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## Benzodiazepine prescribing in Irish children receiving free medical care.

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Benzodiazepine prescribing in children

Benzodiazepine prescribing in children receiving free medical care.

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## Benzodiazepine prescribing in children

**Abstract**

**Objective:** To examine the prevalence and secular trends in Benzodiazepine (BDZ) prescribing in the Irish paediatric population. In addition, we examine co-prescribing of antipsychotic, antidepressant and psychostimulants in children receiving BDZ drugs and compare BDZ prescribing in Ireland to other European countries.

**Setting:** Data was 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 ( $\leq$  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. Prescribing rates of BZD where the safety is not established in children were reported. European prescribing data were retrieved from the literature.

**Results:** Rates decreased from 2002 (8.56/1,000 GMS population: 95% CI: 8.20-8.92) to 2011 (5.33/1,000 GMS population: 95% CI: 5.10-5.55). 6% of children were prescribed BDZ for  $>90$  days. Rates were higher for boys in the 0-4 and 5-11 age ranges whereas girls were higher in the 12-15 age groups. A substantial proportion of children receiving BZD drugs are also prescribed antiepileptic (27%), antidepressant (11%), antipsychotic (4%) and psychostimulant (2%) medicines. 26% of children were prescribed BDZ yet to be deemed safe in children. Prescribing rates follow a similar pattern to other European countries.

**Conclusions:** BDZ prescribing has decreased over the study period. Long-term rates and age and gender trends were established. Rates of prescribing of concomitant medications, and BDZ were established. Results indicate the need for further investigation and guidelines for BDZ prescribing in children.

Benzodiazepine prescribing in children

Article summary

Strengths and limitations of this study

- This is the first study to examine the prevalence and trends in benzodiazepine (BDZ) prescribing in an Irish paediatric population, as well as concomitant use of antipsychotic, antidepressant and psychostimulant drugs.
- However, the HSE-PCRS GMS 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 over-estimation of the true trends in BDZ prescription rates, given that children from lower socioeconomic backgrounds are more likely to be prescribed a psychotropic medication and are at greater risk of epilepsy and anxiety related disorders.
- Furthermore, the database does not contain information about the indication for prescriptions or the setting in which the prescription was initiated (e.g. primary care, hospital or specialist setting). Therefore, it is unclear why certain classes of BDZ were prescribed, and why changes in the rates of prescribing were observed over the ten-year period.

## Benzodiazepine prescribing in children

### Introduction

The use of psychotropic medications among children and adolescents has increased markedly in the last two decades [1-4]. In the US, for example, paediatric use of psychotropic drugs increased three-fold between 1987 and 1996.[5] A similar trend was observed in 9 countries worldwide between 2000 and 2002.[6] Reports suggest this trend is driven by a greater use of stimulants, antidepressants and antipsychotics [7]. Fewer studies have reported data on the use of benzodiazepines (BDZs) in children. Furthermore, no studies have considered prescribing patterns of z drugs to children<sup>1</sup>. Those that have examined BDZ prescribing practices in children and adolescents report slight increases over time.[5] Despite these trends the literature supporting such increases is sparse and it remains unclear what information is guiding clinicians BDZ prescribing practices.[5]

BDZs are often used to control several types of seizures in young children. Amongst the most common BDZs for this indication are diazepam, clonazepam and lorazepam. Diazepam is most frequently used in the treatment of status epileptics and cerebral convulsions.[8] Clinicians recommend caution when prescribing BDZ to children and research into long term prescribing in this population advocate short term courses (6-12 weeks) because of their depressant properties and potential for tolerance and dependency.[9, 10] Furthermore, long term use can result in increased risk of cognitive deficits[11, 12] and presentation of mild withdrawal syndrome.[13]

To-date very little work has been conducted to systematically assess the role of BDZs in child and adolescent psychiatric disorders. Little is known about the efficacy of BDZs in the treatment of psychiatric symptoms in children[5, 14, 15] and there is no firmly established indication for their use with childhood psychiatric disorders.(10) Studies that have examined the efficacy of BDZs in the treatment of childhood psychiatric disorders report significant improvements in symptoms. For example, several studies have shown that alprazolam reduces anxiety in children who meet the criteria for anxiety disorder.[16-18] However, there are inconsistencies in the literature. For example, a well controlled double-blind pilot study revealed no clinically significant effects on anxiety in a small sample of children with a diagnosis of one or more anxiety disorders.[19] Furthermore, a study of social phobia in children and adolescents did not support the use of BDZ in anxiety treatment.[20] The differences

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<sup>1</sup> Z drugs are considered under the same umbrella of BDZ from this point onwards in this article due to the similar effects and indications for which they are prescribed.

