Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration

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EDITORIAL by Cunnington

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STUDY QUESTION

What is the effectiveness of non-benzodiazepine (Z drug) hypnotics and what were the associated placebo responses in adults in a dataset used to approve these drugs?

SUMMARY ANSWER

Compared with placebo, Z drugs (eszopiclone, zaleplon, zolpidem), currently approved by the US Food and Drug Administration (FDA), produced slight improvements in subjective and polysomnographic sleep latency, regardless of type of drug.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Though Z drug hypnotics have short term benefits for treatment of insomnia, their effectiveness has been questioned because of publication bias reported in previous meta-analyses and little is known about the extent of the placebo response. This review of data submitted to the FDA showed that Z drugs decreased subjective and polysomnographic sleep latency compared with placebo, especially with larger doses and in younger or female patients and regardless of type of drug. The drug effect and the placebo response were small and of questionable clinical importance, but the two together produced a reasonably large clinical response.

Selection criteria for studies

Randomised double blind placebo controlled trials of currently approved Z drugs in adults submitted to the FDA (eszopiclone, zaleplon, zolpidem); other designs and studies including healthy patients with normal sleep or single night studies with induced insomnia were excluded.

Primary outcome

Polysomnographic and subjective sleep latency. Secondary outcomes included waking after sleep onset, number of awakenings, total sleep time, and sleep efficiency and quality.

Main results and role of chance

We included 13 studies containing 65 separate drug-placebo comparisons by type of outcome, type of drug, and dose. The trials included 4378 participants from different countries and varying drug doses, treatment lengths, and study years. Z drugs showed significant, albeit small, improvements (reductions) in our primary outcomes: polysomnographic sleep latency (weighted standardised mean difference −0.36, 95% confidence interval −0.57 to −0.16) and subjective sleep latency (−0.33, −0.62 to −0.04) compared with placebo. Analyses of weighted mean raw differences indicated that Z drugs decreased polysomnographic sleep latency by 22 minutes (−33 to −11 minutes) compared with placebo. Although we found no significant effects in secondary outcomes, there were insufficient studies reporting these outcomes to allow firm conclusions. Moderator analyses indicated that sleep latency was more likely to be reduced in studies published earlier, with larger drug doses and longer treatment duration, and including a greater proportion of younger and/or female patients or using zolpidem.

Bias, confounding, and other reasons for caution

Because of the small number of reports for some outcomes, and the heterogeneity of statistical data reported, we could not compare some studies directly or robustly impute missing data. There was insufficient information about characteristics of the sample, drug side effects, and other factors that might have explained heterogeneity to fully account for these. The entry criteria for studies varied, with some studies focusing just on sleep latency, particularly for shorter acting drugs, such as zaleplon, which could have affected the capacity of some studies to identify effects other than on sleep latency. Another weakness of our analysis was that all of the trials were industry sponsored, which has been shown to overestimate the drug effect.

Study funding/potential competing interests

This study was funded by the College of Social Science Research Fund at the University of Lincoln.

Weighted standardised mean differences (95% confidence interval) for effect sizes of Z drugs and placebo

	Within groups			Between groups	
	No of comparisons	Treatment	Control	No of comparisons	Treatment *v* control
Sleep latency					
Polysomnographic	16	−0.93 (−1.32 to −0.54)	−0.39 (−0.54 to −0.23)	22	−0.36 (−0.57 to −0.16)
Subjective	4	−0.67 (−1.30 to −0.03)	−0.33 (−0.63 to −0.03)	11	−0.33 (−0.62 to −0.04)
Secondary outcomes					
Wake after sleep onset (PSG)	2	−0.52 (−1.40 to 0.36)	−0.29 (−0.67 to −0.08)	3	−0.24 (−0.72 to 0.24)
No of awakenings (PSG)	2	−0.36 (−1.28 to 0.56)	−0.21 (−0.60 to 0.17)	4	−0.33 (−0.80 to 0.14)
No of awakenings (subjective)	2	−0.91 (−1.90 to 0.09)	−0.28 (−0.66 to 0.10)	6	−0.06 (−0.42 to 0.29)
Total sleep time (PSG)	2	1.06 (−1.37 to 3.49)	0.65 (−0.67 to 1.98)	2	0.41 (−0.51 to 1.32)
Sleep efficiency (PSG)	2	0.52 (−1.23 to 2.28)	0 (−0.59 to 0.59)	5	0.59 (−0.12 to 1.29)

PSG=polysomnographic.

