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Mortality risk associated with insomnia and sleeping pill use[1]

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ABSTRACT. Insomnia and sleeping pills use have a high prevalence worldwide and epidemiological evidence suggests that they may be associated with a decreased longevity. From this theoretical study, a review of the literature to examine that relationship between insomnia, sleeping pills and decreased longevity was undertaken. Insomnia and sleeping pills use were not consistently associated with an increased mortality rate. The definition of insomnia was poor and inconsistent. In most of the studies it was not determined what "sleeping pills" participants were taking. The design of the studies, the sample sizes, the age of the subjects, and the follow up period were variable across the studies, which made comparisons difficult. Well designed, prospective double blind, randomized, long-term clinical trials with an adequate number of subjects, and the use of the DSM-IV-TR definition of insomnia are needed to improve our understanding of the relationship between insomnia, hypnotic use and decreased longevity.

KEYWORDS. Insomnia. Sleeping pill. Mortality risk. Theoretical study.

RESUMEN. El insomnio y el uso de fármacos para dormir tienen una alta prevalencia a nivel mundial y la evidencia epidemiológica sugiere que tal vez estén asociados con una disminución de la longevidad. Desde este estudio teórico, se efectuó una revisión de la literatura para examinar esa relación entre el insomnio, los fármacos para dormir

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y la disminución de la longevidad. El insomnio y el uso de fármacos para dormir no resultaron consistentemente asociados con un incremento en la tasa de mortalidad. La definición de insomnio fue insuficiente e inconsistente. En la mayoría de los estudios no fue determinado qué fármacos para dormir tomaron los participantes. El diseño de los estudios, los tamaños de las muestras, la edad de los sujetos, y el periodo de seguimiento fueron distintos a través de los estudios, dificultándose así las comparaciones. Ensayos clínicos prospectivos, de doble ciego, aleatorizados, a largo plazo con un adecuado número de participantes y el uso del *DSM-IV-TR* para definir el insomnio son necesarios para mejorar nuestro entendimiento sobre la relación entre el insomnio, el uso de hipnóticos y la disminución de la longevidad.

PALABRAS CLAVE. Insomnio. Fármacos para dormir. Riesgo de mortalidad. Estudio teórico.

RESUMO. A insónia e o uso de fármacos para dormir têm uma lata prevalência a nível mundial e a evidência epidemiológica sugere que talvez estejam associados com uma diminuição da longevidade. A partir deste estudo teórico, efectuou-se uma revisão da literatura para analisar essa relação entre a insónia, os fármacos para dormir e a diminuição da longevidade. A insónia e o uso de fármacos para dormir não se mostraram consistentemente associados com um aumento na taxa de mortalidade. A definição de insónia foi insuficiente e inconsistente. Na maioria dos estudos não foi determinado que fármacos os participantes tomaram para dormir. O plano dos estudos, os tamanhos das amostras, a idade dos sujeitos, e o período de seguimento foram distintos ao longo dos estudos, dificultando assim as comparações. Para melhorar o nosso entendimento sobre a relação entre a insónia, o uso de hipnóticos e a diminuição da longevidade, são necessários ensaios clínicos prospectivos, cegos, aleatórios, a longo prazo com um adequado número de participantes e usando a *DSM-IV-TR* para definir a insónia.

PALAVRAS CHAVE. Insónia. Fármacos para dormir. Risco de mortalidade. Estudo teórico.

Introduction

Insomnia is a distressing and disabling condition that is often associated with functional impairments, reduced quality of life and increased psychophysiologic distress. Ohayon (2002) reviewed the prevalence of insomnia according to four parameters: a) insomnia symptoms; b) insomnia symptoms accompanied by daytime consequences; c) dissatisfaction with sleep quality or quantity; and d) insomnia as a diagnosis. In the first group the prevalence was between 10% and 48%, in the second 9-15%, in the third 8-18%, and the prevalence of insomnia as a diagnosis was 6%.

