Melatonin, Hypnotics and their association with fracture: a matched cohort study

Martin Frisher[1], Nicholas Gibbons[1], James Bashford[1,] Steve Chapman[1], Scott Weich

1. Keele University, School of Pharmacy, Staffordshire ST5 5BG, UK
2. Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick, Coventry, UK

Address correspondence to M. Frisher. Tel: 01782 733568; Fax 01782 713586, Email: m.frisher@keele.ac.uk

ABSTRACT

Objectives: although melatonin prescribing in England has been increasing in recent years there have been no large scale studies on the safety of melatonin compared to other medical treatments for insomnia. The primary aim of this study was to examine the association between exposure to melatonin, hypnotic benzodiazepines (temazepam, nitrazepam) or Z-drugs (zolpidem, zopiclone) and fracture risk.

Design: retrospective cohort study

Setting: 309 general practices contributing to the Health Improvement Network (THIN) between 2008 and 2013.

Participants: 1,377 patients aged 45 years and older prescribed melatonin; 880 patients prescribed hypnotic benzodiazepines; 1,148 patients prescribed Z-drugs and 2,752 unexposed controls matched by age, gender and practice.

Main outcome: fracture following prescription of study drugs ascertained from practice records.

Results: the unadjusted hazard ratios for fracture during the follow-up period were 1.90 (95% CI 1.41-2.57) for melatonin, 1.70 (95% CI 1.18-2.46) for hypnotic benzodiazepines and 2.03 (95% CI 1.45-2.84) for Z-drugs. After adjustment for 26 covariates, the hazard ratios were 1.44 (95% CI 1.01-2.04) for melatonin, 1.26 (95%

CI 0.82-1.92) for hypnotic benzodiazepines and 1.52 (95% CI 1.04-2.23) for Z-drugs. Only patients with three or more melatonin prescriptions had elevated risk. The mean time to fracture was 1.04 years and there was no significant different in mean time to fracture between the cohorts.

Conclusions: In this large cohort of patients attending UK primary care, melatonin and Z-drugs were associated with a significantly increased risk of fracture. With the use of melatonin increasing steadily over time, this study adds to the literature on the safety profile of this drug.

Keywords: older people, melatonin, hypnotics, cohort study, fracture.

Introduction

Medicines used to treat insomnia include hypnotic benzodiazepines, non-benzodiazepine sedatives (Z-drugs) and melatonin agonists [1,2]. These drugs are licensed on the basis that they are effective with regard to sleep parameters [3]. However, older people have an increased risk of hip fracture associated with anxiolytic or hypnotic drug use including short acting benzodiazepine anxiolytics and Z-drugs [4]. Psychotropic drugs including anxiolytics and hypnotics are reported to increase the risk of falling [5] while zolpidem is associated with fractures requiring hospitalization [6]. Falls and fractures are a major health issue for older adults. One study reported that "more than 30% of people over 65 years of age fall each year and in half of the cases falls are recurrent" [7]. Drugs that increase the propensity to fall are therefore a cause for concern. The literature does not appear to contain any studies assessing the risk of fracture associated with the use of melatonin.

Prolonged-release (PR) melatonin has been shown to reduce sleep onset latency and increase subjective sleep quality in two large trials in patients over 55 years and has no known motor side effects [3]. Another review of PR-melatonin noted that, while evidence was based on three randomised, placebo-controlled trials, the outcomes are highly subjective [8]. Whilst data on the efficacy and safety of melatonin were satisfactory [9,10,11,12] for the granting of a marketing authorisation in 2008 there is little detailed information on the safety of melatonin. In 2014 there were 491,000 prescriptions for melatonin in England compared to 262,000 in 2011. Melatonin prescriptions accounted for 5% of total hypnotic scripts in England compared to 2.5% in 2011 [13]. Over the 10 years between 2004 and 2014,

melatonin prescribing increased by 21% [14]. The reason for this increase is probably because of the safety concerns over sedative hypnotics and Z-drugs[15].

One meta-analysis concluded that melatonin has a “relatively benign” side effect profile [16]. Melatonin has also been assessed as having “no-reported side effects” [17]. Reported benefits of melatonin include cerebroprotective and anticancer properties [14] and improved bone biomechanical competence [18]. However other “scientific pre-clinical studies” suggest that the “pharmacological profile of melatonin constitutes…. a basis for prediction of adverse drug reactions or side effects” [19]. Drowsiness is a reported side effect in studies of human subjects given melatonin [20,21]. The current study cannot, however, provide the data for evaluating the pharmacological profile of melatonin or the mechanism that is responsible for increased fracture risk.

Given concerns about adverse events associated with hypnotic drug use and the lack of information about melatonin, the aim of this study is to assess the fracture risk of melatonin and hypnotic drugs among older adults.

