Benzodiazepine prescribing in children under 15 years of age receiving free medical care on the General Medical Services scheme in Ireland

K O’Sullivan,1 U Reulbach,1,2 F Boland,1 N Motterlini,1,† D Kelly,2 K Bennett,3 T Fahey1

ABSTRACT

Objective: To examine the prevalence and secular trends in benzodiazepine (BZD) prescribing in the Irish paediatric population. In addition, we examine coprescribing of antiepileptic, antipsychotic, antidepressant and psychostimulants in children receiving BZD drugs and compare BZD prescribing in Ireland to that in other European countries.

Setting: Data were obtained from the Irish General Medical Services (GMS) scheme pharmacy claims database from the Health Service Executive (HSE)—Primary Care Reimbursement Services (PCRS).

Participants: Children aged 0–15 years, on the HSE-PCRS database between January 2002 and December 2011, were included.

Primary and secondary outcome measures: Prescribing rates were reported over time (2002–2011) and duration (≤ or >90 days). Age (0–4, 5–11, 12–15) and gender trends were established. Rates of concomitant prescriptions for antiepileptic, antipsychotics, antidepressants and psychostimulants were reported. European prescribing data were retrieved from the literature.

Results: Rates decreased from 2002 (8.56/1000 GMS population: 95% CI 8.20 to 8.92) to 2011 (5.33/1000 GMS population: 95% CI 5.10 to 5.55). Of those children currently receiving a BZD prescription, 6% were prescribed BZD for >90 days. Rates were higher for boys in the 0–4 and 4–5 age groups. A substantial proportion of children receiving BZD drugs are also prescribed antiepileptic (27%), antidepressant (11%), antipsychotic (5%) and psychostimulant (2%) medicines. Prescribing rates follow a similar pattern to that in other European countries.

Conclusions: While BZD prescribing trends have decreased in recent years, this study shows that a significant proportion of the GMS children population are being prescribed BZD in the long term. This study highlights the need for guidelines for BZD prescribing in children in terms of clinical indication and responsibility, coprescribing, dosage and duration of treatment.

INTRODUCTION

The use of psychotropic medications among children and adolescents has increased markedly in the past two decades.1–4 In the USA, for example, paediatric use of psychotropic drugs increased threefold between 1987 and 1996.5 A similar trend was observed in nine countries worldwide between 2000 and 2002.6 Reports suggest that this trend is driven by a greater use of stimulants, antidepressants and antipsychotics.7 Fewer studies have reported data on the use of benzodiazepines (BZDs) in children. Furthermore, no studies have considered prescribing patterns of z drugs to...
Z drugs are considered under the same umbrella of BZD from this point onwards in this article due to the similar effects and indications for which they are prescribed.
Data analyses were performed using Stata V.11 (StataCorp, College Station, Texas, USA) and SAS V.9.3 (SAS Institute Inc Cary, North Carolina, USA).

Comparison to European studies
Comparison studies examining overall psychotropic medication trends in paediatric populations were identified from a search of the published literature from 1980 to 2013. Articles were included if they reported paediatric BZD prescribing rate in a community setting and provided overall rates of BZD prescribing. Studies which reported overall percentage prevalence were transformed to per 1000 prevalence rate to facilitate comparison.

RESULTS
Population sample
During the study period January 2002 to December 2011, the number of children ≤15 years in Ireland, as identified from the HSE-PCRS pharmacy database, ranged between 188 833 and 311 579. On average, 51% of the study population were male and 49% were female.

Prescribing time trends
Table 1 shows the prevalence of benzodiazepines for 2002–2011. In 2002, 8.56/1000 GMS population (95% CI 8.20 to 8.92) received at least one benzodiazepine prescription and this rate decreased to 5.33/1000 GMS population (95% CI 5.10 to 5.55) in 2011. Benzodiazepine prescribing decreased nearly every year over the study period, except for 2005 and 2011 where there were slight increases from the previous year (table 1).

