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Pharmacology and therapeutics - Research:
Hypnotics' association with mortality or cancer: a matched cohort study
Daniel F Kripke, Robert D Langer, Lawrence E Kline
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[Abstract] [Full text] [PDF] [Review history] [Supplementary Data]

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Hypnotics' association with mortality or cancer: bias related to the study design and analysis

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In BMJ Open, Kripke et al have presented a study on risks associated with the use of hypnotics (1). In their two-in-one study, the authors report an about fourfold increased risk of death and a 35% increased risk of cancer when comparing users of hypnotics with non-users. The authors present the analyses as a cohort study using a survival analysis model with Cox regression. However, several approaches in both the study design and analysis do not fulfil the conditions for a survival analysis, primarily because the authors do not respect the time sequence of exposure and events. We believe it is important to draw attention to these limitations, because the applied approaches are likely to have introduced bias that may have contributed substantially to the findings.

Firstly, the main criterion for being selected as a non-user is that the study subject has not redeemed any prescriptions for hypnotics anytime during the entire study period. If we have understood this correctly, the consequence of this exposure criterion is that study subjects who received their first hypnotic dispensing after a cancer diagnosis, something reasonable and quite common (2), were excluded from the reference group. These cancer events were, however, occurring among non-exposed study subjects and should be included among these. The selective exclusion creates a spurious association between hypnotics and cancer, with a magnitude depending on the incidence of hypnotic use among cancer patients. A calculation suggests that a cumulative incidence of hypnotic use of 25% among cancer patients would create a 30% spuriously elevated cancer risk through this mechanism. Kripke et al's design violates one of the fundamentals of cohort study design: one should not base the exposure definition on future events - "you should never use a crystal ball".

Secondly, Kripke et al did not use a time-dependent exposure model. Hypnotic exposure began at the time of first prescription and an average exposure was calculated over the entire observation period to either censoring or occurrence of an outcome event. Among persons with a low average exposure we would expect a considerable proportion of "remote users", i.e., persons with only few dispensings who may not even have been exposed at the time of cancer or death. The more than three-fold increased risk of death observed for the lowest average dose level could imply that use of hypnotics was a marker of some underlying condition (e.g., psychiatric disease) that the analysis was not able to adjust for rather than the cause of death per se. A model with time-dependent exposure classification would provide more information on the relationship between exposure patterns and risk.

Similarly, in the cancer substudy, a dose-response analysis based on the average amount of dispensed hypnotics was performed, but analyses taking into account exposure duration and time-dependent cumulative exposure were not presented. We consider the latter analyses essential for evaluating the plausibility of a causal effect. The authors exclude study subjects where cancer is diagnosed less than 18 days from exposure, which they state is "too soon after for it to be at all plausible that the hypnotic caused the cancer". This period is much too short. A sensitivity analysis excluding exposure in different time intervals close to the cancer diagnosis would have been informative regarding the potential prescribing of hypnotics related to early symptoms of the cancer (reverse causation bias) or sleep disturbances during the diagnostic work-up for cancer. A similar pattern might be occurring in the mortality analysis; subjects may have used small quantities of hypnotics to treat distress over a fatal disease shortly before their death. Unfortunately, Kripke et al do not account for the temporal pattern, which renders the paper difficult to interpret.

Thirdly, when adjusting for confounding, Kripke et al used information on comorbidity from the entire observation period, i.e., both before and after start of hypnotic exposure. Usually, adjusting for covariates observed during the entire period from exposure to outcome event(s) is discouraged, because it may induce bias, unless a model reflecting time-dependent exposure is used (3, 4).

With the approach applied in the present study, the amount of information on confounders accumulates over time. This could lead to impaired adjustment for confounding among those who leave the study cohorts early. We note that there was very little difference between crude and adjusted estimates. This could imply lack of confounding, but also that the adjustment was deficient. An additional reason for inefficient confounder control despite the thorough matching could be that comorbidity was defined in rather broad categories. One way of evaluating confounders would be to examine associations between confounders and outcome, but the use of a comorbidity -stratified Cox model unfortunately obscures this possibility.

In summary, we believe that the associations between hypnotic use and cancer or death in the study by Kripke et al may to a large degree be explained by selection bias affecting the controls, and to a lesser degree by suboptimal control of confounding. Kripke et al may inadvertently have introduced bias by some of the choices they have made in their study design and analysis. Furthermore, analyses taking into account time- dependent exposure and - in the analysis of cancer risk - both exposure duration and cumulative exposure would have added much to the interpretation of results.

Finally, we would like to add that we share the authors' view on hypnotics in general. Prescription of hypnotics should generally be avoided, and these drugs should almost exclusively be reserved for short- term use in selected patients.

