Sleep Medicine 57 (2019) 151–152

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Editorial

Benzodiazepines vs mortality - Causation or confounding?

The article "Trajectories in hypnotic use and approaching death: a register-linked case–control study" in this issue provides a next step in the dialogue on the benzodiazepine (BZD)/mortality association [1].

The earliest study on the BZD/mortality association was published in 1979 [2] and over the years more and more articles have been published. (eg, 3–7) Potential confounders such as age, sex, prior cancer, health, and marital status, ethnicity, etc. were inserted as part of multivariate equations for their effect on the BZD/mortality association but no variables were able to explain this association [3]. As a result Kripke and others concluded that the BZD/mortality association was causal [2–7].

In 2015, Neutel et al., provided a different perspective [8]. They found that the frequency of filling BZD prescriptions increased with time as death approached, culminating with the greatest frequency in the last few months before death. This pattern of gradually increasing BZD use is consistent with a gradual increase in symptoms with approaching death. Thus, the time to death was used as an indicator for the amount of discomfort which increased with the severity of the disease and the nearness of death [8]. This pattern of use could explain the BZD/mortality association.

The causal model provided in Fig. 1 provides a visual representation of the causal path relating BZD use and mortality or morbidity. Box B1 show some of the major causes of death, which were the major causes of death in most of the studies listed. The arrow A1 indicates the strong association of these causes of death with ensuing mortality. Prior to death, these same diseases led to uncomfortable symptoms such as those listed in box B2. These symptoms include the indications for BZD leading to the prescribing of BZD use as shown by arrow A3. Wherever the three relationships, A1, A2 and A3 exist, one can be sure that there will be an association between BZD use and mortality which is not causal. Adjusting for the conditions in B2 would be like adjusting for BZD use itself and therefore would eliminate any such relationship. We can only conclude the association between BZD use and mortality is a classic case of confounding by indication.

Among the so-called confounders considered in previous studies there are some which affect the risk of contracting the diseases, such as smoking, obesity, increasing the risk of mortality, while the others, such as culture and training, affect drug taking behaviour. None affect both mortality and BZD use which is what is needed for a factor to be considered. This explains why no matter how many variables were included in multivariate equations, little difference was seen in the resulting BZD/mortality association.

The causal path of our Fig. 1 does explain several observations which were rather puzzling if one postulates a causal relationship between BZD use and mortality. First of all several other medications show a similar pattern of increasing association as death nears, such as opioids, [3] antidepressants [9] and antipsychotics [10]. That the use of opioids, antidepressants, and antipsychotics increase with nearness of death is not surprising considering the need for controlling pain and depression when death draws near, similar to the increasing need for BZD to control insomnia and anxiety at that time. More surprising is perhaps that no one seems very concerned about the associations of antidepressants and antipsychotics with mortality while being very concerned with the BZD/mortality association.

Another puzzling observation for those considering the BZD/mortality causal association is the lack of specificity in cause of death. The same association was shown to occur not only for all-cause mortality but also for cancer, cardiovascular diseases, and kidney disease [11–15]. It seems unlikely that there is a biological reason underlying a causal association with such a wide range of conditions. However, what all these diseases have in common are uncomfortable symptoms which can be alleviated by BZD use.

Here Kronholm et al., added to the evidence [1]. They were able to show that while the BZD/mortality associations existed with several causes of death, there were different patterns of BZD use typical for specific causes of death. They used an approach called Group-Based Trajectory Modelling (GBTM) which showed that patterns of BZD use varied according to underlying illness [13]. Thus, patients with baseline cardiovascular disease were often associated with the trajectory of new users in the end period; ischemic heart disease was most frequent for a trajectory of continuous high use of BZD; cancer was typical of a trajectory of new users during the end period or a continuously increasing use of BZD; a continuously decreasing use of BZD was typical of the degenerative diseases [1]. Therefore, changes in BZD use are in accordance with the changes in symptoms as the disease progresses. Thus, BZD treats symptoms, not diseases and any associations found are due to symptoms rather than the disease.

In conclusion, it is becoming increasingly obvious that the association between BZD use and mortality is due to confounding by indication. Neutel and Johansen showed that BZD use increases with nearness of death. Kronholm et al., showed progress in BZD use was not uniform but differed according to the course of the terminal disease from which that patient suffered. We must conclude that the association of BZD and mortality is not due to a causal relation between BZD and mortality. Therefore, the apparent association of BZD and mortality is related to causal path of A1, A2, and A3.

This is not to say that BZD use does not have its problems. In the last few decades, the use of BZD has been rising steadily [16,17]. BZD use has been shown to result in increased risk of traffic accidents and falls [18,19]. Moreover, with long-term use BZD becomes less

DOI of original article: https://doi.org/10.1016/j.sleep.2018.02.005.

https://doi.org/10.1016/j.sleep.2018.12.016

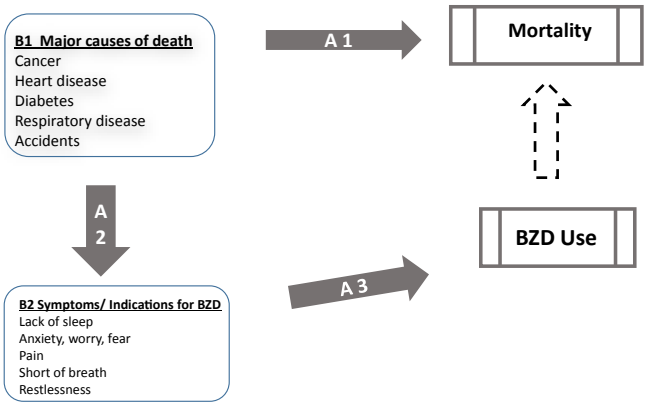

Fig. 1. Web of causation.

effective in controlling the symptoms that they are expected to alleviate. We would agree with Kripke that BZD use should be decreased [3] but not because the drugs themselves hasten all-cause mortality or cause mortality from cancer or heart disease. BZD should be available for symptom control as appropriate, without worrying that BZD use will hasten death.

Conflict of interest

Neither of the authors have any conflicts of interest for this article.

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Available online 13 February 2019