Methods

Data Source

The data for this study were obtained from The Health Improvement Network-THIN [22]. THIN is a database of electronic medical records from over 1500 GPs in over 380 UK practices.

Participants

Melatonin is licensed in the UK for patients aged 55 or over for a short period of time (up to 13 weeks) [23].However as the objective was to assess the fracture risk of melatonin and hypnotic drugs among older adults we extended the age range. Capturing data from the age of 45 and above may also reflect “real life” use of the drug. Full details of study participants may be found in the on-line appendix.

Cohort 1 comprised patients who were 45 years and older when they were first prescribed melatonin (BNF 4.1.1; melatonin) between 01/07/2008 and 30/06/2013.
Cohort 2A comprised patients who received at least 2 prescriptions of hypnotic benzodiazepines (BNF 4.1.1; temazepam, nitrazepam) between 01/07/2008 and 30/06/2013 and whose electronic record contained no prescriptions for melatonin.

Cohort 2B comprised patients prescribed at least 2 prescriptions of Z-drugs (BNF 4.1.1; zolpidem and zopiclone) between 01/07/2008 and 30/06/2013 and whose electronic record contained no prescriptions for melatonin.

Cohort 3 comprised patients who had never been prescribed melatonin or hypnotic benzodiazepines or Z-drugs, and who met the matching criteria. Their observation period began on the date of the first melatonin prescription for the Cohort 1 member to whom they were matched.

The initial aim was to have 1:1:1 matching for cohorts 1, 2a and 2b, and 1:2 matching for cohorts 1 and 3. However, due to the matching and exclusion criteria it was not possible to achieve these ratios. The final achieved cohorts were: melatonin

(N=1,377), hypnotic benzodiazepines (N=880), Z-drugs (N=1,148) and controls (N=2,752). Cohort members were recruited from 309 practices.

Study outcome was any fracture following study entry. The reason for selecting all fractures was because of various mechanisms cited in the literature that could result in a fracture [4]. Since, as noted above, this study is not evaluating the mechanism that may lead to fracture, it was decided not to exclude particular kinds of fracture. Fracture was therefore defined by a comprehensive list of READ codes [24](See Supplementary data, available at Age and Ageing online for frequency of fracture codes).

Each case was followed from study entry date to date of first fracture or censorship (i.e. the patient leaves the practice for any reason) or the end of the observation period [30-05-2013]).

Covariates and potential confounders

Potential confounders were: gender, age at study entry, medical morbidity, prescriptions for non-study drugs, Body Mass Index (BMI), Townsend quintile score (a measure of material deprivation), smoking and alcohol status. Smoking and alcohol use were recorded within the dataset as current, previous or never.

Medical morbidity was ascertained using READ codes for arthritis, anxiety, asthma, dementia/Alzheimer's disease, cancer, COPD, diabetes, gastrointestinal disorders, epilepsy, hypertension, ischaemic heart disease, musculoskeletal conditions,

psychiatric conditions (excluding anxiety) stroke, sleep disorders, ophthalmic disorders and pre-study fractures.

As with similar studies [25], the observation period for the ascertainment of covariates was the entire interval for which data are available for a patient between the time their record starts (prior to recruitment) and either the end of the study period, censorship or death.

Analysis

Hazard ratios for fracture following recruitment into the study (defined as the first prescription of a study drug) were estimated using Cox proportional hazards models. Two models were run. The first model was unadjusted for any covariate while the second was adjusted for the 26 covariates described above.

Results

Crude fracture rates over the study period were 6.0% for melatonin, 5.8% for hypnotic benzodiazepines, 5.9% for Z-drugs and 3.2% controls. The average age at study entry was 64.7 (SD=11.6). Average exposure time (i.e. from study entry to end of follow up) was 2.6 years (SD=1.2 years) There were no significant differences between the cohorts in terms of age or exposure time. Average time to fracture was 1.04 years. There was no significant different in average time to fracture between the cohorts.

Table 1 shows that compared to the hypnotic benzodiazepines and Z-drug cohorts, the melatonin cohort had a higher rate of sleep disorders, dementia/Alzheimer's

disease, a lower rate of cancer and fewer lifetime prescriptions for all drugs. Pre-study facture rates and musculoskeletal problems were similar across these cohorts. Table 1 also shows that compared to the control cohort, the melatonin cohort had higher rates of anxiety, arthritis, asthma, cancer, CHD, COPD, diabetes, musculoskeletal problems, psychiatric disorders, sleep disorders and stroke.

[Table 1 about here]

Table 2 shows the unadjusted and adjusted hazard ratios for the study cohorts. There was a downward adjustment after controlling for comorbidity. Thus some of the effect attributed to cohort membership is accounted for by comorbidity. However, hazard ratios for associations between melatonin, Z-drugs and fractures remained statistically significant after adjustment.

