Ingunn Fride Tvete, Trine Bjørner and Tor Skomedal

A 5-year follow-up study of users of benzodiazepine:

starting with diazepam versus oxazepam

Abstract

Background
Drug dependency may develop during long-term benzodiazepine use, indicated, for example, by dose escalation. The first benzodiazepine chosen may affect the risk of dose escalation.

Aim
To detect possible differences in benzodiazepine use between new users of diazepam and oxazepam over time.

Design and setting
This 5-year prescription database study included 19 747 new benzodiazepine users, inhabitants of Norway, aged 30–60 years, with first redemption for diazepam or oxazepam.

Method
Individuals starting on diazepam versus oxazepam were analysed by logistic regression with sex, age, other drug redemptions, prescriber's specialty, household income, education level, type of work, and vocational rehabilitation support as background variables. Time to reach a daily average intake of ≥1 defined daily doses (DDD) over a 3-month period was analysed using a Cox proportional hazard regression model.

Results
New users of oxazepam had a higher risk for dose escalation compared with new users of diazepam. This was true even when accounting for differences in sociodemographic status and previous drug use (hazard ratio [HR] 1.33, 95% confidence interval = 1.17 to 1.51).

Conclusion
Most doctors prescribed, according to recommendations, oxazepam to individuals they may have regarded as prone to and at risk of dependency. However, these individuals were at higher risk for dose escalation even when accounting for differences in sociodemographic status and previous drug use. Differences between the two user groups could be explained by different preferences for starting drug, DDD for oxazepam being possibly too low, and some unaccounted differences in illness.

Keywords
anxiety; benzodiazepines; Cox models; diazepam; general practice; logistic models; oxazepam.

INTRODUCTION

Benzodiazepines (BZD) act on the central nervous system (CNS) by enhancing the effect of $GABA_A$ receptors. They are used as sedatives, hypnotics, anxiolytics, and muscle relaxants. BZDs are not recommended for more than 2–4 weeks of continuous use, as tolerance and dependence can develop after even a short time.[1–3] Important adverse effects are dependency, drowsiness, falls among older people, mood swings, violent and impulsive behaviour, and depression.[4–6] Previous studies[7,8] have shown that BZDs are mainly prescribed according to guidelines, and only a small percentage of patients became excessive users. Previous analyses also suggested differences in the risks of patients becoming excessive users depending on the first prescribed BZD choice.[7,8] This study examined new users of diazepam and oxazepam to obtain a better understanding of differences between these two user groups.

METHOD

Data collection and study population

This is an observational prescription registry study. Data on prescription fulfilments were extracted from the Norwegian Prescription Registry (NorPD),[9] linked with socioeconomic data from Statistics Norway (SSB).[10]

Information was collected about Norwegian inhabitants aged 30–60 years who had a first redemption for diazepam (ATC code N05BA01) or oxazepam (N05BA04) during 2006. To follow new users, only individuals without redemptions for alprazolam (N05BA12), nitrazepam (N05CD02), flunitrazepam (N05CD03), hydroxyzine (N05BB01), or buspirone (N05BE01) from January 2004 (first registration in NorPD) through to December 2005 were included. To further ensure only new users of BZD were included, it was also required that first redemption was between 10 and 30 defined daily doses (DDDs)[11] and that average DDD per day redeemed in the first 3 months was <1. The study included 19 747 individuals.

Information was obtained about the participants' sex, age, and prescribers' specialty. Individuals who died during the observation period were excluded.

Information from 2004 about redemptions for other drugs was used as an indicator of any comorbidity: antidepressants and antipsychotics as indicators of psychiatric disease; opioids, anti-alcohol, and smoking cessation treatment as indicators of dependency and craving; drugs for cardiac diseases and for chronic obstructive pulmonary disease (COPD) as indicators for serious somatic disease; and drugs for rheumatic diseases as indicators for pain. The prescriber's specialties were: GP (no specialty or specialist in general practice), internal medicine, psychiatry, surgery, or other specialties.

