BMJ Open

A 3-year survey quantifying the risk of dose escalation of benzodiazepines and congeners to identify risk factors to aid doctors to more rationale prescribing

Ingunn Fride Tvete,[1] Trine Bjørner,[2] Ivar Andreas Aursnes,[3] Tor Skomedal[3]

Co-author and initiator of the project, Professor Ivar Aursnes, MD PhD, died in the autumn 2011.

[1]The Norwegian Computing Center, Oslo, Norway
[2]Department of General Practice/Family Medicine, Institute of Health and Society, University of Oslo, Oslo, Norway
[3]Department of Pharmacology, University of Oslo, Oslo, Norway

Correspondence to
Ingunn Fride Tvete; ingunn.fride.tvete@nr.no

ABSTRACT

Objectives: This study investigated and quantified risk factors of dose escalation, as an indication of drug misuse and dependency of benzodiazepines and congeners, among presumably drug naïve patients in the Norwegian drug prescription database, observed over 3 years.

Design: Observational study.

Setting: Prescription database study.

Participants: We defined an excessive user as one redeeming more than two defined daily doses per day in 3 months.

Primary and secondary outcome measures: We examined the risk of excessive use over time and the effect of risk factors through multistate logistic regression and scenarios.

Results: Most of the 81 945 patients had zopiclone or zolpidem as the initial drug (63.8%), followed by diazepam (25.3%), oxazepam (6.1%), nitrazepam/flunitrazepam (2.9%), hydroxyzine/buspirone (1.6%) and alprazolam (0.3%). At any time 23% redeemed prescriptions, about 34% did not redeem any prescriptions beyond any 3-month period and 0.9% ended up as excessive users. Patients previously using drugs, such as opioids, antialcohol or smoke cessation treatment, had a higher risk to become excessive users compared to patients who had not. Patients whose first prescription was for oxazepam or nitrazepam/flunitrazepam had a higher risk of becoming an excessive user compared to those who started with diazepam. A specialist in general practice as the first-time prescriber was associated with a lower risk compared to doctors without specialty.

Conclusions: Most benzodiazepine use occurred according to guidelines. Still, some experienced dose escalation over time, and risk factors were previous use of other psychotropic drugs, long time use, choice of first-time drug and prescriber's specialty. This could incite doctors to have a cessation plan when issuing first-time prescriptions.

INTRODUCTION

Long-term use of benzodiazepines (BZD) and congeners as z-hypnotics (collectively denoted BZD) for anxiety and insomnia can

ARTICLE SUMMARY

Strengths and limitations of this study

■ This is the first study to quantify risk factors for dose escalation of benzodiazepines and congeners in an entire population over a longer time period in order to aid doctors to more appropriate prescribing.

■ With the Norwegian prescription register only existing from 2004 we had to make some plausible assumptions regarding patients being drug naïve.

■ As in all register based studies, we had to assume that the amount dispensed is the amount consumed.

cause adverse effects (eg, falls and road accidents), tolerance, dependence and dose escalation.[1–4] Among long-term users 50% considered themselves BZD dependent.[5] It has been claimed, studying up to 8 months treatment, that 'there are no data to suggest that long-term therapeutic use of benzodiazepines by patients commonly leads to dose escalation'.[6 7] Some doubt this,[8] while others claim that restriction to short-term use is not applicable in clinical practice.[9] A study of BZD use over years for different user levels have been carried out, but without focus on excessive use or dose escalation.[10] Studies of BZD consumption over years with respect to amount and change in frequency seemed warranted.

With data from the Norwegian Prescription Database (NorPD),[11] patients' redemptions over time were calculated and patients with dose escalation identified.

The aim of this study was to observe BZD naïve patients redeeming BZD at pharmacies for 3 years and examine the amount and frequency of redemptions to assess the degree of dose escalation and the effect of risk factors: age, gender, physicians' specialty, first BZD redeemed and previous use of other

drugs. Given our statistical model we conducted scenarios over 3 years for patients previously given other drugs, first BZD redeemed and physicians' specialty to study risk differences in becoming excessive BZD users over time. We have emphasised these risk factors as they are of practical relevance for physicians.