71% of melatonin prescriptions for the prolonged release formulation, while 29% were for immediate release formulation. 79% of those prescribed melatonin were prescribed the drug once or twice, while 21% were prescribed three times or more. Among the latter group, the average number of prescriptions was 11.9. Only those with three or more melatonin prescriptions had elevated risk (data are not shown in the paper).

[Table 2 about here]

Table 3 shows that predictors of higher rates of post study fracture were: dementia/Alzheimer's disease, musculoskeletal problems, pre-study fracture and

lifetime receipt of more than 501 prescriptions. The only predictor of a lower rate of post study fracture was being overweight.

Table 3 about here

Discussion

The main finding of this study is that both Z-drugs and melatonin were found to be independently associated with increased fracture risk. One of the strengths of this study was the inclusion of a large number of covariates that potentially might have explained the hazards associated with these drugs.

Only for hypnotic benzodiazepines did the inclusion of covariates result in a downward adjustment that resulted in a non-significant hazard ratio. However the size of this cohort was considerably smaller than the other drug cohorts so this may be an indicator of statistical power.

As noted in the introduction, there were reasons to indicate that melatonin might be safer than the hypnotic drugs, although other studies indicated that there could be adverse events[16]. As this study only shows an increased risk for the large diagnostic category of “fracture”, further work could explore if the study drugs are associated with particular types of fracture that occur as a result of falling (e.g. hip fractures), which in turn may be caused by specific risk factors such as drowsiness [16]. Furthermore this study did not examine if there was a dose-response relationship between the study drugs and fracture risk. In the case of melatonin, the risk was only observed for those prescribed the drug three or more times.

This study supports the growing evidence that Z-drugs are not safer than benzodiazepines with respect to the risk of fracture [26,27]. Given the caution now attached to the prescribing of hypnotic drugs, this study may indicate that similar considerations should be attached to melatonin.

Strengths and limitations of the study should be noted. The THIN data set provided large cohorts of patients prescribed melatonin, together with matched controls receiving hypnotic benzodiazepines and Z-drugs and controls receiving neither melatonin nor hypnotic drugs. Exposure was based on prescription recorded by General Practitioners rather than self-report. The study was able to control for a wide range of potential confounders and several possible explanations were considered, e.g. that the risk of fractures could be attributed to ophthalmic disorders or musculo-skeletal conditions.. The study also controlled for sleep disorders and these were not significantly associated with fracture. The length of follow-up was a further strength of this study as few of the earlier studies of melatonin have looked at a time frame of over 2 years following receipt of the drug. The main limitation of this study is that the design was non-randomised. It is impossible to exclude confounding arising from unmeasured factors, or measurement error [28]. The study controls for the presence of medical conditions but not their severity.

In conclusion, prescriptions for melatonin and hypnotic drugs were associated with significantly increased risk of fracture over a two-year period after adjusting for a range of potential confounders. The study design has a number of strengths which suggest that these findings are robust but we also note important limitations.

Key points

- In this large cohort of patients attending UK primary care, melatonin and Z-drugs were associated with a significantly increased risk of fracture over a two year period.
- This study controlled for a wide range of potential confounders including sleep disorders, musculoskeletal and ophthalmic conditions.
- With the use of melatonin increasing steadily over time in the UK, this study adds to the small literature on the safety profile of this drug.

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Conflict of interest
None.

Authors' contributions
MF performed the analysed and drafted the article. NG extracted the data and helped with the analysis. JB, SC and SW contributed to the revised manuscript.

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Ethical Statement
The THIN scheme was approved by the National Health Service South-East Multi-centre Research Ethics Committee. The present study was approved by an independent Scientific Review Committee administered by IMS Health Real World Evidence Solution (protocol reference: 13-049).

Tables

Table 1. Prevalence (%) of covariates for all study cohorts.

