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Sjöstedt, Cecilia; Ohlsson, Henrik; Li, Xinjun; Sundquist, Kristina

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Authors:

Cecilia Sjöstedt, Henrik Ohlsson, Xinjun Li, Kristina Sundquist

Affiliations:

Center for Primary Health Care Research, Lund University, Malmö, Sweden

Cecilia Sjöstedt: cecilia.sjostedt@med.lu.se

Henrik Ohlsson: henrik.ohlsson@med.lu.se

Xinjun Li: xinjun.li@med.lu.se

Kristina Sundquist: kristina.sundquist@med.lu.se

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Address for correspondence:

* Xinjun Li

Center for Primary Health Care Research, CRC, Building 28, Floor 11, Jan Waldenströms gata 35, Skåne University Hospital, 205 02 Malmö, Sweden

Phone: +4640391381

Fax: +46-40-391370

E-mail: xinjun.li@med.lu.se

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Abstract

Former studies that have attempted to characterize individual socio-demographic factors associated with long-term benzodiazepine use were based on relatively small sample sizes and/or self-reported data. Our aim was to clarify this using large-scale primary health care data from Sweden. The present study covered 71 primary health care centres containing individual-level data from a total of 919 941 individuals who visited a primary health care centre (PHCC) during the period 2001-2007. From this database we selected individuals 25 years or older with depression, anxiety and/or insomnia and who were prescribed a benzodiazepine within 0-90 as well as 91-270 days after their first clinical diagnosis of depression, anxiety and/or insomnia. Older age (OR, 2.92, 95% CI, 2.28-3.84), middle SES (OR, 1.22, 95% CI, 1.08-1.38), being on social welfare (OR, 1.40, 95% CI, 1.23-1.62) and not being married were associated with higher long-term benzodiazepine use. The PHCCs only explained a small part of the individual variation in long-term benzodiazepine use. Awareness of the impact on long-term benzodiazepine use of certain individual-level socio-demographic factors is important for health care workers and decision-makers who should aim at targeting general interventions at all primary health care centres.

Key words: anxiety; benzodiazepines; depression; primary care

Highlights

*Older age, middle SES, being on social welfare, and not being married were associated with higher long-term benzodiazepine use.

*The PHCCs only explained a small part of the individual variation in long-term benzodiazepine use.

* Awareness of the impact on long-term benzodiazepine use of certain individual-level socio-demographic factors is important.

Introduction

Benzodiazepines represent some of the most frequently prescribed tranquilizers in the world (Fang et al., 2009; Fassaert et al., 2007; Moerman and Haafkens, 1993; Quigley et al., 2006; Zandstra et al., 2002). If properly used, benzodiazepines possess sedative, hypnotic, and anti-anxiety properties and have therefore an obvious role in the therapeutic arsenal (Fang et al., 2009; Fassaert et al., 2007; Rogers et al., 2007) when initiating medical and/or psychotherapeutic treatment of depression, anxiety and insomnia disorders. Long-term use of benzodiazepines, however, is associated with complications such as withdrawal symptoms, therapeutic dose dependence, relapse anxiety, falls and fractures and impairment in long-term cognitive functioning (which can remain for several months after benzodiazepines have been withdrawn) (Anthierens et al., 2007; Cunningham et al., 2010; Fang et al., 2009; Fassaert et al., 2007; Rogers et al., 2007; Zandstra et al., 2002).