METHODS AND PROCEDURES
Database extraction
Data from NorPD contains drug redemptions according to physicians' prescriptions in Norway from 2004 on anonymous patient identifications, patients' age, gender, county of residence, physician's specialty, date of redemption, numbers of defined daily doses (DDDs) redeemed and ATC-category (Anatomical Therapeutic Chemical classification system[12][13]) of the drug. Our study was based on data extraction from NorPD.

The drugs
The drug groups are listed in table 1. The first four are the benzodiazepines diazepam, oxazepam, alprazolam and nitrazepam/flunitrazepam. They act on the central nervous system by reinforcing the γ-amino butyricacid ($GABA_A$) receptor mediated effects in the brain, calming the patient or inducing sleep. The z-hypnotics zopiclone and zolpidem act similarly by reinforcing effects of subtypes of $GABA_A$ receptors and thus inducing sleep. Hydroxyzine acts mainly by blocking histamine H_1 and serotonin $5-HT_{1A}$ receptors and buspirone acts as a partial agonist on serotonin $5-HT_{1A}$ receptors.

Patient characteristics
We identified BZD-naïve patients, defined as persons who had no prescription fulfilments prior to July 2004 for any of the aforementioned drugs and had at least one prescription within a year. Patients, between 18 and 67 years of age in 2004, were followed for 3 years, giving 12 3-month periods. They had a first prescription of between 10 and 30 DDDs and an average daily dose of less than 1 DDD during the first 3 months.

As BZDs are not associated with excessive mortality[14] and intoxication deaths caused by BZD alone are unusual[15] we omitted patients who died during the study period. Figure 1 displays the data selection procedure, giving 81 945 patients. Patient characteristics were
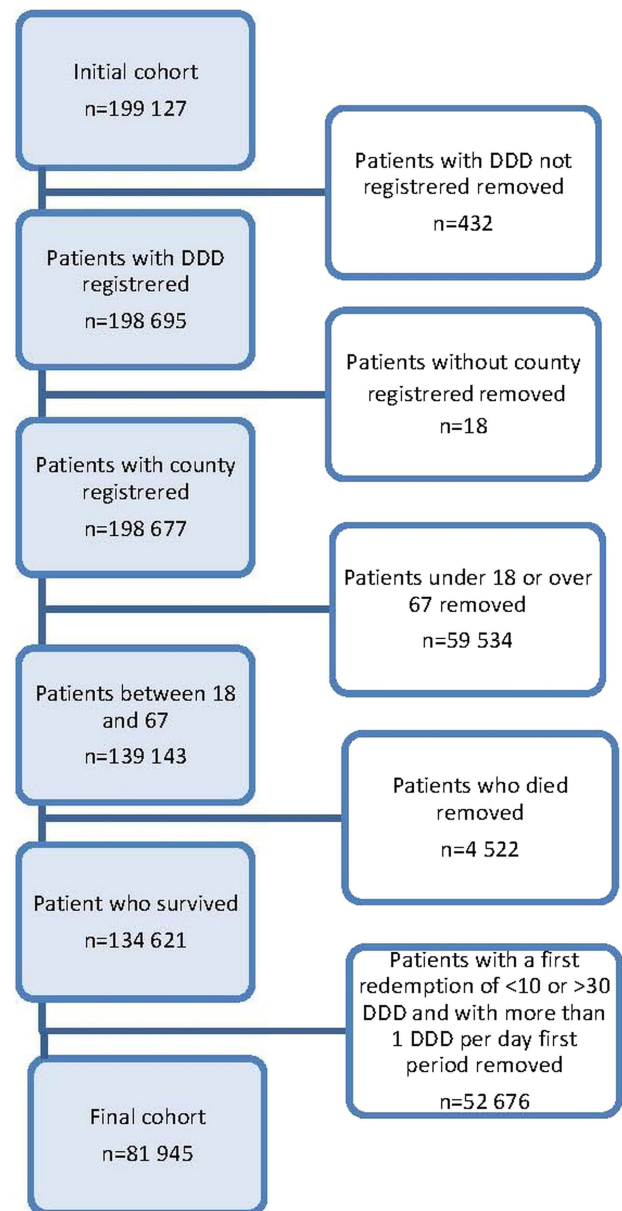

Figure 1 Data selection procedure.

gender, age at first redemption, first BZD redeemed, country of residence and redeemed drugs as indication of diseases: drugs for alcohol and smoke cessation treatment, opioids, antidepressants or lithium, antipsychotics,

