

Call for action: Benzodiazepine prescription prevalence analysis shows off-label prescription in one in eleven citizens.

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Abstract

Objective: Benzodiazepines have a good safety profile. Nevertheless, off-label use of these drugs may increase the risk of falls, dependence, and memory loss. Off-label prescription use is not highly prevalent. Studies have not researched the factors that influence off-label prescription use. We aim to identify the prevalence of off-label use of benzodiazepines in Barcelona and explore socio-demographic factors that may be involved for professionals and patients.

Method: A cross-sectional study in Barcelona was carried out. Data from professionals were obtained from the Medical Official College of Barcelona. Patients' healthcare data were extracted from the electronic prescription system DataMart and from the Catalan Health System Observatory (catchment of 97% of the prescription system). Two multivariate analyses were performed to identify risk factors of off-label prescription use; one focused on the patients' characteristics and the other focused on professionals' characteristics.

Results: 9.7% of Barcelona's citizens used benzodiazepine prescriptions; 96.1% of them were off-label uses. The most common reason was long-term use (95.8%). Elderly patients were the most common demographic that was exposed to off-label use (OR =

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1.05, CI95% = 1.04–1.05). Family doctors (B= 38.87, CI95% =25.25-35.50) and psychiatrists (B = 16.93; CI95% = 11.50–22.35) were the largest groups of off-label prescribers.

Conclusions: The prevalence of benzodiazepine off-label prescriptions in our environment is very high, especially when the length of the treatment is considered. Implementation of evidenced-based strategies to facilitate more effective prescription practices is required.

Keywords: prescription drugs, anxiety, benzodiazepines, healthcare professionals, off-label.

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Introduction

Benzodiazepines are prescribed for several medical conditions, such as anxiety disorders, insomnia, alcohol withdrawal, anesthesia induction, or acute muscular pain[1–3]. Despite their usefulness and good tolerance in clinical practice, benzodiazepines produce relevant side effects (e.g. sedation, dry mouth, dependence, falls, memory loss)[4]. Long-term use is not recommended because of the severity of the side effects of these drugs and the unknown risk–benefit ratio [4]. Guidelines and regulatory institutions recommend the use of benzodiazepines for a short period, usually less than 12 weeks including withdrawal, avoiding dangerous drug combinations, and using the lowest effective dose available[5–8]. Off-label use of medication is allowed when it is clinically required and the risk–benefit ratio should be higher benefit, lower risk. In this case, the associated increase in risk[9] and the prescription require close follow-up. As the Psychopharmacology Special Interest Group of the Royal College of Psychiatrists and the British Association for Psychopharmacology states “the risks of dependence associated with long-term use should be balanced against the benefits that in many cases follow from the short or intermittent use of benzodiazepines and the risk of the underlying conditions for which treatment is being provided[10]”. For example, it is known that the risk of benzodiazepine dependence increases with length of use; a previous study reported a risk of 20% after 3 months and 50% after 12 months[11]. In addition, benzodiazepines and other psychiatric drugs are among the most frequent off-label

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prescriptions[12,13]. The estimated off-label use ranges from 6% to 76% when the criterion of prescription length > 6 months is applied[14]. This information is especially relevant in Spain because benzodiazepine consumption is 37% greater than the European mean[15]. According to the Spanish Survey of Drug Use (EDADES) 2017, the 11.1% of the Spanish population uses benzodiazepines with or without a prescription; 1.3% of these individuals use benzodiazepines without a prescription[16]. With these data, we can assume that the ratio of unprescribed-prescribed users is 1:10. In addition, a recent study in the USA showed that 17% of benzodiazepine users were misusers[17]. Sensitive populations such as elderly people and psychiatric patients are among those who frequently receive benzodiazepines[18,19]. However, studies of off-label benzodiazepine prescriptions and factors associated with them are lacking. Cross-sectional studies can be used to describe the situation and identify potential risk factors that can then be confirmed in longitudinal studies. In Catalonia, electronic prescriptions (e-prescriptions) are widely implemented and account for 97% of all prescriptions, and the data from these prescriptions are readily available. The e-prescription system allows access to dose, prescription time, and socio-demographic data from users—e.g. gender, age, and neighborhood—but patients' diagnoses are not a mandatory field. Consequently, we had to restrict our off-label criteria to the following: length of use, combination with other benzodiazepines, and prescribed doses. A total of 177,964 benzodiazepine prescriptions were retrieved (November 8th 2016) for the analyses (see methods).