During the study period, diazepam was the most frequently prescribed benzodiazepine. Following the overall benzodiazepine trend, the prevalence decreased from 5.14/1000 GMS population (95% CI 4.86 to 5.42) in 2002 to 3.20/1000 GMS population (95% CI 3.02 to 3.38) in 2011. Rates of zopiclone, alprazolam, clobazam, zolpidem and clonazepam remained relatively stable over the 10 years (figure 1).

Long-term use
Between January 2002 and December 2006, a total of 7844 children had at least one benzodiazepine prescription and 5.7% of these children were taking benzodiazepines for longer than 90 days. From January 2007 to December 2011, 7453 children had at least one benzodiazepine prescription and 6.2% of these children were taking benzodiazepines for longer than 90 days. Table 2 shows the breakdown of children taking benzodiazepines on a long-term basis by gender and age group. This table shows that the highest percentage of children taking benzodiazepines on a long-term basis are between 5 and 11 years of age. Additionally, from 2002–2006 to 2007–2011, the percentage of males and females with long-term use increased slightly for all age groups except for males aged 12–15 years.

Gender and age
Figure 2 shows the prevalence rates of benzodiazepines for all years for males and females and all age groups (0–4, 5–11 and 12–15). The interactions between age group×year (p<0.01) and age group×gender (p<0.01) were significant. This means that the effect of age group on the prevalence of benzodiazepines differed over the years, and over males and females separately. Significant differences were observed between males and females for all age groups; males had higher rates at 0–4 and 5–11 years, whereas females had higher rates at 12–15 years. Additionally, significant differences were seen for all years between age groups whereby 12–15 years had significantly higher rates of prescribing than 0–4 years and also 5–11 years.

Concomitant medications
An antiepileptic was coprescribed to 28% of BZD users, an antidepressant to 11% of users, antipsychotics to 5%

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence rate per 1000 GMS population (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>8.56 (8.20 to 8.92)</td>
</tr>
<tr>
<td>2003</td>
<td>8.64 (8.28 to 9.00)</td>
</tr>
<tr>
<td>2004</td>
<td>8.20 (7.84 to 8.56)</td>
</tr>
<tr>
<td>2005</td>
<td>8.42 (8.06 to 8.78)</td>
</tr>
<tr>
<td>2006</td>
<td>7.34 (7.01 to 7.67)</td>
</tr>
<tr>
<td>2007</td>
<td>6.88 (6.57 to 7.19)</td>
</tr>
<tr>
<td>2008</td>
<td>6.32 (6.04 to 6.60)</td>
</tr>
<tr>
<td>2009</td>
<td>5.95 (5.69 to 6.21)</td>
</tr>
<tr>
<td>2010</td>
<td>5.27 (5.03 to 5.50)</td>
</tr>
<tr>
<td>2011</td>
<td>5.33 (5.10 to 5.55)</td>
</tr>
</tbody>
</table>

GMS, General Medical Services.
and a psychostimulant to 2% of users (Table 4). The proportion of concomitant medications changed significantly during the observation period. Rates of concomitant antiepileptic prescribing increased between 2002 and 2004, and between 2006 and 2008. Rates of concomitant prescribing of psychostimulants increased from 2002 to 2009 inclusively (Table 4). Excluding patients who took antiepileptics, antipsychotic medication was prescribed to 4% of all benzodiazepine users, an antidepressant to 14% and psychostimulants to 2% of users (Figure 3).

Comparison with European countries

Studies examining overall psychotropic medication trends in paediatric populations and reporting a BZD prescribing rate in a community setting between 1990 and 2013 were identified. Two studies were identified from the Netherlands, one from France and one from Finland.

The overall prescribing rate of BZD for this study was 6.7/1000 GMS population. This is higher than 4.4/1000 in Finland (1994–2005) but lower than 7.8/1000 in France (2003–2005). Two studies were identified from the Netherlands with rates of 6.5/1000 (1995–1999) and 9/1000 (1995–2001). This shows that the rates of BZD prescribing in paediatrics in Europe varies a lot and indicates that Ireland is ranked near the median. However, there is high heterogeneity across the different studies, in terms of age groups, sample size and year in which the data are assessed.