Table 1 The six drug groups considered, together with their ATC-codes and their recommended DDD values (in mg) and whether they are benzodiazepines or z-hypnotics

Drug group	ATC-code	Type	DDD (mg)
Diazepam	N05BA01	Benzodiazepine	10
Oxazepam	N05BA04	Benzodiazepine	50
Alprazolam	N05BA12	Benzodiazepine	1
Nitrazepam/flunitrazepam	N05CD02/N05CD03	Benzodiazepines	5/1
Zopiclone/zolpidem	N05CF01/N05CF02	z-Hypnotics	7.5/10
Hydroxyzine/buspirone	N05BB01/N05BE01	Non-benzodiazepine	75/30

ATC, Anatomical Therapeutic Chemical; DDD, defined daily doses.

antiasthmatics or chronic obstructive pulmonary disease (COPD) drugs, drugs for cardiac diseases or methotrexate or steroids as an indication other serious somatic diseases.

Prescriber characteristics

The prescriber's specialty was: specialist in general practice, internal medicine, psychiatry, surgery, other specialities or no specialty. Frequent BZD prescribers (FBZDP) were defined as doctors with more than 24 BZD prescriptions during the first 6 months of 2004 and who prescribed more than twice the average of their peers.[16]

Redemption characteristics

Patients were allocated to four groups during each period according to level of use: level 0=no BZD redeemed, level 1=average of less than 1 DDD/day, level 2=1–2 DDD and level 3=more than 2 DDDs (excessive user). If last redemption occurred less than 5 days prior to period-end and remaining DDDs per day were more than three, this redemption was defined first in the subsequent period. We will hereafter refer to the redeemed drugs as drugs used by the patients.

Statistical analysis

We defined a multistate logistic regression model for the patients' BZD levels over time.[17–19] A patient's probability to remain or to enter another level from one period to another depended on factors previously listed. We

also related a patient's level in a given period to previous periods' levels. We included a period effect and four interaction terms: level in the previous period and log (period), average of all previous levels and log (period), gender and log (period) and age and log (period). This model was selected using the Bayesian Information Criterion.[20] The data were analysed with R[21] using the function multinom by Venables and Ripley.[22]

Scenarios

To examine the risk of becoming excessive users over time given certain patient and prescriber characteristics and not just examining from one period to another, we conducted Monte-Carlo simulation scenarios. We simulated patients' levels from the estimated model for given characteristics, giving the isolated risk due to the sole fact of having, for example, diazepam as first BZD.

With particular interest in the importance of first BZD redeemed, previous use of other drugs and physician's specialty we simulated patients' levels for values of these. We defined a risk group of patients with a first redemption for oxazepam with a general practitioner without specialty as first prescriber (group 1), compared to a group of patients who initially used diazepam with a specialist of general practice as first prescriber (group 2). The groups were defined based on adjusted estimates, table 2, making the latter a lower risk group. For detecting significant differences we took the uncertainty in risk factors and simulation into consideration.

Table 2 Some estimated factors from the model

	Effect of gender, age and physician prescribed high amount of BZD				
To level	Gender	Age	FBZDP		
1	−0.008 (ns)	0.006	0.040		
2	−0.146	0.007	0.262		
3	−0.552	−0.021	0.127		
	Effect of first drug choice (compared to diazepam)				
	Oxazepam	Alprazolam	Nitrazepam/ flunitrazepam	Zopilone/zolpidem	Hydroxyzine/ buspirone
1	0.146	0.014 (ns)	−0.046	0.032	−0.200
2	0.167	0.165 (ns)	0.515	0.465	−0.168
3	0.204	−0.010 (ns)	0.375	0.063 (ns)	−0.230 (ns)
	Effect of other drugs				
	Opioids/ antialcohol/ smoke cessation	Antidepressants/ lithium	Antipsychotics	Antiasthmatics/ COPD drugs	Cardiac drugs	Methotrexate/ steroids
1	0.136	0.214	0.152	0.100	0.030	0.035
2	0.272	0.280	0.398	0.146	0.090	0.249
3	0.738	0.334	0.570	0.266	0.002 (ns)	0.194 (ns)
	Effect of prescribers specialty (compared to no specialty)				
	General practitioner	Internist	Psychiatrist	Surgeon	Another specialty
1	0.017	−0.108	−0.054	−0.136	−0.043
2	−0.048	0.200	0.178	0.003 (ns)	0.003 (ns)
3	−0.152	0.066 (ns)	−0.013 (ns)	−0.119 (ns)	−0.042 (ns)

ns indicates not significant, 5% level.
BZD, Benzodiazepine; COPD, chronic obstructive pulmonary disease; FBZDP, Frequent BZD prescriber

