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Surprising View of Insomnia and Sleeping Pills:

Commentary on Chen et al. A 9-year Follow-up Study of Sleep Patterns and Mortality in Community-Dwelling Older Adults in Taiwan (SP-00502-12).

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Chen, Su, and Chou in this issue of SLEEP[1] present a study that challenges several pervasive beliefs about sleep disorders. They used a novel hierarchical approach to classifying types of insomnia-like disturbances, a well-characterized aging population sample, and a long follow-up reaching 9 years. The new methodology provided a better understanding of the complex inter-relationships of insomnia, short sleep, and use of sleeping pills.

The first surprise in the findings of Chen et al.[1] was that "...of those who scored >5 on the PSQI, only 9.3% and 20.5% of subjects satisfied the definitions of 1-month and 6-month insomnia disorder, respectively..." Poor sleep quality by PSQI and insomnia usually were NOT the same thing. Indeed, the authors of the PSQI never asserted that their scale for "sleep quality" was an index of insomnia or well correlated with any polysomnographic parameters.[2,3] Rather, PSQI was developed to assess a mixture of sleep quality items indicating insomnia, excessive sleepiness, sleep apnea, restless legs syndrome, perhaps circadian rhythm sleep disorders, and uncharacterized disturbances. PSQI should not be used as an assessment of insomnia, for which there are better instruments.

The second surprise in the findings of Chen et al.[1] was that substantial percentages of those with PSQI>5 or who took sleeping pills on at least 21 days per month said that they slept at least 8 hours. Indeed, the percentage taking sleeping pills at least 21 days per month was almost as high among those who said they slept 8 hours as among those who said they slept ≤4 hours a night. Over half of those taking sleeping pills at least 21 days per month fell into the no-insomnia group. Controlled trials do not suggest that sleeping pills are that successful in eliminating insomnia, but there is much evidence that sleeping pills are often prescribed for patients who do not complain of insomnia or short sleep. The third surprise in the findings of Chen et al.[1]was that a PSQI>5 was not associated with significantly elevated mortality in the

fully-controlled Cox model. In fact, they found that with control for hypnotic consumption, insomnia disorders were not associated with mortality for 1-month insomnia disorder (hazard ratio [HR] = 0.84; 95% C.I. = 0.50-1.43), and with control for hypnotic consumption, they found decreased mortality associated with 6-month insomnia disorder (HR = 0.64; 95% C.I. = 0.43-0.96). The majority of studies have not suggested that insomnia is protective, but the results of Chen et al.[1] emphasize that insomnia cannot explain excess mortality associated with hypnotics consumption.[4]

The data of Chen et al.[1] did reveal an elevation in mortality hazard ratio associated with depression, unlike some other studies controlling for hypnotic use.[4,5] However, controlling for depression had no significant effect on the mortality hazard associated with sleeping pill use. Sleep duration less than 7 hours was not associated with increased mortality, but sleep greater than 8 hours was associated with increased mortality. This adds to evidence recently reviewed by Kurina and colleagues that mortality is more consistently elevated in association with long sleep than with short sleep,[6] but Kurina et al. remark that objective sleep of 9 hours or more is rarely observed by PSG. Since it is well-known that among elderly people, reported sleep tends to be longer than objective sleep, it may be that optimal survival with 7 hours reported sleep may correspond to 5.0-6.5 hours of objectively recorded sleep.[7] Objective sleep exceeding 390-420 min. per night might carry a long-sleep mortality risk.

In conclusion, the findings of Chen et al.[1] reconfirmed that sleeping pill use was associated with excess mortality, but that excess hypnotic-associated mortality risk could NOT be explained by confounding with insomnia, short sleep, or depression risks. Their study has many excellent elements worthy of emulation, but like many studies examining mortality associated with sleep medications, the manuscript acknowledges limitations due to the lack of

data concerning which specific medications were associated with excess mortality, and the lack of measurement of the sleeping pill exposure of participants during the mortality follow-up. If the study participants of Chen et al.[1] initially taking sleeping pills soon discontinued them or those initially drug-free commenced using sleeping pills during follow-up, this study might mis-estimate the risks associated with hypnotics. Future studies must resolve the conflicting strategies of prospective selection of cohorts versus need for monitoring of sleeping pill consumption during follow-up.

The report by Chen and colleagues[1] points to greater risks associated with sleeping pill use and long sleep than with risks of short sleep or insomnia. Epidemiologic attention is better directed to risks of sleeping pills and long sleep. However, association does not necessarily indicate causality. To date, it appears the U.S. Food and Drug Administration (FDA) has not required controlled safety trials of whether hypnotics cause mortality risks. The alternative will be genetic analyses based on Mendelian randomization to determine how much morbidity (e.g., cancer) and mortality may be caused by sleeping pills and by long sleep.[8] Mendelian randomization studies might exploit existing data bases that combine information on participant hypnotic use and subsequent mortality with GWAS genetic data on the same participants. If it can be shown that particular polymorphisms influence the amount of hypnotics consumed, that those same randomly-inherited polymorphisms influence morbidity or mortality, and that those polymorphisms mediate mortality or cancer through hypnotic consumption, a causal component of hypnotic risks will have been demonstrated.[9-13]

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