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Original Article

Primary care hypnotic and anxiolytic prescription: Reviewing prescribing practice over 8 years

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Abstract

Introduction: Over the last few years, hypnotic and anxiolytic medications have had their clinical efficacy questioned in the context of concerns regarding dependence, tolerance alongside other adverse effects. It remains unclear how these concerns have impacted clinical prescribing practice. **Materials and Methods:** This is a study reviewing community-dispensed prescribing data for patients on the East Practice Medical Center list in Arbroath, Scotland, in 2007, 2011 and 2015. Anxiolytic and hypnotic medications were defined in accordance with the British National Formulary chapter 4.1.1 and chapter 4.1.2. All patients receiving a drug within this class in any of the study years were collated and anonymized using primary care prescribing data. The patients' age, gender, name of the prescribed drug(s), and total number of prescriptions in this class over the year were extracted. **Results:** The proportion of patients prescribed a benzodiazepine medication decreased between 2007 and 2015: 83.8% (n = 109) in 2007, 70.5% (n = 122) in 2011, and 51.7% (n = 138) in 2015 (P = 0.006). The proportion of these patients prescribed a nonbenzodiazepine drug increased between 2007 and 2015: 30% (n = 39) in 2007, 46.2% (n = 80) in 2011, and 52.4% (n = 140) in 2015 (P = 0.001). There was a significant increase in the number of patients prescribed melatonin (P = 0.020). **Discussion:** This study reports a reduction in benzodiazepine prescriptions in primary care alongside increases in nonbenzodiazepine and melatonin prescribing, with an increase in prescribing rates of this drug class overall. **Conclusion:** Changes in this prescribing practice may reflect the medicalization of insomnia, local changes in prescribing practice and alongside national recommendations.

Keywords: Anxiolytic, benzodiazepines, hypnotic, nonbenzodiazepines, prescribing, primary care

Introduction

Insomnia, agitation, and anxiety are common presentations to primary care clinicians, with these frequently being treated with anxiolytic and hypnotic medications (defined by the British National Formulary [BNF] chapters 4.1.1 and 4.1.2).[1] These medications may also be used as part of a program of alcohol withdrawal, treatment for epilepsy or muscle spasms although this represents a minority of prescriptions in clinical practice.[1,2]

It is recognized that the long-term use of these medications in general practice is generally not appropriate and should be limited to short-term prescriptions and kept off repeat prescription.[2] The combination of perceived effectiveness by patients and risks associated with long-term use such as dependence and tolerance make this medication group challenging to manage in primary care. Indeed, there are ongoing concerns about the rates of prescribing of this medication group in clinical practice,[1,2] with particular concerns voiced for patients over 65 including falls and cognitive impairment.[3,4] Over the last few years, these medications have had their clinical efficacy questioned in the context of increasing concerns regarding dependence, tolerance, and alongside other adverse effects.

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A 2012 meta-analysis and systematic review of the US Food and Drug Administration data reported that after reviewing 13 studies containing 65 Z-drug-placebo comparisons, Z-drugs produce only slight improvements in subjective polysomnographic sleep latency, regardless of the type of drug used.[5] The authors noted that although the drug effect and placebo response were small and of uncertain clinical significance, the two together produced reasonable clinical response.[5] Furthermore, a retrospective cohort study published in 2014 of 34,727 aged 16 years old and older attending the UK primary care reported that anxiolytic and hypnotic drugs were associated with significantly increased risk of mortality over a 7-year period, after adjusting for a range of potential confounders.[6] There has been recent work noting that there is a clear evidence that the use of hypnotic and anxiolytic medications are associated with an increased risk falls and hip fractures in older people.[7] Furthermore, these medications may lead to cognitive problems in older patients, with a meta-analysis reporting increased rates of memory problems, confusion, and disorientation more common in patients receiving benzodiazepines and Z-drugs.[8] There have even been reports that benzodiazepine use increases the risk of developing Alzheimer's disease, with this association increasing with prolonged exposure.[9]

It remains unclear how these concerns have impacted clinical prescribing practice on the coalface of primary care clinical practice. This is particularly relevant as they have been changes in guidelines in 2014, which have promoted an active approach to reducing the prescription of these medications.[1] This was adopted locally by a Clinic B monitoring program where patients on repeat doses of these medications were actively reviewed and either had doses reduced or switched to less harmful agents.