Information from SSB was obtained

IF Tvete, PhD, senior researcher, The Norwegian Computing Center, Oslo, Norway. **T Bjørner**, MD, PhD, associate professor, Department of General Practice, Institute of Health and Society; **T Skomedal**, MD, PhD, professor emeritus (pharmacology), Specialty Clinical Pharmacology, Department of Pharmacology, University of Oslo, Oslo, Norway.

Address for correspondence
Ingunn Fride Tvete, Norwegian Computing Center, SAMBA, Gaustadalleen 23a, Oslo 0373 Norway.

E-mail: ingunn.fride.tvete@nr.no

Submitted: 28 September 2015; **Editor's response:** 2 November 2015; **final acceptance:** 8 December 2015.

This is the full-length article (published online 11 Mar 2016) of an abridged version published in print. Cite this article as: **Br J Gen Pract 2016; DOI: 10.3399/bjgp16X684385**

How this fits in

Many doctors regard the various benzodiazepines as different with respect to abuse liability, and oxazepam has been recommended as a drug of lower risk. This study provides an analysis of new users of diazepam and oxazepam, in which the latter group was found to be more prone to dose escalation. Possible explanations for the discrepancy between given recommendations and present findings representing the actual user patterns are discussed.

on the individuals' household income, education level, type of work, and vocational rehabilitation support (all in 2004). Only individuals whose education level was registered in SSB were included. Education was categorised as low (until lower secondary school) or high (upper secondary school or higher). Household income was categorised as low — from 0 to 3G [176 364 NOK — roughly 14 500 GBP], medium — from 3G to 6G [352 728 NOK — roughly 22 000 GBP], or high — from 6G [352 728 NOK — roughly 29 000 GBP], and upwards. In Norway G is the National Insurance basic amount, forming the basis for estimating social benefits and pension schemes.[12] Work type was categorised as private sector, public sector, or no registered work. The last category included, for example, unemployment, working from home, and being ill and/or disabled. Individuals were followed for 5 years from their first redemption of their prescription. The follow-up time for each individual was divided into 3-month periods. For each period each individual was categorised in one of three redemption levels:

- 0 — no prescription fulfilments;
- 1 — <1 DDD per day on average redeemed; or
- 2 — ≥1 DDD per day on average redeemed.

Statistical analysis

The statistical analysis consisted of background analysis of those patients who started on diazepam or oxazepam and pattern of BZD use over time. In the first part univariate and multivariate logistic regression analyses were conducted to study how new users of diazepam and oxazepam differed with respect to background variables: sex, age, other drug redemptions, prescriber's specialty, household income, education level, type of work, and vocational rehabilitation support. In the second part, univariate and multivariate Cox proportional hazard regression models were constructed for the time to reach the highest redemption level given the background variables, including which BZD was first redeemed. In the multivariate analyses, first, a 'full' model was specified with all the background variables, and then an automatic model selection procedure was used (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/step.html), based on the Akaike information criterion for model evaluation, for optimal model fitting. This gave odds ratios (part one) and hazard ratios (part two) for different levels of background variables. In the second part, the time-varying factors redeemed for different BZDs and prescription fulfilments from psychiatrists during the observation period were also considered. The statistical analysis was conducted using the statistical software R (2010 version). A 5% significance level was used.

RESULTS

All results are significant unless stated otherwise.

Background analysis: starting on diazepam versus oxazepam

Of 19 747 new users, 15 927 (80.7%) started on diazepam and 3820 (19.3%) started on oxazepam. Of these, 37.7% and 42.6% were male, respectively (Table 1). A greater percentage of those starting on oxazepam compared with those starting on diazepam had previously used antidepressants and lithium (26.8% versus 19.2%), antipsychotics (9.1% versus 5.3%), and opioids, anti-alcohol, and smoking cessation treatment (1.7% versus 0.6%). A greater percentage of those starting on oxazepam had a first prescription from a psychiatrist (5.3%) compared with those starting on diazepam (3.0%). A somewhat greater percentage of those who started on oxazepam had previously received vocational rehabilitation support (11.6%) compared with those who started on diazepam (9%). There was a greater percentage of individuals with low education, low income, and no registered work among those starting on oxazepam compared with diazepam (Table 1).