	Prevalence (Full Medical Record)	Study Cohorts			
Covariate	Prevalence (%)	Melatonin (N=1,371)	Hypnotic benzodiazepines (N=880)	Z-drugs (N=1,148)	Controls (N=2,751)
1	Anxiety disorder	30.2	32.4	33.6	12.5
2	Arthritis	31.8	32.5	29.9	24.0
3	Asthma	17.9	16.2	15.3	10.1
4	Cancer	23.3	32.4	29.6	19.5
5	Coronary Heart Disease (CHD)	17.2	18.6	17.7	9.3
6	Chronic Obstructive Pulmonary Disease (COPD)	14.2	15.4	13.2	9.3
7	Diabetes	14.5	12.9	14.5	11.6
8	Dementia/ Alzheimer's disease	7.4	4.1	5.0	3.0
9	Epilepsy	3.8	4.3	3.4	2.1
10	Gastrointestinal disorder	2.3	2.4	2.3	1.5
11	Hypertension	36.1	37.4	38.4	36.5
12	Ischaemic heart disease	17.2	18.6	18.4	13.5
13	Musculoskeletal problems	89.6	89.4	86.5	77.4
14	Psychiatric diagnoses (excluding anxiety)	46.9	49.3	47.6	20.7
15	Sleep disorder	25.7	18.9	16.5	2.5
16	Stroke	9.2	8.9	7.8	5.7
17	Ophthalmic Conditions	23.9	23.7	22.3	19.5
18	Fracture pre-study	24.7	24.6	26.9	21.3
19	Smoking Status (% current)	20.7	26.4	27.1	17.3
20	Alcohol Status (% current)	68.4	67.5	66.5	70.1
21	Number of prescriptions (all drugs) [MEAN/SD]	486 [530]	542 [772]	503 [636]	409 [561]

Table 2. Unadjusted and adjusted cohort hazard ratios for post-study entry fracture

			Unadjusted				Adjusted			
			Hazard Ratio	95.0% CI for Hazard Ratio		Sig. Level	Hazard Ratio	95% C.I. for Hazard Ratio		Sig. Level
Cohort	N cases	N controls		Lower	Upper	p-value		Lower	Upper	p-value
Controls			1				1			
Melatonin	1377	2752	1.90	1.41	2.57	<0.001	1.44	1.01	2.04	0.04
Hypnotic benzodiazepines	880	1759	1.70	1.18	2.46	<0.001	1.26	0.82	1.92	0.29
Z-drugs	1148	2294	2.03	1.45	2.84	<0.001	1.52	1.04	2.23	0.03

Table 3. Adjusted covariate hazard ratios for post-study entry fracture

	N	Hazard Ratio	95% C.I. for Hazard Ratio		Sig. Level
			Lower	Upper	p-value
Anxiety disorder	1440	1.04	0.8	1.37	0.76
Arthritis	1738	0.97	0.75	1.25	0.8
Asthma	847	1.29	0.95	1.76	0.1
Cancer	1490	1.07	0.82	1.4	0.63
Coronary Heart Disease (CHD)	864	0.75	0.46	1.24	0.26
Chronic Obstructive Pulmonary Disease (COPD)	741	1.1	0.76	1.59	0.62
Diabetes	801	1.24	0.87	1.77	0.23
Dementia	255	1.55	0.95	2.53	0.08
Epilepsy	190	0.92	0.48	1.75	0.79
Gastrointestinal disorder	120	0.87	0.38	1.98	0.74
Hypertension	2284	0.9	0.69	1.18	0.45
Ischaemic heart disease	988	1.08	0.68	1.72	0.75
Musculoskeletal problems	5170	1.97	1.19	3.26	0.01
Other psychiatric diagnoses	2210	0.96	0.74	1.25	0.78
Sleep disorder	784	1.14	0.83	1.55	0.42
Stroke	455	1	0.65	1.53	0.99
Ophthalmic Disorders	859	1.23	0.93	1.62	0.14
Fracture pre-study	1460	1.72	1.35	2.2	<.01
Number of Prescriptions (all drugs); 1-99; reference category:	1847	1			
100-300	1740	1.15	0.79	1.68	0.48
301-500	925	1.22	0.79	1.9	0.37
501+	1675	1.62	1.07	2.46	0.02
Body Mass Index; “healthy” BMI [18-24.9]; reference category:	1766	1			
underweight [10-18.4]	172	1.49	0.88	2.53	0.14
overweight [25-29.9]	2134	0.62	0.46	0.83	<.01
obese [30+]	1597	0.72	0.52	1	0.05
Alcohol; lifelong teetotal; reference category	1136	1			
current drinker	4248	1.22	0.9	1.66	0.2
ex-drinker	233	1.44	0.8	2.58	0.22
Smoking; lifelong non-smoker; reference category	3149	1			
current smoker	1312	1.01	0.72	1.4	0.97
ex-smoker	1666	1.04	0.78	1.38	0.81
Townsend score; most deprived quintile; reference category	1592	1			
2nd most deprived quintile	1378	0.93	0.66	1.32	0.7

middle quintile	1144	0.81	0.55	1.19	0.29
2nd most affluent quintile	964	1.28	0.9	1.82	0.17
most affluent quintile	905	0.96	0.65	1.43	0.85
Gender, Male; reference category	2518				
Gender, Female	3669	2.15	1.61	2.87	<.01
Age:45-54; reference category	1451				
Age:55-64	1976	1.02	0.73	1.44	0.89
65-74	1475	0.91	0.62	1.36	0.66
75+	1285	1.33	0.87	2.05	0.19