,116,936	6 yr	1.24-1.25	P<<0.05
Lack et al., 2006[19]	2,087	13 yr	1.12	P=0.001
Mallon et al., 2002[20]	1,870	12 yr	6.4 & 3.8	P<0.05
Mallon et al., 2009[21]	3,523	20 yr	3.285	P<0.001
Merlo et al., 1996[22]	498	10 yr	1.0	NS
Phillips & Mannino, 2005[23]	13,563	6.3 yr	1.4	NS
Rod et al., 2010[24]	16,989	19 yr	1.07-1.30	P<0.05 & NS
Rumble & Morgan, 1992[25]	577	5 yr	1.19-1.24	P=.027 to 0.275
Sundquist, et al.,1996[26]	unclear	10 yr	N/A	P<0.001
Thorogood et al., 1992[27]	112	3 yr	3.7-12.0	P<<0.05
Winkelmayer et al, 2007[28]	3,630	2-4 yr	1.15	P<0.05

As Supplementary Table 1 shows, the great majority of previous studies observed a significant association of sleeping pill consumption with mortality. These studies were highly diverse in methodologies, numbers of subjects, and duration of observation. The risk ratios reported were variable, ranging from 1.0 to 12.0, but in only one of 22 studies did the risk ratio fail to exceed 1.0. It seems plausible that factors producing variability in risk ratios included sample age and health status, the various hypnotics used by the samples, frequency and duration of hypnotic use, accuracy of ascertainment of consumption, methods of covariate control, and whether hypnotic consumption was ascertained during the follow-up period or only prior to the mortality follow-up. In studies such as the American Cancer Society studies,[16 18] participants might have discontinued hypnotic usage soon after initial questionnaires were completed, whereas other subjects who initially reported no sleeping pill use at commencement of the study may have begun taking sleeping pills during the prospective follow-up.

Additional Methods

Anonymization.

The size of the total Geisinger electronic health record data base is so large that dates such as birth dates and clinic visit dates are not uniquely identifying. Nevertheless, dates of visits, births, and deaths were disguised and ages of patients over age 89 years were disguised to strengthen anonymization in the working files. Although medical record numbers were employed when compiling the research files so that various extracted data files could be linked, the medical record numbers were replaced by randomly-selected study identification numbers to denote each participant within a completely de-identified data set. Usage of the deidentified data for research purposes was approved by the IRBs with waiver of consent.

User vs control nonuser extraction and matching.

A total of 19,547 patients receiving outpatient hypnotic drug orders between January 1, 2002 and September 31, 2006 were initially identified in the electronic records, but about one third were excluded for issues such as age <18 years, not having a Geisinger primary care physician, non-availability of at least one control, or inadequate interval of follow-up available, leaving 12,465 hypnotic users available for further exclusions. The primary care population (patients having 2 or more visits within the study time period in the departments of internal medicine and/or Family Practice) also included 212,292 patients who received no hypnotic. Thus, the primary care population consisted of 224,757 patients, of whom 5.5% had received a hypnotic prescription. Two control nonusers for each user were selected when possible; matched by gender, age within 5 years, beginning of observation, and whether the patient had ever smoked. Controls had not had a prescription for any hypnotic recorded during the interval from January 1, 2002 to September 31, 2006. Data for anonymized users and nonusers included disguised age when entering a period of observation (defined below), disguised date of death if deceased, gender, ethnicity, and usually included smoking status, alcohol status, marital status, height and weight, records of selected office diagnoses, cancer diagnoses on medical problem lists, cancer registry data (when available), and all prescriptions for hypnotic medications recorded electronically from 1996-2007, including exact drug and dosage identification, numbers of doses prescribed, numbers of refills, and some information concerning indications of prescriptions.

There were a small number of initially-extracted users who had been selected because of a medication order which—when dosage directions and indications were reviewed—was not considered a true hypnotic prescription (e.g., phenobarbital TID for epilepsy or intravenous midazolam for anesthesia) or whose hypnotic prescriptions did not occur during the period of observation. These users were then excluded. Likewise, 131 patients intended as control nonusers were found to have hypnotic medication orders before the period of observation, and these controls were excluded. Finally, we were concerned that the rate of cancer diagnoses was higher in users than nonusers before the commencement of the periods of observation. Since it is possible that a cancer diagnosis would cause anxiety and insomnia leading to hypnotic prescription, in which case the cancer would be causing the hypnotic consumption rather than the converse, we excluded all users and nonusers that received any diagnosis of cancer (other than nonmelanoma skin cancer) recorded before the period of observation or earlier than 18 days after commencement of the period of observation. This restriction excluded patients whose first hypnotic prescription might have occurred at the same office visit when the cancer diagnosis was made or too soon after for it to be at all plausible that the hypnotic caused the cancer.

For the users, the period of observation usually commenced with the first hypnotic prescription after January 1, 2002. However, 18.5% of the users had records of hypnotic prescription prior to January 1, 2002, and thus, prior to the period of observation. For users, periods of observation commenced rather steadily throughout the interval from January 1, 2002 to September 30, 2006 as hypnotic orders were recorded. For both users and controls, the initially-extracted periods of observation ended at the last contact before December 31, 2006 unless a patient was lost to contact earlier or deceased. No users were entered after September 30, 2006, because both user and control data were analyzed only if the period of observation was at least 0.23 year (a cut point selected from consideration of the data distributions). A period of observation of at least 0.23 year was required to assure at least that much observation was available in which a hypnotic drug action could develop. Sufficient matching controls were available for 53.7% of the initially-extracted control periods of observation to begin on January 1, 2002. It was noted that the strategy of initial extraction yielded longer periods of observation starting at younger ages for nonuser controls than for users. To better match users and nonusers, the commencement of the statistical period of observation for each nonuser control was delayed to match the start of period of observation for the matched user, unless that produced a period of observation <0.23 years for the control. Analyses were conducted using a matched-cohort design with Cox regression procedures.

As shown in Table 1 of the main manuscript, as a result of these various exclusions and the redefinitions of periods of observation, the female/male proportions of users and controls were no longer quite identical and the user/nonuser ratio was no longer quite 1:2, but the more important age-matching and period-of-observation matching were improved after exclusions and redefinition. The exclusions and employment of a more complex smoking status variable than that used for matching (e.g., separate categories for quit smoking and for passive smoking were included) resulted in the percentages of current smokers no longer perfectly matched between users

and controls. However, these minor imbalances of gender, age, and smoking status between users and nonusers were controlled as covariates in the Cox proportional hazards models.

Data base development.

First, the various data files were converted to SPSS files. They were then compiled using Excel 2007 and SPSS 12.0.0 for Windows. The file containing basic demographic data was merged with files containing cancer diagnoses from 3 electronic files: the cancer registry, the patient problem list, and the records of office cancer diagnoses, yielding 5470 patients with at least one cancer diagnosis entry.