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Our aim is to identify the prevalence of off-label benzodiazepine use in Barcelona and to identify socio-demographic factors involved in off-label prescriptions as a first step toward designing and implementing specific strategies to prevent inappropriate off-label benzodiazepine use.

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Method

Design

We designed a cross-sectional study using data from November 8, 2016 based on the DataMart e-prescription system from the Catalan Health Service (CatSalut) for the city of Barcelona (97% of e-prescription implementation in 2017). In Spain, the public healthcare system is universal and free of charge with variable levels of medication copayment.

Sample

All active benzodiazepine and z-drug prescriptions (zolpidem, zopiclone) in the city of Barcelona on November 8, 2016 were identified. We were able to track how long each prescription had been active during the last 12 months. The compounds that we assessed were lorazepam, diazepam and combinations that included diazepam, alprazolam, lormetazepam, clonazepam, zolpidem, clorazepate, bromazepam, clometiazol, ketazolam, clobazam, flurazepam, loprazolam, midazolam, zopiclone, clotiazepam, brotizolam, triazolam, bentazepam, pinazepam, quazepam and chlordiazepoxide. Current indications according to the Spanish Drugs Agency (*Agencia Española del Medicamento y Productos Sanitarios*, AEMPS) for the four most prescribed benzodiazepines in our study are described in Table 5.

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The population of Barcelona in 2016 was 1,610,427[20], and it accounted for 21.4% of the Catalan population (7,522,596)[21] and 3.5% of the Spanish population (46,468,102)[21].

Variables and Data Extraction

Data from the professionals were extracted confidentially and anonymously from the Official Medical College of Barcelona (COMB) and from the electronic prescription database and comprised: age, gender, specialty, and benzodiazepine prescriptions. The research team identified anonymous IDs via a code number and assigned new anonymous code numbers that were independent of prescription behavior. This second number allowed us to track the information and restructure the database later. Both codes were sent without other information to those responsible for informatics support at the COMB, and they sent us socio-demographic characteristics of each doctor, which consisted of only 2 codes without any identifiable data.

The patients' data were extracted anonymously by a public insurance number from the electronic prescription system of the Catalan Health Service and from the Catalan Health Observatory and were: age; gender; neighborhood; socio-demographic index with reference to his/her healthcare provider; and characteristics of the benzodiazepine prescriptions, number and identification of prescriptions, total daily dose, duration, and association of 2 or more benzodiazepines.

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The socio-demographic index (SDI) was created by the Catalan Health Quality and Assessment Agency (“Agència de Qualitat i Avaluació Sanitàries de Catalunya”—AQUAS). SDI refers to the population that visits a specific primary health center. SDI is based on: 1) number of patients who are exempted from paying for their medications; 2) population with income < €18,000; 3) population with income > €100,000; 4) population with low education level; 5) rate of premature death; 6) rate of preventable hospital admissions; 7) rates of manual workers. Higher levels in the SDI index imply a lower socio-economic level, which ranged from -3.7 to 3.0 [22]. We used recent data from 2015[23].

Our criteria for identifying off-label prescriptions were for any prescription that did not fit the recommendations of the official information leaflet (edited by the Agencia Española del Medicamentos y Productos Sanitarios, AEMPS) according to the identifiable data in the electronic system. Three off-label prescription criteria were identified according to this definition: 1) a prescription with doses above the maximum recommendation; 2) a duration of treatment > 3 months; and 3) a prescription of ≥ 2 benzodiazepines simultaneously during > 3 weeks.

Our database did not allow us to track the following situations: 1) prescriptions for non-approved medical conditions; 2) combinations of prescriptions with contraindicated medications; and 3) prescriptions in contraindicated medical conditions.