This study aimed to assess changes in prescribing practice of hypnotic and anxiolytic medications between 2007 and 2015 which would encompass local and national changes in clinical practice using routinely collected prescribing data in a single primary care practice in Arbroath (Scotland).

Materials and Methods

The analysis used community-dispensed prescribing data for patients from the East Practice, Springfield Medical Centre in Arbroath in Scotland held by NHS Tayside and community prescribing bodies in 2007, 2011, and 2015. Data were held by the medical practice as a matter of normal clinical care.

Service characteristics

The East Practice Springfield Medical Centre is one of four practices providing primary care services to the population of Arbroath and is staffed with three-partner general practitioners (GPs): one nurse practitioner, one practice nurse, and one health-care assistant alongside support staff. The practice serves approximately 4000 patients in a densely populated town with marked deprivation, based on the Scottish Index of Multiple Deprivation Quintile (SIMD). The SIMD is based on information from major population surveys in Scotland and allows comparison between the most deprived and the rest of the population in Scotland in numerous domains.[10] In 2007, there was a local process of coding patients being prescribed benzodiazepines (particularly those on repeat) to aid GP review of their prescriptions and facilitate reduction in benzodiazepine prescriptions. This process was extended in 2014 following the national guideline recommendations.

Data collected and analysis

For each individual, all community-dispensed prescriptions for anxiolytic and hypnotic medications were extracted between January 01 and December 31 for the study years of 2007, 2011, and 2015. The prescriptions were reviewed on a four yearly basis to assess for changes following the introduction of Clinic B monitoring in 2007 with subsequent update and review in 2011 and adjusted national guideline recommendations in late 2014/early 2015. There were also difficulties in obtaining other years as a result of local information technology challenges, so these year groups represented a pragmatic approach.

Anxiolytic and hypnotic medications were defined in accordance to BNF drug groupings, hypnotics (drugs defined in BNF chapter 4.1.1), and anxiolytics (BNF chapter 4.1.2).[11] Information regarding the patients' age, gender, medication name, and number of prescriptions in this drug class over the course of the year were extracted. Over the course of the year, all prescriptions were reviewed with the number of different drug classes documented with the maximal number being 5 (benzodiazepines, nonbenzodiazepine hypnotics, sedative antihistamines, azapirones, and melatonin).

These data were fully anonymized, and any patient identifiable information was removed before analysis. The analysis was carried out in SPSS v22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY).[12] Baseline data were compared using one-way ANOVA for normally distributed continuous variables, Kruskal–Wallis test for nonnormally distributed variables, and Chi-squared test for categorical variables. *P* values reported note the significance of differences between the 3 years groups in each of the data comparisons. As a result of the small sample size, medications were compared between years as an overall drug class (e.g., benzodiazepines) rather than individual agents. This study was deemed not to require ethical approval as it entailed analysis of routinely collected clinical data.

Results

There were 4155 patients, 4239 patients, and 4255 patients registered at East practice in 2007, 2011, and 2015, respectively. Of this group, 3.1% ($n = 130$), 4.1% ($n = 173$), and 6.3% ($n = 267$) were prescribed a hypnotic or anxiolytic medication at least once over the course of 2007, 2011, and 2015, respectively ($P = 0.375$).

Table 1 summarizes baseline patient characteristics alongside individual drug group comparisons.