Chronic insomnia may be associated with a negative impact on the quality of life (Roth and Ancoli-Israel, 1999), a decreased job performance and increased absenteeism (Zammit, Weiner, Damato, Sillup, and McMillan, 1999). Insomnia is associated with

poorer general health (Bixler, Kales, Soldatos, Kales, and Healey, 1979; Mellinger, Balter, and Uhlenhuth 1985; Zammit *et al*., 1999) and increased health care costs (Ford and Kamerow, 1989; Simon and Von Korff, 1997). And, insomnia is a risk factor for depression, anxiety disorder, alcohol and drug abuse (Johnson and Breslau, 2001; Weissman, Greenwald, Nino-Murcia, and Dement, 1997). Insomnia may be associated with a decreased longevity (Kojima *et al*., 2000). Treatment of insomnia includes both pharmacological treatment and non-pharmacological interventions. Long-term use of hypnotics has generally been discouraged by experts because of concerns about: a) residual sedative effects, b) memory impairment, c) falling, d) rebound insomnia, e) respiratory depression, f) tolerance development and dose escalation, g) dependency and withdrawal difficulties, h) medication abuse, and i) a possible increased risk of death (Kramer, 2000).

The most important and unresolved of these concerns is the possibility that both chronic insomnia and the use of hypnotics may contribute to an increased mortality. A major concern would be for the elderly as they consume 31% of all hypnotic prescriptions and over-the-counter drugs (Mellinger *et al*., 1985) often on a daily basis for years. From this theoretical study (Montero and León, 2005), a review of the literature on the relationship of longevity to both insomnia and to the use of hypnotics seemed appropriate and was undertaken.

Method

We conducted a search of Medline (1966 through April 2006) and PubMed (1966 through April 2006) databases using the terms insomnia, sleeplessness, sleep problem, sleep disorder, sleeping pill, hypnotic and mortality. The search found 136 articles when terms insomnia and mortality were used and 1,346 articles when terms hypnotic and mortality were used. The references of the selected articles were also reviewed to identify any studies that were missed in the search. We identified 16 studies reporting association between insomnia or sleep disturbance symptoms and mortality, and 9 studies reporting sleeping pill use as a risk factor for an increased mortality risk.

Results

Insomnia (see Table 1)

Increased risk present

Kripke, Simons, Garfinkel, and Hammond (1979) reexamining the Cancer Prevention Study I data (CPS I), which involved more than one million subjects over the age of thirty, found that in men, who reported a current complaint of insomnia “often”, the 6-year mortality risk was 1.30, after controlling for age, sleeping pill use and reported sleep duration. Females who reported insomnia “fairly often” had a significant 10% decrease in mortality risk. In a replication, based on the data from Cancer Prevention

Study II (CPS II) with 1.1 million participants aged 30-102 years, Kripke, Garfinkel, Wingard, Klauber, and Marler (2002) found that a self-report of insomnia was associated with a decreased mortality risk of 4-13% for men, and 13-19% for females after controlling for 32 risk factors. A definition of insomnia was not provided in either study.

Pollak, Perlick, Linsner, Wenston, and Hsieh (1990) found in 1,855 residents of an urban community, that insomnia was associated with a 300% increase in mortality risk in men. The relationship between insomnia and mortality was U-shaped. Participants reporting no insomnia or frequent insomnia (4-12 episodes over 14 nights) had a higher mortality risk than participants reporting occasional insomnia (1-3 episodes over 14 nights). In women, insomnia was a borderline predictor of mortality (RR, 1.36; 95% CI, 0.98-1.88).

Kojima *et al*. (2000) in a population based cohort study of 5,322 participants, aged 20 to 67 years, reported a two fold increase in mortality risk (RR, 2.03; 95% CI, 1.10-3.74) in females complaining of poor awakening state compared to those who reported normal awakening state.

Manabe *et al*. (2000) reported an increased mortality risk of 1.59 (95% CI, 1.05-2.40) for insomnia among 272 chronically institutionalized, geriatric hospital patients after a 2-year-follow-up. Patients were checked hourly by nursing staff, and insomnia was defined as sleep less than 6.4 hours at night.

In the Cardiovascular Health Study (CHS), with 5,888 participants older than 65, recruited in four US communities, Newman *et al*. (2000) reported an increased mortality risk of 1.43 (95% CI, 1.14-1.80) in men with difficulties falling asleep. The risk remained significant (RR, 1.29; 95% CI, 1.03-1.63) after adjustment for age. An association between frequent awakenings in men and women and early morning awakening in men was positive, but did not reach statistical significance. Follow-up was an average of 4.85 years.