A file of comorbid diagnoses made at office visits was supplied, focusing on diagnostic categories prospectively predicted to be risk factors for mortality. These consisted of 491,492 records of ICD9 diagnostic codes, recorded between 1996 and September, 2006. Each record was associated with the anonymized patient's study identification number and the disguised time when the diagnosis was recorded. The same ICD9 diagnosis might be recorded many times for a given patient, as might be appropriate when a patient made repeated office visits, and many different ICD9 diagnoses might be recorded for a given patient, so that there was an average of more than 13 diagnosis entries per patient. To simplify and to obtain categories of sufficient size for statistical reliability, these ICD9 codes were reduced to 12 classes, shown in Supplementary Table 2 below, plus a combining category for all cardiovascular diseases. Of the 43,593 non-duplicated entries for all patients, 39,665 or 91% of diagnoses could be included in one of these 12 classes. The remaining diagnoses, each too infrequent to constitute a separate analyzable class, were not further considered as covariates. Due to IRB concern with confidentiality and legal issues, psychiatric diagnoses were not available. For each patient (user or nonuser), the time when a diagnosis was first recorded in each category was compiled and then merged into the master data base.

Supplementary Table 2. Definitions of common comorbidity classes

Disease	ICD9 Codes	N
Asthma	493	2749
Cardiovascular Disease, any except hypertension (CVD)	410-414, 429, 433, 435, 436, 441, 443	6198
Cerebrovascular disease	433, 435, 436	1552
Chronic Kidney Disease (CKD)	585, 586	404
Chronic Obstructive Pulmonary Disease (COPD)	491, 492, 496	2265
Coronary Heart Disease (CHD)	410-414, 429	3746
Dementias	290	199
Diabetes	250	5333
Heart Failure (HF)	428	1467
Hypertension (HTN)	401	13393
Obesity	278	2690
Reflux and Peptic Disease (PUD)	530 & 533	6487
Peripheral Vascular Disease (PVD)	441, 443	900

For each disease, **N** is the number of combining prevalent plus incident diagnosed comorbidities. The Cardiovascular Disease category is an instructive compilation of Coronary Heart Disease, Cerebrovascular Disease, and Peripheral Vascular Disease.

Every hypnotic medication order was compiled for each patient in the medications file, identified by the patient's study identification number and providing the specific drug name (brand or generic), dosage strength, number of doses prescribed, number of refills, and diagnostic code indication. This file was edited to delete medication orders that were judged not to represent hypnotic administration for sleep. For example, entries for intravenous midazolam (used as a surgical anesthetic) were deleted. Orders for multiple doses per day (e.g., phenobarbital TID for epilepsy) were removed along with prescriptions for morning or afternoon administration not

apparently intended for sleep. The edited file detailed 58,228 prescriptions for drugs indicated as hypnotics. To compress the medication types to make each type large enough for analysis, the hypnotic medications were grouped into 9 classes: 1) zolpidem, 2) temazepam, 3) eszopiclone, 4) zaleplon, 5) triazolam, 6) flurazepam, quazepam, or estazolam combined to obtain a large enough class of long-acting benzodiazepines, 7) all barbiturates, mostly phenobarbital, 8) antihistamines, almost entirely diphenhydramine, 9) all other hypnotics, mainly ethchlorvynol, chloral hydrate, and ramelteon. The other hypnotics grouped in class 9) were each prescribed too infrequently to be analyzed individually in separate classes, but it would not be logical to analyze them in combination because of their widely-disparate pharmacology. Thus, Class 9) was defined only to keep these rarely-prescribed drugs from being confounded with the other classes of medication. For each class of medication, the numbers of unit doses (e.g., pills) prescribed (including those prescribed through refills) were summed for each patient up to the end of the period of observation (defined above). The number of unit doses prescribed for that class was merged into the master file.

Statistical models.

Cox proportional hazards models (SPSS 12.0.0 for Windows) were computed using backwards stepwise elimination specifying all covariates with criteria of $p \leq 0.10$ to retain, and $p \leq 0.05$ to re-enter. The two control nonusers matched to each user were assigned the same start of their period of observation as the user unless that resulted in a period of observation <0.23 year for the control nonuser, in which rare instances, January 1 2002 or the first recorded visit thereafter was selected to start the period of observation for this control nonuser. Thus, the proportional hazards models covered intervals starting with the first hypnotic prescription after January 1, 2002 for users (and for almost all control nonusers matched to each user) and extended until death, a lost-to-follow-up date, or December 31, 2006. Because it was recognized that many deaths occurred in the first month after the final clinic visit which had ended the period of observation, evidently because many patients could not be seen in the clinic in their terminal months and may have received care at home, in the hospital, or in hospice, deaths occurring in this first month following the period of observation were included as outcome events in the models. Medication prescriptions ordered in a terminal month after the end of the defined period of observation were not included in the models. For the comorbidities listed in Supplementary Table 2, strata were constructed of patients (both users and nonusers) with no comorbidities (the largest category), with any one of the 12 separate comorbidity classes (the cardiovascular disease supercategory would have been redundant), and with each unique combination of multiple comorbidity classes. This yielded 116 usable strata for the main model, matching almost all the hypnotic user cohort with nonusers diagnosed with exactly the same combinations of the 12 classes of comorbidity. Infrequent combinations of several comorbidities with fewer than 5 users and 5 nonusers or without a single outcome event before censoring (i.e., death) were combined into larger strata defined by the number of comorbidity classes from 2 to ≥7, to avoid creating strata too small to be useful for computaton. The Cox proportional hazards models were then computed as stratified models, so that users were compared with nonusers of matched comorbidity status within each stratum to compute the hazard ratios (HR) associated with hypnotic use. The use of stratified models provided matching on comorbidity status as well as age, gender, and smoking in the comparisons of users and nonusers, and also minimized the potential problems of interactions and colinearities among comorbidities. Besides this, the stratified models were additionally adjusted for age and the categorical risk factors of gender, smoking status (to adjust for minor failures in matching), BMI, ethnicity, marital status, alcohol use, and prior cancer.

The investigators elected to control for comorbidities first recorded before or during the periods of observation, in order to control for comorbidities which might have covertly led to hypnotic prescriptions even before the comorbidity was explicitly recognized and its diagnosis was recorded. This was a highly conservative decision to minimize the risk that comorbidities causing hypnotics to be prescribed would exaggerate the hazard ratios. By increasing the risk that conversely a comorbidity caused by a hypnotic might be over-controlled, we accepted the possibility that adjustment for comorbidities arising during the periods of observation would create a bias underestimating the true hazard ratios. Somewhat to our surprise, the conservative stratified analyses usually produced HR as high as Cox models employing only unstratified comorbidities ascertained prior to the periods of observation as covariates. These alternative Cox models which did or did not control for comorbidities first diagnosed in the period of observation almost always yielded hazard ratios with overlapping 95% Confidence Intervals. Models which did not control for comorbidities at all yielded generally consistent results with only slightly higher hazard ratios.