Statistical Analyses

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Continuous variables were described as mean (standard deviation). Categorical variables were described by counts and percentages. To analyze the impact of patients' socio-demographic characteristics on off-label prescription use, we ran a logistic regression considering our off-label criteria (see above for definition) as the dependent variable and age, gender, and socio-economic index as the independent variables. To analyze the impact of the professionals' demographic characteristics on the off-label prescription use, we ran a linear regression with the dependent variable as the percentage of off-label benzodiazepine prescriptions out of all benzodiazepine prescriptions (off-label/total benzodiazepine prescriptions*100), and the independent variables were age, gender, and specialty. The results of the multivariate logistic regression analysis were expressed as odds ratios (ORs), and linear regression analyses (unstandardized coefficient B) were considered to be the main outcomes; these determined which variables were independently associated with the outcome. The SPSS statistical package (SPSS Inc., version 20.0, Chicago, IL) was used.

Ethics

This study was approved by the ethical committee of the Hospital Clínic de Barcelona (2013/8446) according to the Helsinki declaration and Spanish national laws. The anonymity of participants was guaranteed.

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Results

Sample description: patients and professionals

In November 2016, there were 157,019 citizens with at least one active prescription for benzodiazepines, and a total of 177,964 benzodiazepine prescriptions were active in the electronic prescription system at that date.

This indicates that 9.8% of Barcelona's population had a benzodiazepine prescription.

69.6% of the patients were women, the mean age was 67.2 years (SD 16.3), and the mean socio-economic index was 0.85 (SD 1.4). Regarding the ages of the patients, 60.1% (n=71,326) of the patients were older than 64 years, and 14.6% were older than 85 years; 0.3% (n=466) were younger than 18 years (0–5 years old: n=38, 8.1%; 6–10 years old: n=70, 15%; 11–15 years old: n=142, 30.5%; 16–18 years old: n=216, 46.4%).

According to the official report from the COMB, there were 32,714 doctors (December 12, 2016) in Barcelona [24]. A total of 3,714 medical doctors (11.4%) had prescribed at least 1 benzodiazepine during the last 12 months that was still active on November 8, 2016. The average number of prescriptions in the last 12 months was 37.9 per practitioner among those who had at least prescribed once (SD 61.2). They were mainly women (n=2,268; 63.9%), and the mean age was 45.4 years (SD 11.6). Of these practitioners, 57.8% were general practitioners (n=1,509), 12.2% were psychiatrists (n=319), 4.7% internists (n=124), 3.9% pediatricians (n=103), and 2.5% neurologists (n=65). The mean number of off-label benzodiazepine prescriptions by practitioner

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was 36.2 (SD 59.9). The average ratio of off-label prescriptions/total prescriptions (Σ % ratio of off-label prescription/number of practitioners) was 0.75 (SD 0.41).

Prescriptions and Off-label Prescriptions

Benzodiazepine prescriptions were mainly delivered in primary health practices (n=158,585; 89.1%) and mental health practices (n=16,261; 9.1%). Lorazepam was the most prescribed benzodiazepine (n = 66,134; 38%), then diazepam (n=24,753; 14%), alprazolam (n=23,159; 12%), and clonazepam (n = 12,176; 7%). The majority (84%) of prescriptions was lorazepam, diazepam, alprazolam, or clonazepam; no other benzodiazepines exceeded 5% of the total amount of prescribed benzodiazepine.

Considering our selected criteria of dose, combination, and length, 96.1% of the benzodiazepine prescriptions were off-label ((number of off-label benzodiazepine prescription/total of benzodiazepine prescription) x 100).

Regarding the duration of prescriptions, 95.8% of patients received long-term prescriptions for benzodiazepines (> 3 months; n=150,454), 7.4% receive ≥ 2 benzodiazepines at the same time (n=14,806), and 1.2% of patients received a high dose of benzodiazepine (n=1,823). For benzodiazepines, 7.7% (n=13,720) were prescribed for more than 3 months but less than 6 months, and 87.7% (n=156,356) were prescribed for at least 6 months. Of those who received a prescription for 2 or more benzodiazepines, the vast majority received 2 (n=14,042; 94.8%), a minority received 3 (n=728; 4.9%), and only 36 patients (0.2%) received more than 3 prescriptions. More details are available in Figure 1.