Nilsson, Nilsson, Hedblad, and Berglund (2001) reported an increased mortality risk of 1.76 (95% CI, 1.51-2.06) in men and 1.40 (95% CI, 1.07-1.84) in women with insomnia among 33,346 participants from Malmo, Sweden. The author points to the relationship between insomnia and sympathetic nervous activation and hypothesizes that both are consequences of chronic stress exposure.

In a prospective population based study, in Sweden, Mallon, Broman, and Hetta (2002) investigated the relationship between sleep complaints and total mortality, coronary artery disease (CAD) mortality, cancer mortality and “all other causes” mortality among 1,870 subjects aged 45-65 years after a 12-year follow-up. They found that difficulties falling asleep (DIS) (RR, 1.9; 95% CI, 1.4-2.7), and difficulties maintaining sleep (DMS) (RR, 1.4; 95% CI, 1.1-1.9) in men and DIS (RR, 1.6; 95% CI, 1.1-2.3) in females were related to total mortality after age adjustment. After further adjustment for several risk factors DIS (RR, 3.1; 95% CI, 1.5-6.3) was related to an increased mortality risk from CAD, and DMS (RR, 3.1; 95% CI, 1.3-7.6) to an increased risk for “all other causes” in males. In females, DIS (RR, 2.9; 95% CI, 1.3-6.3) was correlated to an increased risk for “all other causes” mortality.

No risk found

Eight other studies, with 38,917 participants aged 45 to 89 years, and follow-up between 3 and 9 years, found no relationship between insomnia and an increased mortality risk.

In a prospective Nottingham Longitudinal Study of Activity and Ageing (Rumble and Morgan, 1992) there was no significant relationship between mortality and subjective insomnia among 1,042 survey respondents after 5-year follow-up.

Brabbins *et al*. (1993) did not find association between insomnia and increased mortality in a sample of 1,070 subjects aged 65 and over living in Liverpool after 3-year follow-up.

The three-center "Established Population for Epidemiologic Studies of the Elderly" (EPESE) (Foley *et al*., 1995) did not show association between insomnia and decreased longevity in 9,282 participants aged 65 years and older after 3-year follow-up.

Hays, Blazer, and Foley (1996) did not find an association between insomnia and an increased mortality risk in a prospective cohort study in North Carolina among 3,962 participants aged 65-101 years after a 4-year follow-up.

Althuis, Fredman, Langenberg, and Magaziner (1998) reported no relationship between insomnia and 6-year survival among 778 white women from Baltimore area, 65 years and older.

Jensen, Dehlin, Hagberg, Samuelsson, and Svensson (1998) found no significant difference in survival rate between a group of subjects with no insomnia and mild insomnia and group of subjects with moderate and severe insomnia in a longitudinal study of 333 80-year-old subjects from the city of Lund, Sweden, who were followed up for 9 years.

The Canadian Study of Health and Aging (CSHA) (Rockwood, Davis, Merry, MacKnight, and McDowell, 2001) found no association between insomnia and an increased risk of death among 9,008 Canadians age 65 and older after a 5-year follow-up.

A recent study by Phillips and Mannino (2005) has shown insomnia was not associated with an increased mortality rate among 13,563 participants, aged 45 to 69 years from four communities in United States after 6.3 years of follow-up.

Sleeping pill use (see Table 1)

A correlative relationship between sleeping pill use and increased mortality risk was shown in both Caner Prevention Studies (Kripke *et al*., 1979; Kripke *et al*., 2002). In CPS I the mortality risk was increased 1.57 times in men who indicated taking sleeping pills "often" and 1.54 in women after a 6-year follow-up. An increased mortality risk was also statistically significant in participants who reported using sleeping pills "seldom", with a 15% increase in males and 13% in females. In 1959, when the study was done, the most commonly used hypnotics were barbiturates. In CPS I no distinction was made between prescribed hypnotics and over-the-counter drugs. After controlling for 32 risk factors, mortality risk for "prescription sleeping pills" users after a 6-year follow-up in CPS II was significantly increased, yet lower than in CPS I. The mortality

risk in subjects with hypnotic use 30 times per month was increased 25% in men and 24% in females. The use 1-29 times per month was associated with a statistically increased mortality risk of 15% in men and 10% in females.