Former studies have been able to establish that individual socio-demographic factors are associated with psychiatric disorders, such as depression, anxiety and insomnia (Andersen and Frydenberg, 2011; Bayard-Burfield et al., 2001; Demyttenaere et al., 2008; Fang et al., 2009; Hjern, 2001; Quigley et al., 2006; Sonnenberg et al., 2012). Former studies have also attempted to characterize individual socio-demographic factors associated with the occurrence of long-term use of benzodiazepines. Some of the most consistent predictors of long-term use of benzodiazepines are older age (Andersen and Frydenberg, 2011; Cunningham et al., 2010; Demyttenaere et al., 2008; Fang et al., 2009) and low socio-economic status (Andersen and Frydenberg, 2011; Demyttenaere et al., 2008; Sonnenberg et al., 2012; Zandstra et al., 2004). A slight female-associated long-term use has also been observed (Andersen and Frydenberg, 2011; Fang et al., 2009). Being married and having social support have been shown to be associated with decreased benzodiazepine use in general (Andersen and Frydenberg, 2011)

but the association between these factors and long-term use of benzodiazepines is unknown. Contextual factors may also have an impact on prescription patterns. Former studies have shown that there is a considerable variation in prescription patterns between health care centres (Fang et al., 2009; Mercuri and Gafni, 2011; Mousques et al., 2010; Rogers et al., 2007). Such contextual factors may include the location of the health care centre (urban/rural), neighbourhood socioeconomic factors, the prescribing culture of physicians, and resources available in the health care centre. Despite such potential differences between health care centres, treatment with benzodiazepines should be based on evidence and principles of equity rather than on social constructs and variation in medical practice between health care centres. An appropriate use of benzodiazepines will also prevent medical complications as well as save limited economic resources in the health care budget.

A majority of previous studies investigating long-term use of benzodiazepines have been based on relatively small sample sizes and/or self-reported data (Anthierens et al., 2007; Demyttenaere et al., 2008; Fassaert et al., 2007; Manthey et al., 2012; Manthey et al., 2011; Quigley et al., 2006; Zandstra et al., 2002). The present study contributes to the body of knowledge as it is based on data from a large primary health care population of 919 941 individuals. In addition, the sociodemographic variables (i.e., the predictor variables) and the long-term use of benzodiazepines (i.e., the outcome variable) are objective rather than being based on self-report. The data sources include highly complete prescription data and individual-level population register data as well as clinical diagnoses from primary health care doctors' examinations. The combined strengths of these large-scale, highly complete data sources that were unbiased by self-report represents a novel contribution to previous literature.

The aim of this study was to investigate the potential impact of several individual-level socio-demographic variables on long-term use of benzodiazepines in primary health care patients with depression, anxiety and/or insomnia. In addition, we also examined how much of the total variation in long-term use of benzodiazepines could be attributed to the primary health care centres.

Material and Methods

The study population was obtained from a primary health care database covering 71 primary health care centres in the Swedish counties of Stockholm (n=687 310), Värmland (n=145 943), Gotland (n=84 898), and Uppsala (n=12 790). The participation rate for the primary heath care centres included in the database was generally high and reached almost 100% in the smallest counties (e.g. Gotland). In addition, the primary health care centres were located in urban and rural areas as well as in both the Southern and Northern parts of Stockholm County. The primary health care database contains individual-level clinical data from a total of 919 941 individuals who visited a primary health care centre during the period 2001-2007. The clinical data have been linked to the sociodemographic variables (i.e., age, gender, country of origin, income, education, social welfare and marital status, listed below) from the Total Population Register in Sweden, provided to us by Statistics Sweden, the Swedish Government-owned statistics bureau. The individual-level data linkages were possible to perform because Swedish residents have a unique personal identification number, which is used by the authorities and at utilization of health care. The personal identification number was replaced by a serial number in order to protect people's integrity.