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Socio-demographic variables and Off-label Prescriptions

Table 1 shows the univariate analysis of socio-demographic characteristics of patients with off-label prescriptions versus those without off-label prescriptions. Multivariate analyses (see Table 3) showed that older patients had a greater risk of receiving an off-label benzodiazepine prescription (OR = 1.05, 95% CI = 1.04–1.05, $p < 0.001$).

Table 2 shows the univariate analysis of socio-demographic characteristics of professionals regarding off-label prescriptions. The following demographic characteristics of the professionals, including female gender, specialist in family medicine or in psychiatry, and older professionals, tended to have higher rates of off-label prescriptions. The results suggest that female practitioners had higher rates of off-label prescription between 7% and 13%. Each added year to the age of a practitioner increased the off-label ratio between 0.3% and 0.5%. Regarding the effect of the type of specialty, a prescriber who was a family doctor had an increased ratio of 38.9%, and a prescriber who was a psychiatrist had an increased ratio of 16.9%. For more details, see Table 4. All these data should be observed with caution because of potential cofounders that were not studied in our sample.

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Discussion

Nearly 10% of the analyzed population had a benzodiazepine prescription and 96.1% of these were off-label; the only criteria considered to determine whether a prescription was off-label were length, dose, and combination of 2 or more benzodiazepines. Most of the off-label prescriptions were because of long-term use (96%). Older people were the most exposed to the risks of off-label use. Since family doctors and psychiatrists were the largest groups of off-label prescribers, efforts for improving benzodiazepine prescribing practices must be addressed to them.

Off-label use in the general population

1 out of 11 citizens in Barcelona received a benzodiazepine prescription. Our results confirmed the following data previously provided by surveys in our country: the prevalence of prescription benzodiazepine use in the Spanish population was 9.8% in 2017[16]. However, we had objective data available from prescriptions, which was in contrast to surveys that are always affected by desirability bias or concerns from responders about privacy. Thus, the reliability of our measures is more accurate than that of previous studies. A recent cross-sectional study in the US based on surveys (National Surveys on Drug Use and Health) and drug distributions of pharmacies (IMS Health Total Patient Tracker) showed that 12.5% of the United States population used benzodiazepines in the last year, which was a slightly higher value than in our study. From this population, 17.1% of users misused benzodiazepines and 1.5% of users had a benzodiazepine-use disorders[17]. As in our sample, the elderly population and

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women were the most exposed groups to benzodiazepines. We did not have available data for misuse or use disorders that allow us to compare with other population. Further studies with appropriate methods, such as longitudinal studies and including prevalence and incidence of the different patterns of use, are required. In Europe, data are scarce concerning the prevalence of benzodiazepine use, misuse, and use disorders, but one study in German found that 1.4% of hospitalized patients had sedative use disorder[25]. Magrini et al (1996) found a prevalence of 8.6% for past-week use for elderly patients and women, both of which were commonly exposed to both chronic and short-term use[26]. Lagnaoui et al (n=4007; year 2004) based on telephone interviews found a prevalence of current use of 7.5%; age and female gender were the primary risk factors for these prescriptions [27]. Pradel et al (2003) based on pharmacy registers found a prevalence of benzodiazepine use of about 12%[28]. In the UK (2016), only 2.6% of primary care patients received a benzodiazepine prescription (without considering z-drugs)[29]. Although there were different methods (face-to-face interviews, telephone interviews or registers), different time-frames (past year, past week, current use), different countries (US, Spain, Italy, Germany, or France), or different years of publication (1996, 2004, 2012, 2017), we can affirm that prevalence of use ranges from 2.6% to 12.5%. Our sample is in this window. However, an isolated study in southern Spain showed an increase in benzodiazepine prescriptions (26%) between 2006 and 2015, but this study had high variability between areas[30]. A different study in Asturias (northern Spain) found an increasing rate of use between the period from point A (2003-2008) to point B (2009-

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2013) of 32% for anxiolytic drugs and 74% for hypnotic drugs for all of Spain, 7.9% and 5.9%, respectively[31]. These data suggest that any conclusions drawn from these studies should be made cautiously because of the regional differences between the studies. Although clonazepam has been linked to an increased use in the black market during the last years (e.g. Norway)[32], it is the fourth most prescribed benzodiazepine in Barcelona probably due to the perception that it is a safe benzodiazepine.