Mallon *et al*. (2002) reported in a 12 year follow-up study among 1,870 subjects aged 45-65 years that habitual sleeping pill use ("often" and "very often") was significantly related to total mortality, with risk ratios of 3.0 (95% CI, 1.5-5.9) for men and 3.8 (95% CI, 2.1-7.0) for women. However, after adjustment for a range of important risk factors, there was statistically significant relationship between sleeping pill use and death from cancer in males (RR, 5.3; 95% CI, 1.8-15.4) and death "from all other causes" (non cancer and non-coronary artery disease deaths) in females (RR, 3.3; 95% CI, 1.1-10.1).

Kojima *et al*. (2000) found positive association between sleeping pill use in females (RR, 1.81; 95% CI, 0.92-3.56), but this association was not statistically significant. There was no clear association between sleeping pill use and longevity in men. The average follow-up time was 11.9 years. The prevalence of sleeping pill use was low, only 2.2% of men and 3.4% of women were sleeping pill users.

In the Atherosclerosis Risk in Communities Study (Phillips and Mannino, 2005), which included 13,563 participants, sleeping pill use was not associated with an increased mortality risk (RR, 1.4; 95% CI, 0.9-2.1). Only 296 participants were identified as sleeping pill user; 44 subjects used barbiturates (RR, 2.0; 95% CI, 0.9-4.6), 104 used antihistamines (RR, 2.0; 95% CI, 0.9-4.4), and 148 participants used benzodiazepines (RR, 1.1; 95% CI, 0.6-2.0). The small number of subjects may have prevented the study of detecting a modest risk.

Elderly individuals are the greatest users of hypnotics. An examination of the mortality risk for the elderly related to their hypnotic use is of great concern. In three studies (Brabbins *et al*., 1993; Hays *et al*., 1996; Pollak *et al*., 1990) with 6,887 subjects older than 65, and a follow-up period of between 3 and 5 years, a relationship between hypnotic use and decreased longevity could not be confirmed in any study.

Rumble and Morgan (1992) found among 1,042 subjects that the 5-year mortality was increased 40% (RR, 1.39; 95% CI, 0.99-1.93) among sleeping pill users aged 65 years. However, there was a statistically significant increase in deaths only among analgesic users (RR, 2.46; 95% CI, 1.28-4.74), but not among users of recognized hypnotics (RR, 1.20; 95% CI, 0.83-1.73).

TABLE 1. Insomnia, sleeping pill use and a mortality risk.