Benzodiazepine prescribing in children

observed in research findings may be attributed to a number of issues such as a shortage of well-designed studies with longitudinal examination of the effects, an inability to replicate the studies that do demonstrate promising results and the long term safety concerns of prescribing BDZ in younger age groups. Furthermore, research to date has focused mostly on adult populations, with limited focus on paediatric prescribing of BDZs in community settings.[5] This is a common feature among many psychotropic medications whereby they are not trialled in children so little or no information is available on their effectiveness and safety.

The aim of the current study is to investigate BDZ and z drug prescribing in an Irish paediatric population from a predominately low socio-economic group receiving free medical care over a ten-year period (2002-2011) and to establish long-term prescribing patterns, gender and age trends, and concomitant and prescribing rates of BDZ where the safety and efficacy is not established in children. An additional aim is to compare the prescribing Irish rates to European studies.

## Benzodiazepine prescribing in children

**Methods***Study population and study design*

Data was obtained from the Irish General Medical Services (GMS) scheme pharmacy claims database from the Health Service Executive (HSE) – Primary Care Reimbursement Services (PCRS). The pharmacy claims database contains basic demographic information and details on monthly dispensed medications, coded using the WHO Anatomical Therapeutic Chemical (ATC) classification system, for each individual within the scheme. The scheme is means tested and provides free health services. It represents approximately 28% of Irish children but over-represents socially deprived populations. Permission was given by the data controller to use the GMS dataset if anonymised and analysed at group level. Therefore, it was unnecessary to seek specific ethical approval for this study.

Children aged 0-15 years on the HSE-PCRS database between January 2002 and December 2011 was included in this study. All BDZ medication prescriptions, (ATC codes: N03AE, N05BA, N05CD and N05CF),<sup>[21]</sup> were extracted from the database. Concomitant psychotropic medication prescriptions were also extracted all antipsychotic medications (N05A), psychostimulant medications (N06B), antiepileptic medications (N03) and antidepressants (N06A).

*Data analysis*

The prevalence of benzodiazepines per 1000 GMS population per year and associated 95% confidence intervals for children aged 0-15 years were calculated as a proportion of all eligible children (0-15 years) entitled to free health services, as identified from the annual reports produced by the PCRS. Prevalence rates are to be interpreted as the prevalence of children receiving at least one benzodiazepine prescription per 1000 GMS population, as determined from the GMS database. Prevalence rates per 1000 eligible population and associated 95% confidence intervals (CIs) were also calculated across years (2002-2011). Prevalence of short term ( $\leq 90$  days) and long-term ( $> 90$  days) use among children ( $\leq 15$  years) was investigated. Additionally, age groups (0-4 years, 5-11 years and 12-15 years) and gender trends were established. Rates of concomitant prescribing of other psychotropic medication and prescribing of BDZs where the safety and efficacy are not established in childhood were calculated.

Benzodiazepine prescribing in children

Insert Table 1 here

A negative binomial regression model was used to determine trends in prescribing rates. The log of the GMS population was used as the offset term and year, age group, gender and all possible interactions between these variables were included as fixed effects in the model. The Bonferroni method was used to control the overall Type I error rate in making multiple comparisons and *p*-values <0.05 were deemed significant.

Data analyses was performed using Stata version 11 (StataCorp, College Station, Tx, USA) and SAS version 9.3 (SAS Institute Inc. Cary, NC, USA).

*Comparison to European studies*

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

## Benzodiazepine prescribing in children

**Results***Population sample*

During the study period, January 2002 to December 2011, the number of children  $\leq 15$  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.

**Insert figure 1 here**

*Prescribing time-trends*

Table 1 shows the prevalence of benzodiazepines for 2002-2011. In 2002, 8.56/1,000 GMS population (95% CI: 8.20-8.92) received at least one benzodiazepine prescription and this rate decreased to 5.33/1,000 GMS population (95% CI: 5.10-5.55) 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 5.14/1,000 GMS population (95% CI: 4.86-5.42) in 2002 to 3.20/1,000 GMS population (95% CI: 3.02-3.38) in 2011. Rates of zopiclone, alprazolam, clobazam, zolpidem and clonazepam remained relatively stable over the ten 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 highest percentage of children taking benzodiazepines on a long-term basis are between 5-11 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.