The multivariate analysis results are shown in Table 2. Compared with males, females were less likely to start on oxazepam than on diazepam (OR 0.82). Individuals starting on oxazepam were

slightly older than those starting on diazepam (OR 1.01). Previous use of antidepressants and lithium; antipsychotics; and opioids, anti-alcohol, and smoking cessation drugs gave OR of 1.38, 1.40, and 2.49, respectively, compared with no such previous use, for starting on oxazepam versus diazepam. Having an internist or a psychiatrist as first prescriber gave OR for starting on oxazepam versus diazepam of 1.49 and 2.48, respectively, compared with a GP as first prescriber. To have previously received vocational rehabilitation support compared with no such support was nominally, but not significantly higher (OR 1.13). High education compared with low education gave an OR of 0.92. Working within the private or public sector compared with no registered work gave OR of 0.79 and 0.84, respectively. In a univariate analysis low income was a significant risk factor, but this was removed by the automatic model selection procedure.

Table 1. Number of individuals who started on diazepam or oxazepam for background variables

Variable	Group	Diazepam (15 927 individuals), *n* (%)	Oxazepam (3820 individuals), *n* (%)
Sex	Male	5998 (37.7)	1629 (42.6)
	Female	9929 (62.3)	2191 (57.4)
Average age, years		46.74	47.29
Previous medication	Antidepressants and lithium	3085 (19.2)	1023 (26.8)
	Antipsychotics	848 (5.3)	348 (9.1)
	Opioids, anti-alcohol, and smoking cessation drugs	89 (0.6)	66 (1.7)
	Drugs for cardiac diseases	3467 (21.8)	870 (22.8)
	Drugs for rheumatic diseases	852 (5.3)	197 (5.2)
	Drugs for COPD	1648 (10.3)	411 (10.8)
Specialty of first prescriber	GP	14 543 (91.3)	3318 (86.9)
	Internist	480 (3.1)	157 (4.1)
	Surgeon	339 (2.1)	80 (2.1)
	Psychiatrist	317 (2.0)	201 (5.3)
	Other	248 (1.6)	64 (1.7)
Vocational rehabilitation		1439 (9)	443 (11.6)
Education	Low	4981 (31.3)	1311 (34.3)
	High	10 946 (68.7)	2509 (65.7)
Income	Low	5943 (37.3)	1657 (43.4)
	Average	6663 (41.8)	1443 (37.8)
	High	3321 (20.9)	720 (18.8)
Type of work	Not registered	4716 (29.6)	1410 (36.9)
	Private sector	5309 (33.3)	1080 (28.3)
	Public sector	5902 (37.1)	1330 (34.8)

COPD = chronic obstructive pulmonary disease.

Table 2. Multivariate logistic regression analysis

Variable (baseline)	Group	OR (95% CI)	*P*-value
Intercept		0.34 (0.292 to 0.394)	<0.001
Sex (male)	Female	0.815 (0.755 to 0.879)	<0.001
Age[a]		1.011 (1.007 to 1.015)	<0.001
Previous medication	Antidepressants and lithium	1.382 (1.268 to 1.506)	<0.001
	Antipsychotics	1.404 (1.223 to 1.609)	<0.001
	Opioids, anti-alcohol, and smoking cessation drugs	2.489 (1.788 to 3.446)	<0.001
Specialty of first prescriber (GP)	Internist	1.493 (1.237 to 1.793)	<0.001
	Surgeon	1.126 (0.873 to 1.434)	0.349
	Psychiatrist	2.479 (2.057 to 2.981)	<0.001
	Other	1.155 (0.867 to 1.517)	0.312
Vocational rehabilitation		1.125 (0.998 to 1.266)	0.051
Education (low)	High	0.924 (0.854 to 0.999)	0.047
Type of work (not registered)	Private sector	0.787 (0.715 to 0.865)	<0.001
	Public sector	0.837 (0.765 to 0.916)	<0.001

[a]*The only continuous variable. COPD = chronic obstructive pulmonary disease.*

Development of BZD use over time

Among individuals starting on diazepam, 5.36% (854 individuals) reached the highest consumption level, whereas the corresponding number for oxazepam was 8.48% (324 individuals). Table 3 displays the number (%) of individuals starting on diazepam or oxazepam and who reached consumption level 2 (≥1 DDD per day on average) or not, for background variables.