Sample

We selected individuals from the primary health care database using the following criteria: 1) a clinical diagnosis of depression, anxiety and/or insomnia (ICD10 codes: F32, F33, F38, F39, F40, F41, F43, F511, F519) between Jan 1st, 2002 and April 1st, 2007; 2) a prescription of a benzodiazepine (ATC code: N05BA, N05CD, N05CF) between 0 and 270 days after the first diagnosis of depression, anxiety and/or insomnia; and 3) age 25 years or older at diagnosis. We excluded individuals with depression, anxiety and/or insomnia during 2001. No exclusions due to previous prescriptions with benzodiazepines were made. These inclusion criteria yielded 12,536 individuals. The outcome variable long-term use of benzodiazepines was defined as a prescription of a benzodiazepine between 1-90 (short-term use) *as well as* between 91- and 270 days after the first diagnosis of depression, anxiety and/or insomnia. Short-term use was defined as a benzodiazepine prescription within 90 days from diagnosis, which is in accordance with the WHO (WHO Collaboratioin Centre for Drug Statistics Methology, 2010). Those with a prescription between 91- and 270 days after the first diagnosis of depression, anxiety and/or insomnia only were not considered in the analyses. The following covariates were included in the model: age, gender, country of origin, income, education, social welfare and marital status. These covariates were included because previous research has shown that sociodemographic factors are related to psychiatric disorders (Andersen and Frydenberg, 2011; Bayard-Burfield et al., 2001; Demyttenaere et al., 2008; Fang et al., 2009; Hjern, 2001; Quigley et al., 2006; Sonnenberg et al., 2012). Age was divided into five categories: 25-44, 45-64, 65-74, and 85+ years. The group 25-44 years was used as reference. For the variable gender, women were used as reference. Country of origin was divided into six categories: Sweden (reference), Finland (the largest immigrant group in Sweden), Western Countries (including Western Europe, the United States of America and Australia), Eastern Europe, the Middle East, and Other countries. Income, education, social welfare and marital status were measured the year prior to the diagnosis of depression,

anxiety and/or insomnia. Income by quartile comprised information on personalized family income for each year of interest, derived from the total population register. We used this information to determine the distribution of personalized family income and then used this distribution to calculate empirical quartiles. The highest income quartile was used as reference. Educational level was classified into three categories: completion of compulsory schooling or less (≤ 9 years), completion of high school or some high school (10–12 years), and college or university studies (>12 years). The highest education was used as reference. Social welfare was categorized into two groups: yes or no (reference). Marital status was categorized into two groups: married or unmarried/widowed/divorced (reference).

Statistical analysis

As individuals were nested within Primary Health Care Centres (PHCC), we used multilevel logistic regression to investigate the association between age, gender, country of origin, income, education, social welfare and marital status and the outcome long-term use of benzodiazepines. Several models were used with long-term use of benzodiazepines as the outcome. Model A was an empty model that was used in order to disentangle the variance into the first and second levels of analysis, i.e., the individual level and PHCC level. Model B1 also included age and gender while model B2-B6 included age and gender as well as the other covariates in combination with age and gender. Model B2 included age, gender and country of origin; model B3 included age, gender and income; model B4 included age, gender and education; model B5 included age, gender and social welfare; and model B6 included age, gender and marital status. Model C included all covariates added simultaneously in the same model. Fixed effects are reported as Odds ratios (ORs) with corresponding 95% confidence intervals. In the multilevel logistic regression the evaluation of the variance is of substantive interest. The intra class correlation (ICC) indicates how much of the total variance belongs to

the second level, i.e., the PHCC level. A high ICC indicates that individuals from the same PHCC are more similar to each other (with regard to long-term use of benzodiazepines) than to individuals from other PHCCs. We used the latent variable method to calculate the ICC. It assumes that the propensity for long-term benzodiazepine use is a continuous latent variable underlying our binary response. Each individual has a propensity to long-term benzodiazepine use, but only individuals whose propensity exceeds a certain cutpoint will have it. The unobserved individual variable follows a logistic distribution with individual variance equal to 3.29 (Π 2/3). The ICC can then be calculated according to the following formula: variance*PHCC* /(variance*PHCC* + Π 2/3). All calculations were performed using SAS version 9.3 and MLwiN version 2.27.

Ethical considerations

This study was approved by the Ethics Committee of Lund University, Sweden. Registers used in this study were retrieved from Statistics Sweden and the Swedish National Board of Health and Welfare.