**Insert Table 2 here**

Benzodiazepine prescribing in children

Gender and Age

Figure 2 shows the prevalence rates of benzodiazepines for all years for males and females and all age groups (0-4 years, 5-11 years and 12-15 years). The interactions age group  $\times$  year ( $p < 0.0001$ ) and age group  $\times$  gender ( $p < 0.0001$ ) were significant. This means that the effect of age group on the prevalence of benzodiazepines differed over years, and 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.

Insert Figure 2 here

Concomitant medications

An antiepileptic was co-prescribed to 28% of BDZ users, an antidepressant to 11% of users, antipsychotics to 5% 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, 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% of users and psychostimulants to 2% of users (Figure 3).

Safe Prescribing

26% of children receiving a prescription for BDZ were prescribed zopiclone, alprazolam, zolpidem or flurazepam – BDZs yet to be deemed safe and efficacious for children. Table 3 shows the number and percentage of children, per age group, taking these both short and long-term. 2000 children were prescribed these BDZs between 2002 and 2006. Similarly from 2007-2011, 2045 children were prescribed the above BDZs.

Insert table 3 here

3.6 % of BDZ prescribed children were taking these BDZ for more than 90 days from 2002 and 2006. Similarly, 3.8% of BDZ prescribed children were taking them for longer than 90 days from 2007 – 2011. The percentage of children on long-term prescriptions of BDZ that have yet to be deemed safe in children varied between 2.9% and 5.6% with the highest percentages lying in the 5-11 years groups. From 2002-2006 to 2007-2011 the percentage of females aged 5-11 and 12-15 on long term use of this type BDZ remained the same and males aged 0-4 and 5-11

## Benzodiazepine prescribing in children

decreased. However, the percentage of males aged 12-15 and females aged 0-4 increased from 2002-2006 to 2007-2011.

**Insert Figure 3 here**

### *Comparison with European countries*

Studies examining overall psychotropic medication trends in paediatric populations and reporting a BDZ prescribing rate in a community setting between 1990 and 2013 were identified (Table 5). Two studies were identified from the Netherlands, one from France and one from Finland.

The overall prescribing rate of BDZ 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 BDZ 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 the data are assessed (Table 5).

**Insert table 4 here**

Benzodiazepine prescribing in children

**Discussion and conclusion:**

*Prescribing Trends*

The overall rate of BDZ 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 GMS children population in Ireland rate of prescribing 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 BDZ have found it difficult to overcome the concern about potential for addiction or other adverse events (e.g. disinhibition).[1] While trends indicate a decrease in prescribing rates in recent times, there are still a significant proportion of the GMS children population being prescribed BDZ without clear evidence for its safety and effectiveness. The current trends highlight the need for more large scale, well designed studies that address the safety concerns associated with prescribing BDZ to children, especially on a long term basis.

*Long-term use*

The long-term prescribing of BDZ in Ireland was investigated and it was found that 5.9% of children prescribed BDZ were taking them for a period longer than 90 days. The prevalence of long-term use increased across the study period and the highest percentage of children taking BDZ long-term in the 5-11 year age group. No formal studies of the long term safety of children on BDZ were found. Long term use in adults has resulted in significant cognitive deficits,(18) withdrawal syndrome [20-22] and increased risk of dependency [10]. The current findings suggest that the proportion of children being prescribed BDZ long-term may be at increased risk of these effects and this may merit further investigation.

*Gender and Age*

The age differences that were observed here are consistent with literature from Denmark[23] and France[24] with prevalence of prescription rates of BDZ increasing with age. The current data shows that 12-15 year olds were prescribed more BDZ. The prevalence rate, for 12-15 year olds, in the current study was slightly higher than that

## Benzodiazepine prescribing in children

observed in Denmark [23]. Significant differences in gender rates of prescribing of BDZ were also seen. Compared to females, males were prescribed more BDZ in the 0-4 year and 5-11 year age groups. However, this pattern reversed for the 12-15 year olds and females were prescribed significantly more. This observation is consistent with the European comparison studies whereby the frequency of BDZ prescribing is higher in boys until age 13 when adolescent girls are then prescribed double that of adolescent boys[24, 25]. 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[26] and gender differences in prevalence of general anxiety disorder usually emerges in early adolescence[27].