Additional models were computed separately using each class of hypnotics as a single independent variable, excluding those users who had received a prescription for any other hypnotic class. To further explore dose-response, models were defined with a category dividing hypnotic prescriptions into 4 levels of prescription per year of observation: a zero-prescription level (nonusers) and 3 levels dividing users who received the hypnotic approximately into thirds: 3 almost-equal-sized tertiles with low, middle, and high quantities prescribed. These dose-response models were computed by considering a patient's total dosage per year of any hypnotic, for zolpidem alone using milligrams (a defined daily dosage or DDD for zolpidem is 10 mg.) per year, and for temazepam alone using the total milligrams prescribed per year.

Additional Results

More information about participants who were prescribed only one of the less-commonly-used hypnotics is provided in Supplementary Table 3 below.

Supplementary Table 3. Characteristics of study participants: less common hypnotics.

	Eszopiclone	Zaleplon	Triazolam	Flurazepam	Barbiturates	Antihistamines	Mixed
N	266	331	64	133	228	495	2543
% female	68	66.2	70.3	60.2	60.1	70.1	64
Age (years, mean ±SD)	50.5 ±13.9	51.1 ±17.2	61.2 ±16.2	59.1 ±16.2	54.7 ±16.6	57.9 ±16.6	54.0 ±16.3
Years Observation (mean ±SD)	0.80 ±0.43	2.72 ±1.29	2.82 ±1.42	3.14 ±1.29	3.67 ±1.05	2.39 ±1.35	2.78 ±1.39
Comorbidity Classes (N ±SD)	1.12 ±1.31	1.36 ±1.44	1.98 ±1.54	1.60 ±1.64	1.11 ±1.27	1.48 ±1.48	1.71 ±1.62
Died during Observation	6	18	5	6	13	26	156
% Deceased	2.3	5.4	7.8	4.5	5.7	5.3	6.1
BMI %							
<18.5	0.8	1.8	1.6	0.8	2.2	1.2	1.7
18.5-24.9	21.1	14.8	20.3	24.8	16.7	17.4	20.1
25-29.9	20.3	23	25	21.8	19.7	30.9	23.4
30-34.9	18.4	15.1	17.2	12.8	17.5	15.8	16.4
>35	15.4	13.3	7.8	13.5	11	17.4	15.7
unknown	24.1	32	28.1	26.3	32.9	17.4	22.8
Marital Status %							
Married	60.9	56.2	50	54.1	45.2	59.4	54.1
Divorced	14.3	12.7	12.5	9.8	9.6	9.7	13.5
Single	13.9	16	14.1	16.5	30.3	12.9	14.8
Separated	3	2.4	1.6	2.3	1.3	0.8	2.6
Widowed	7.9	12.4	21.9	17.3	13.6	17.2	14.9
Unknown	0	0.3	0	0	0	0	0.1
Ethnicity %							
White	97.4	97.9	96.9	98.5	98.7	98.4	96.4
Asian, Black,Hisp	2.6	1.5	3.1	1.5	1.3	1.4	3.1
Native or Other	0	0.6	0	0	0	0.2	0.4
Smoking Status%							
Never	38.7	39.9	43.8	41.4	55.7	49.1	40.5
Unknown	0.4	4.8	3.1	4.5	4.8	2.6	2.6
Passive	0.4	0.9	1.6	0	0	0.2	0.6

Quit	34.6	27.8	29.7	30.1	17.1	32.1	31
Yes, now	25.9	26.6	21.9	24.1	22.4	16	25.4
Alcohol Use %							
Yes	42.1	44.4	35.9	31.6	20.6	40.4	39
No	47.7	47.4	54.7	55.6	70.2	52.9	52.5
Unknown	10.2	8.2	9.4	12.8	9.2	6.7	8.5

Supplementary Table 3 extends the main manuscript's Table 1 for the less-commonly-prescribed hypnotics. **N:** Number of patients prescribed only the named hypnotic. **Years Observation**: the mean period of observation in years. **Comorbidity Classes:** the number of comorbidity classes in which a diagnosis was made either before or during the period of observation. **BMI %:** the percentage of the total group within the BMI range defined as m^2/kg. **Ethnicity %:** the percentage in each self-reported ethnicity category (Asians, Blacks, and Hispanics were combined because of the small numbers). **Alcohol Use %:** is a simple yes/no self-report by the patient whether the patient drinks alcohol. **Mixed:** are data for patients who received at least two of the hypnotic classes. Data for the 9th class (Other hypnotics) are not listed, as it was prospectively decided not to analyze data for this hypnotic class because of the small numbers of prescriptions and the inhomogeneity of their pharmacologic effects.

Prior prevalence and incidence of comorbidities.

Before the periods of observation, hypnotic users were diagnosed with more comorbidities than nonusers for each of the comorbidities, that is, before the first-recorded hypnotic prescription for 81.5% of users (Supplementary Table 4). The percentages for each comorbidity class are also listed for users of each medication class uniquely and for those who were prescribed more than one hypnotic class (mixed). The estimates for zolpidem, temazepam, and the mixed group may be reasonably stable, but estimates for the less frequently-prescribed hypnotics had too few patients in each group to be reliable.

Supplementary Table 4. Prevalence of comorbidities prior to the periods of observation: Percents of patients diagnosed

Prior Comorbidities	nonusers	users	Zolpid.	Temaz.	Eszop.	Zalepl.	Triazol.	Fluraz.	Barbit.	Antihist.	Mixed
Asthma	4.4	8.8	8.5	8.7	7.9	10.3	10.9	3.0	6.1	5.7	10.0
Cerebrovascular	2.0	4.1	3.8	4.2	1.5	2.1	3.1	3.0	6.1	6.5	4.8
Coronary Heart Dis.	6.3	11.4	11.5	12.4	9.0	8.2	15.6	10.5	4.8	10.1	12.2
Chronic Kidney Dis.	0.3	0.8	0.9	0.7	0.0	1.2	1.6	1.5	0.9	0.8	0.9
COPD	3.4	6.4	6.7	6.3	7.1	6.6	6.3	5.3	3.9	4.6	6.6
Cardiovascular Disease	9.0	16.5	16.6	17.1	10.9	11.2	20.3	15.0	11.0	16.8	17.9
Dementia	0.3	0.4	0.5	0.1	0.4	0.3	0.0	0.0	0.4	1.0	0.2
Diabetes	9.8	13.9	14.0	14.6	7.9	10.9	20.3	11.3	9.2	13.9	14.8
Heart Failure	1.7	4.6	4.9	4.2	2.6	2.4	10.9	5.3	1.3	5.1	4.9
Hypertension	26.8	35.0	34.8	36.2	33.8	27.5	37.5	36.1	23.7	34.5	36.5
Obesity	4.0	8.0	7.4	7.9	9.0	8.8	6.3	9.0	4.8	8.1	9.1
Reflux & peptic	9.2	20.3	20.2	19.3	22.9	19.3	23.4	18.8	9.2	17.2	22.7
Peripheral Vascular Dis.	1.3	3.0	3.3	2.8	0.8	2.1	1.6	3.8	1.3	3.2	3.0

In Supplementary Table 5, the incidence of diagnoses in each comorbidity class during the periods of observation is shown as a percent of the total patients in that class for each group of hypnotics nonusers and users. Note that the more patients were diagnosed with the comorbidity before the period of observation (Supplementary Table 4), the fewer could be diagnosed with new incidence during the period of observation.