Starting on diazepam, 6.94% of the males and 4.41% of the females reached level 2. The corresponding numbers for starting on oxazepam were 10.19% and 7.21%, respectively. Individuals reaching level 2 were, on average, somewhat older than those who did not reach level 2. Among the new users of diazepam and oxazepam who reached level 2 there was a greater number of individuals who had previously used antidepressants and lithium, antipsychotics, opioids, anti-alcohol and smoking cessation drugs, drugs for rheumatic diseases, and COPD drugs. A greater percentage of those starting on oxazepam and reaching level 2 had a first prescription by a surgeon, psychiatrist, or other specialist compared with those who did not reach level 2. This was not the case for those starting on diazepam. A greater percentage of both new users of diazepam and oxazepam who reached level 2 had received vocational rehabilitation support, had low income and education, and did not have registered work.

The multivariate Cox proportional hazard regression model analysis results are given in Table 4. Female sex and higher age indicated lower risk for reaching level 2 (HR 0.57 and HR 0.98, respectively). Starting on oxazepam versus diazepam gave an HR of 1.33 for reaching level 2. Previous use of antidepressants or lithium; antipsychotics; opioids, anti-alcohol, and

smoking cessation drugs; and drugs for COPD was associated with increased risks for reaching level 2 (HR 1.69, 1.75, 3.04, 1.29). There was a nominal, but not significant, increased risk for reaching level 2 for those who had previously used drugs for rheumatic diseases (HR 1.22). In a univariate analysis the corresponding HR was 1.36 and significant. High versus low education gave an HR of 0.65. Average or high income and working within both private and public sector indicated reduced risk for reaching level 2 compared with low income and no registered work (HR 0.72 and 0.57 and HR 0.62 and 0.61, respectively). Having received vocational rehabilitation and specialty of prescriber were factors removed by the automatic model selection procedure.

Among those starting on diazepam or oxazepam and ending up in level 2, 9.6% (82 individuals) and 14.81% (48 individuals), respectively, had prescription fulfilments from a psychiatrist during the observation period. The corresponding numbers for those not reaching level 2 were 3.55% (535 individuals) and 7.64% (267 individuals), respectively. Among those who started on diazepam or oxazepam and ended up in level 2, 57.61% (492 individuals) and 55.86% (181 individuals) redeemed several BZDs. Corresponding numbers for those who did not reach level 2 were 19.54% (2945 individuals) and 21.31% (745 individuals). Based on these findings a model was examined with the time-varying factors: having redeemed several BZDs and having visited a psychiatrist.

These variables were important for describing the process of reaching level 2. To have redeemed for different BZDs and to have prescription fulfilments from a psychiatrist were not risk factors themselves, but they described characteristics of the process to becoming level 2 users.

Average times to reach level 2 were 26 (diazepam) and 23 (oxazepam) months, respectively, for individuals redeeming single BZDs. Corresponding times for those redeeming different BZDs were 31 and 26 months, respectively.

Hence, most of these excessive users of BZD used BZD far beyond the recommended time period.

Table 3. Number of individuals who started on diazepam and oxazepam who reached consumption level 2 and not, for various background variables