Study	*N*	*Gender*	*Age*	*Main finding(s)*	*F/U*
1. Kripke *et al*. (1979)	> 1 million	Both	30-over 90	Insomnia was associated with an increased mortality risk in men (RR, 1.30).[a] Sleeping pill use was associated with a higher mortality risk in men (RR, 1.57)[a] and women (RR, 1.54).[a]	6 years
2. Pollak *et al*. (1990)	1,855	Both	65-98	Insomnia was associated with an increased mortality risk in men (RR, 3.15).[b] Sleeping pill use was not associated with an increased mortality risk.	3.5 years
3. Rumble and Morgan (1992)	1,042	Both	over 65 years	No relationship between insomnia and mortality risk. Higher mortality risk found only in analgesic users (RR, 2.46), but not in users of recognized hypnotics (RR,[#] 1.20).	5 years
4. Brabbins *et al*. (1993)	1,070	419 M 651 F	65 and older	No relationship was found between mortality and insomnia or hypnotic use (RRs not reported).	3 years
5. Foley *et al*. (1995)	9,282	Both	65 and older	No positive relationship found between insomnia and an increased mortality risk (RR, 0.98).[c]	3 years
6. Hays *et al*. (1996)	3,962	Both	65 and older	Sleeping pill use was not associated with an increased mortality risk (RR, 0.89).[d]	4 years
7. Althuis *et al*. (1998)	778	Females	65 and older	No positive relationship found between insomnia and an increased mortality risk (RR, 0.74).[e]	6 years
8. Jensen *et al*. (1998)	212	Both	80 years old	Subjects with moderate and severe insomnia did not have increase mortality risk compared with subjects who reported no insomnia or mild insomnia (RR not reported).	9 years
9. Kojima *et al*. (2000)	5,322	2,438M 2,884F	20-67	Females complaining of poor awakening state had a higher mortality risk than those who woke up normally (RR, 2.03).[f] Female sleeping pills users had an increased mortality risk (RR, 1.81).[f]	12 years
10. Manabe *et al*. (2000)	272	107M 181F	65 and older	Insomnia was associated with an increased mortality risk (RR, 1.59).[g]	2 years
11. Newman *et al*. (2000)	5,888	2,495M 3,393F	65 and older	Difficulties falling asleep in men associated with an increased mortality risk (RR, 1.29).[h]	4.85 years
12. Nilsson *et al*. (2001)	33,346	22,444 M 10,902 F	Middle age	Insomnia was a risk for total (RR, 1.76)[i], CVD (RR, 1.71) and "other mortality (RR, 2.78)[i] in men and for total (RR, 1.40)[i] and "other" mortality (RR, 2.43)[i] in females.	17 years M 12 years F
13. Rockwood *et al*. (2001)	9,008	Both	65 and older	No relationship found between sleep disturbance symptoms and an increased mortality risk.	5 years
14. Kripke *et al*. (2002)	1.1 million	480,841M 636,095 F	30-102	No relationship found between insomnia and an increased mortality risk. Sleeping pill use had a higher mortality risk in males (RR, 1.25)[j], and in females (RR, 1.24).[j]	6 years
15. Mallon *et al*. (2002)	1,870	906 M 964 F	45-65	Insomnia not associated with total mortality after adjustment for known risk factors (RR not reported). DIS (RR, 3.1)[k] was related to CAD mortality in males. Sleeping pill use was not associated with total mortality after adjustment for known risk factors (RR not reported). Female sleeping pill users had an increased risk (RR, 3.3)[k] for non-CAD, non-cancer mortality.	12 years
16. Phillips and Mannino (2005)	13,563	7,482 M 6,081 F	45-69	Insomnia (RR, 0.9)[l] and sleeping pill use (RR[#], 1.4)[l] were not associated with an increased mortality risk.	6.3 years

NOTES.CAD: coronary artery disease; CVD: cerebrovascular disease; DIS: difficulties initiating sleep; RR: relative risk.

[#] Non-significant.

[a] Adjusted for age, gender, reported hours of sleep, prior histories of heart disease, high blood pressure, stroke, and diabetes.

[b] Adjusted for reported sleep duration, insomnia, symptoms of restless leg syndrome and periodic leg movements, symptoms of sleep apnea, excessive daytime sleepiness, frequent use hypnotic/sedative drugs, age, activities of daily living, self-assessment of general health, income, cognitive impairment, living arrangement.

[c] Adjusted for age, sex, community and number of physical limitations.

[d] Adjusted for age, sex, race, residence, marital status, living arrangements education, income, cognitive impairment, depressive symptoms, chronic illness, activities of daily living, gross mobility, physical activity, body mass index, smoking, and alcohol use.
[e] Adjusted for age, prescription medication use, functional limitations, self-rated health, and number of chronic conditions.
[f] Adjusted for baseline age, present and past history of hypertension, cerebrovascular, heart and renal diseases and diabetes, sleep duration, and use of sleeping pills (smoking and drinking habits only in males).
[g] Adjusted for age, gender, and activities of daily living scores.
[h] Adjusted for age.
[i] Adjusted for smoking, body mass index, systolic blood pressure, cholesterol, smoking and problematic alcohol drinking habits.
[j] Adjusted for age, race, occupation, education, marital status; habits: exercise level, smoking at intake, years of smoking, churchgoing, fat in diet, reported sleep duration, insomnia frequency, "sick now," "upset," body mass index, leg pain, history of heart disease, history of hypertension, history of cancer, history of diabetes, history of stroke, history of bronchitis, history of emphysema, history of kidney disease, "prescription sleeping pills," Valium, Librium, "blood pressure pills," diuretics, Tylenol, Tagamet.
[k] Adjusted for age, not married, living alone, smoking, body mass index>28, hypertension, cardiac disease, respiratory disease, diabetes, joint pain, gastrointestinal disease, depression, sleep duration<6h, sleep duration>8h, DIS, DMS, habitual snoring, habitual sleeping pill usage and urogenital disease.
[l] Adjusted for age, sex, menopausal status, education level, body mass index, depressive symptoms, presence of cardiac disease, lung function status, presence of hypertension, smoking status, alcohol intake, diabetes, and hypnotic use.

