

## Letter to the Editors

# Reply to 'Evidence for harm, comment on . . .' by Kripke & Langer

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In our reply to the letter by Kripke & Langer [1], we have focused on what we believe to be the two most important points of discussion: (i) how to interpret an outcome measure that is very close to unity, yet still statistically significant; and (ii) our critique of the control cohort selection in the original study by Kripke *et al.* [2].

We respectfully disagree with Kripke & Langer's assertion that a statistically significant odds ratio (OR) of 1.09 supports the notion of a carcinogenic effect of benzodiazepines or benzodiazepine-related drugs (BZRD). This is a very weak association that is likely to be explained by the known confounders in this relationship. The only reason this weak association becomes statistically significant is because we were allowed to tap into a database that covered the cumulative BZRD use in a population of 5.6 million persons over a 15 year period. The same argument applies to the 'dose-response effect', which comfortably could (and should) be interpreted as residual confounding and only becomes statistically significant as a result of the vast amount of data.

We agree with Kripke & Langer that it is a weakness that we could not account for smoking; a fact we also acknowledged in our paper. However, the direction of this bias is given, because users of BZRD smoke more than other individuals [3, 4]. Thereby, some of the 'elevated' risk of 1.09 that Kripke & Langer attribute to BZRD use is most probably due to the smoking behaviour among BZRD users. This is also supported by our finding of an OR of 1.01 for nontobacco-related cancers. Had we been able to account for smoking, our OR estimates for all cancers would have been even lower than 1.09.

Our main concern with the analysis performed by Kripke *et al.* [2] relates to the selection of unexposed subjects, i.e. control subjects, as described in our previous letter [5]. In the study by Kripke *et al.*, 'non-use' was defined as 'no BZRD use at any time during the study period' [2]. Basically, this implies that the eligibility of a

given individual in, for example, 2002, is dependent on the same individual's drug exposure in, for example, 2005. Such classification of exposure dependent on future events violates one of the fundamentals of epidemiological study conduct.

Consider this example. A man who has never used any BZRD in his life is diagnosed with cancer at age 70 years. A week later, the general practitioner for the patient prescribes him a BZRD to help him sleep. Although this use of BZRD could obviously not have influenced the occurrence of the cancer disease (as this occurred before the BZRD use), this patient would not be eligible to enter the unexposed cohort in the study by Kripke *et al.* as he would no longer be classified as a 'BZRD never-user', and thus be excluded from the study.

Exclusion of patients in cancer risk analyses due to drug exposure after the cancer diagnosis is clearly wrong. In the above example, the problem is accentuated by the fact that the erroneous exclusion criterion is applied only for non-users of BZRD prior to the cancer diagnosis, i.e. if the same patient had used BZRD prior to the cancer diagnosis, he would have been eligible to enter the exposed cohort. Furthermore, it is well known that a recent cancer diagnosis is associated with increased use of BZRD and other psychotropics [6]. In the study by Kripke *et al.*, valid non-users of BZRD were not only excluded selectively from the non-exposed cohort, but the erroneous exclusion was also performed with a preference for study subjects who experienced the outcome of interest, i.e. cancer. In other words, the sampling strategy defining non-use as 'no BZRD use at any time during the study period' conferred a spurious protective effect against cancer that selectively applied to BZRD non-users.

As highlighted by Kripke & Langer [1], subsequent studies by Kao *et al.* [7, 8] have replicated their findings of an increased cancer risk associated with use of BZRD. However, the selection procedure applied in these studies

seems to suffer from the same flaw as explained above [7, 8].

In our study [9], we included a supplementary analysis that mimicked the erroneous control selection in the study by Kripke *et al.* [2, 5]. This analysis yielded a result strikingly similar to the result in the study by Kripke *et al.* However, we strongly disagree with the interpretation offered by Kripke & Langer [1] that this supplementary analysis should be a confirmation of their results.

The selection bias illustrated above bears close resemblance to 'immortal time bias' described by Suissa [10]. We encourage readers with an interest in epidemiology to read this excellent paper, illustrating the reasons why future events should have no influence on the selection criteria in epidemiological studies.

In conclusion, we maintain that the weak association seen in our study should not be interpreted as evidence of a causal association. Furthermore, we claim that the associations seen in the study by Kripke *et al.* [2] are heavily influenced by erroneous selection of the unexposed control cohorts.

Lastly, we do agree with Kripke & Langer on one important aspect, which is that use of BZRD should generally be avoided for several reasons [11] or at least reserved for short-term use in select patient groups.

## Competing Interest

All authors have completed the Unified Competing Interest form at [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: MA and JH have 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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