		Diazepam (15 927 individuals)		Oxazepam (3820 individuals)	
Variable	Group	Not reached level 2 (15 073), *n* (%[a])	Reached level 2 (854), *n* (%)	Not reached level 2 (3496), *n* (%)	Reached level 2, (324)*n* (%)
Sex	Male	5582 (37.0)	416 (48.7)	1463 (41.8)	166 (51.2)
	Female	9491 (63.0)	438 (51.3)	2033 (58.2)	158 (48.8)
Average age, years		45.43	46.81	45.06	47.50
Previously used	Antidepressants and lithium	2778 (18.4)	307 (35.9)	907 (25.9)	116 (35.8)
	Antipsychotics	721 (4.8)	127 (14.9)	287 (8.2)	61 (18.8)
	Opioids, anti-alcohol, and smoking cessation drugs	63 (0.4)	26 (3.0)	40 (1.1)	26 (8.0)
	Drugs for cardiac diseases	3284 (21.8)	183 (21.4)	809 (23.1)	61 (18.8)
	Drugs for rheumatic diseases	789 (5.2)	63 (7.4)	177 (5.1)	20 (6.2)
	Drugs for COPD	1522 (10.1)	126 (14.8)	367 (10.5)	44 (13.6)
Specialty of first prescriber	GP	13 753 (91.2)	790 (92.5)	3047 (87.2)	271 (83.6)
	Internist	462 (3.1)	18 (2.1)	145 (4.1)	12 (3.7)
	Surgeon	325 (2.2)	14 (1.6)	71 (2.0)	9 (2.8)
	Psychiatrist	296 (2)	21 (2.5)	179 (5.1)	22 (6.8)
	Other	237 (1.6)	11 (1.3)	54 (1.5)	10 (3.1)
Vocational rehabilitation		1307 (8.7)	132 (15.5)	394 (11.2)	49 (15.1)
Education	Low	4565 (30.3)	416 (48.7)	1151(32.9)	160 (49.4)
	High	10 508 (69.7)	438 (51.3)	2345 (67.1)	164 (50.6)
Income	Low	5445 (36.1)	498 (58.3)	1459 (41.7)	198 (61.1)
	Average	6402 (42.5)	261 (30.6)	1353 (38.7)	90 (27.8)
	High	3226 (21.4)	95 (11.1)	684 (19.6)	36 (11.1)
Type of work	Not registered	4260 (28.3)	456 (53.4)	1225 (35.0)	185 (57.1)
	Private sector	5138 (34.1)	171 (20.0)	1022 (29.2)	58 (17.9)
	Public sector	5675 (37.7)	227 (26.6)	1249 (35.8)	81 (25)

[a]*Percentage starting on diazepam and oxazepam. COPD = chronic obstructive pulmonary disease.*

Table 4. Multivariate Cox proportional hazard regression model analysis

Variable (baseline)	Group	HR (95% CI)	*P*-value
Sex (male)	Female	0.571 (0.505 to 0.645)	<0.001
Age[a]		0.984 (0.977 to 0.99)	<0.001
First BZD (diazepam)	Oxazepam	1.328 (1.167 to 1.512)	<0.001
Previous medication	Antidepressants and lithium	1.687 (1.491 to 1.91)	<0.001
	Antipsychotics	1.753 (1.488 to 2.066)	<0.001
	Opioids, anti-alcohol, and smoking cessation drugs	3.042 (2.285 to 4.049)	<0.001
	Drugs for rheumatic diseases	1.216 (0.968 to 1.529)	0.093
	Drugs for COPD	1.288 (1.089 to 1.523)	0.003
Education (low)	High	0.647 (0.574 to 0.73)	<0.001
Income (low)	Average	0.719 (0.615 to 0.841)	<0.001
	High	0.569 (0.453 to 0.714)	<0.001
Type of work (no registration)	Private sector	0.622 (0.520 to 0.743)	<0.001
	Public sector	0.613 (0.518 to 0.725)	<0.001

[a]*The only continuous variable. BZD = benzodiazepines. COPD = chronic obstructive pulmonary disease.*

DISCUSSION

Summary

The main finding in this study was that patients starting with oxazepam, compared with diazepam, increased their risk for reaching consumption level 2 during a 5-year period. This was true even when accounting for differences in

sociodemographic status and previous drug use (HR 1.33, 95% CI = 1.17 to 1.51).

New users of oxazepam had more often used antidepressants, lithium, antipsychotics, opioids, anti-alcohol and smoking cessation drugs, and drugs for COPD previously, than had new users of diazepam. They had a somewhat lower education and income, and had to a greater extent no registered work. Thus, former drug consumption and sociodemographic profiles characterising new users of oxazepam were associated with reaching level 2.