Table 3 The percentage of patients in BZD levels over time periods

	Period										
Level	2	3	4	5	6	7	8	9	10	11	12
0	78.57	78.84	77.91	76.69	78.05	78.63	77.32	76.34	77.30	77.69	76.17
1	19.66	19.16	19.82	20.58	19.06	18.36	19.36	20.00	18.91	18.30	19.31
2	1.60	1.78	1.95	2.33	2.43	2.52	2.79	3.03	3.13	3.27	3.61
3	0.16	0.22	0.32	0.40	0.45	0.48	0.53	0.63	0.66	0.74	0.91

Level 0=no redemption, level 1=redeemed an average of less than 1 DDD per day, level 2=1 DDD or more per day, but not more than 2 DDDs per day and level 3=more than 2 DDDs per day.
DDD, defined daily doses.

RESULTS

Overall patient characteristics and user patterns

The study included 50 309 women and 31 636 men. Altogether 52 293 patients (63.8%) had zopiclone/zolpidem as the initial drug, followed by diazepam (20 706; 25.3%), oxazepam (4995; 6.1%), nitrazepam/flunitrazepam (2365; 2.9%), hydroxyzine/buspirone (1321; 1.6%) and alprazolam (265; 0.3%). Most patients' first-time prescribers were specialists in general practice (42 007; 51.3%), followed by general practitioners with no specialty (25 178; 30.7%), other specialty (10 380; 12.7%), psychiatrists (2033; 2.5%), internists (1569; 1.9%) and surgeons (778; 0.9%). About 23% had a FBZDP as first-time prescriber (18 808). Almost 35% (28 435) of the patients previously redeemed other drugs, most prevalent for cardiac diseases (15 208), followed by antidepressants or lithium (9571), antiasthmatics or COPD drugs (5646), antipsychotics (2206), methotrexate or steroids (1949) and opioids, antialcohol and smoke cessation treatment (921). Only 7.5% (6082) received drugs from at least two different drug groups. Of all redemptions 57.3% were for less than 30 DDD, 35.9% and 6.8% for between 30 and 60 and 60 and above DDDs.

Table 3 shows the fractions of patients in level 0–3 over time. Of 81 945 BZD naïve users 27 619 (33.7%) received BZD only in the first period. During any period 77% had no redemptions. There were 1315 and 133 patients in levels 2 and 3 in the second period, steadily increasing to respectively 2955 (3.6%) and 749 (0.9%) in the last period.

The fitted model for BZD dose escalation

Table 2 presents the estimated effects of relevant characteristics.

Patients who had previously been using antidepressants or lithium, antiasthmatics or COPD drugs, antipsychotics, opioids, antialcohol and smoke cessation treatment had a higher risk to enter level 3 compared to patients without such use. We found no such difference for previous use of drugs for cardiac diseases, methotrexate or steroids.

Patients with a first redemption for oxazepam, nitrazepam/flunitrazepam and zopiclone/zolpidem (the latter not significant) had a higher risk of entering level 3 compared to patients with a first redemption for diazepam (baseline). Patients with a FBZDP had a somewhat higher risk to enter all user levels compared to patients without. When the first prescriber was a specialist in general practice the patient had a lower risk of entering the highest level compared to when the first prescriber had no specialty. There were some regional differences, most of them not significant.

The odds for entering the highest level was about two times (exp (0.738)) compared to no use for patients who had previously used opioids and drugs for alcohol or smoke cessation compared to patients without previous use. This odds describes a period-to-period effect. To make statements about risk over time we considered scenarios.

Unadjusted and adjusted patient characteristics

The crude and adjusted numbers for the last period for the two highest levels are displayed in table 4. The crude percentages of women and men in the highest level in the end were 0.73 and 1.2, while adjusted values were 0.81 and 0.38. More men than women had used opioids and drugs for alcohol or smoke cessation treatment and had a first prescriber with no specialty, explaining the lower adjusted value. A larger fraction of patients starting with oxazepam compared to those starting with diazepam ended up in the two highest user levels (14.6% and 8.4%). The adjusted numbers were 9.6% and 6.7%. These were similarly compound groups, but a few more oxazepam users had previously been treated with other drugs. All 18% of the oxazepam patients had previously been treated with antidepressants and lithium, compared to 14% of the diazepam patients.