Risk of presentation to hospital with epileptic seizures after vaccination with monovalent AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix): self controlled case series study

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- Research: Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine (*BMJ* 2011;343:d3908)
- Research: Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine (*BMJ* 2011;343:d5956)
- Research: Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death (*BMJ* 2012;344:e2794)

STUDY QUESTION

What is the risk of presentation to hospital with epileptic seizures after vaccination with a monovalent AS03 adjuvanted pandemic A/H1N1 influenza vaccine in people with and without a previous diagnosis of epilepsy?

SUMMARY ANSWER

People vaccinated with a monovalent AS03 adjuvanted pandemic A/H1N1 influenza vaccine were not at an increased risk of epileptic seizures diagnosed in hospital.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Vaccination against A/H1N1 has previously been associated with an increased risk of neurological events such as Guillain-Barré syndrome and narcolepsy. In this large study in Sweden, vaccination against A/H1N1 PDM09 did not seem to be a risk factor for epileptic seizures in people with a previous diagnosis of epilepsy nor in those without such a diagnosis.

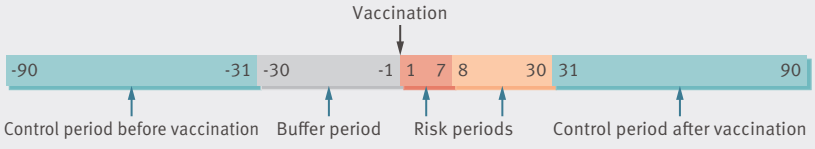
Participants and setting

People (age 0-106, median 41.2) vaccinated with a monovalent AS03 adjuvanted pandemic A/H1N1 influenza vaccine in three counties in Sweden (n=373 398).

Design, size, and duration

Register based self controlled case series with all vaccinated individuals in three counties in Sweden presenting to hospital with a diagnosis of epilepsy at any time from 90 days before until 90 days after any dose of vaccine.

Risk periods after vaccination and control periods before and after vaccination
Numbers represent days from vaccination (day 1)



Primary outcome

Relative incidence between risk and control periods within individuals with 95% confidence interval.

Main results and the role of chance

Out of 373 398 vaccinated individuals, 859 experienced epileptic seizures during the study period. In the first 1-7 day risk period (day 1 being the day of vaccination) there was no increased risk of seizures in people with epilepsy before the study period (relative incidence 1.01, 95% confidence interval 0.74 to 1.39) and a non-significant decrease in risk for people without epilepsy before the study period (0.67, 0.27 to 1.65). In the second risk period (days 8-30) there was a slight but non-significant increased risk of seizures in people without epilepsy (1.11, 0.73 to 1.70) and no increase in risk for those with epilepsy (1.00, 0.83 to 1.21). The results remained stable in sensitivity analyses.

Bias, confounding, and other reasons for caution

The self controlled case series method implicitly controls for all confounders that do not vary with time over the observation period, such as genetics, location, socioeconomic status, sex, individual frailty, and severity of underlying disease. The observation period was too short for age to realistically influence the results. We used a control group of people without indications of epilepsy before the onset of the study to assess whether the probability of exposure was affected by the occurrence of an outcome. This did not seem to be the case. We included only diagnoses of epilepsy in inpatient and outpatient hospital care. This means that epileptic events diagnosed in other settings might have been missed, with the inclusion only of more severe events leading to hospital visits.

Generalisability to other populations

The results are generalisable to all of Sweden and possibly to other populations with similar conditions.

Study funding/potential competing interests

This work was supported by a grant from GlaxoSmithKline Biologicals in Belgium.

Familial risk of early and late onset cancer: nationwide prospective cohort study

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STUDY QUESTION

Is familial risk of cancer limited to early onset cases?

SUMMARY ANSWER

There is an increased familial risk of a concordant cancer in offspring of parents who received a diagnosis at an advanced age (even ≥90 years). Although the highest familial risk was seen in cases with diagnoses at an earlier age in both parents and offspring, our findings suggest that familial cancers might not be early onset in those with parents who were elderly at diagnosis.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Early onset cancers tend to have a more pronounced hereditary component than late onset cancers. This study found that familial risks of cancers exist even in cancers of advanced ages, although the highest familial risk was seen in cases in young people whose parents were also younger at diagnosis. This study suggests that age at onset of familial cancers might be to some extent genetically determined.

Participants and setting

The nationwide Swedish Family-Cancer Database, including all Swedes born after 1931 and their biological parents. This unique database was created in the 1990s by linking information from the multi-generation register, national censuses, Swedish Cancer Registry, and death notifications and has been updated every two years since then.

