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Sanna-Mari Tähtäpää<sup>1</sup>, Leena Saastamoinen<sup>2\*</sup>, Terhi Kurko<sup>2</sup>, Annamari Tuulio-Henriksson<sup>2,3</sup>, Terhi Aalto-Setälä<sup>4,5</sup>, Marja Airaksinen<sup>6</sup>

## Decreasing trend in the use and long-term use of benzodiazepines among young adults

1 Tikkurilan Uusi Apteekki, Talvikkitie 37, 01300 Vantaa; Finland

2 Research unit, The Social Insurance Institution, Po. Box 450, 00056 Kela, Finland

3Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland.

4 The Social Insurance Institution, Po. Box 450, 00056 Kela, Finland

5 Family Councelling Center, Helsinki, Finland.

6 Clinical Pharmacy Group, Division of Pharmacology and Pharmacotherapy, Faculty of Pharmacy, University of Helsinki. P.O. Box 56, 00014 University of Helsinki, Finland

\*Corresponding author: Terhi Kurko, [terhi.kurko@kela.fi](mailto:terhi.kurko@kela.fi), +358-50-5219905

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30 **Objective** Patterns of benzodiazepine (BZD) use and long-term use among young adults are not well  
31 known. Our aim was to study trends in BZD use and long-term use among 18–25-year-old young  
32 adults by gender and active substance in a nationwide retrospective longitudinal register-based  
33 setting.

34 **Methods** All Finns aged 18–25 years with reimbursed purchases of BZDs in 2006–2014 recorded to  
35 the Finnish Prescription Register were included. Annual prevalence rates of BZD use and long-term  
36 use among young adults were reported overall, and according to gender, drug group (anxiolytic or  
37 hypnotic) and active substance. Long-term use of BZDs was defined as purchasing  $\geq 180$  Defined  
38 Daily Doses (DDD) in at least two drug purchases during a calendar year.

39 **Results** Overall prevalence of BZD use among young adults decreased from 24.0 to 18.8 per 1000  
40 inhabitants in 2006–2014. Prevalence of long-term use decreased from 5.5 to 3.3 per 1000 inhabitants.  
41 Overall BZD use was higher among females, whereas long-term use was more common among males.  
42 Use of anxiolytics was more common than use of hypnotics. Oxazepam, alprazolam, zopiclone and  
43 zolpidem were the most used BZDs, whereas alprazolam and clonazepam were the substances with  
44 most long-term use. The use and long-term use of BZDs have decreased annually since 2008 among  
45 Finnish young adults. Further research is needed to investigate the reasons behind the decline.

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48 **Keywords:** Benzodiazepines, young adults, anxiolytics, hypnotics

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## 57 Introduction

58 Young adulthood is a developmentally critical phase associated with several challenges, such as  
59 achievement of independence, identity formation and important decision making for the future (Patel  
60 et al. 2007). Many mental disorders become prevalent during adolescence and young adulthood, and  
61 approximately three fourth of lifetime psychiatric disorders have emerged by the age of 24 (Kessler  
62 et al.2005). Studies have shown that psychotropic drug use has increased among adolescents and  
63 young adults in recent decades (Autti-Rämö et al 2009; Hsia et al 2009, Hartz et al. 2016). However,  
64 most of the pharmacoepidemiological research assessing the use and long-term use of BZDs has  
65 focused on adult population or the aged (Kurko et al. 2016) who consume BZDs more commonly  
66 than younger age groups and are at an increased risk for adverse effects associated with regular BZD  
67 use (Barker et al. 2004, Glass et al. 2005)

68  
69 Previous studies on BZD use among young adults have concerned specific populations, such as  
70 patients with substance use disorders, or focus on abuse of BZDs (McCabe et al 2005, Kornor et al.  
71 2010, Riska et al. 2014). In studies assessing BZD use in general populations, young adults have been  
72 included as one of the age-groups (Lagnaoui et al 2004, Cunningham et al. 2010, Hollingworth et al.  
73 2010, Nordfjaern et al 2012, Olfson et al. 2015). In United States, the prevalence of BZD use was 2.6  
74 % and 0.4 % for long-term use among young adults (aged 18–35) (Olfson et al. 2015). In a Norwegian  
75 study cohort, 4 % of young adults aged 18–25 years had received a prescription for BZDs, 1 % used  
76 BZDs at least 180 DDD per year, and 0.5 % were defined as chronic users (Nordfjaern et al. 2012).  
77 Among Taiwanese incident BZD users (aged 16–19), 5 % were long-term users (Yeh et al. 2011)