Figure 2 displays estimated risks for entering the highest level over time for patients with and without previous use of opioids/antialcohol/smoke cessation, antidepressants/lithium, antipsychotics or antiasthmatics/COPD drugs (figure 2A–D), for patients given first oxazepam or nitrazepam/flunitrazepam compared to diazepam (baseline) (figure 2E and F) and for patients with a first-time prescriber who was a specialist in general practice compared to no specialty (baseline) (figure 2G) and the two defined risk groups (figure 2H), with 95% confidence bands. The fraction of excessive users for those previously using opioids or drugs for alcohol or smoke cessation treatment
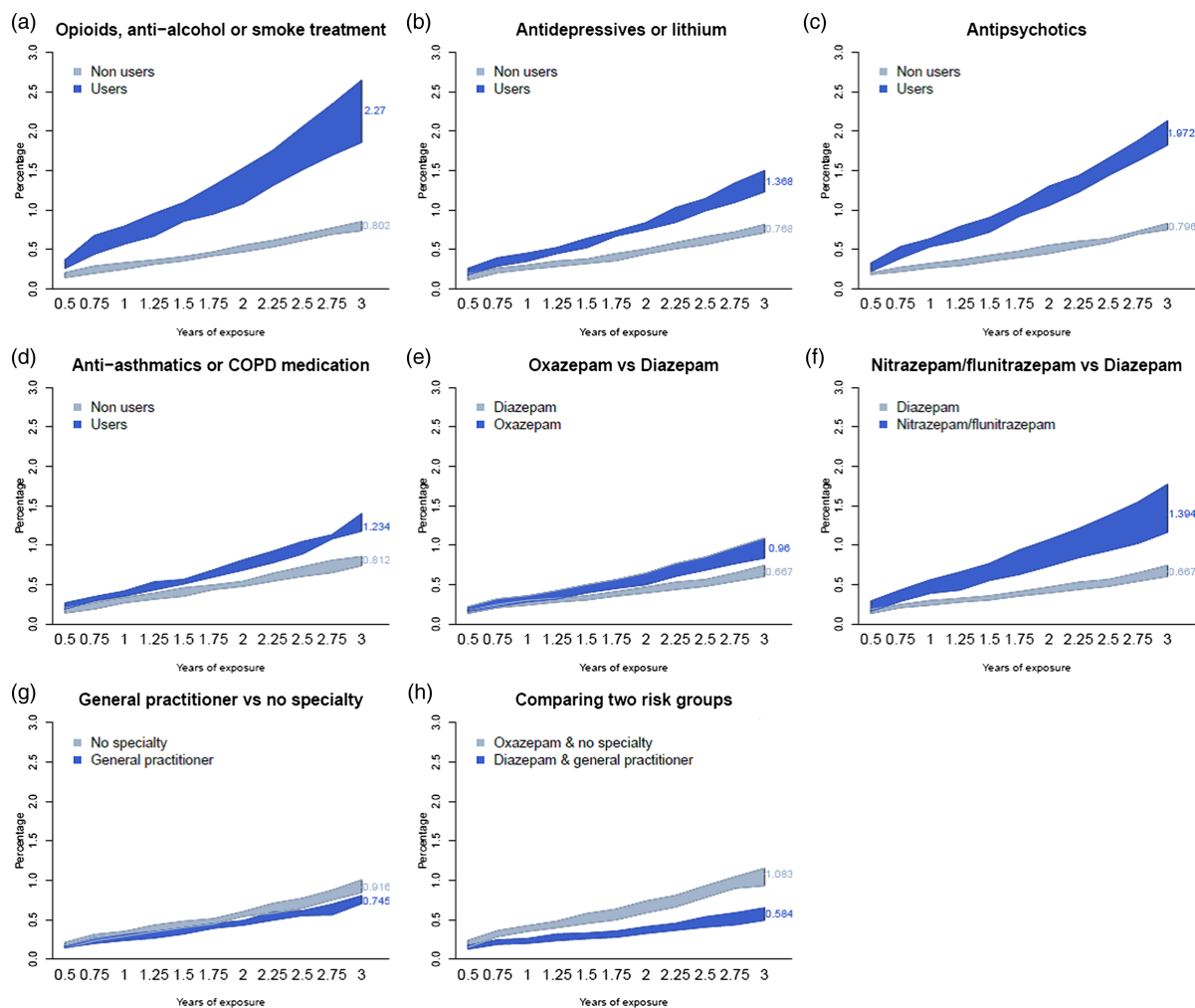
Figure 2 Estimated percentages of patients in benzodiazepine (BZD) level 3 (redeemed more than 2 defined daily doses per day on average) for previous use of other drugs A–D) compared to no previous use, first redeemed BZD compared to diazepam as first BZD (E–F), specialty of first BZD prescriber compared to no specialty (G) and a comparison of patients first BZD and first BZD prescriber's specialty (H).

