

A Citizens Petition was submitted to the Food and Drug Administration on 10/26/15 to revise warnings about hypnotics (sleeping pills), including possible black box warning for evidence of a serious hazard associated with their use. The petition was submitted by Dr. Daniel Kripke, professor emeritus at the University of California at San Diego and an internationally recognized sleep researcher. Dr. Kripke's petition is based on an analysis of 50 recent sleeping pill studies published between 2012-2015.

These studies reveal that sleeping pills were consistently associated with an elevated mortality risk in 33 of 34 studies that measured mortality risk. No studies showed that sleeping pills lower mortality risk. Moreover, the increased mortality risk appears to be dose dependent: the more frequently sleeping pills were used, the greater the mortality risk. This mortality risk was not explained by insomnia or depression since researchers controlled for these factors, and insomnia patients or depressed patients with insomnia who did not take hypnotics did not exhibit elevated mortality risk. This consistent and significantly elevated mortality risk suggests that sleeping pills may be responsible for hundreds of thousands of excess deaths annually- comparable to the leading causes of deaths annually in the United States:

Heart disease 600,000

Cancer 580,000

Cigarettes 550,000

Sleeping pills 300,000-500,000

Murders 15,000

The increased mortality risk associated with sleeping pills is due to respiratory depression and cardiac arrest, depression and suicide, car accidents, falls and fractures, immune suppression and cancer. This risk is particularly elevated in elderly and obese individuals due to longer half lives of the drugs and rapid accumulation in the brain, comorbidities such as sleep apnea and COPD (both increase with age and obesity and are made worse by sleeping pills), and use of other sedatives (such as benzodiazepines) and narcotics.

Sleeping pills increase cancer risk because they are clastogenic, which means they disrupt chromosomes. Hypnotics also increase infections (upper respiratory and pneumonia and other infections) and inflammation, both of which can lead to cancers. The fact that the association between hypnotics and cancer risk has been found consistently in epidemiological studies, animal studies, controlled clinical trials, and in vitro studies likely suggests that hypnotics cause cancer and cancer deaths.

Toxicology studies of suicides have found hypnotics in the blood in the majority of suicides and combined with alcohol in 30-40% of suicides. Depression also increases suicide risk, and hypnotics and benzodiazepine medications such as Klonopin, Xanax, and Ativan are also associated with a doubling of depression rates. Hypnotics also increase states that lead to suicide such as aggression and lack of impulse control.

Hypnotics are often used in combination with narcotics, which poses an even greater mortality risk. Hypnotics in combination with alcohol or benzodiazepines medications also pose an elevated death risk, and Ambien is ranked first among psychotropic drugs for emergency room visits according to the Centers for Disease Control. The use of hypnotics with narcotics or alcohol also significantly increases the risk of dependence and addiction due to their additive effects, particularly in the elderly, obese individuals and women due to longer half lives and rapid accumulation in the brain. The Agency for Healthcare Research and Quality (AHRQ) found that 68% of ambien users are sustained users (three or more prescriptions) and that 22% of sustained users are also sustained users of narcotics. Since 40 million prescriptions were written for Ambien in 2013, millions of Ambien users are also using narcotics. The same is probably true for millions of users of other hypnotics and benzodiazepines. The AHRQ also found that only 5% of women and 10% of elderly are prescribed the recommended doses of 5 mg of ambien. The remaining 90-95% exceed the recommended dose, which significantly increases the risk of side effects, dependence and addiction, and mortality risk.

Dr. Kripke's petition also summarizes data documenting that, although sleeping pills produce modest subjective improvements in sleep (in part due to the fact that poor sleepers do not remember being awake as a result of the

amnesic effects of the drugs), sleeping pills such as Ambien produce no objective improvement in sleep even at doses higher than current recommended doses. They provide an average of 11 minutes of additional sleep compared to a placebo, which was not statistically significant. The current lowered recommended doses are likely to have no objective effect on sleep. Indeed, the drug manufacturers advised the FDA that the currently recommended 5 mg dose of Ambien is ineffective (the FDA reduced the recommended dose of Ambien to 5mg for women and the elderly after new tests showed that 10 mg produced impaired driving in a significant percentage of women). No studies have shown show that sleeping pills improve daytime functioning. In fact, the opposite is true: sleeping pills impair daytime performance.