**Insert table 5 here**

### *Concomitant medications*

Co-prescribing was most common with antiepileptic medication (27%), followed by antidepressants (11%), and less so, with antipsychotics (4%) and psychostimulants (2%). The comparative European data shows that antidepressants were most commonly prescribed with BDZ (24%) and this was at a higher rate than the Irish population[28]; however, in one comparison study concomitant BDZ prescribing was so low it was not reported[29]. When patients who were prescribed antiepileptics were excluded from the analysis the percentage of concomitant prescribing of antidepressants increased, whereas antipsychotics and psychostimulant prescribing remained similar. This may indicate that children who are being prescribed BDZs with antidepressants are doing so for psychiatric symptoms.

The efficacy of drug combinations in treating paediatric symptoms is under explored. In adult clinical practice, BDZ is regularly co-prescribed with antidepressants in the treatment of depression. For example, a study in Japan found that 60% of patients who presented with major depression were prescribed a combination of BDZ and antidepressant on their first psychiatric visit.[30] In spite of high rates of co-prescribing the efficacy of combined antidepressant and BDZ in the treatment of psychiatric symptoms has not been established. A systematic review examined the treatment of depression with a BDZ and antidepressant combination versus an antidepressant only approach. Results showed that the BDZ and antidepressant combination had a significant impact on patient behaviour whereby it decreased dropout rates. However, 6-8 week follow-up revealed no differences in depression symptoms. The review did however highlight an increased risk of dependence in the combination group (1 in 3 patients) and discussed the

Benzodiazepine prescribing in children

likelihood of reduced effects of BDZ in the combination group due to increased tolerance levels and drug interactions.[30]

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. Research has shown that these can reduce the rate of metabolism of BDZ[31] and in one recent study the combination of fluoxetine and BDZ actually reversed fluoxetine’s anxiogenic effects.[32] These findings, and the observation that a significant proportion of children on BDZ are also being prescribed antidepressants, suggest that an examination of the interactive effects of BDZ and other psychotropic drugs are an important area of further investigation in paediatric prescribing.

*Safe Prescribing*

The difficulty with examining prescribing of BDZ in the current population is not knowing the indication for which the prescription was administered. BDZ is often indicated to treat epilepsy or used as an analgesic in children. In an on-label and off-label capacity it can be also used to treat anxiety in young children. In order to establish any level of inappropriate prescribing, classes of BDZ that are yet to be deemed safe and efficacious in children were examined. This revealed that significant proportion of the children taking BDZs had been prescribed one that is not specifically recommended in childhood and that 3.7% were being prescribed this category of BDZ long-term. The highest percentage of children taking such BDZs was seen in the 12-15 year age category. Practitioners may be more comfortable prescribing psychotropic medication that is approved for adults to the older age group because the efficacy of these medications is well established in adult clinical trials.[33] Nevertheless, the proportion of children on long-term BDZ prescriptions in the current sample and the observation that some potentially inappropriate prescribing of BDZ yet to be deemed safe in children is occurring, indicates the need for further investigation and guidelines for BDZ prescribing in children.

*Limitations*

The HSE-PCRS GMS 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 over-estimation of the

## Benzodiazepine prescribing in children

true trends in BDZ prescription rates, given that children from lower socioeconomic backgrounds are more likely to be prescribed a psychotropic medication[34, 35] and are at greater risk of epilepsy[36] and anxiety related disorders[27] Direct comparison of European prescribing rates for low socioeconomic populations was not possible because of a lack of published data in this sub-population.

The 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 BDZ were prescribed, and why changes in the rates of prescribing were observed over the ten-year period. It could be speculated that the reduced incidence of BDZ prescribing in children may be related to physician preferences, changes in knowledge about the long term effects of BDZ or the development of new medications. Not knowing the indication for which the prescription was administered makes it difficult to fully comment on the quality and appropriateness of BDZ prescribing rates.

### *Conclusions*

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

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Benzodiazepine prescribing in children

**Declarations:**

All authors contributed to the development of this article. T.F., K.B., N. M., & U.R., jointly conceived the study with designed and implemented the analytical model and prepared the manuscript; D.K., & F.B., created the analytic model with contributions from K. OS., and N.M. K.OS., prepared the manuscripts. K.B., T. F., F.B., & K.OS. edited the manuscript.

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The Authors declare that they have no conflict of interest relating to this work.