DISCUSSION AND CONCLUSION

Prescribing trends

The overall rate of BZD prescribing according to the dispensed medication data has decreased between 2002 and 2011, with the exception of 2005 and 2011 where small increases were observed. Over the study period, it was also seen that diazepam was prescribed most frequently. The rate of prescribing to children on the GMS scheme was close to the median value, relative to the European countries with data available for comparison. Ireland reported lower rates than France and the Netherlands but higher rates than Finland.

Paediatric clinical trials into the safety and efficacy of BZD have found it difficult to overcome the concern about the potential for addiction or other adverse events (e.g., disinhibition). While trends indicate a decrease in prescribing rates in recent times, there is still a significant proportion of the GMS children population who are being prescribed BZD. The rate of children being prescribed BZD is lower than that of adults on the GMS scheme; in 2002, an Irish report revealed that 11.6% of adults were in receipt of a BZD prescription and that this rate was steadily increasing. This shows that a lower proportion of children on the GMS scheme are being prescribed BZD than adults, and while the current trends show reduced prescribing rates, they also highlight the need for more large-scale, well-designed studies that address the safety concerns associated with prescribing BZD to children, the clinical indication for the BZD, the dosage and duration of prescribing.

Long-term use

The long-term prescribing of BZD in Ireland was investigated and it was found that 5.9% of children prescribed BZD were taking them for a period longer than 90 days.

### Table 2

<table>
<thead>
<tr>
<th>Year</th>
<th>Males</th>
<th></th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤90 days</td>
<td>&gt;90 days</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>≤90 days</td>
<td>&gt;90 days</td>
<td>Total</td>
</tr>
<tr>
<td>2002–2006</td>
<td>0–4 years</td>
<td>1360 (95.6%)</td>
<td>62 (4.4%)</td>
</tr>
<tr>
<td></td>
<td>5–11 years</td>
<td>1381 (93.7%)</td>
<td>93 (6.3%)</td>
</tr>
<tr>
<td></td>
<td>12–15 years</td>
<td>1162 (93.6%)</td>
<td>80 (6.4%)</td>
</tr>
<tr>
<td>2007–2011</td>
<td>0–4 years</td>
<td>1166 (95.4%)</td>
<td>56 (4.5%)</td>
</tr>
<tr>
<td></td>
<td>5–11 years</td>
<td>1325 (92.9%)</td>
<td>101 (7.1%)</td>
</tr>
<tr>
<td></td>
<td>12–15 years</td>
<td>1234 (94.0%)</td>
<td>79 (6.0%)</td>
</tr>
</tbody>
</table>
| Figure 2     | Prevalence rates of benzodiazepines per 1000 General Medical Services population aged 0–15 years for 2002–2011 classified by gender and age group.
The prevalence of long-term use increased across the study period and the highest percentage of children taking BZD in the long term were in the 5–11 age group. No formal studies of the long-term safety of children on BZD were found. Long-term use of BZD in adults has resulted in significant cognitive deficits, and increased risk of dependability. The current findings suggest that the proportion of children being prescribed BZD in the long term may be at increased risk of these effects. A report in 2002 reviewed BZD prescribing in adults and provided clinical guidelines for BZD prescribing. Clinicians were advised that they should examine the benefit–risk ratio in each individual case early in BZD treatment. Furthermore, clinical guidance is that if BZD are used as anxiolytics for children, there should be a careful assessment of the clinical indication, and treatment duration should be kept to a minimum due to the risk of dependence. The observation that long-term use is increasing over this study period, while overall rates are decreasing, may indicate the need for specific clinical practice recommendations for BZD prescribing to children.