Table 1: Baseline Characteristics and Prevalence of Hypnotic & Anxiolytic Prescribing

	2007	2011	2015	*P* value
Total Number Practice Patients (as of 1st Jan in each year)	*n*=4155	*n*=4239	*n*=4255	0.375
Total Number of Patients Prescribed Hypnotic and/or Anxiolytic (%)	*n*=130 (3.1)	*n*=173 (4.1)	*n*=267 (6.3)	0.368
Mean Age (years) (SD)	52.03 (14.57)	49.94 (16.08)	53.37 (20.42)	0.112
Male Sex (%)	42 (32.3)	60 (34.7)	87 (32.6)	<0.001
Mean Number of Prescriptions Per Year Per Patient Receiving At Least One Anxiolytic/Hypnotic Drug (SD)	5.7 (8.25)	4.83 (7.15)	5.33 (6.86)	0.526
Mean Number of Different Anxiolytic/Hypnotic Drugs Prescribed (SD)	1.14 (0.43)	1.20 (0.48)	1.20 (0.47)	0.319
Benzodiazepine (%)	109 (83.8)	122 (70.5)	138 (51.7)	0.006
Diazepam	72 (55.4)	82 (47.4)	115 (43.1)	
Temazepam	13 (10)	20 (11.6)	9 (3.4)	
Chlordiazepoxide	9 (6.9)	3 (1.8)	3 (1.1)	
Lorazepam	6 (4.6)	10 (7.3)	6 (2.2)	
Nitrazepam	4 (3.1)	2 (1.2)	3 (1.1)	
Lormetazepam	3 (2.3)	2 (1.2)	0 (0)	
Loprazolam	1 (0.8)	1 (0.6)	1 (0.4)	
Oxazepam	1 (0.8)	1 (0.6)	1 (0.4)	
Clobazam	0 (0)	1 (0.6)	0 (0)	
Nonbenzodiazepine hypnotic drugs (%)	39 (30)	80 (46.2)	140 (52.4)	0.001
Zolpidem	1 (0.8)	4 (2.3)	13 (4.9)	
Zopiclone	38 (29.2)	75 (43.4)	126 (47.2)	
Clomethiazole	0 (0)	1 (0.6)	1 (0.4)	
Sedative Antihistamines (%)	1 (0.8)	0 (0)	1 (0.4)	0.712
Promethazine HCl	1 (0.8)	0 (0)	1 (0.4)	
Azapirones (%)	1 (0.8)	1 (0.6)	2 (0.7)	0.354
Buspirone HCl	1 (0.8)	1 (0.6)	2 (0.7)	
Melatonin (%)	4 (3.1)	6 (3.5)	15 (5.6)	0.020

The mean number of prescriptions of anxiolytic and hypnotic drugs over the course of the year in 2007 was 5.7, in 2011 was 4.83, and in 2015 was 5.33 ($P = 0.526$). The mean number of different anxiolytic and hypnotic drugs were 1.14, 1.2, and 1.2 in 2007, 2011, and 2015, respectively ($P = 0.319$).

The proportion of patients prescribed a benzodiazepine medication decreased between 2007 and 2015: 83.8% ($n = 109$) in 2007, 70.5% ($n = 122$) in 2011, and 51.7% ($n = 138$) in 2015 ($P = 0.006$). The percentage of patients prescribed diazepam reduced from 55.4% ($n = 72$) of all prescribed hypnotic and anxiolytic medications in 2007 to 43.1% ($n = 115$) in 2015.

The proportion of these patients prescribed a nonbenzodiazepine drug increased between 2007 and 2015: 30% ($n = 39$) in 2007, 46.2% ($n = 80$) in 2011, and 52.4% ($n = 140$) in 2015 ($P = 0.001$). The vast majority of these prescriptions in this drug class were for zopiclone, 97% in 2007, 93.7% in 2011, and 90% in 2015.

The proportion of patients prescribed melatonin also increased: 3.1% ($n = 4$) in 2007, 3.5% ($n = 6$) in 2011, and 5.6% ($n = 15$) in 2015 ($P = 0.020$). Sedative antihistamines and azapirones were prescribed in very small numbers, with between zero and two patients receiving the medication in each of the study years.

Discussion

Key findings

Between 2007 and 2015, the percentage of patients prescribed anxiolytic and/or hypnotic medications increased from 3.1% of the practice population to 6.3% of the practice population although this did not reach statistical significance. When looking at individual drug classes, there was a statistically significant reduction in benzodiazepine prescriptions in primary care alongside increases in nonbenzodiazepine and melatonin prescribing. During each of the study time points, males made up approximately a third of the group prescribed hypnotic and/or anxiolytic medications.