Supplementary Table 5: Incidence of comorbidities during the periods of observation: Percent of all patients diagnosed

Incidence	nonusers	users	Zolpid.	Temaz.	Eszop.	Zaleplon	Triazol.	Fluraz.	Barbit.	Antihist.	Mixed
Asthma	2.2	2.5	2.4	2.6	1.9	0.9	3.1	3.8	2.2	1.4	3.1
Cerebrovascular	1.8	2.1	2.1	1.8	0.4	1.5	3.1	4.5	1.8	3.2	2.1
Coronary Heart Dis.	3.0	3.1	2.6	3.5	0.0	3.9	4.7	3.8	3.1	3.8	3.6
Chronic Kidney Dis.	0.6	0.9	0.6	1.2	0.4	1.2	3.1	0.8	0.9	1.4	1.0
COPD	2.1	2.7	2.0	2.6	0.4	3.9	7.8	6.0	3.1	2.0	4.0
Cardiovascular Disease	5.1	4.9	4.4	5.1	0.8	5.1	6.3	8.3	5.7	4.4	5.7
Dementia	0.3	0.3	0.2	0.1	0.0	0.3	0.0	0.8	0.9	0.4	0.4
Diabetes	4.8	4.0	3.8	3.9	0.4	3.3	6.3	5.3	3.9	4.0	4.7
Heart Failure	1.5	2.0	1.7	2.4	0.0	1.2	1.6	4.5	1.8	0.8	2.8
Hypertension	10.7	7.8	7.1	7.7	3.0	8.5	17.2	7.5	8.8	9.5	9.1
Obesity	2.7	2.5	2.2	2.1	0.4	3.0	1.6	1.5	3.5	2.6	3.5
Reflux & peptic	5.8	7.6	6.7	7.0	2.3	7.9	12.5	12.0	7.9	7.3	9.8
Peripheral Vascular Dis.	0.8	0.9	0.7	0.9	0.4	0.3	0.0	2.3	0.9	1.2	1.5

The impression from Supplementary Table 5 might be that nonusers were more likely to be newly diagnosed with certain comorbidities than hypnotic users during the periods of observation. However, if we consider the number in each group who had not been previously diagnosed with the comorbidity (Supplementary Table 4 subtracted from the total participants) as the denominator, the percents of the remaining patients diagnosed with new incidence of each comorbidity during the periods of observation were greater in the group of hypnotics users for most classes (Supplementary Table 6).

Supplementary Table 6: Incidence of comorbidities during the periods of observation: Percent of patients not previously diagnosed

Remainder Incidence	nonusers	users	Zolpid.	Temaz.	Eszop.	Zaleplon	Triazol.	Fluraz.	Barbit.	Antihist.	Mixed
Asthma	2.3	2.7	2.6	2.8	2.0	1.0	3.5	3.9	2.3	1.5	3.5
Cerebrovascular	1.8	2.1	2.2	1.9	0.4	1.5	3.2	4.7	1.9	3.5	2.2
Coronary Heart Dis.	3.2	3.5	2.9	4.0	0.0	4.3	5.6	4.2	3.2	4.3	4.1
Chronic Kidney Dis.	0.6	0.9	0.6	1.2	0.4	1.2	3.2	0.8	0.9	1.4	1.0
COPD	2.2	2.9	2.2	2.7	0.4	4.2	8.3	6.3	3.2	2.1	4.3
Cardiovascular Disease	5.6	5.8	5.3	6.2	0.8	5.8	7.8	9.7	6.4	5.3	6.9
Dementia	0.3	0.3	0.2	0.1	0.0	0.3	0.0	0.8	0.9	0.4	0.4
Diabetes	5.3	4.6	4.4	4.6	0.4	3.7	7.8	5.9	4.3	4.7	5.5
Heart Failure	1.5	2.1	1.8	2.5	0.0	1.2	1.8	4.8	1.8	0.9	2.9
Hypertension	14.7	12.0	10.8	12.0	4.5	11.7	27.5	11.8	11.5	14.5	14.3
Obesity	2.8	2.7	2.4	2.2	0.4	3.3	1.7	1.7	3.7	2.9	3.9
Reflux & peptic	6.4	9.5	8.4	8.7	2.9	9.7	16.3	14.8	8.7	8.8	12.7
Peripheral Vascular Dis.	0.8	1.0	0.7	0.9	0.4	0.3	0.0	2.3	0.9	1.3	1.6

Hazard ratios for subsamples diagnosed with specific disease classes.

To further examine any influence of specific comorbidities on the death HR, Cox Regression models were computed for those patients having each of 12 diagnostic classes, as defined in Supplementary Table 2. Within each disease group, the users of any hypnotic were separated into the same dosage tertiles defined in the main manuscript, and mortality within each tertile of users was contrasted with that of nonusers having the same disease, as shown in Supplementary Table 7. Results were not statistically significant in the model for the 192 patients with dementia, most likely due to the small sample size, so that disease class is not shown.

Supplementary Table 7: Adjusted hazard ratios (95% confidence limits) for death from Cox regression* for subpopulations defined by the presence of specific diseases, comparing tertiles of users of any hypnotic with nonusers (reference).

Disease class	N	Pills per year (mean)		
		0.4 to 18 (8)	18 to 132 (57)	>132 (469)
Hypertension	13116	4.14 (3.17 to 5.40)	5.90 (4.68 to 7.45)	5.85 (4.74 to 7.23)
Peptic Ulcer Disease	6286	3.72 (2.35 to 5.87)	5.73 (3.81 to 8.62)	7.27 (5.14 to 10.29)
Diabetes	5215	5.23 (3.72 to 7.37)	5.16 (3.72 to 7.14)	6.78 (5.08 to 9.03)
Cardiovascular Disease	5451	3.94 (3.01 to 5.16)	5.05 (3.96 to 6.43)	5.70 (4.59 to 7.07)
Coronary Heart Disease	3663	4.63 (3.29 to 6.52)	5.43 (3.96 to 7.43)	6.60 (5.00 to 8.71)
Obesity	2665	8.07 (3.64 to 17.89)	6.37 (2.73 to 14.88)	9.34 (4.47 to 19.52)
Asthma	2193	2.95 (1.25 to 6.96)	4.17 (1.87 to 9.31)	3.65 (1.71 to 7.80)
COPD	2220	4.48 (2.84 to 7.01)	7.46 (5.06 to 10.99)	6.18 (4.30 to 8.90)
Cerebrovascular Disease	1504	4.97 (3.09 to 7.99)	6.23 (3.93 to 9.85)	6.34 (4.26 to 9.44)
Heart Failure	1427	3.67 (2.55 to 5.29)	3.76 (2.70 to 5.26)	4.53 (3.37 to 6.11)
Peripheral Vascular Disease	876	3.14 (1.70 to 5.78)	3.95 (2.32 to 6.73)	5.21 (3.23 to 8.25)
Chronic Kidney Disease	396	6.89 (2.96 to 16.05)	3.62 (1.58 to 8.30)	11.31 (5.56 to 23.03)
NO Comorbidity	13493	1.93 (0.94 to 3.97)	3.97 (2.23 to 7.07)	8.63 (5.43 to 13.72)

* From Cox regression using backwards stepwise elimination, criteria of $p<0.10$ to retain and $p<0.05$ to re-enter. The reference groups were nonusers with disease in the same class. Covariates entered were hypnotic use category, age, sex, BMI, smoking status, ethnicity, marital status, and alcohol use. Disease diagnoses are defined in Supplementary Table 2.