## Benzodiazepine prescribing in children

## References:

1. Hugtenburg JG, Heerdink ER, Egberts ACG. Increased psychotropic drug consumption by children in the Netherlands during 1995–2001 is caused by increased use of methylphenidate by boys. *Eur J Clin Pharmacol* 2004; **60**(5): 377-9.
2. Chirdkiatgumchai V, Xiao H, Fredstrom BK, et al. National Trends in Psychotropic Medication Use in Young Children: 1994–2009. *Pediatrics* 2013; **132**(4): 615-23.
3. Zito J, Safer D, Berg L, et al. A three-country comparison of psychotropic medication prevalence in youth. *Child Adolesc Psychiatry Ment Health* 2008; **25**: 26 - 32.
4. Wong I, Murray M, Camilleri-Novak D, Stephens P. Increased prescribing trends of paediatric psychotropic medications. *Arch Dis Child* 2004; **89**: 1131 - 2.
5. Witek MW, Rojas V, Alonso C, Minami H, Silva RR. Review of Benzodiazepine use in Children and Adolescents. *Psychiatric Quarterly* 2005; **76**(3): 283-96.
6. Wong I, Camilleri-Novak D, Stephens P. Rise in psychotropic drug prescribing in children in the UK: an urgent public health issue. *Drug Saf* 2003; **26**: 1117 - 8.
7. Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry* 2006; **63**: 679 - 85.
8. Walkup JT, Labellarte MJ, Ginsburg GS. The pharmacological treatment of childhood anxiety disorders. *International Review of Psychiatry* 2002; **14**(2): 135-42.
9. Donoghue J, Lader M. Usage of benzodiazepines: A review. *International Journal of Psychiatry in Clinical Practice* 2010; **14**(2): 78-87.
10. Ilomäki R, Ilomäki E, Hakko H, Räsänen P. Psychotropic medication history of inpatient adolescents — Is there a rationale for benzodiazepine prescription? *Addictive Behaviors* 2011; **36**(1–2): 161-5.
11. Kutcher SP, MacKenzie S. Successful clonazepam treatment of adolescents with panic disorder. *Journal of clinical psychopharmacology* 1988; **8**(4): 299-301.
12. Simeon JG, Ferguson HB. Alprazolam effects in children with anxiety disorders. *Canadian journal of psychiatry Revue canadienne de psychiatrie* 1987; **32**(7): 570-4.
13. Simeon JG, Ferguson HB, Knott V, et al. Clinical, cognitive, and neurophysiological effects of alprazolam in children and adolescents with overanxious and avoidant disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* 1992; **31**(1): 29-33.
14. Graae F, Milner J, Rizzotto L, Klein RG. Clonazepam in childhood anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* 1994; **33**(3): 372-6.
15. Bernstein GA, Garfinkel BD, Borchardt CM. Comparative studies of pharmacotherapy for school refusal. *Journal of the American Academy of Child and Adolescent Psychiatry* 1990; **29**(5): 773-81.
16. Hsia Y, Neubert A, Sturkenboom MCJM, et al. Comparison of antiepileptic drug prescribing in children in three European countries. *Epilepsia* 2010; **51**(5): 789-96.
17. O'Brien CP. Benzodiazepine use, abuse, and dependence. *Journal of Clinical Psychiatry* 2005; **66**(SUPPL. 2): 28-33.
18. Paterniti S, Dufouil C, Alperovitch A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *Journal of clinical psychopharmacology* 2002; **22**(3): 285-93.
19. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 2004; **19**(3): 437-54.
20. Busto U, Sellers EM. Pharmacologic aspects of benzodiazepine tolerance and dependence. *Journal of substance abuse treatment* 1991; **8**(1-2): 29-33.
21. Methodology WCCfDS. Guidelines for ATC classification and DDD assignment 2012. *Oslo* 2011.
22. Rickels K, Case W, Downing RW, Winokur A. Long-term diazepam therapy and clinical outcome. *JAMA* 1983; **250**(6): 767-71.
23. Steinhausen HC, Bisgaard C. Nationwide time trends in dispensed prescriptions of psychotropic medication for children and adolescents in Denmark. *Acta psychiatrica Scandinavica* 2014; **129**(3): 221-31.

Benzodiazepine prescribing in children

24. Acquaviva E, Legleye S, Auleley G, Deligne J, Carel D, Falissard B B. Psychotropic medication in the French child and adolescent population: prevalence estimation from health insurance data and national self-report survey data. *BMC Psychiatry* 2009; **9**(1): 72.

25. Madsen H, Andersen M, Hallas J. Drug prescribing among Danish children: a population-based study. *Eur J Clin Pharmacol* 2001; **57**(2): 159-65.

26. Pigott TA. Anxiety disorders in women. *The Psychiatric clinics of North America* 2003; **26**(3): 621-72, vi-vii.

27. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *The Psychiatric clinics of North America* 2009; **32**(3): 483-524.