78  
79 There is limited population-based knowledge on the use of BZDs among young people due to the fact  
80 that most research has been conducted either among adults in general or among older adults (Kurko  
81 et al 2016). The objective of this study was to assess nationwide trends in the prevalence of BZD use  
82 and long-term use among young adults 18–25 years of age over a nine-year period of 2006–2014  
83 overall and according to gender and active substance.

## 84 Materials and Methods

85  
86 Data sources

87  
88 This nationwide, retrospective register-based study is based on data from the Finnish Prescription  
89 Register of the Social Insurance Institution of Finland. The Finnish National Health Insurance covers

90 all Finnish residents. The Prescription Register contains individual level information on all  
91 reimbursed drug purchases dispensed to Finnish residents in outpatient care. In the database, all drugs  
92 are classified according to the World Health Organization's, (WHO 2017) Anatomical Therapeutic  
93 Chemical (ATC) classification system. The data compiled for the present study contains information  
94 on each patient's personal identifier based on person's personal identification number in encrypted  
95 form, age at the end of the year, gender, ATC code of the dispensed drug, dispensing date, number of  
96 dispensed packages and number of defined daily doses (DDDs) dispensed. According to Finnish  
97 legislation, ethical approval was not required to conduct this register-based study with anonymized  
98 patient data. Permission to use data was given by the register holder, the Social Insurance Institution  
99 of Finland.

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101

102 The BZDs included in this study are presented in supplementary table 1. These were anti-epileptic  
103 clonazepam (ATC-code N03AE01), traditional BZD anxiolytics (N05BA), traditional BZD  
104 hypnotics (N05CD), BZD related drugs, also called z-hypnotics (N05CF) and combination of  
105 chlordiazepoxide and amitriptyline (N06CA01). Purchases of orally administered dosage forms were  
106 included in this study with the exception of oral suspensions.

107

108 The study population consisted of all 18–25-year-old young adults with at least one reimbursed  
109 purchase of BZD between 1 January 2006 and 31 December 2014. Young adults were selected as a  
110 study population because the majority (94.3%, n=68 167) of 0–25-year-old BZD users (n=72 266)  
111 were 18–25-year-old young adults (Figure 1), and the definition for DDD by WHO (2016) concerns  
112 only adults. Person's age was calculated at the end of each calendar year. Numbers of BZD users,  
113 dispensed prescriptions and persons aged 0–25 covered by National Health Insurance in 2014 are  
114 presented in Figure 1.

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118 Study variable construction

119

120 Anti-epileptic clonazepam was included in this study when used for other than epileptic indications,  
121 i.e. when purchased without special reimbursement for epilepsy. In the Finnish system, patients'  
122 entitlement for special reimbursement is based on doctor's certificate fulfilling certain diagnosis  
123 criteria. These purchases with special reimbursements are distinguished in a register with special

124 coding. In the non-epileptic indications, the dosing is lower compared to dosing for epilepsy (8mg).  
125 The dosage of 1mg was used as the defined daily dose for clonazepam use based on the literature and  
126 clinical experience (White 2009, Drug and Alcohol Services 2012, Ashton 2013).

127

128 BZDs in ATC-classes N03AE01, N05BA, N06CA01 were classified as anxiolytics, and drugs in  
129 ATC-classes N05CD and N05CF as hypnotics.

130

131

132 Reimbursed drug purchase of BZDs was used as a proxy for BZD use (Haukka et al 2007). Long-  
133 term use of BZDs was defined as at least 180 DDD purchases of BZDs and two or more drug  
134 purchases during a calendar year corresponding to six months' use. This definition of six months' use  
135 was based on the WHO's recommendation as the definition for long-term use and a systematic review  
136 concerning long-term use BZD use (World Health Organization 1996; Kurko et al 2015). Drug  
137 consumption of BZDs per patient per year was calculated by using DDDs recommended by WHO  
138 (2016). DDDs of each patient's drug purchases were combined according to the patient's personal  
139 identifier.