Discussion

Insomnia

Insomnia was not found to be consistently associated with an increased mortality rate. The design of the studies, the definition of insomnia, the sample sizes, the age and sex of the subjects, the control of covariates and the follow up period were variable across the studies, which may have affected the results. Insomnia was inconsistently and poorly defined with the two CPS studies (Kripke *et al*., 1979; Kripke *et al*., 2002) not providing any definition of insomnia at all. The severity and duration of insomnia were not included in the definitions of insomnia in many studies, which could have caused great within-group variability. The inclusion of covariates in predictive models in some studies, which may be consequences or side effects of insomnia (for example: depression or anxiety), may have lead to an underestimation of the mortality risk. The possible importance of gender differences was not appreciated as some studies found increased mortality only in males, some only in females, while some studies did not even report results by gender. The possible differential effect of age on mortality in insomniacs was dealt with in a limited manner as some studies included only middle-aged people, but most studies appropriately were of people over 65 who have the highest prevalence of insomnia. The follow-up period was highly variable, from 2 to 17 years, making comparison across studies very difficult.

The question is often raised as to what the mechanism might be to account for an increased mortality in insomnia if that were indeed the case. The mechanism by which insomnia may contribute to increased mortality has not been coherently and comprehensively delineated. Insomnia is often associated with perceived acute or chronic stress. Stress has been associated with an immediate response mediated through the

release of catecholamines (epinephrine and norepinephrine), and a slower response mediated through the hypothalamic-pituitary-adrenal (HPA) axis resulting in an increased secretion of cortisol. These pathophysiologic changes could lead to physiologic or psychological activation *i.e*. "hyperarousal" in insomniacs. There is evidence that patients with insomnia have an increased amount of beta EEG activity throughout the night, affecting NREM and REM sleep (Merica, Blois, and Gaillard, 1998; Perlis, Smith, Andrews, Orff, and Gilles, 2001) and Nofzinger *et al*. (2004) using PET scanning, has found that patients with insomnia had greater glucose brain metabolism during sleep and while awake.

An association between insomnia and sympathetic hyperactivation has been additionally demonstrated in several studies. Insomniacs have elevated heart rate, increased core body temperature and 24-hour metabolic rate (Bonnet and Arand, 1995). Insomnia is associated with nocturnal elevations of circulating levels of norepinephrine (Irwin, Clark, Kennedy, Gillin, and Ziegler, 2003), and 24-hour increased urinary epinephrine secretion (Adam, Tomeny, and Oswald, 1986). Sympathetic activation is associated with hypertension, metabolic syndrome, and it is involved in the pathogenesis of atherogenesis (Hugget, Burns, Mackintosh, and Mary, 2004). Tachycardia is related to an increased risk for cardiovascular as well as for all-cause mortality (Greenland *et al*., 1999; Kannel Kannel, Paffenbarger, and Cupples, 1987).

There is evidence which suggests that the HPA system is activated in chronic insomnia. Insomnia is associated with an increase of ACTH and cortisol secretion throughout the 24-hour period without disturbances in the circadian pattern of excretion (Vgontzas *et al*., 2001), increased evening and nocturnal levels of cortisol (Rodenbeck, Huether, Ruether, and Hajak, 2002), and elevated urine excretions of cortisol in poor sleepers (Johns, Gay, Masterton, and Bruce, 1971). Hypercortisolism is associated with mood disturbances (depression and anxiety), hypertension, metabolic syndrome and osteoporosis. HPA activation in chronic insomniacs may explain the close link between insomnia on one hand, and depression and anxiety on the other. This link may also contribute to an explanation of the increased suicide risk in insomnia (Agargun, Kara, and Solmaz 1997; Singareddy and Balon, 2001).