Note that the hazard ratio for each tertile within each comorbidity class met one-tailed $P<0.05$ significance criteria for greater hazard among hypnotic users, confirming that excess death hazard was seen in every comorbidity category (except dementia as noted above). Hazard ratios among subsamples with specific comorbidities were generally consistent with the hazard ratios by tertiles of use for the entire sample, but those with diabetes, obesity, COPD, cerebrovascular disease, and chronic kidney disease, as well as those with peptic ulcer disease in the highest tertile of use, seemed particularly sensitive to hypnotic effects as compared to nonusers with the same comorbidity.

Sensitivity analysis for specific sleep-related indications.

The small groups prescribed hypnotics without a sleep-related diagnosis being the recorded indication had somewhat higher death HR in the two tertiles prescribed the fewest hypnotic doses. The death HR in the tertile who were prescribed most of the hypnotic doses was about the same regardless of whether or not a sleep-related diagnostic indication was recorded, and 85.5% of patients in the third tertile had sleep-related diagnoses.

Contrasting hazard ratios for men and women.

In Supplementary Table 8, we contrast hazard ratios (HR) for men and women, examining the dose-responses for those taking any hypnotic with Cox models controlled for demographic covariates and stratified by comorbidities. The death HR for men and women were very similar, and the 95% confidence intervals (C.I.) entirely overlaped.

Supplementary Table 8. Hazard ratios for deaths with dose-response analyses for males and females

Gender & Hypnotic Dose	P	HR (95% C.I.)
MALES: Any hypnotic	<.001	
NO hypnotics, N=8839	Reference	
0.4-18 pills/yr, mean 8, N=1200	<.001	3.91 (2.91 to 5.25)
18-132 pills/yr, mean 57, N=1289	<.001	4.86 (3.70 to 6.39)
>132 pills/yr, mean 469, N=1311	<.001	5.70 (4.44 to 7.33)
FEMALES: Any hypnotic	<.001	
NO hypnotics, N=14837	Reference	
0.4-18 pills/yr, mean 8, N=2291	<.001	3.34 (2.45 to 4.56)
18-132 pills/yr, mean 57, N=2259	<.001	4.29 (3.26 to 5.65)
>132 pills/yr, mean 469, N=2179	<.001	4.88 (3.84 to 6.21)

Hazard Ratios for 8 hypnotic classes.

To examine the HR for the 8 hypnotic classes separately, it was necessary to compute HR encompasing the entire dosage range for each hypnotic, since there were too few patients taking the less popular hypnotics to reasonably divide these HR by dosage tertiles. Analyses of the 8 hypnotic classes included the patients who had taken only one hypnotic drug class and excluded those who had taken more than one class of hypnotic drugs. These were analyses with comorbidities stratified for users of that particular hypnotic class, and controlled for age, gender, smoking, etc. The death HR for 8 hypnotic classes are shown in Supplementary Table 9. The HR 95% Confidence Interval for 6 of the other hypnotics included the mean HR for zolpidem, so these drugs did not have a significantly different death hazard from that of zolpidem. The exception was eszopiclone, which had an estimated death HR of 30.62 (12.90-72.72, 95% Confidence Interval.) The extreme elevation of the eszopiclone death HR is difficult to interpret because there were only 6 deaths among the small group prescribed only eszopiclone, and their periods of observation averaged only 0.79 years, partly because eszopiclone was not marketed before mid-2005. Note that patients prescribed hypnotics were not randomly assigned to the different drugs, and there may have been biases for particular drugs in prescribing among patients of varying ages, genders, smoking status, etc., as well as differing numbers of hypnotic doses received by patients in different drug classes. The control cohorts were not extracted for matching to the particular cohorts taking each single class of hypnotic. Thus, although the analyses in Table 9 were stratified for comorbidity classes for each drug and controlled for covariates, comparisons of HR between individual hypnotic classes could be misleading. This may have been particularly a concern for barbiturates and antihistamines, for which the prescribing intentions may not have been fully comparable to those for the benzodiazepines and benzodiazepine agonists.

Supplementary Table 9. Hazard ratios for unique use of 8 hypnotics (all doses for each hypnotic)

Hypnotic	P	HR (95% C.I.)
No hypnotic use, N=23671 (295 deaths)	reference	
Zolpidem N=4336 (265 deaths)	.000	4.82 (4.06 to 5.74)
Temazepam N=2076 (143 deaths)	.000	4.98 (4.05 to 6.14)
Eszopiclone N=266 (6 deaths)	.000	30.62 (12.90 to 72.72)
Zaleplon N=331 (18 deaths)	.000	3.75 (2.29 to 6.12)
Triazolam N=64 (5 deaths)	.001	4.50 (1.83 to 11.10)
Flurazepam, et al., N=133 (6 deaths)	.056	2.21 (0.98 to 4.98)
Barbiturates N=228 (13 deaths)	.000	2.78 (1.57 to 4.92)
Antihistamines N=495 (26 deaths)	.000	4.57 (3.01 to 6.94)

N: Number of incident deaths in the period of observation for each hypnotic. **P:** probability that HR = 1 from Cox proportional hazards models. **HR** Hazard ratio for death. **C.I.:** 95% confidence interval.

Age Effects on HRs for Death and Cancer.

To plot age effects and accommodate limits in SPSS plotting capabilities, Cox proportional hazards models were computed in which the comorbidity classes were implemented as covariates rather than strata, and a complex categorical covariate was created from a combination of 4 age groups among hypnotic users and 4 age groups among nonusers. The results of these models are summarized below in Supplementary Table 10 and in Figure 1 in the main manuscript and in Supplementary Figure 1 below. In Supplementary Table 10, the third column represents the "Age HR" reflecting combinations of categories of age range and user or nonuser status, with the group of nonusers with age of 18 to 55 years as the reference group. As might be anticipated, as compared to age 18-55 nonusers, these HR increased with age among both nonusers and users, but note that the users had higher HR than nonusers in every age category. The fourth column indicates the ratio of the HR of users divided by the HR for nonusers within each age category, suggesting the HR associated with hypnotic use for each age range. In general, the age-categorized hypnotic HR computed in these models were quite similar to those computed with the primary Cox proportional hazards models. The hypnotics-associated HR for deaths was highest in the youngest age range, but were relatively stable from age 55-65 to the >75 age range. The cancer hypnotic HR of users to nonusers was relatively stable among the 4 age groups.