28. Gyllenberg D, Sourander A. Psychotropic drug and polypharmacy use among adolescents and young adults: findings from the Finnish 1981 Nationwide Birth Cohort Study. *Nordic journal of psychiatry* 2012; **66**(5): 336-42.

29. Schirm E, Tobi H, Zito J, de Jong-van den Berg L. Psychotropic medication in children: a study from the Netherlands. *Pediatrics* 2001; **108**: E25.

30. Furukawa TA, Streiner DL, Young LT. Antidepressant and benzodiazepine for major depression. *The Cochrane database of systematic reviews* 2002; (1): CD001026.

31. Saber-Tehrani AS, Bruce RD, Altice FL. Pharmacokinetic drug interactions and adverse consequences between psychotropic medications and pharmacotherapy for the treatment of opioid dependence. *The American Journal of Drug and Alcohol Abuse*. 2011;**37**(1):1-11. PubMed PMID: 21247284.

32. Birkett MA, Shinday NM, Kessler EJ, Meyer JS, Ritchie S, Rowlett JK. Acute anxiogenic-like effects of selective serotonin reuptake inhibitors are attenuated by the benzodiazepine diazepam in BALB/c mice. *Pharmacology Biochemistry and Behavior*. 2011 6//;**98**(4):544-51.

33. Zito J, Psychopharmacology ASoC. Pharmacoepidemiology: recent findings and challenges for child and adolescent psychopharmacology. *J Clin Psychiatry*. 2007;68:966 - 7. PubMed PMID: doi:10.4088/JCP.v68n0622.

34. McLaughlin KA, Costello EJ, Leblanc W, Sampson NA, Kessler RC. Socioeconomic Status and Adolescent Mental Disorders. *American Journal of Public Health* 2012; **102**(9): 1742-50.

35. Currie J, Stabile M. Socioeconomic Status and Child Health: Why Is the Relationship Stronger for Older Children? *American Economic Review* 2003; **93**(5): 1813-23.

36. Currie J, Stabile M. Socioeconomic Status and Child Health: Why Is the Relationship Stronger for Older Children? *American Economic Review* 2003; **93**(5): 1813-23.

## Benzodiazepine prescribing in children

**Table 1: Prevalence rates (95% confidence intervals) of prescribing benzodiazepines to children aged 0-15 years from 2002-2011.**

Year	Prevalence rate per 1,000 GMS population (95% confidence interval)
2002	8.56 (8.20-8.92)
2003	8.64 (8.28-9.00)
2004	8.20 (7.84-8.56)
2005	8.42 (8.06-8.78)
2006	7.34 (7.01-7.67)
2007	6.88 (6.57-7.19)
2008	6.32 (6.04-6.60)
2009	5.95 (5.69-6.21)
2010	5.27 (5.03-5.50)
2011	5.33 (5.10-5.55)

Benzodiazepine prescribing in children

**Table 2: The number and percentage of children, per age group, identified as taking Benzodiazepines long-term (> 90 days).**

Males				Females		
	≤90days	>90 days	Total	≤90days	>90 days	Total
<u>2002-2006</u>						
0-4 years	1360 (95.6%)	62 (4.4%)	1422	1114 (96.0%)	46 (4.0%)	1160
5-11 years	1381 (93.7%)	93 (6.3%)	1474	1101 (91.9%)	97 (8.1%)	1198
12-15 years	1162 (93.6%)	80 (6.4%)	1242	1280 (95.0%)	67 (5.0%)	1348
<u>2007-2011</u>						
0-4 years	1166 (95.4%)	56 (4.5%)	1222	923 (94.6%)	53 (5.4%)	976
5-11 years	1325 (92.9%)	101 (7.1%)	1426	956 (91.6%)	88 (8.4%)	1044
12-15 years	1234 (94.0%)	79 (6.0%)	1313	1388 (94.3%)	84 (5.7%)	1472

## Benzodiazepine prescribing in children

**Table 3: The number and percentage of children, per age group, identified as taking zopiclone (N05CF01), alprazolam (N05BA12), zolpidem (N05CF02) or flurazepam (N05CD01) long-term (> 90 days).**

	Males			Females		
	≤90days	>90 days	Total	≤90days	>90 days	Total
<u>2002-2006</u>						
0-4 years	220 (94.4%)	13 (5.6%)	233	196 (97.0%)	6 (3.0%)	202
5-11 years	372 (96.1%)	15 (3.9%)	387	310 (96.9%)	10 (3.1%)	320
12-15 years	366 (97.1%)	11 (2.9%)	377	464 (96.5%)	17 (3.5%)	481
<u>2007-2011</u>						
0-4 years	200 (95.2%)	10 (4.8%)	210	140 (95.9%)	6 (4.1%)	146
5-11 years	373 (96.4%)	14 (3.6%)	387	250 (96.9%)	8 (3.1%)	258
12-15 years	449 (95.9%)	19 (4.1%)	468	556 (96.5%)	20 (3.5%)	576