Gender and age
The age differences that were observed here are consistent with the literature from Denmark and France, with the prevalence of prescription rates of BZD increasing with age. The current data show that children aged 12–15 year were prescribed more BZD. The prevalence rate for children aged 12–15 year in this study was slightly higher than that observed in Denmark. Significant differences in gender rates of prescribing of BZD were also seen. Compared with females, males were prescribed more BZD in the 0–4 and 5–11 age groups. However, this pattern reversed for the children aged 12–15 year and females were prescribed significantly more. This observation is consistent with the European comparison studies whereby the frequency of BZD prescribing is higher in boys until age 13 when adolescent girls are then prescribed double that for adolescent boys. This observation may relate to gender differences in the incidence of anxiety disorders. Women are twice as likely to meet the criteria for generalised anxiety disorder as men, and gender differences in prevalence of general anxiety disorder usually emerge in early adolescence.

### Table 3
Characteristics of studies included for comparative data and a comparison of average prescribing rates per 1000 GMS children between 2001 and 2011 with European rates per 1000 children

<table>
<thead>
<tr>
<th>Study (publication year)</th>
<th>Country (year data represent)</th>
<th>Sample size</th>
<th>Age</th>
<th>Rate of BZD prescribing (per 1000)</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMS data</td>
<td>Ireland (2002–2011)</td>
<td>311 579</td>
<td>0–15</td>
<td>6.7</td>
<td>Primary care reimbursement service pharmacy claims</td>
</tr>
</tbody>
</table>

BZD, benzodiazepine; GMS, General Medical Services.

### Table 4
Percentage of benzodiazepine users (aged 0–15 years) from 2002 to 2011 taking concomitant medications

<table>
<thead>
<tr>
<th>Year</th>
<th>Benzodiazepine users (n)</th>
<th>Concomitant antipsychotics n (%)</th>
<th>Concomitant antiepileptics n (%)</th>
<th>Concomitant antidepressants n (%)</th>
<th>Concomitant psychostimulants n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>2127</td>
<td>81 (3.81)</td>
<td>498 (23.41)</td>
<td>272 (12.79)</td>
<td>20 (0.94)</td>
</tr>
<tr>
<td>2003</td>
<td>2154</td>
<td>87 (4.04)</td>
<td>553 (25.67)</td>
<td>266 (12.35)</td>
<td>35 (1.62)</td>
</tr>
<tr>
<td>2004</td>
<td>1990</td>
<td>84 (4.22)</td>
<td>572 (28.74)</td>
<td>215 (10.80)</td>
<td>21 (1.06)</td>
</tr>
<tr>
<td>2005</td>
<td>2031</td>
<td>91 (4.48)</td>
<td>633 (31.17)</td>
<td>219 (10.78)</td>
<td>45 (2.22)</td>
</tr>
<tr>
<td>2006</td>
<td>1928</td>
<td>92 (4.77)</td>
<td>556 (28.84)</td>
<td>215 (11.15)</td>
<td>37 (1.92)</td>
</tr>
<tr>
<td>2007</td>
<td>1916</td>
<td>116 (6.05)</td>
<td>579 (30.22)</td>
<td>204 (10.65)</td>
<td>36 (1.88)</td>
</tr>
<tr>
<td>2008</td>
<td>1895</td>
<td>91 (4.80)</td>
<td>549 (28.97)</td>
<td>213 (11.24)</td>
<td>51 (2.69)</td>
</tr>
<tr>
<td>2009</td>
<td>1996</td>
<td>116 (5.81)</td>
<td>550 (27.56)</td>
<td>211 (10.57)</td>
<td>50 (2.51)</td>
</tr>
<tr>
<td>2010</td>
<td>1951</td>
<td>95 (4.87)</td>
<td>528 (27.06)</td>
<td>222 (11.38)</td>
<td>36 (1.85)</td>
</tr>
<tr>
<td>2011</td>
<td>2067</td>
<td>130 (6.29)</td>
<td>557 (29.95)</td>
<td>255 (12.34)</td>
<td>40 (1.94)</td>
</tr>
</tbody>
</table>