140

141 One-year prevalence of BZD use and long-term BZD use were assessed overall and according to  
142 gender, drug group (anxiolytic or hypnotic, based on the ATC-classification) and active substance  
143 during 2006–2014. Prevalence rates (number of users per 1000 inhabitants) were calculated according  
144 to the number of the same age Finnish population.

145

#### 146 Statistical analysis

147 While this study concerns a whole population, data were analyzed with descriptive statistical  
148 methods. Binomial distribution was used to compare changes in prevalence rates between 2006 and  
149 2014. For these prevalence rates, the 95% confidence intervals were calculated. The overall yearly  
150 trends of each studied drug were assessed by comparing these confidence intervals. If the confidence  
151 intervals were not overlapping, the trend during the assessed period was considered to be statistically  
152 significantly changed. Descriptive data analyses were performed using statistical software IBM SPSS  
153 Statistics version 22.0 and binomial distribution was tested by R version 3.1.3.2015.

154

155

## 156 Results

157 Overall prevalence of BZD use among young adults decreased statistically significantly, by 21.5%  
158 from 24.0 to 18.8 / 1000 inhabitants over a nine-year period (Figure 2). The annual prevalence of  
159 BZD use increased between 2006 and 2008, the highest prevalence (28.6 / 1000 inhabitants) being  
160 observed in 2008. The use of BZDs was more common in females than males during the study period.  
161 In 2014, prevalence of BZD use among females was 22.8 / 1000 inhabitants and among males 15.1 /  
162 1000 inhabitants.

163  
164 Overall prevalence of long-term use of BZDs among 18–25-year-old Finns decreased statistically  
165 significantly, by 39.8% from 5.5 to 3.3 per 1000 inhabitants during 2006–2014. In 2014, the last  
166 studied year, 17.5% of all 18–25-year-old BZD users were defined as long-term users. The prevalence  
167 of long-term use was higher among males than females during the entire study period.

168  
169 Use of anxiolytic BZDs was more common than use of hypnotics among Finnish young adults (Figure  
170 3). The overall prevalence of anxiolytic use decreased 20.6%, from 15.2 to 12.1 / 1000 inhabitants  
171 during the study period. The use of hypnotics decreased from 12.5 to 8.5 / 1000 inhabitants, 31.8%  
172 between 2006 and 2014. Long-term use of anxiolytics was more common than long-term use of  
173 hypnotics among young adults during the study period. In 2014, the prevalence of long-term use of  
174 anxiolytics was 2.6 / 1000 inhabitants and hypnotics 0.7 / 1000 inhabitants. Both long-term use of  
175 anxiolytics and long-term use of hypnotics decreased during 2006–2014.

176  
177 Oxazepam and alprazolam were the most commonly used anxiolytics. The most commonly used  
178 hypnotics were z-drugs zopiclone and zolpidem. Over the nine-year study period, there was a decline  
179 in the use of almost every studied substance. Alprazolam use decreased the most (53.5%) between  
180 2006 and 2014. Only the prevalence of oxazepam use increased by 17.4%, from 5.3 in 2006 to 6.2  
181 per 1000 inhabitants in 2014. Use of diazepam and clonazepam was lower than that of oxazepam and  
182 alprazolam. During the study period, prevalence of diazepam use ranged between 2.0 and 3.4 / 1000  
183 inhabitants, while clonazepam use ranged between 1.6 and 2.3 / 1000 inhabitants, respectively.

184  
185 Long-term use of BZDs was relatively low among young adults during the study period. The highest  
186 prevalence of long-term use was observed in alprazolam users during 2006–2009 and in clonazepam  
187 users during 2010–2014. The substance-level prevalence of long-term use decreased in users of all  
188 BZD substances between 2006 and 2014. The decline of long-term use was most significant in  
189 diazepam (58.7 %) and alprazolam (57.9 %) users. Compared to other BZDs, long-term use was more

190 prevalent among subjects using diazepam and clonazepam. The relative proportions of long-term use  
191 among diazepam and clonazepam users were higher compared to other BZDs. More than half (59.9–  
192 64.6 %) of clonazepam users were long-term users during 2006–2014. Corresponding proportions  
193 were 24.9–37.5% among diazepam users and 26.8–32.3% among alprazolam users during the study  
194 period.