was 2.27%, almost three times that for non-users (0.802%). For all comparisons (figure 2A–H) we found the differences in risk of dose escalation increasing over time. For the two defined risk groups (figure 2H) the increasing difference was mainly due to the highest risk groups' risk increase, ending with 1.083% of the patients, twice that of the other group (0.584%). Table 5 displays the final estimated percentages in the highest level and the estimated difference between the contrasting groups, with 95% confidence bands.

DISCUSSION

Most patients used BZD for a short time, and 33.7% of the users stopped after 3 months or less. About 77% did not redeem BZD in any other period. This indicates high prevalence of short-term treatment, which is in accordance with guidelines.[23] Many patients had intermittent use, as also found by Nelson and Chouinard.[24] The risk of dose escalation increased over time, but only

749 (0.9%) ended up as excessive users. Earlier studies[6] have found no dose escalation among patients over short (1 year) or longer periods, the latter contradicting our findings.[25–27] This might be due to our selection of BZD naïve patients.

Patients with previous opioids, antialcohol, smoke cessation treatment or use of antipsychotics had an increased risk of becoming excessive users compared to patients without such use and the difference increased over time. This was to some degree also the case for previous use of antidepressants/lithium and antiasthmatics/COPD drugs. This should call for awareness when prescribing to patients with such drug history.

Patients starting on oxazepam had higher risk of becoming excessive users compared to those starting on diazepam. This might be explained by different elimination half-lives, diazepam lasting longer.[28] A belief is that oxazepam strikes slower, hence less-addictive, than diazepam. Practitioners uncertain about indications for BZD might chose oxazepam to prescribe according to

Table 4 Numbers (n) of patients in the various cohort subgroups after 3 years, corresponding numbers per 1000 patients with 1–2 and above 2 DDDs on average per day used during the last period and adjusted estimates as described in method.

	n	Between 1 and 2 DDDs		Above 2 DDDs	
		Crude	Adjusted	Crude	Adjusted
Subgroups					
Woman	50 309	35.2	33.8	7.3	8.1
Man	31 636	37.5	33.4	12.0	3.8
First drug prescribed					
Diazepam	20 706	23.0	20.4	8.1	6.7
Oxazepam	4995	37.0	27.0	14.6	9.6
Alprazolam	265	30.2	25.9	0	6.8
Hydroxyzine/buspirone	1321	17.4	13.8	6.8	4.1
Nitrazepam/flunitrazepam	2365	41.9	40.2	11.4	13.4
Zopiclone/zolpidem	52 293	41.4	38.8	9.0	8.7
Specialty of first prescriber					
None	25 178	35.4	34.2	10.6	9.5
General practitioner	42 007	35.6	31.9	8.3	7.6
Internist	1569	45.9	43.1	8.9	10.8
Psychiatrist	2033	49.2	42.4	12.3	9.9
Surgeon	778	41.13	32.1	9.0	7.6
Other specialty	10 380	35.1	33.2	8.5	8.8
First prescription by frequent prescriber	18 808	48.5	44.0	10.9	10.5
Other drugs					
Opioids, antialcohol and smoke cessation	921	68.40	50.0	32.57	24.3
Antidepressives or lithium	9571	55.7	50.3	15. 8	13.5
Antipsychotics	2206	70.7	59.9	30.8	19.8
Antiasthmatics or COPD drugs	5646	51.4	41.7	15.8	12.1
Cardiac drugs	15 208	46.1	37.3	9.2	8.7
Methotrexate or steroids	1949	62.6	48.2	15.4	12.2

COPD, chronic obstructive pulmonary disease; DDD, defined daily doses.

guidelines,[29] focusing on drug choice rather than on amount. This might also be due to unobserved differences in the population groups.