There is an association between insomnia and immune functioning. Insomniacs have a reduction of natural killer (NK) cell activity (Irwin *et al*., 2003), significantly increased nocturnal interleukin-6 (IL-6) secretion (Burgos *et al*., 2005), and a shift of IL-6 and tumor necrosis factor (TNF) secretion from nighttime to daytime (Vgontzas *et al*., 2002). Primary chronic insomnia is associated with lower counts of T-lymphocytes (Savard, Laroche, Simard, Ivers, and Morin, 2003). These findings suggest immunologic abnormalities in insomniacs and a possible link between insomnia, cancer morbidity (Savard *et al*., 1999), and inflammatory diseases.

These metabolic alterations could individually or in combination provide a series of possible mechanisms for the development of illness which could decrease longevity in insomniacs. They also open the possibility for alternative strategies for the treatment of insomnia. More carefully designed and executed studies establishing the mortality, morbidity and pathophysiology of insomniacs to establish the prevalence of each factor and/or their concomitance would foster the pursuit of mechanisms underlying such effects and perhaps open new treatment approaches.

Sleeping pill use

Two Cancer Prevention Studies (CPS I and II) of the American Cancer Society (Kripke *et al*., 1979; Kripke *et al*., 2002) showed that people who reported taking sleeping pills had a higher mortality rate. The strongest relationship was between sleeping pill use and increased risk for suicide and death from cancer. The data from these two large population surveys did not reflect the demographics of the population of the USA. Subjects who were geographically mobile, institutionalized, from minority groups and low-income groups were underrepresented. The mortality rate in CPS II was 20% less than in the general population, which makes the results more impressive as they are positively health skewed. Two other studies with 7,192 participants (Kojima *et al*., 2000; Mallon *et al*., 2002) were able to partially replicate these results.

In five studies with 21,492 subjects the relationship between sleeping pill use and an increased mortality rate could not be confirmed. The failure to replicate may be due to insufficient power in the smaller sample size in each of these studies and the generally shorter follow-up time.

How sleeping pills may cause death is not clear. In CPS II use of hypnotics was particularly associated with an increased risk for suicide and cancer. Another study (Mallon *et al*., 2002) has found that men with habitual use of sleeping pills have an increased risk for cancer. A casual mechanism which explains the relationship between hypnotics and carcinogenesis is not known at this time. Overdose may explain in some cases link between sleeping pill use and increased mortality, especially for barbiturates. Barbiturate overdose mortality is usually secondary to coma and respiratory depression. On the other hand benzodiazepines are generally safe in overdose. In the USA in 2003 a total of 60,014 exposures to benzodiazepines were reported, of which 180 (0.003%) resulted in death (Watson *et al*., 2004). Sleeping pills may have synergistic action with alcohol and other CNS depressants. Other suggested mechanisms which may explain an increased mortality are: exacerbation of sleep apnea, suppression of self-care functions, confusion, amnesia and disinhibition (Kripke *et al*., 1998).

In most of the studies it was not determined what “sleeping pills” participants were taking. “Sleeping pills” in these studies, depending on when they were done, may have included different classes of medications: barbiturates, meprobamates, benzodiazepines, antihistamines, analgesics, melatonin, valerian root and other OTC drugs. It is essential to know the chemical substances that are potentially implicated in the increased mortality, if the pursuit of a mechanism of action is to be undertaken.

Conclusion

The evidence linking insomnia or sleeping pills use and an increased mortality rate is suggestive but inconclusive. Well designed, longitudinal studies with a) an adequate number of subjects, b) a clear definition of insomnia as a syndrome, c) a rigorous assessment of the frequency, duration, and severity of insomnia symptoms, d) a careful choice of covariates to be included in predictive models, and e) a comparison of equivalent groups of treated with the type of hypnotic specified and untreated insomniacs with healthy controls are needed to improve our understanding of the relationship between

insomnia, sleeping pill use, and decreased longevity. A prospective study may not be feasible and careful examinations of large demographically representative data bases such as those at the VA or a large HMO might serve the same purpose.

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