Benzodiazepine prescribing in children

**Table 4: Percentage of benzodiazepine users (aged 0-15 years) from 2002-2011 taking concomitant medications.**

Year	Benzodiazepine users (n)	Concomitant Antipsychotics n (%)	Concomitant Antiepileptics n (%)	Concomitant Antidepressants n (%)	Concomitant Psychostimulants n (%)
2002	2,127	81 (3.81)	498 (23.41)	272 (12.79)	20 (0.94)
2003	2,154	87 (4.04)	553 (25.67)	266 (12.35)	35 (1.62)
2004	1,990	84 (4.22)	572 (28.74)	215 (10.80)	21 (1.06)
2005	2,031	91 (4.48)	633 (31.17)	219 (10.78)	45 (2.22)
2006	1,928	92 (4.77)	556 (28.84)	215 (11.15)	37 (1.92)
2007	1,916	116 (6.05)	579 (30.22)	204 (10.65)	36 (1.88)
2008	1,895	91 (4.80)	549 (28.97)	213 (11.24)	51 (2.69)
2009	1,996	116 (5.81)	550 (27.56)	211 (10.57)	50 (2.51)
2010	1,951	95 (4.87)	528 (27.06)	222 (11.38)	36 (1.85)
2011	2,067	130 (6.29)	557 (26.95)	255 (12.34)	40 (1.94)

Legend Table 2: Percentage of benzodiazepine users aged 0-15 years who also received concomitant psychotic (column 3) or antiepileptic (column 4) or antidepressant (column 5) or psychostimulant (column 6) medication from 2002-2011.

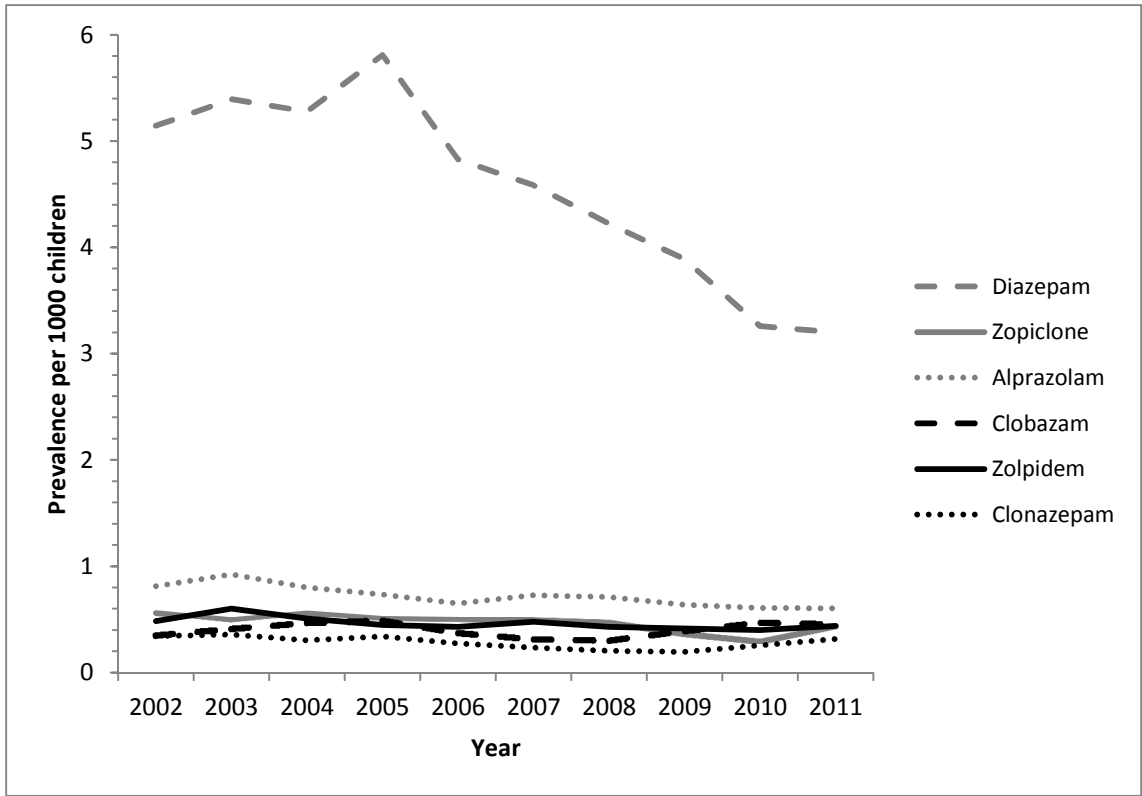
## Benzodiazepine prescribing in children