The prevalence of use is itself alarming but the high rate of off-label prescriptions based on long-term use is even more concerning. Long-term use (> 3 months) was globally estimated to apply to 3% of the population and 65–67% of adult benzodiazepine users in Japan and Switzerland[14]. Our result was 96%, which was higher than that of previous studies. In Barcelona, 150,454 citizens—68,000 of these were >64 years old—were at-risk of consequences of long-term benzodiazepine use (e.g., 2.5 times more risk of falls in elderly patients)[33]. These consequences affected older patients, which are those who received off-label prescriptions most frequently in our study. Probably, this is a shared problem with other countries like Italy, where a study conducted in pharmacies showed that 80% of those who took benzodiazepines did so during more than one year [34], and elderly patients were the citizens that were most exposed to this risk[35]. In the United States, prescription and long-term (> 12 months) prescription use were more frequent in women and the elderly (14–32%) [36].

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Less than 8% of users took >1 benzodiazepine at the same time, and 1.2% of users had a prescription that was higher than the recommended dose by the drug agency.

Unfortunately, there is not much data to compare. A US study from 1998 found a rate of 4.5% for combined benzodiazepine use[37], which was slightly lower than in our sample. From a clinical point of view, using >1 benzodiazepine does not make sense and ideal prevalence should approach 0, but we have to highlight that the data from our study might include those patients who were shifting from one benzodiazepine to another (i.e., from a short half-life to long half-life). Another American study from 2003 found that there were 1.6% of high dose users (defined by expert consensus) among long-term users (at least two years treatment)[38]; the results in our study were even better.

Primary care context and barriers to the prevention of off-label use

Understanding the opinion and risk perception of general practitioners (GPs) and psychiatrists—those who use off-label benzodiazepines more intensively—is relevant in order to design and implement strategies to reduce off-label prescription. A previous study in Barcelona showed that psychiatrists and GPs were aware of the risk of benzodiazepine prescriptions. They thought that there was compelling scientific evidence that this was a relevant and well-known problem, and that was easily controllable by the doctor. On the other hand, they thought that it was not a well-known problem by patients and, consequently, the patients' informed consent was not always sufficient[39] because the informed consent requires to know and understand

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the ratio risk-benefit of intervention. Another study reported that GPs perceived that knowledge about risks has improved during recent years [40]. If they know the problem, what prevents them from addressing it? Some doctors believe that benzodiazepine is a *lesser evil* for psychosocial problems and they do not have non-drugs alternative for managing them or, despite the evidence of their effectiveness, they do not trust psychotherapeutic approaches. Also, they think that it is a quick option compared to other treatments [40]. External limitations also play a relevant role. Doctors think that referring services are lacking or difficult to access; high workload and lack of financial incentives for referrals are also viewed as barriers[41].

Evidence-based interventions for reducing benzodiazepine use

Fortunately, there are promising strategies to diminish the risk and the effects of off-label benzodiazepine use. According to a Cochrane review on reducing benzodiazepine use (2015), cognitive-behavioral therapy is effective in short-term but is not effective at six months; a tailored letter from the General Practitioner to the patient, standardized interviews, and relaxation techniques could be effective[42]. Alerts to pharmacist in order to discuss benzodiazepine prescriptions with patients who are using long-term prescriptions have shown effectiveness in reducing these prescription rates[43]. The evidence of minimal interventions in primary care is consistent. A meta-analysis showed that letters or single consultations in this setting decreased doses or stopped the use of benzodiazepines[44].