Patients starting on nitrazepam/flunitrazepam had a greater risk of becoming excessive BZD users compared to those starting on diazepam. We found no increased

Table 5 The estimated percentages of patients in the highest level in the last-period, and the estimated difference between the contrasting groups in figures 2A–H (95% confidence bands)

Figure	Comparing groups	Estimate 1	Estimate 2	Difference
Effect of other drugs				
2A	Opioids/antialcohol/smoke cess. (1) versus none (2)	2.27 (1.858, 2.646)	0.802 (0.736, 0.855)	1.468 (1.074, 1.853)
2B	Antidepressants/lithium (1) versus none (2)	1.368 (1.23, 1.501)	0.768 (0.711, 0.818)	0.6 (0.437, 0.726)
2C	Antipsychotics (1) versus none (2)	1.972 (1.824, 2.131)	0.796 (0.749, 0.831)	1.176 (1.006, 1.336)
2D	Antiasthmatics/COPD drugs (1) versus none (2)	1.234 (1.178, 1.4)	0.812 (0.739, 0.859)	0.422 (0.357, 0.543)
Effect of 1st drug choice				
2E	Oxazepam (1) versus diazepam (2)	0.96 (0.835, 1.091)	0.667 (0.602, 0.745)	0.293 (0.154, 0.476)
2F	Nitrazepam/flunitrazepam (1) versus diazepam (2)	1.394 (1.164, 1.772)	0.667 (0.602, 0.745)	0.727 (0.447, 1.131)
Effect of prescribers specialty				
2G	General practitioner (1) versus no specialty (2)	0.745 (0.705, 0.806)	0.916 (0.844, 1.007)	−0.171 (−0.294, −0.092)
Compare the two defined groups				
2H	Oxazepam and no specialty (1) versus diazepam and specialist in general practice (2)	1.083 (0.931, 1.155)	0.584 (0.494, 0.652)	0.499 (0.361, 0.618)

risk with the z-hypnotics zopiclone and zolpidem or with hydroxyzine and buspirone compared to diazepam as the initial drug. For the latter two this is reasonable, as these are non-benzodiazepines and less expected to induce drug dependency.[24 29]

There was a somewhat decreased risk for patients to become excessive users over time if the first physician was a specialist of general practice. We found an increased risk for patients with oxazepam as initial BZD and if the treatment was started by a physician with no specialty compared to patients with an initial BZD of diazepam and a specialist in general practice starting treatment and the difference in risk increased over time. It would be interesting to study this discrepancy pattern over a longer-time window.

We found some geographical differences, but had no socioeconomic variables to explain differences.

As we have no data registrations prior to 2004 we defined BZD-naïve patients based on only half a year without redemptions. We therefore required that the first redeemed prescription was between 10 and 30 DDDs combined with having less than 1 DDD/day the first period, giving conservative estimates as compared to having a population of known BZD naïve patients over a longer period.

As in all register-based studies, we only know the amount dispensed and not the amount consumed. If consumption deviate much from the amount dispensed the results will be partly flawed. We have, regrettably, no way to estimate a possible discrepancy.

We could have considered the influence of other drugs and BZD choice throughout the observation period and not just previously. As this is a more complicated task, it was not pursued.

The study was retrospective, but as a population analysis this should give no bias. We have in this work not focused on drug dependency that could occur without dose escalation. Still, also long-term use could be a surrogate marker for dependency, and a more comprehensive analysis could give an answer to this.

CONCLUSION

Most BZD use occurred according to guidelines. Only 0.9% ended up as excessive users after 3 years. Patients who previously had opioids, antialcohol or smoke cessation treatment or medication indicating previous psychiatric or chronic pulmonary disease had a higher risk for excessive BZD use. If nitrazepam/flunitrazepam or oxazepam was the first prescribed BZD, the risk of dose escalation was higher as compared to diazepam. The risk for dose escalation increased with long-term use. This should incite doctors to have a cessation plan when patients get their first BZD prescription.