The difference in dose escalation risk for the two user groups was interesting as diazepam is described as having higher liability for dependence compared with oxazepam.[13,14] Diazepam is absorbed more rapidly, followed by a fast distribution phase (distribution half-life of about 1 hour) and a terminal elimination phase with a half-life of 20–200 hours,[15] whereas oxazepam is absorbed more slowly, covering also the distribution phase, followed by a terminal elimination phase with a half-life of 4–15 hours.[15] These pharmacokinetic differences are mainly a result of diazepam being more lipophilic than oxazepam. The fast invasion of the central nervous system (CNS, fast 'on-rate') during the absorption phase and the fast fall in the CNS concentration (fast 'off-rate') during the distribution phase by diazepam compared with oxazepam are expected to be the typical pattern for causing dependency. Thus, these differences constitute the basis for the recommendation to start with oxazepam rather than diazepam if prescribers suspect substance use disorder.[1,2,13,14]

Previous use of psychopharmacological drugs, opioids, and anti-alcohol and smoking cessation drugs could indicate a psychiatric disorder and problems with pain, and perhaps also a more general proneness to dependency. The present study findings indicate that prescribers took such patient histories into account and chose drugs regarded as less addictive. For individuals with previous COPD medication, oxazepam was perhaps considered to be a safer drug regarding respiratory problems.

Overall 8.48% (oxazepam) and 5.36% (diazepam) reached level 2 and hence consumed above the recommended dosage. There could be several explanations for this. A greater fraction of new users of oxazepam may have wanted a faster-acting drug and experienced an insufficient initial drug effect, and therefore compensated for the slow absorption by increasing the dose. DDD for diazepam and oxazepam are 10 and 50 mg, respectively.[15] Another possible explanation for the different patterns of use between the two drugs could simply be that DDD for oxazepam has been set too low. Some individuals perhaps did not experience a sufficient effect with the average dose.[13,14,16]

Even when accounting for differences in sociodemographic status and previous drug use, there was a difference in BZD consumption between new users of diazepam and oxazepam. Perhaps a greater fraction of users of oxazepam had more serious psychiatric conditions, not accounted for by the available background variables, and therefore experienced an insufficient effect with recommended dosages.

A higher fraction of patients redeeming different BZDs reached level 2 compared with those who only used one BZD. This could indicate that those switching BZDs were dissatisfied and perhaps also more prone to dose escalation. As expected, individuals redeeming different BZDs needed a longer time to reach level 2. This is reasonable as it takes time to try new drugs and thereafter increase the dose. Furthermore, to have prescriptions issued by a psychiatrist also characterised the path to reach level 2. Those visiting a psychiatrist may encompass a group of more seriously ill patients with psychiatric conditions in need of more extensive treatment regimes.

Strengths and limitations

As a population-based analysis there was no observational bias. However, drug dependency was only discussed in terms of reaching consumption level 2. A study focusing on low-dosage long-term use could also indicate drug dependency. Also, observational cohort studies may have unmeasured/unmeasurable confounders. For example, the lack of knowledge of indications for prescribing BZDs and of clinical data on psychiatric history is important missing information from the analysis.

There were no redemptions registered prior to 2004. New users had had 2 years without redemptions. Still, only individuals with a first redemption between 10 and 30 DDDs, and individuals who redeemed <1 DDD daily on average in the first 3 months, were considered. This made the new-user assumption reasonable. Register-based studies can only consider the amount of drugs redeemed, not the amount consumed. Unfortunately, possible discrepancies could not be controlled for.

Comparison with existing literature

This study confirmed that most prescribers and consumers follow recommendations regarding dosage and treatment duration.[17] This is in line with previous findings.[7] This gives credit to the robustness of the analysis regarding the new findings on new users of oxazepam.

The present finding of higher BZD consumption for individuals with lower socioeconomic status is in line with findings for more deprived members of the population in previous studies.[18,19] Clearly, many doctors unsure of the risk for dependency chose oxazepam rather than diazepam for these patients.

Implications for research and practice

Many doctors acted according to recommendations by prescribing oxazepam to individuals for whom they feared dependency problems. This study describes the real 'post prescription situation' and showed that these individuals to a larger degree reached a consumption level beyond what was recommended compared with those starting on diazepam. These findings could be considered by guideline providers and by doctors initiating BZD treatment, and could help prescribers identify patients who might need a closer follow-up throughout treatment.