Results

Table 1 shows descriptive statistics for the 12,536 individuals included in the study. Of these, 3,395 individuals (27.3%), met our criteria for long-term use of benzodiazepines, i.e., they had a prescription of benzodiazepine within 1-90 as well as 91-270 days from diagnosis. Long-term benzodiazepine users seemed to be older than short-term users; 25 % of long-term users were older than 65 years while the corresponding figure for short-term users only was 16 %. Women were in majority both among short-term and long-term users. Approximately 75% of the study population was Swedish-born. Individuals with long-term use of benzodiazepines seemed to be less educated and have lower income.

Table 1 here

Table 2 shows the results from the multilevel logistic regression analysis on the 12,536 individuals. Age was significantly associated with long-term use; compared to the youngest age group (25-44 years) the odds increased with higher age. For example, the oldest age group (85+ years) had an OR of 3.04 (95% CI = 2.46-3.77). Gender was not associated with long-term use. Compared to individuals born in Sweden, individuals born in Finland had higher odds for long-term use (OR of 1.16) but the results were non-significant. Those originating from the Middle East had lower odds of long-term use: the OR was 0.86 (borderline significant, 95% CI = 0.72-1.00). Compared to individuals with high income, individuals with mid-low income had 30% higher odds for long-term use (OR = 1.30, 95% CI 1.15-1.46). The same pattern was seen for education; those with middle educational status had higher odds of long-term use compared to those with the highest education (OR = 1.25, 95% CI 1.15-1.38). Those with social welfare had the highest odds (OR = 1.41, 95% CI = 1.24 - 1.61) while being married decreased the odds for long-term use (OR = 0.80, 95% CI = 0.73-0.86). Including all variables in the same model (i.e., model C) attenuated the results only to a small degree. The random part of the multilevel model shows that the ICC is low; in both model A and model C, the ICC was 0.2%, i.e., the Primary Health Care Centres only explained a small part of the individual variation in long-term use of benzodiazepines.

Table 2 here

Discussion

The main finding of the present study is that several individual-level sociodemographic factors are associated with long-term use of benzodiazepines in primary health care patients with depression, anxiety and/or insomnia. Older age, middle SES (defined as income and education), being on social welfare and not being married were associated with higher long-

term use of benzodiazepines. Gender was not associated with long-term use and country of birth only seemed to have a minor influence on long-term use of benzodiazepines. The primary health care centres only explained a small part of the individual variation in long-term use of benzodiazepines.

Older age was a strong predictor for long-term use of benzodiazepines, which is consistent with previous studies (Andersen and Frydenberg, 2011; Cunningham et al., 2010; Demyttenaere et al., 2008; Fang et al., 2009). It is possible that these findings are partly explained by other health problems or co-morbidities in older age. Former studies show that long-term use of benzodiazepines is more common among persons with somatic illnesses and chronic pain (Manthey et al., 2011). In addition, individuals with somatic illnesses and/or chronic pain may have sleeping difficulties to a higher extent than healthy individuals, which may explain the higher odds of long-term use of benzodiazepines in older age.

Our findings of a higher long-term use of benzodiazepines among individuals with middle SES (vs. individuals with high SES) or social welfare recipients are consistent with previous research (Fang et al., 2009; Moerman and Haafkens, 1993). Somatic illnesses are more common among individuals wth low SES and comorbidity is a factor shown to increase long-term use of benzodiazepines (Manthey et al., 2011). The poorer health among individuals with low SES might partly be explained by difficulties in leading a healthy lifestyle including being physically active and having a moderate intake of alcohol. In contrast, individuals with high SES, such as those with high incomes and higher educational levels, often have better opportunities to lead a healthy life due to better financial possibilities and more knowledge. Although socio-demographic factors are associated with depression, anxiety and insomnia, it is important not to expose these vulnerable patients to a long-term use of benzodiazepines,

which may lead to several somatic and psychiatric complications. The results of the present study are important to keep in mind when striving to achieve social equity in the medical treatment of psychiatric disorders, which may include additional treatment approaches such as different types of therapies.

