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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

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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 amount and change in frequency seemed warranted.

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

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Introduction

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

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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) 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 butyric acid (GABA) 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 receptors and thus inducing sleep. Hydroxyzine acts mainly by blocking histamine H1 and serotonin 5-HT1A receptors and buspirone acts as a partial agonist on serotonin 5-HT1A receptors.

Patient characteristics

We identified BZD-naive patients, defined as persons who had no prescription fulfilsments 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 and intoxication deaths caused by BZD alone are unusual we omitted patients who died during the study period. Figure 1 displays the data selection procedure, giving 81 945 patients. Patient characteristics were 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 specialties 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 R21 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 |
|---------|---------------------------------------|
| To level | Gender | Age | FBZDP | Effect of gender, age and physician prescribed high amount of BZD |
| 1       | –0.008 (ns) | 0.006 | 0.040 |
| 2       | –0.146 | 0.007 | 0.262 |
| 3       | –0.552 | –0.021 | 0.127 |
|          | Oxazepam | Alprazolam | Nitrazepam/ flunitrazepam | Zopiclon/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 first drug choice (compared to diazepam) |
| 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 other drugs |
| 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) |
| 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.

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

| Period | Level 0 | Level 1 | Level 2 | Level 3 |
|--------|---------|---------|---------|---------|
| Period |
| 0      | 78.57   | 78.84   | 77.91   | 76.69   |
|        | 78.05   | 76.63   | 77.32   | 76.34   |
| 1      | 19.66   | 19.16   | 19.82   | 20.58   |
|        | 20.05   | 19.06   | 18.36   | 19.36   |
| 2      | 1.60    | 1.78    | 1.95    | 2.33    |
|        | 2.43    | 2.52    | 2.79    | 3.03    |
| 3      | 0.16    | 0.22    | 0.32    | 0.40    |
|        | 0.45    | 0.48    | 0.53    | 0.63    |
| 4      |         |         |         | 0.81    |
|        |         |         |         | 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), antipsychotics 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, antipsychotics 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 (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 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...
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. Many patients had intermittent use, as also found by Nelson and Chouinard. The risk of dose escalation increased over time, but only 749 (0.9%) ended up as excessive users. Earlier studies have found no dose escalation among patients over short (1 year) or longer periods, the latter contradicting our findings. 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 antiasmatics/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. 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

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**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).
guidelines, 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 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 | 41.1 | 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 |
| Antiprosthetics 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.

| 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.

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 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/fluxitrazepam 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.

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Contributors

IAA conceived the underlying idea. IFT designed and did the statistical analysis. IAA, TB and TS contributed in interpreting the findings. All authors contributed to the writing of the paper with IFT having the main responsibility.

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Competing interests

None.

Ethics approval

The prescription data registered for our purpose were anonymous patient identifications and by its nature accepted from the Local Ethics Committee sanction. The study was approved by the Regional Committees for medical and health research ethics in Norway.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

The prescription data analysed is commercially available from the Norwegian Prescription Database.

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