The present findings indicate that, although in theory pharmacokinetic profiles with longer absorption time and slower availability in the CNS, such as for oxazepam, should account for differences in liability for dose escalation, this might not apply in practical use. This is because slower absorption and availability can be compensated for by higher consumption.

Funding

This work was done under the Norwegian Research council project number 190420/V50.

Ethical approval

The data were released from NorPD and SSB by approval from the Regional Committee for Medical and Health Research Ethics (2010/1514) and the Norwegian Data Protection Authority (12/00730-5/RCA).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

Acknowledgements

We acknowledge the Norwegian Prescription Registry and Statistics Norway for their helpful services.

Discuss this article

Contribute and read comments about this article: **bjgp.org/letters**

REFERENCES

1. Lader M. Benzodiazepines revisited — will we ever learn? *Addiction* 2011; **106(2):** 2086–2109.
2. Helsedirektoratet. *Nasjonal faglig veileder vanedannende legemidler — rekvirering og forsvarlighet. [Health Directorate. National academic tutor addictive drugs — requisitioning and soundness].* https://helsedirektoratet.no/retningslinjer/vanedannende-legemidler (accessed 1 Mar 2016).
3. Royal College of Psychiatrists. *Benzodiazepines.* http://www.rcpsych.ac.uk/healthadvice/treatmentswellbeing/benzodiazepines.aspx (accessed 1 Mar 2016).
4. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. *CNS Drugs* 2004; **18(1):** 37–48.
5. Lader M. Effectiveness of benzodiazepines: do they work or not? *Expert Rev Neurother* 2008; **8(8):** 1189–1191.
6. Ashton H. Adverse effects of prolonged benzodiazepine use. *Adverse Drug React Bull* 1986; **118:** 1–7.
7. Tvete I, Bjørner T, Aursnes IA, Skomedal T. 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 *BMJ Open* 2013; **3(10):** e003296.
8. Tvete I, Bjørner T, Skomedal T. Risk factors for excessive benzodiazepine use in a working age population: a nationwide 5 year survey. in Norway. *Scand J Primary Health Care* 2015; **33(4)**: 252–259.
9. The Norwegian Prescription Database. http://www.norpd.no (accessed 1 Mar 2016).
10. Statistics Norway. http://www.ssb.no/ (accessed 1 Mar 2016).
11. WHO Collaborating Centre for Drug Statistics Methodology. *DDD: Definition and general considerations.* 2009. http://www.whocc.no/ddd/definition_and_general_considera/ (accessed Mar 2016).
12. OECD iLibrary. *OECD economic surveys: Norway 2014.* http://www.oecd-ilibrary.org/economics/oecd-economic-surveys-norway-2014_eco_surveys-nor-2014-en (accessed 1 Mar 2016).
13. Griffiths RR, McLeod DR, Bigelow GE, *et al.* Relative abuse liability of diazepam and oxazepam: behavioral and subjective dose effects. *Psychopharmacology* 1984; **84(2):** 147–154.
14. Griffiths RR, McLeod DR, Bigelow GE, *et al.* Comparison of diazepam and oxazepam: preference, liking and extent of abuse. *J Pharmacol Exp Ther* 1984; **229(2):** 501–508.
15. WHO Collaborating Centre for Drug Statistics Methodology. *ATC/DDD index 2016.* http://www.whocc.no/atc_ddd_index/ (accessed 1 Mar 2016).
16. Resource Site for Involuntary Benzodiazepine Tranquilliser Addiction, Withdrawal & Recovery. *Benzodiazepine equivalence table.* 2007. http://www.benzo.org.uk/bzequiv.htm (accessed 1 Mar 2016).
17. Griffiths RR, Weerts EM. Benzodiazepine self-administration in humans and laboratory animals — implications for problems of long-term use and abuse. *Psychopharmacology (Berl)* 1997; **134(1):** 1–37.
18. Quigley P, Usher C, Bennett K, Feely J. Socioeconomic influences on benzodiazepine consumption in an Irish Region. *Eur Addict Res* 2006; **12(3):** 145–150.
19. Williams D, Teiljeur C, Bennet K, *et al.* Influence of material deprivation on prescribing patterns within a deprived population. *Eur J Clin Pharmacol* 2003; **59(7):** 559–563.