Supplementary Table 10: Age-categorized death HR associated with hypnotic use

GROUP	DEATHS P	AGE HR (95% C.I.)	Hypnotic HR
age 18-55, no hypnotics, N=13039	REFERENCE: HR=1.0		
age 55-65, no hypnotics, N=4049	0.000	3.72 (2.08 to 6.66)	
age 65-75, no hypnotics, N=3641	0.000	6.38 (3.79 to 10.76)	
age>75, no hypnotics, N=2945	0.000	14.81 (8.99 to 24.39)	
age 18-55, had hypnotic, N=5807	0.000	9.71 (5.92 to 15.94)	9.71
age 55-65, had hypnotics, N=1758	0.000	15.54 (9.20 to 26.28)	4.18
age 65-75, had hypnotics, N=1477	0.000	29.88 (18.01 to 49.36)	4.68
age >75, had hypnotics, N=1489	0.000	60.40 (36.98 to 98.65)	4.08
GROUP	**CANCERS P**	**AGE HR (95% C.I.)**	**Hypnotic HR**
age 18-55, no hypnotics, N=13039	REFERENCE: HR=1.0		
age 55-65, no hypnotics, N=4049	0.000	2.55 (2.11 to 3.08)	
age 65-75, no hypnotics, N=3641	0.000	4.78 (4.03 to 5.67)	
age>75, no hypnotics, N=2945	0.000	5.73 (4.77 to 6.90)	
age 18-55, had hypnotic, N=5807	0.198	1.16 (0.93 to 1.44)	1.16
age 55-65, had hypnotics, N=1758	0.000	3.05 (2.42 to 3.84)	1.25
age 65-75, had hypnotics, N=1477	0.000	5.53 (4.51 to 6.79)	1.20
age >75, had hypnotics, N=1489	0.000	6.85 (5.57 to 8.44)	1.22

Supplementary Table 11: Hazard Ratios for Hypnotic Users Associated with Specific Incident Cancers

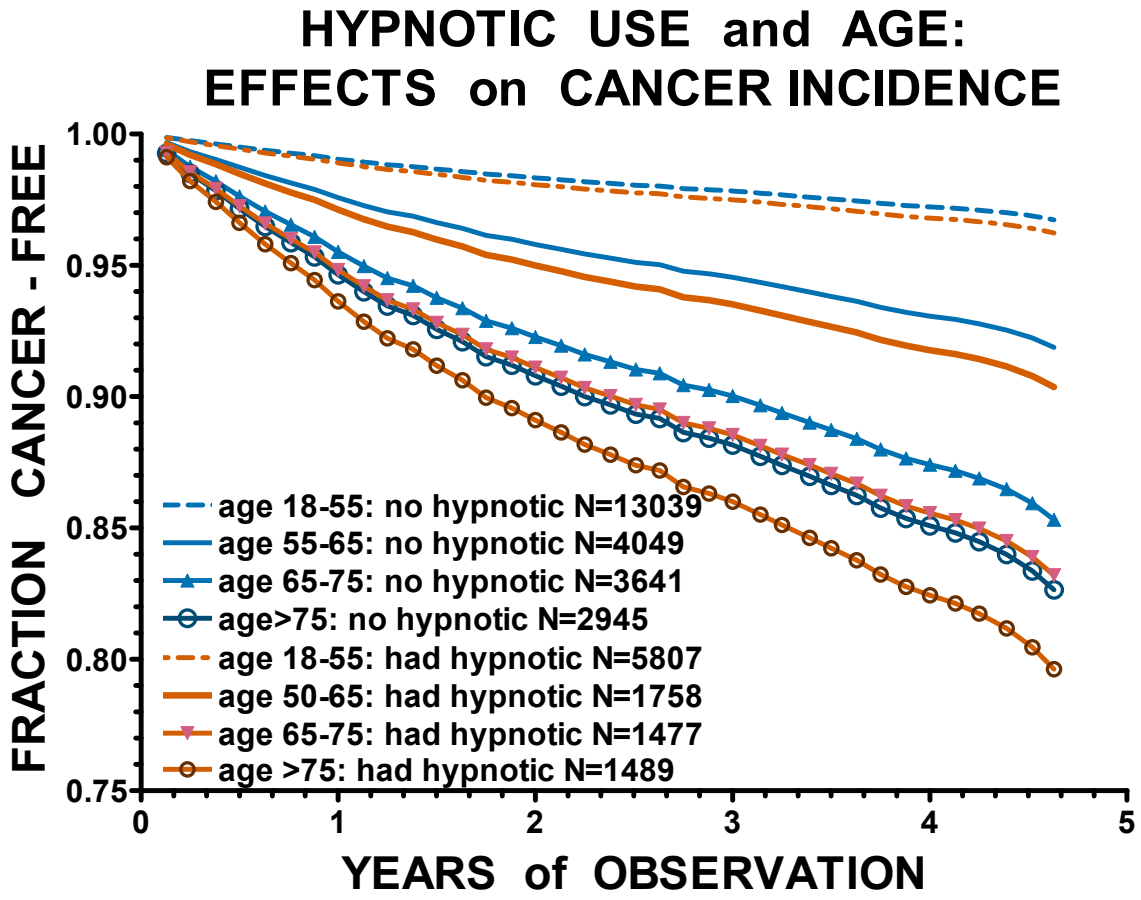
To further explore the possibility that hypnotics may increase hazards of major cancer, we performed exploratory analyses for the association of any hypnotic prescription with the incidence of 10 specific categories of major cancers (Supplementary Table 11.) In addition, HRs were computed for all other major cancers not included in the 10 diagnostic groups and separately for non-melanoma skin cancers. The hypnotic-associated HRs for lymphomas, lung cancers, colon cancers, and the "all other cancers" were distinctly elevated, with 95% Confidence Intervals not overlapping the HR for cancers such as leukemia, melanoma, bladder cancers, uterus/cervix cancers, breast cancers, and non-melanoma-skin cancers. The HR for esophageal cancers was also high and significant, but the confidence interval was wide due to only 20 esophageal cancers being observed. The HR for prostate cancer was statistically significant but modest. Neither temazepam nor zolpidem was associated with specific cancer incidences significantly different from that for users of all hypnotics. It was observed that the HR associated with hypnotic prescribing exceeded the HR associated with current smoking in the same stratified proportional hazards models for lymphomas, lung, colon, prostate, and "all other cancers."