Design, size, and duration

This was a nationwide prospective cohort study. Parents' ages were not limited but offspring were aged 0-76. We included >12.2 million individuals and >1.1 million cases of first primary cancer. Participants were followed from 1961 to 2008.

Main results and the role of chance

Risks for the occurrence of a concordant cancer in offspring were significantly increased for colorectal, lung, breast, prostate, and bladder cancer, and melanoma, skin squamous cell carcinoma, and non-Hodgkin's lymphoma, even when parents had received a diagnosis at an advanced age (≥70). Even when parents were diagnosed at more advanced age (≥90), the risk of concordant cancer in offspring was still significantly increased for skin squamous cell carcinoma (hazard ratio 1.9), colorectal (1.6), breast (1.3), and prostate cancer (1.3). We found no significant familial risk for offspring with late onset cancer (aged 60-76 at diagnosis) whose parents were younger (<40) at their diagnosis. When a parent was aged <50 at diagnosis, the familial risk for concordant cancer in offspring at older ages was substantially lower compared with offspring with a diagnosis at younger ages. The latter group had the highest familial risk when parents had received a diagnosis at earlier ages.

Bias, confounding, and other reasons for caution

Because of the structure of our data, the number of familial cases with parents aged <40 at diagnosis is slightly underestimated. We had data on obesity and alcohol consumption and on chronic obstructive pulmonary disease (as a proxy for smoking) only on the basis of admission to hospital for these conditions, which would of course include only extreme conditions. Therefore, further studies with more complete information on these and other possible confounding factors are warranted.

Generalisability to other populations

The Swedish Family-Cancer Database is the largest of its kind in the world and risk estimates generated by these data are relatively precise. Our results are probably generalisable to populations with the same background incidence of cancer, encompassing many developed countries.

Study funding/potential competing interests

This study was supported by the Swedish Council for Working Life and Social Research and the German Cancer Aid (Deutsche Krebshilfe).

Risk of cancer in offspring whose parents were affected with concordant cancer compared with offspring without affected parents. Figures are hazard ratios* (95% confidence interval)

	Parental age (years) at diagnosis							
	<40	40-49	50-59	60-69	70-79	80-89	≥90	All ages
Colorectal	8.3 (5.7 to 12.1)	4.4 (3.6 to 5.4)	2.8 (2.5 to 3.2)	2.1 (2.0 to 2.3)	1.7 (1.6 to 1.8)	1.6 (1.4 to 1.7)	1.6 (1.2 to 2.0)	1.9 (1.8 to 2.0)
Lung	3.2 (0.8 to 12.7)	1.3 (0.7 to 2.4)	2.7 (2.3 to 3.2)	2.0 (1.8 to 2.3)	2.1 (1.9 to 2.3)	1.8 (1.6 to 2.1)	1.4 (0.7 to 2.8)	2.1 (1.9 to 2.2)
Breast	4.7 (3.9 to 5.7)	2.9 (2.7 to 3.2)	2.5 (2.3 to 2.6)	2.0 (1.9 to 2.1)	1.8 (1.7 to 1.9)	1.6 (1.5 to 1.7)	1.3 (1.0 to 1.6)	2.0 (1.9 to 2.1)
Prostate	—	5.2 (2.5 to 10.9)	3.3 (2.8 to 3.8)	2.9 (2.8 to 3.1)	2.4 (2.3 to 2.4)	1.9 (1.8 to 2.0)	1.3 (1.1 to 1.6)	2.3 (2.2 to 2.4)
Urinary bladder	—	3.8 (2.1 to 7.1)	2.3 (1.7 to 3.2)	2.2 (1.8 to 2.6)	1.8 (1.6 to 2.1)	1.9 (1.5 to 2.3)	1.7 (1.0 to 3.1)	2.0 (1.8 to 2.2)
Melanoma	5.4 (4.1 to 7.2)	4.5 (3.7 to 5.5)	3.7 (3.2 to 4.4)	2.9 (2.5 to 3.4)	2.2 (1.9 to 2.6)	2.3 (1.9 to 2.8)	0.5 (0.2 to 1.5)	2.9 (2.7 to 3.2)
Skin squamous cell carcinoma	—	2.1 (0.5 to 8.4)	1.8 (0.9 to 3.4)	3.1 (2.3 to 4.1)	2.4 (2.0 to 2.9)	2.0 (1.7 to 2.4)	1.9 (1.4 to 2.7)	2.2 (2.0 to 2.5)
Non-Hodgkin's lymphoma	1.9 (0.5 to 7.5)	0.8 (0.3 to 2.6)	2.3 (1.5 to 3.3)	2.3 (1.8 to 3.0)	1.4 (1.1 to 1.8)	1.7 (1.3 to 2.3)	0.9 (0.3 to 2.9)	1.8 (1.5 to 2.0)

*Presented if at least two familial cases were available in that strata. Adjusted for age, sex, calendar period, geographical region, socioeconomic status of index cases as well as age at start and end of follow-up of parents; further adjustment for admission to hospital for obesity, chronic obstructive pulmonary disease (as proxy for smoking), and alcohol consumption did not change results.