Being married was associated with decreased odds of long-term use of benzodiazepines in our study, which is consistent with previous knowledge. Individual variables as marital status and social support have been shown to be associated with a decreased benzodiazepine use in previous studies (Andersen and Frydenberg, 2011). However, gender was not associated with long-term use of benzodiazepines, which is in contrast to our expectations; this is because women have higher rates of depression, anxiety and insomnia than men.

Finnish-born residents had slightly increased odds of long-term use of benzodiazepines albeit not to a significant extent. Previous studies performed in Sweden have shown a more frequent use of benzodiazepines and increased rates of psychiatric illnesses in certain foreign-born residents (Bayard-Burfield et al., 2001; Hjern, 2001); for example, people originating from Finland are to a greater extent exposed to psychiatric illness and drug abuse (Leao et al., 2006a; Leao et al., 2006b). In contrast, slightly decreased odds were observed in our study in people born in the Middle East. The mechanisms behind our findings in people born in the Middle East may be due to differences in attitudes towards use of tranquilizers and/or poorer access to primary health care.

The main reason for using a multilevel regression model was to assess the clustering of cases of long-term users at the PHCC level. However, the ICC was low, suggesting that long-term users were randomly distributed among PHCCs in Sweden. This means that the variation

between PHCCs regarding their propensity to prescribe benzodiazepine for more than 91 days (i.e., long term use) is low. Most of the individual variation in long-term use of benzodiazepines was due to individual-level factors rather than factors at the PHCC level. The low variation between PHCCs in prescribing patterns for benzodiazepines is encouraging and may be a result of the universal health care system in Sweden, which is provided to the entire population, irrespective of individual income. These findings can be helpful for planning interventions. For example, general interventions targeting all PHCCs rather than certain PHCCs might be more efficient, as the long term users were not clustered within certain PHCCs. The finding of a very low ICC at the PHCC level is in contrast to several other studies investigating variation in prescription patterns between health care centres (Fang et al., 2009; Mercuri and Gafni, 2011; Mousques et al., 2010; Rogers et al., 2007). However, those studies used other outcomes and it is possible that prescription patterns regarding long-term use of benzodiazepines are more related to individual-level factors than area-level factors.

Strengths and limitations

Our results should be interpreted in the context of certain limitations. First, even though we had data showing that the benzodiazepines had been prescribed, we had no data on whether the pharmacy had dispensed the medication or not. Second, our results are based on Swedish data and may therefore not extrapolate to other populations, particularly in developing countries where the socioeconomic conditions are very different from those in industrialized countries. Third, our measures of diagnoses of depression, anxiety and insomnia are based on the detection from official medical records, which implies that they may not represent the ”true” number of cases in the population.

The present study also has several strengths. Key strengths include the large sample size of 12 536 individuals with clinically diagnosed depression, anxiety and/or insomnia. Another important key strength is that we were able to link clinical diagnoses made by physicians on individual patients, using a large primary health care database, to national demographic and socioeconomic data, using a national population register. This gave us access to several different types of sociodemographic variables in our analysis, which enhanced the comprehension of what sociodemographic variables influence long-term use of benzodiazepines the most. By using national population data, we also avoided self-report bias, which is common when assessing socioeconomic status.

Conclusions

Individual-level sociodemographic factors seem to have an influence on long-term use of benzodiazepines in primary health care patients with depression, anxiety and/or insomnia. However, the primary health care centres only explained a small part of the individual variation in long-term use of benzodiazepines. The findings are of interest for health care workers as well as for the society as a whole. Decision-makers should aim at targeting general interventions at all primary health care centres. Further research is needed to identify mechanisms influencing long-term use of benzodiazepines in certain subgroups of the population.

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Declaration of interest

None

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