Patients received between a mean of 5.7 and 4.83 prescriptions of anxiolytic and/or hypnotic medications per year, with a mean of between 1.14 and 1.2 different hypnotic and anxiolytic medications over the course of the year. The mean number of prescriptions of hypnotic or anxiolytic medications has remained stable between 5.7 and 4.83 over the study period, and for most of these medications, more than three prescriptions would suggest prescriptions more frequent than recommended guidelines.[13]

Prescribing by gender

This study reports that males have been consistently been prescribed less hypnotic and anxiolytic medications. This is in line with the current evidence, with a Norwegian study of

approximately 15,000 middle-aged adults with a mean 18-year follow-up reported that the proportion of anxiolytic or hypnotic drug users was 6.6% among men and 16.2% among women.[14] Furthermore, women are more likely to be treated for a mental health problem that men (29% vs. 17%)[15,16] and are more likely attend the primary care physician for management of their mental health diagnoses.[17] It is pertinent to note that there is a national strategy for women's mental health but no equivalent for men although there is a new drive to manage suicide risk in young men.[17,18] Finally, men are more likely to have mental health disorders such as alcohol and substance misuse where prescription of these medications is not as commonly utilized.[15]

Changes anxiolytic and hypnotic drug class as a whole

Over the course of the review, there was an increase in the percentage of patients prescribed hypnotic and/or anxiolytic medications to 6.3%, which is similar albeit lower when compared to a larger population-based studies in Scotland that have placed hypnotic/anxiolytic prescriptions at between 7.5%[3] and 8.1%.[15] Rates of hypnotic and anxiolytic prescriptions are lower when compared to other nations including Norway,[14] Australia,[19] and France.[20] East practice appears to have lower rates of hypnotic and anxiolytic prescribing although the rates are increasing closer to the published Scottish prevalence for these agents.

Changes in specific drug classes

The reduction in benzodiazepine prescribing is likely to have been combination of nationally driven targets for reducing benzodiazepine prescribing,[21] locally driven targeted intervention for patients on benzodiazepine through "Clinic B" monitoring and increasing recent research linking benzodiazepines to the development of Alzheimer's disease,[9] falls and fractures in older patients[7] and overall all-cause mortality[6,14] changing prescribing practice. There is a good body of evidence that some of the newer antidepressants can manage symptoms with anxiety,[22,23] with nondrug options for managing anxiety[24] and insomnia[13,21,25] having a strong evidence basis. However, it should be noted that a meta-analysis reviewing the use of antidepressant medications (selective serotonin reuptake inhibitors [SSRIs]) and benzodiazepines for anxiety disorder reported that the change in the prescribing pattern favoring newer SSRIs over benzodiazepines in the treatment of anxiety disorders has occurred without supporting evidence and direct comparison is recommended.[23]

The reported increase in nonbenzodiazepine may reflect patients being prescribed short-courses of these agents rather than short-acting benzodiazepines. There has been recent concern about the possible medicalization of sleep disorders which may explain increases in these prescriptions.[26] The expectation of uninterrupted sleep by patients with the availability of new medications has certainly impacted clinical practice. Indeed, an American study reported a large increase in patient complaints of sleeplessness with associated increases in the use of benzodiazepine and nonbenzodiazepine hypnotic medications between 1993 and 2007.[26] Indeed this US study suggested that life problems may be being treated with medical solutions, after reporting that there was a 21 fold increase in non-benzodiazepine medications between 1993 and 2007 in the context of only a 5 times increase in imsomnia diagnoses made by clinicians.[26]