Percentage of benzodiazepine users aged 0–15 years who also received concomitant antipsychotics (column 3) or antiepileptics (column 4) or antidepressants (column 5) or psychostimulants (column 6) medication from 2002 to 2011.
When considering paediatric prescribing practices, the potential for interaction between psychotropic drugs is an area of concern. Fluoxetine and paroxetine are antidepressants that are regularly prescribed to children with depression. Animal and human research has shown that these can reduce the rate of metabolism of BZD, and in one recent animal study the combination of fluoxetine and BZD actually reversed fluoxetine’s anxiogenic effects. These findings, and the observation that a significant proportion of children on BZD are also being prescribed antidepressants, suggest that an examination of the interactive effects of BZD and other psychotropic drugs are an important area of further investigation in paediatric prescribing.

**Limitations**

The HSE-PCRS GMS scheme pharmacy claims database represents approximately one-third of Irish children and over-represents more socially disadvantaged children in the Irish population. This may result in an overestimation of the true trends in BZD prescription rates, given that children from lower socioeconomic backgrounds are more likely to be prescribed a psychotropic medication and anxiety-related disorders. Direct comparison of European prescribing rates for low socioeconomic populations was not possible because of a lack of published data in this subpopulation.

The HSE-PCRS GMS data set does not collect information about the indication for prescriptions or about the setting in which the prescription was initiated (e.g., primary care, hospital or specialist setting). Therefore, it is unclear why certain classes of BZD were prescribed, and why changes in the rates of prescribing were observed over the 10-year period. It could be speculated that the reduced incidence of BZD prescribing in children may be related to physician preferences, changes in knowledge about the long-term effects of BZD or the development of new medications. Not knowing the clinical indication for which the prescription was administered makes it difficult to fully comment on the quality and appropriateness of BZD prescribing rates, especially as BZDs are often indicated to treat epilepsy. In this study, it is impossible to know whether BZD was prescribed to treat anxiety or epilepsy. To the best of our knowledge, in Ireland, there is no publication giving an estimation of the rates of benzodiazepines used against anxiety or epilepsy together. However, as was observed in other studies, the proportion of benzodiazepines used to treat epilepsy is likely to be very low compared with psychiatric/psychological indications.

**CONCLUSIONS**

Trends of BZD prescribing in the GMS population in Ireland show that BZD prescribing has decreased over the study period and that prescribing rates are close to the median value relative to available European...
countries. However, it remains that children are still being prescribed BZDs, both for short-term and long-term use, and little is known about the long-term effects of BZD prescribing. Future studies should examine the long-term effects of BZD prescribing set against initial clinical indication for initiating and continuing BZD drugs.

Acknowledgements The authors acknowledge the HSE-PCRS for supplying the data.

Contributors All the authors contributed to the development of this manuscript. TF, KB, NM and UR conceived and designed the study; they also contributed to the analysis and preparation of the manuscript. DK and FB created the analytical model with contributions from KJ and NM. KJ prepared the manuscript. KB, TF, FB and KJ edited the manuscript.

Funding This work was supported by the Health Research Board (HRB) of Ireland through the HRB Centre for Primary Care Research under grant HRC/2007/1.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES


Benzodiazepine prescribing in children under 15 years of age receiving free medical care on the General Medical Services scheme in Ireland

K O'Sullivan, U Reulbach, F Boland, N Motterlini, D Kelly, K Bennett and T Fahey

BMJ Open 2015 5:
doi: 10.1136/bmjopen-2014-007070

Updated information and services can be found at:
http://bmjopen.bmj.com/content/5/6/e007070

These include:

References
This article cites 32 articles, 3 of which you can access for free at:
http://bmjopen.bmj.com/content/5/6/e007070#BIBL

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See:
http://creativecommons.org/licenses/by-nc/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Paediatrics (305)
Pharmacology and therapeutics (277)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/