References

1. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850

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4. van Walraven C, Davis D, Forster AJ, Wells GA. Time-dependent bias was common in survival analyses published in leading clinical journals. J Clin Epidemiol 2004;57(7):672-82.

Conflict of Interest:

MA and JH has participated in research projects funded by Nycomed, the manufacturer of Nitrazepam, and Pfizer, the manufacturer of Halcion (triazolam) and Tafil (alprazolam), with grants paid to institutions where they have been employed. JH has personally received fees for teaching from Nycomed. AP and SF declare no conflicts of interest.

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Published 21 June 2012

Is it hypnotics that kill, or is it psychiatric illness?

Kenneth G Terkelsen, MD, General psychiatrist, Assistant Director, Behavioral Health Services James P McGuire, MD and Michael B Friedman

Community Health Center of Cape Cod

Is it hypnotics that kill, or is it psychiatric illness? * Kenneth G. Terkelsen, M.D. General Psychiatrist, Assistant Director * James P. McGuire, M.D. Child and Adolescent Psychiatrist Behavioral Health Services Community Health Center of Cape Cod

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Published 11 June 2012

Re:Conflict of interest: response to Ms Colella

Daniel F. Kripke, M.D.

Scripps Clinic Viterbi Family Sleep Center

Please note that my co-authors have approved our manuscript, but Dr. Langer and Dr. Kline have no previous publications about hypnotic drugs and no affiliation with the www.DarkSideOfSleepingPills.com web site. Some people would think it scientifically proper that I participated in a

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Published 19 April 2012

Conflict of interest

Angela M Colella, PharmD Candidate

Dear Editor: I appreciated and read Dr. Kripke's manuscript with interest. He and his co-authors present many considerations healthcare providers should acknowledge when prescribing hypnotics. Hypnotics, like all medications, have inherent risks.

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Published 16 April 2012

Propensity score matching to minimize confounding by indication

Sujit D Rathod, PhD Candidate in Epidemiology

University of California, Berkeley

The authors made a concerted effort to control for confounding in the design and analysis phase of this paper, and correctly stated that unmeasured confounding is a limiting feature of the results. Given the understandable concerns about confounding by indication, another approach the authors may wish to consider is propensity score More...

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Published 29 March 2012

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

Devonne M Ryan, Student

Dr. Daniel Kripke,

Thank you for you article entitled "Hypnotics' association with mortality or cancer: a matched cohort study," I enjoyed reading it and found it to be especially interesting.

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Published 16 March 2012

Re:Hypnotics and mortality: A time for action

Daniel F Kripke, M.D.

Scripps Clinic Viterbi Family Sleep Center

We apologize if we created confusion by saying we "adjusted" for prior cancer. Indeed, our method of adjustment was to exclude all patients with any diagnosis of major cancer prior to the interval of observation. Similarly, when examining non-melanoma skin cancers, we excluded

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Published 8 March 2012

Need for accessible non-drug treatments

Daniel F Kripke, M.D.

Scripps Clinic Viterbi Family Sleep Center

As these distinguished authors write, efforts should be made to improve the accessibility of non-drug treatments for insomnia such as cognitive-behavioral approaches. By reducing the use of hypnotics, such treatments might be life-saving.

Conflict of Interest:

Please see our BMJ Open article

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Published 8 March 2012

Insomnia in the UK: who cares?

Colin A Espie, Director, University of Glasgow Sleep Centre Kevin Morgan, David Nutt, Niroshan Siriwardena, Derk-Jan Dijk, Brian McKinstry, June Brown, John Cape, Sue Wilson, Maureen Tomeny, Andrew McCulloch, Neil Douglas

Insomnia is twice as common in the UK as anxiety or depressive symptoms(1). Indeed, chronic insomnia is a risk factor for the development of such mental health problems(2). Yet in a week when new research shows that the prevalence of insomnia is increasing in England(3), and that even

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Published 6 March 2012

Hypnotics and mortality: more evidence is needed

Victor Vallejo-Garcia, Medical Student Pilar Toledano-Valero, Javier Feito-Sancho, Joao Modesto-Santos

University of Navarre

Dear Editor:

We have read with great interest the recent article by Kripke DF, Langer RD and Kline LE that assessed the risk of all cause mortality and cancer incidence in patients using

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Published 6 March 2012

richard link, internist

nydt hosp.

Why weren't people with insomnia who didn't take hypnotics included in the control group-could insomnia and not hypnotics be the factor causing excess death???Is the dose relationship just an indication of the severity of insomnia?

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Published 6 March 2012