Supplementary Table 11: Hazard Ratios for incidence of specific cancers associated with use of any hypnotic

CANCER TYPE	N	P	HR
Esophagus	20	.048	2.51 (1.01 to 6.25)
Bladder	111	.138	.68 (.40 to 1.14)
Lymphoma *	135	<.001	2.99* (2.11 to 4.25)
Leukemia	78	.667	1.14 (.70 to 1.85)
Melanoma	121	.391	.83 (.55 to 1.26)
Uterus/cervix	175	.291	.83 (.59 to 1.16)
Lung*	189	<.001	2.97* (2.20 to 4.01)
Colon*	213	<.001	1.61* (1.21 to 2.13)
Prostate*	320	.007	1.39* (1.09 to 1.76)
Breast	400	.262	1.13 (.91 to 1.39)
All other major cancers*	443	<.001	1.67* (1.38 to 2.03)
Non-melanoma skin cancer	934	.440	1.05 (.91 to 1.22)

There were 10524 in the hypnotic users cohort and 23,671 nonusers selected for each Cox proportional hazards model before a small percent were excluded due to stratification. Analyses were controlled for age, gender, ethnicity, smoking status, BMI, marital status, and alcohol use and stratified by records of diagnoses in 12 classes of comorbidity. The skin cancer model excluded patients with non-melanoma skin cancer prior to the period of observation, but prior skin cancer was not an exclusion when considering major cancer incidence. **N**: number of cancers in the model for both hypnotic users and non-users. **P**: probability that the HR = 1.000. **HR:** Hazard ratio for incidence of the specific cancer during the period of observation (95% confidence interval).

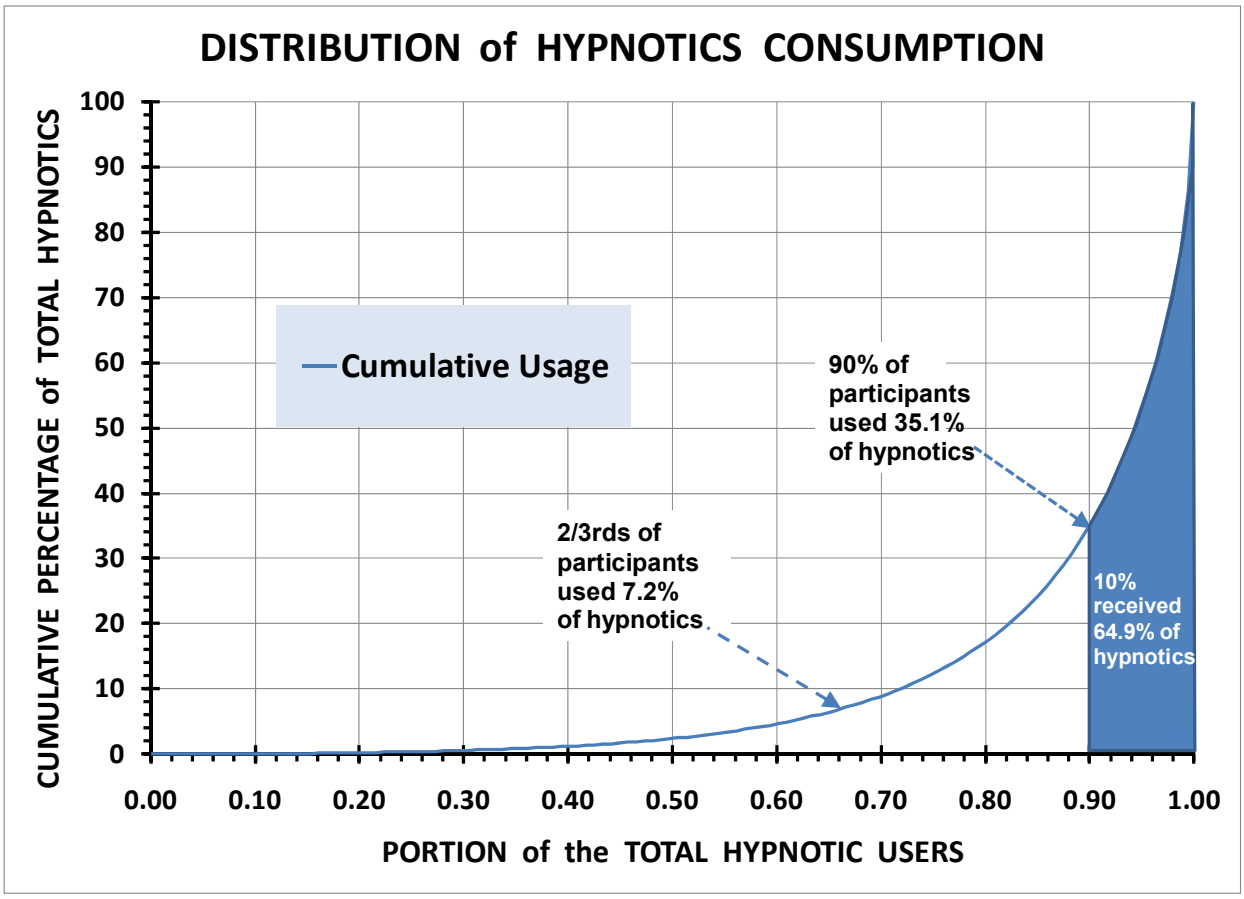
***** indicates the HR for hypnotic users exceeded the HR for current smoking in the same model for this specific cancer.



Supplementary Figure 1. The cancer-free survival of patients is plotted versus the years of observation before censoring. The plot illustrates the same cancer HR from the special Cox proportional hazards model summarized in eTable 10, which used comorbidity groups as covariates. Patients were divided into 8 groups: four age groups who received no hypnotic prescriptions and the comparable age groups of patients who received hypnotic prescriptions (age at beginning of period of observation.) The plot illustrates age effects, cancer HR associated with hypnotics, and the incidence of cancer over time since the first hypnotic prescription (for users).

Most hypnotics prescribed for a small proportion of users.

In our study of Geisinger System patients who received prescriptions for any hypnotics, the lowest-consuming two thirds of the participants were prescribed only 7.2% of the total prescribed hypnotic doses, and the bottom 90% received only 35.1%, as illustrated in Supplementary Figure 2. The top 10% of participants received 64.9% of the prescription doses and averaged 1111 total doses per year. The distribution was quite similar for zolpidem, with the top 10% receiving 62% of the prescriptions and averaging 886 pills (either 5 or 10 mg.) per year.



Supplementary Figure 2. The blue line shows the cumulative percentage of the total hypnotic doses prescribed received by each portion of the hypnotic users, ranked by increasing hypnotic use from left to right. The blue-shaded portion highlights the 64.9% of the total doses received by the top-consuming 10% of participants.

Another way of examining this issue is to use the zolpidem portion of the data, for which we could compute more accurately the daily drug dosages consumed and relate them to statistically-defined daily doses. Of the patients included in our Cox models who received any zolpidem, 34.8% were prescribed <15 defined daily doses per year, averaging 7 statistically-defined daily doses of 10 mg. per year. Those patients who were prescribed 15-85 daily doses per year, who were 33% of the sample, were prescribed an average of 40 defined daily doses per year. The top-consuming 32.1% of zolpidem users were prescribed a mean of 366 defined daily doses per year, thus averaging one per night. This top-consuming 32.1% received 88.4% of the total zolpidem prescribed. The other 67.9% of zolpidem users received only 11.6% of the total zolpidem prescribed.