REFERENCES

1. Ashton H. Adverse effects of prolonged benzodiazepine use. *Adverse Drug React Bull* 1986;118:1–7.
2. Smith RG. Fall-contributing adverse effects of the most frequently prescribed drugs. *J Am Podiatr Med Assoc* 2003;93:42–50.
3. Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998;24:1331–6.
4. Oster G, Huse DM, Adams SF, et al. Benzodiazepine tranquilizers and the risk of accidental injury. *Am J Public Health* 1990; 80:1467–70.
5. Melander A. *Benzodiazepines and their analogues*. NEPI Foundation Report 13. 2002; ISBN 91-8627-499-6.
6. American Psychiatric Association. *Practice guideline for the treatment of patients with panic disorder*, 2nd edn, Washington (DC): American Psychiatric Association, 2009.
7. American Psychiatric Association. *Benzodiazepine dependence, toxicity, and abuse*. A task force report of the American Psychiatric Association. American Psychiatric Association, 1990. http://www.appi.org/searchcenter/pages/SearchDetail.aspx?ItemId=2228
8. Donoghue J, Lader M. Usage of benzodiazepines: a review. *Int J Psychiatry Clin Pract* 2010;14:78–87.
9. Veronese A. Benzodiazepine use in the real world of psychiatric practice: low-dose, long-term drug taking and low rates of treatment discontinuation. *Eur J Clin Pharmacol* 2007;63:867–73.
10. Holm E, Fosbol E, Pedersen H, et al. Benzodiazepine use in Denmark 1997–2008. *Eur Geriatr Med* 2012;3:299–303.
11. The Norwegian Prescription Database. http://www.norpd.no
12. WHO. Definitions and general considerations. http://www.whocc.no/ddd/definition_and_general_considera
13. WHO. Structure and principles. http://www.whocc.no/atc/structure_and_principles/
14. Hausken A, Skurtveit S, Tverdal A. Use of anxiolytic or hypnotic drugs and total mortality in a general middle-aged population. *Pharmacoepidemiol Drug Saf* 2007;16:913–18.
15. Reith D, Fountain J, McDowell R, et al. Comparison of the fatal toxicity index of zopiclone with benzodiazepines. *J Clin Toxicol* 2003;41:975–80.
16. Dybwad T, Sundene G, Eskerud J, et al. Control of prescriptions of B-preparations. A registry study of B-preparations in Oslo and Akershus. *Tidsskr Nor Laegeforen* 1994;114:3207–10.
17. McCullagh P, Nelder J. Generalized linear models. London: Chapman & Hall, 1989.
18. Nielsen L, Keiding N. *Describing episodes of drug treatment from joint observation of a prescription registry and a cross-sectional survey*. Copenhagen: Department of Biostatistics, University of Copenhagen, 2009.
19. Jackson C, Sharples L. Hidden Markov models for the onset and progression of bronchiolitis obliterans syndrome in lung transplant recipients. *Stat Med* 2002;21:113–28.
20. Schwarz G. Estimating the dimension of a model. *Ann Stat* 1978;6:461–4.

21. R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2010. http://cran.r-project.org/doc/FAQ/R-FAQ.html

22. Venables W, Ripley B. *Modern applied statistics with S*. 4 edn. New York: Springer, 2002.

23. National institute for health and Clinical Excellence (NICE). http://www.nice.org.uk/Search.do?keywords=benzodiazepine&searchSite=on&searchType=All&newSearch=1

24. Nelson J, Chouinard G. Guidelines for the clinical use of benzodiazepines: pharmacokinetics, dependency, rebound and withdrawal. *Can J Clin Pharmacol* 1999;6:69–83.

25. American Psychiatric Association. *Benzodiazepine dependence, toxicity and abuse: a task force report of the American Psychiatric Association*. Washington, DC: American Psychiatric Association, 1990.

26. Soumerai SB, Simoni-Wastila L, Singer C, *et al*. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv* 2003;54:1006–11.

27. Hallfors D, Saxe L. The dependence potential of short half-life benzodiazepines: a meta-analysis. *Am J Public Health* 1993;83:1300–4.

28. Dybwad TB, Kjølsrød L, Eskerud J, *et al*. Why are some doctors high-prescribers of benzodiazepines and minor opiates? A qualitative study of GPs in Norway. *Fam Pract* 1997; 14:361–8.

29. Fick DM, Cooper JW, Wade WE, *et al*. Updating the beers criteria for potentially inappropriate medication use in older adults results of a US consensus panel of experts. *Arch Intern Med* 2003;163:2716–24.