The current National Institute for Clinical Excellence guidelines only recommended hypnotic drug therapy is used for the management of severe insomnia interfering with normal daily life only after due consideration of the use of nonpharmacological measures for short periods of time only.[13] As there is no evidence suggesting superiority of one hypnotic drug to another,[5,13] patients should be prescribed the medication with lowest purchase cost and patients experiencing side effects from one agent or experiencing lack of benefit from one agent should not be trailed on other hypnotic agents (excluding melatonin).[2,13] Crucially, hypnotics are not particularly effective with high number needed to treat to obtain benefit in the context of high rates of adverse effects. Glass *et al.* reported that for 13 people taking a hypnotic for 1 week, twelve people's sleep would either improve or not irrespective of whether they had taken a hypnotic or a placebo and one person would experience sleep improvement; two patients would experience an adverse event.[8] The increase in this drug group should be seen in context with a reduction in benzodiazepines, but it is a concern that this group of medication is consistently increasing. It is postulated that the medicalization of insomnia and patient expectations are leading to clinician pressure to prescribe hypnotic agents for patients. Efforts are going to be made locally to provide advice and information about nondrug approaches to managing sleep problems, which aims to reduce the use of these medications in the coming years.

There was a statistically significant increase in the number of patients being prescribed melatonin over the course of the 8 years. Melatonin is an endogenous hormone produced in the body in response to darkness that is important in regulating circadian rhythms.[2] Levels are known to be reduced in some middle-aged and elderly patients with insomnia, and studies to date have reported a benign side effect profile compared to other agents.[27]

A recent meta-analysis reported that melatonin decreases sleep onset latency, increases total sleep time, and improves overall sleep quality without any major side effect reported.[26] The benefits noted did not decrease with prolonged use unlike other hypnotic agents, and although the absolute benefits were small given the favorable side effect profile, this agent may have a role for middle-aged and elderly patients.[26] It appears that the increase in data regarding the safety and role of melatonin in primary sleep disorders, alongside the possible role in adolescent,[28,29] has led to a small increase in prescribing which is likely to increase in time as the cost of the medication decreases and further studies are published.

Limitations and further work

This research paper has several limitations. First, the paper reports patients prescribed an anxiolytic and/or hypnotic medications at three time points (2007, 2011, and 2015). Therefore, the data obtained does not allow us to fully ascertain the changes in prescribing practice over this time. However, such work does provide a useful platform for discussing general changes in prescribing and considering for these changes. Second, this was a single center study of a general practice with a small patient list in an urban-deprived area. These results are not necessarily generalizable to other areas of the United Kingdom or further afield. However, the proportion of patients prescribed anxiolytic and hypnotic medications were similar to published Scottish data.[3,15] Third, due to the small sample size, we were unable to break down each of the cohorts into high-risk patient groups such as patients with multi-morbidity or elderly patients. Finally, the study did not include larger number of different drug groups in the analyses due to the nature of the data set. It is possible that by focusing on only two classes of medications, we may have missed broader trends in psychoactive prescribing.

Despite the limitations of this research paper, this study has provided an opportunity to review and assess a single GP practices prescriptions of hypnotic and anxiolytic medications. Following work on the data used for analyses, it is planned to perform further work looking at prescribing rates of psychoactive medications more broadly involving more local GP practices to assess different patient subgroups. There has been published work noting large-scale variation in anxiolytic and hypnotic prescribing by GPs, with demographic factors more powerful determinants of this.[30] However, high prescribing practices were less well developed, in that their quality and outcomes framework scores were lower and they were less likely to be training practices.[30] It is hoped that further work will allow further data be obtained with regard to GP prescribing variation.

Conclusions

This study reports a reduction in benzodiazepine prescriptions in primary care alongside increases in nonbenzodiazepine and melatonin prescribing, with an increase in prescribing rates of this drug class overall. Changes in this prescribing practice may reflect the medicalization of insomnia, local changes in prescribing practice, and alongside national recommendations.

This clinical paper provides a useful platform for discussing community-based prescribing for this challenging group of medications and reports that locally available Scottish prescribing data can be utilized to look in more detail in primary care prescribing practice at a single practice level. This study will be the basis for future work in this area with an increase in the number of practices involved to allow targeted analysis at high-risk patients for the adverse side effects of psychoactive medications alongside other high-risk medications.

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Conflicts of interest

There are no conflicts of interest.

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