Heat and risk of myocardial infarction: hourly level case-crossover analysis of MINAP database

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- Research: The effects of hourly differences in air pollution on the risk of myocardial infarction (*BMJ* 2011;343:d5531)
- Research: Short term effects of temperature on risk of myocardial infarction in England and Wales (*BMJ* 2010;341:c3823)

STUDY QUESTION

Are high ambient temperatures associated with changes in the risk of myocardial infarction on an hourly timescale?

SUMMARY ANSWER

Above a threshold of 20°C, higher temperature was associated with a transiently increased risk of myocardial infarction one to six hours after exposure; reductions in risk at longer lags were consistent with heat triggering myocardial infarctions early in highly vulnerable people who would otherwise have had one up to a few days later.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

High ambient temperatures are associated with increased overall short term mortality, but whether high temperatures are linked to an increased risk of myocardial infarction specifically is unclear, and previous studies have not examined this using data at an hourly temporal resolution. Data at an hourly temporal resolution from 11 conurbations in England and Wales showed that higher temperatures were associated with increased risk of myocardial infarction in the six hours after exposure, above a threshold of 20°C.

Participants and setting

We included people in 11 conurbations in England and Wales with a diagnosis of myocardial infarction recorded in the Myocardial Ischaemia National Audit Project (MINAP) database.

Design, size, and duration

We did a case-crossover study to investigate the associations between ambient temperature and hospital admissions for myocardial infarction occurring in the summer months (June to August) of the years 2003-09. We compared exposure data relating to the day of the myocardial infarction with data on every other day in the same calendar month in a conditional logistic regression model allowing for non-linear associations and delayed effects (up to two weeks) and adjusting for potential time varying confounders. Data were matched on the time of day of the myocardial infarction event.

Main results and the role of chance

We included data from 24 861 myocardial infarction events. We found strong evidence for a heat effect acting one to six hours after exposure to temperatures above an estimated threshold of 20°C (95% confidence interval 16°C to 25°C). For each 1°C increase in temperature above this threshold, the risk of myocardial infarction increased by 1.9% (0.5% to 3.3%; P=0.009). Later reductions in risk seemed to offset early risk increases: the cumulative effect of a 1°C temperature rise above the threshold was 0.2% (−2.1% to 2.5%) by the end of the third day after exposure.

Estimated odds ratio for myocardial infarction associated with temperature increases

Time since exposure (hours)	Odds ratio (95% CI) per 1°C increase in temperature	P value
1-6	1.019 (1.005 to 1.033) per °C>20	0.009
7-12	1.002 (0.991 to 1.014)	0.677
13-18	1.011 (0.997 to 1.026)	0.124
19-24	0.989 (0.977 to 1.001)	0.074
25-48	0.991 (0.981 to 1.001)	0.074
49-192	0.996 (0.986 to 1.006)	0.401
193-360	0.991 (0.981 to 1.002)	0.101

All lag terms were included in model simultaneously; model adjusted for relative humidity, NO_2, holiday, day of week, and residual seasonality within calendar months.

Bias, confounding, and other reasons for caution

We adjusted for potentially important confounders including traffic associated air pollution (nitrogen dioxide), relative humidity, day of the week, public holidays, and residual seasonality within calendar months. Myocardial infarctions resulting in death before hospital admission would not have been recorded in MINAP; if heat associated events were more likely to result in sudden death, associations may have been underestimated. Associations may have been further underestimated owing to measurement error in capturing the true time of onset of events.

Generalisability to other populations

MINAP has comprehensive coverage and does not restrict on demographic criteria, so hospital admissions recorded should be representative of those occurring in the locations under study, and we would expect our findings to generalise to people living in other similar UK cities. We advise caution in generalising to countries with different climates.

Study funding/potential competing interests

This study was funded through grants from the British Heart Foundation, the Wellcome Trust, and the Garfield Weston Trust. KB is supported by a National Institute for Health Research postdoctoral fellowship. LS is supported by a Wellcome Trust senior research fellowship in clinical science.