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## 198 Discussion

199 To our best knowledge, the present study is the first nationwide register-based study focusing on use  
200 and long-term use of BZDs among young adults. Therefore, the present study offers clinically  
201 significant new information on BZD use and long-term use of this less studied user group. We found  
202 a decreasing trend of both BZD use and long-term use among Finnish young adults during the  
203 investigated nine-year study period. The overall prevalence of BZD use decreased by one fifth and  
204 long-term use of BZDs decreased by over one third between 2006 and 2014. Overall BZD use was  
205 more common among females, whereas long-term use was more common among males. The four  
206 most commonly used BZDs among young adults were oxazepam, alprazolam, zopiclone and  
207 zolpidem. Oxazepam was the only substance with increased use between 2006 and 2014. Alprazolam  
208 and clonazepam were the substances mostly used for long-term.

209

210 This study was based on data from the Finnish Prescription Register covering all reimbursed BZD  
211 purchases in Finland among whole population during the investigated period. Key strengths of this  
212 study are the nationwide data and a long nine-year study period. Completeness and accuracy of  
213 records in The Finnish Prescription Register is high.

214

215 Drug purchase was used as a proxy for BZD use, because there is concordance between prescription  
216 database information and self-reported BZD use (Haukka et al 2007). However, this study may  
217 underestimate the total BZD use among young adults in Finland. The Finnish Prescription Register  
218 does not record non-reimbursed drug purchases, inpatients' drug use or illegal drug use (Furu et al  
219 2010). Moreover, some diazepam and oxazepam purchases in small package sizes are not recorded  
220 in the Prescription Register, as they are not usually reimbursable. The coverage of the register was

221 76–90% annually compared to wholesale data of BZD provided by the Finnish Medical Agency  
222 (2017). Information on patient’s diagnosis or severity of psychiatric condition is not included in the  
223 Prescription Register.

224

225 Previous studies on BZD use and long-term use have varied considerably in terms of definition for  
226 long-term use, time-period of the study and age group making it difficult to compare the prevalence  
227 rates between studies. There may also be differences in treatment practices between countries.  
228 However, prevalence of BZD use (1.9 %) among Finnish young adults in 2014 was similar to that  
229 reported in France (1.8 %) but lower than reported in studies in the U.S. (2.6 %), Norway (4.0 %) and  
230 Taiwan (6.7 %) (Lagnaoui et al 2004, Yeh et al. 2011, Nordfjaern et al. 2012, Olfson et al. 2015).  
231 Long-term use of BZDs (0.3 %) by Finnish young adults was slightly less common than that reported  
232 among U.S. young adults (0.4 %) in 2008 (Olfson et al. 2015), and among a sample of French young  
233 adults (0.6 %) in 2001 (Lagnaoui et al. 2004). Further, the prevalence of long-term use in Finland  
234 was lower than that observed in a Norwegian study cohort (1 %) during 2004–2008 (Nordfjaern  
235 2012), and among Taiwanese incident BZD users (5 %) in 2001–2005 (Yeh et al 2011).

236

237 It was not possible to include assessment of indications of BZD prescriptions in the present study.  
238 However, results showed that BZDs classified as anxiolytics were more commonly used than  
239 hypnotics, which may suggest that BZDs are more often used in anxiety than sleep disorders among  
240 young adults. At a substance-level, decreasing trend was observed among almost all BZDs except  
241 oxazepam, which was the only substance with increased use. In the last studied year, oxazepam was  
242 the most commonly used BZD among Finnish young adults. Increased use of oxazepam may be due  
243 to its lower abuse liability (Griffiths et al 1984). This study found that long-term use among oxazepam  
244 users was relatively uncommon. However, a recent study showed that oxazepam users were more  
245 prone to dose escalation compared with diazepam users (Tvette et al 2016). Despite the decreasing  
246 trend of long-term use overall and at a substance-level, long-term use was common among users of  
247 high or medium potency BZDs including clonazepam, diazepam and alprazolam. In this study, a  
248 majority of all clonazepam users used the substance for long-term. Similarly, a recent study found  
249 that clonazepam use is often associated with dose escalation (Alessi-Severini et al. 2016). On the  
250 other hand, in the study of Cloos et al. (2015), clonazepam was associated with a lower risk for high-  
251 dose use compared to hypnotics and anxiolytics alprazolam and prazepam, which were associated  
252 with the highest risk for high-dose use.