Additional Discussion

Possibility of genetic confounding.

Epidemiologic studies cannot today control for genetic susceptibility factors that might conceivably both influence the need or desire for hypnotics and also influence survival. For this to occur, the same set of genetic polymorphisms would have to produce high mortality ratios and very high susceptibility to hypnotic use. Currently, there are no known genetic polymorphisms or combinations of polymorphisms which could produce both markedly elevated death hazard ratios and through a separate pathway, a desire for hypnotics, thus leading to artifactual association. There are some data suggesting that heritability of mortality below age 60 is very modest,[29] although Supplementary Data Table 9 found the highest HR for hypnotics in the age group below age 55. Even were the heritability of mortality very high, much of it would have been indirectly controlled through stratification on comorbidities which would tend to presage mortality. The heritability of insomnia is quite modest,[30 31] though the heritability of a tendency to take hypnotics does not seem to have yet been estimated. Judging from what is known about the heritability of mortality and insomnia, it would appear impossible for confounding with genetic factors to account for much of the HR associated with hypnotic use.

Hypertension hazard ratios.

Of the 12 classes of incident comorbidities, only hypertension had a meaningfully lower incidence rate among the hypnotic users than controls. An earlier generation of physicians prescribed sedatives for hypertension, but noting the abandonment of this strategy, we would be surprised if hypnotics genuinely provided antihypertensive benefit through a sedative effect, while at the same time increasing overall mortality, heart failure, coronary atherosclerosis, and esophageal and stomach complications. We know of no evidence for reductions in blood pressure from controlled trials of hypnotics. No satisfactory explanation appears to us. A higher percentage of the hypnotics cohort than the control cohort were excluded from this analysis due to the high rate of hypertension diagnoses prior to the periods of observation (Supplementary Table 4). Judging from the higher rate of numerous complications among the hypnotics cohort compared to controls before the periods of observation, it seems plausible that patients who received hypnotics had visited their primary practitioners more often before the periods of observation, conceivably leaving more undiagnosed hypertension still to be first-diagnosed among controls.

Heart failure hazard ratios.

Of comorbidities, apart from esophageal and stomach distress, the incidence of heart failure had the most impressively elevated incidence for the cohort using hypnotics as contrasted to controls. Many possible mechanisms are conceivable. One mechanism would be that zolpidem exacerbates sleep apnea,[32] and in turn, sleep apnea is thought to contribute to heart failure.[33]

Hypnotics no benefit for obesity.

Several recent studies have noted associations of short sleep durations with obesity,[34] with the implication that sleeping more might prevent obesity. An association of hypnotic use with lower BMI has been reported in men, but the same study showed increased hypertension and diabetes in both genders associated with hypnotic use, and mortality was higher among men using hypnotics.[24] It is interesting that in the current data set, use of hypnotics provided no protection whatsoever against development of obesity (Supplementary Table 4 and Supplementary Table 6).

Combining the extrapolated Geisinger and International Narcotics Control Board data to estimate the percentage of U.S. adults consuming hypnotics.

As explained at the beginning of this Supplement, for 2006-2008, The International Narcotics Control Board estimated that the U.S. consumed statistically defined daily doses (DDD) of hypnotics which would amount to one DDD (at least one pill) for 3.0625% of the U.S. adult population.[1] In the Geisinger user sample examined for the association of any hypnotic dosage with deaths, as shown at the top of Table 3 of the main manuscript, the

lowest 33.09% of the user sample received an average of 8 pills per year (which would contribute 8 * .3309 = 2.65 pills to the consumption of the average hypnotic user.) The middle 33.72% received an average of 57 pills per year (which would contribute 57 * .3372 = 19.23 pills to the consumption of the average hypnotic user.) Finally, the highest 33.18% received an average of 469 pills per year (which would contribute 469 * .3372= 155.61 pills to the consumption of the average user.) Thus, the average user received 2.65 + 19.23 + 155.61 = 177.49 hypnotic pills per year. If each pill was on average equivalent to The International Narcotics Control Board's statistically-defined daily dose, at this rate of hypnotic consumption per hypnotic user, it would require 3.0625% * (365.25/177.49) = 6.3% of the adult population to consume the U.S. defined daily dose consumption estimated by the International Narcotics Control Board for 2006-2008, that is, 6.3% would be hypnotic users. Since almost half of the zolpidem recipients received 5-6.25 mg. pills (about half of a statistically-defined daily dose), and similar low doses may have been prescribed with some of the other compounds, it might require somewhat more than 6.3% of adults to equal the reported 2006-2008 consumption of statistically-defined daily doses. Moreover, since hypnotic consumption has increased since the average for 2006-2008,[2 3] and considering that the International Narcotics Control Board compilation did not include eszopiclone, zaleplon, and antihistamines which we considered hypnotics, we might roughly extrapolate that 10% of U.S. adults might have consumed hypnotics in 2010. This is a very rough estimate which would not include sedative antidepressants such as trazodone or low-dose doxepin used as hypnotics.

An estimate of hypnotic-associated excess U.S. deaths.

Let us take the estimate presented above that at least 6.3% of U.S. adults were using hypnotics in 2006-2008. Let us combine this with the death hazard ratios associated with the three different levels of hypnotic consumption, hazard ratios of 3.60, 4.43, and 5.32 for the three tertiles of users prescribed hypnotics. From these estimates, we can project that the 6.3% of U.S. adults taking hypnotics would experience deaths approximating (.3309 * 6.3% *3.60) + (.3372 * 6.3% * 4.43) + (.3318 * 6.3% * 5.32) = 28.0% of the deaths which would have occurred in the entire population if everybody had the survival hazards of nonusers. The excess deaths associated with hypnotic consumption would be 28.0% - 6.3% = 21.7% of the deaths which would have occurred if everybody had the survival hazards of nonusers. Accordingly, excess deaths would be 21.7% / (100% + 21.7%) or 17.9% of total deaths. Based on a Census-projected U.S. death rate for 2010 of 7.6 per thousand adults for 235,016,000 adults, 2010 excess deaths associated with hypnotics would be .179 * 235,016,000 * (7.6/1000) = yielding approximately 320,000 deaths in 2010 associated with hypnotics consumption. If we based our approximation on the higher extrapolation of 10% of the adult population consuming hypnotics, the very rough estimate would be 507,000 excess deaths in 2010 associated with hypnotic consumption (about 28.4% of total deaths). These estimates can be only a rough approximation of the order of magnitude of deaths associated with hypnotic consumption. Moreover, as previously discussed, we have no accurate estimate of what portion of the deaths associated with hypnotics prescriptions are actually caused by these hypnotic drugs. In guessing the number of yearly U.S. deaths which might be caused by hypnotics, we should consider the possibility that 1) confounding factors augmenting the order of magnitude of associated deaths over the number actually caused by hypnotics might be balanced by 2) study limitations which might lead to undestimation of the associated deaths.

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