Methodological issues

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This study has several limitations (see below) linked to the cross-sectional design and electronic prescription software. However, other limitations are intrinsic to the study of benzodiazepines in the field of epidemiology. First, there are different definitions of benzodiazepine use that might affect the range of the prevalence of use from 0.2% to 8.9%, but the ratio of male-female use is constant independent of which definition is used [45]. The definition of misuse is also problematic[46] because there are many terms with slight differences in meaning, e.g. abuse, misuse, or non-medical use. A common definition is necessary to compare data from different regions and understand the impact of preventive interventions. Another intrinsic limitation is the timeframe for both use and off-label use, as we have seen in the first section of the discussion. What is considered a sedative drug is also inconsistent between studies; several studies do not include z-drugs in their definition, and other studies draw a distinction between anxiolytic and hypnotic drugs[31]. The heterogeneity of methods (e.g. surveys, registers) and samples (e.g. primary care, general population) are barriers to comparison.

Limitations and Strengths

This study has several limitations. First, we retrieved data from prescriptions, but we do not know how the medications were used. Second, we had no data to differentiate between justified and unjustified off-label prescriptions. This limitation originated in the electronic prescription system, which did not include “diagnosis” as a mandatory field, so >80% of patients lacked information in this field. In addition, the electronic

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prescription system did not query the professional about the reasons for off-label prescriptions. At this point, we would recommend that the prescription system make the “diagnosis” field mandatory and include an alert when off-label prescription is made in order to assess the reasons for it and increase the awareness of the associated professionals. Third, our data are geographically limited, so external validity for other cities or regions is not well-established. Fourth, we could not assess all off-label use (e.g. other indications and association with other medications with potential high-risk interactions). Fifth, we did not have access to private practice data. However, the Catalan health system is universal, free, and is the most-used care. For instance, CatSalut - the Catalan public insurance- provides service to 99.5% of Catalan population and 74.6% of population use the public insurance exclusively (24.9% use both public and private insurances)[47,48]. Almost 60% of expenditure in drugs and other perishable medical products (e.g. saline solutions, gauzes, etc.) in Spain belong to public health insurance[49]. There is no data without “other perishable products”. Indeed, if we could take into account only medications, the relative expenditure of public insurance would be higher because most of the “other perishable medical products” are not covered by public health insurance. In addition, Catalonia spent (2016) 5.3% of gross domestic product in health and more than 66% was destined to the public health system[50]. Sixth, we could not ensure that short-term prescriptions (< 3 months) were not repeated short-term prescriptions that were false negatives for off-label prescriptions. Seventh, patient behavior has not been evaluated in this study because of the study’s cross-sectional design, and behavior might affect the

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prescription behavior of healthcare providers (e.g., patients increase their own daily dose, and later the healthcare provider prescribes the new dose). Future longitudinal studies should focus on the effect of patient behavior on healthcare provider prescription practices.

However, our work also has strengths. First, sample size is large enough (177,964 prescriptions). Second, despite the fact that it was a cross-sectional study, we covered a sufficient time-frame of prescriptions (1-year). Both strengths ensure that the sample is representative of Barcelona population. Third, the electronic prescription system is reliable and well-implemented, which allows reliable data extraction. For instance, the implementation reaches the 97% of public health system that provides service to the 99.5% of population (3/4 of citizens use it exclusively). Fourth, 2 sides of a coin—professionals and patients—were studied and allowed wider analyses. Drug prescription is a professional relationship with at least two actors: the demand (patients' perspective) and the supply (professionals' perspective). The prescriber might have risk factors for inappropriate prescription and the patient might be vulnerable to off-label prescription. To our knowledge there were no previous studies that included both actors.

Conclusion

A high proportion of benzodiazepine prescriptions were off-label (96.1%) being those patients at risk for benzodiazepine misuse and dependence. Because elderly patients are the most prevalent group receiving off-label prescriptions of benzodiazepines, and

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GPs and psychiatrists form the largest group of prescribers, they must be central to efforts to prevent problems with benzodiazepine use. Different strategies—such as minimal interventions, healthcare workload reduction, facilitation of specialist treatment, activities to prevent benzodiazepine use, and withdrawal interventions in primary care facilities and pharmacies—have been effective in reducing benzodiazepine use and must be considered in Barcelona.

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Figure 1. Flowchart sample

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