253



254 The observed gender difference in overall BZD use is consistent with other studies showing that use  
255 of BZDs is more common among females than males (Petitjean et al. 2007, Lagnaoui et al 2004,  
256 Cunningham et al. 2010, Olfson et al 2015). The higher prevalence of anxiety and sleep disorders in  
257 females during young adulthood partly explains this finding (Wittchen et al. 1998, Suvisaari et al.  
258 2009). Yet, in our study, long-term use of BZDs was more prevalent in males than females. This  
259 could be partly explained by the previous finding reporting non-medical, e.g. self-reported possible  
260 abuse or misuse, use of anxiolytics and hypnotics in adolescence to be significantly more common in  
261 males than females in Finland compared to many other European countries (Kokkevi et al 2008).  
262 However, our study did not assess the possible abuse of BZDs.

263  
264 Decreasing trend in BZD use found in this study suggests that prescribing patterns of BZDs have  
265 changed during recent years. Similar decreasing trend of BZD utilization has also been observed in  
266 the entire Finnish population (Saastamoinen et al. 2016). National guidelines on rational BZD  
267 prescribing recommend to restricting the length of BZD treatment to some weeks (National  
268 Supervisory Authority for Health and Welfare 2015, Working Group set up by the Finnish Medical  
269 Society Duodecim and the Finnish Sleep Research Society 2017). However, we found that nearly  
270 one out of five young adult BZD users could be defined as a long-term user. Decreasing trend of long-  
271 term BZD use among young adults raises questions about the factors associated with decreased use.  
272 It is probable that a part of BZD use has been replaced by other pharmaceutical use or psychosocial  
273 treatments. During recent years, mental health services among adolescents and young adults have  
274 increased, which reflects the enhanced recognition of the treatment need, but may also suggest that  
275 stigma associated with mental health service use has decreased (Pylkkänen and Laukkanen 2011).  
276 Availability of mental health services may have improved, and low threshold online therapies are  
277 available, too (Stenberg et al 2016).

278  
279 Based on the findings of this study we suggest that patterns of BZD long-term use among young  
280 people need more research. Long-term treatment with BZDs can be considered medically justified  
281 for some patients. Therefore, it would be of importance to identify specific patient groups, which  
282 would benefit from long-term BZD treatment. However, equally important would be to recognize  
283 those patients who may experience harm of BZD use.

284  
285 In conclusion, both overall use and long-term use of BZDs have decreased annually since the year  
286 2008 among Finnish young adults. Decreasing use may be the consequence of increased awareness  
287 of problems related to long-term BZD use and recommendations introduced to rationalize the use of

288 BZDs. Further research is needed to identify factors associated with the decline in BZD use among  
289 young adults.

290

291

## 292 Clinical Significance

293 In this first nationwide study on BZD use and long-term use focusing on young adults, we found a  
294 declining trend in use and long-term BZD use. Despite this decline, still a nearly one out of five  
295 young adult BZD users could be defined as a long-term user and part of this long-term use may also  
296 be inappropriate. Our findings urge physicians to pay more attention to BZD prescribing and  
297 monitoring for young men who are especially prone to long-term use. In addition, special concern  
298 regarding the prescription practices of high potency BZDs alprazolam and clonazepam is needed, as  
299 these substances were most commonly used for long-term.

300

## 301 Conflicts of interest

302 Terhi Aalto-Setälä, Marja Airaksinen, Leena Saastamoinen, Annamari Tuulio-Henriksson, Sanna  
303 Tähkäpää: Have no conflicts of interests

304 Terhi Kurko has owned a few stocks of pharmaceutical company Orion Pharma in 2014-2015 and  
305 has received an expert fee from Pfizer in 2015.

306

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