**Table 5: Characteristics of studies included for comparative data and comparison of average prescribing rates per 1000 GMS children between 2001 and 2011, to European rates per 1000 children**

Study (publication year)	Country (year data represents)	Sample Size	Age	Rate of BDZ Prescribing (per 1000)	Setting
Acquitiva (2009)	France (2003-2005)	14 070 021	0 – 18	7.8/1000	National health insurance system data
Hugtenburg (2003)	Netherlands (1995-2001)	1 000 000	0 -18	9/1000	Dispensing data from retail pharmacies
Gyllenberg (2012)	Finland (1994-2005)	60 007	0 – 24	4.4/1000	National drug prescription register
Schrim (2001)	Netherlands (1995-1999)	31 140	0 – 19	6.9/1000	Dispensing data from community pharmacy database
<b>GMS data</b>	<b>Ireland (2002 – 2011)</b>	<b>311 579</b>	<b>0 - 15</b>	<b>6.7/1000</b>	<b>Primary care reimburse ment service pharmacy claims</b>

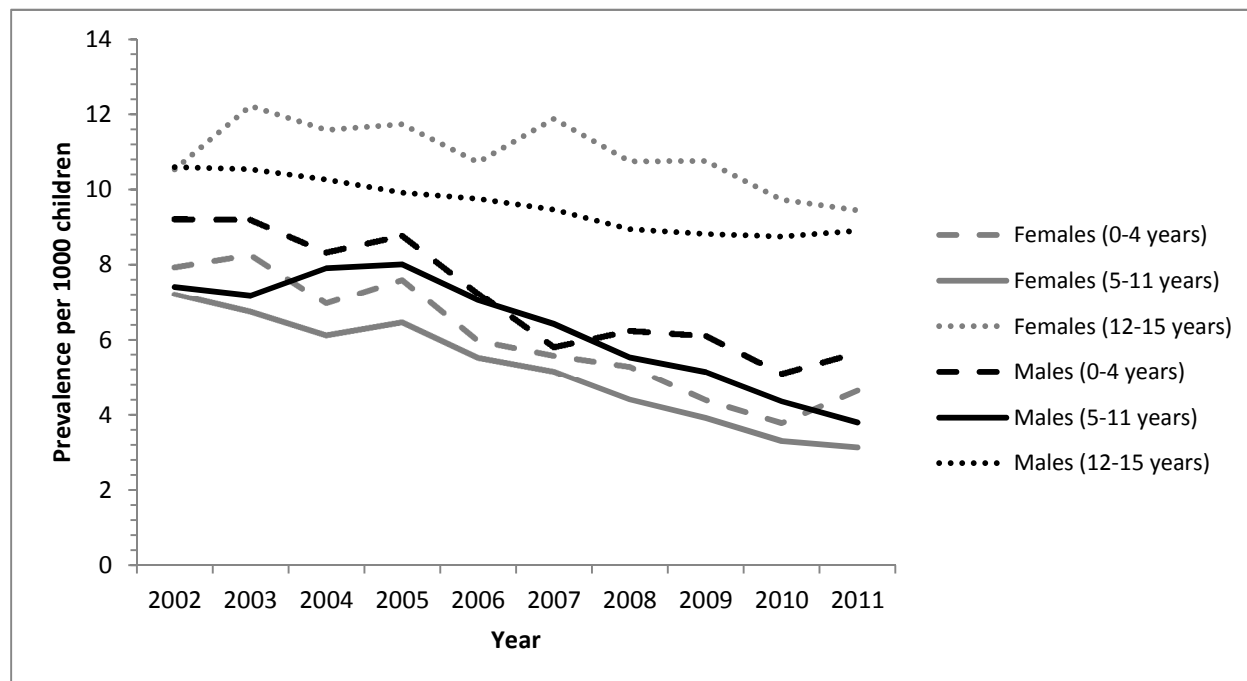
Benzodiazepine prescribing in children

**Fig. 1** Prevalence rates of the six most frequently prescribed benzodiazepines per 1000 GMS population aged 0-15 years old for 2002-2011



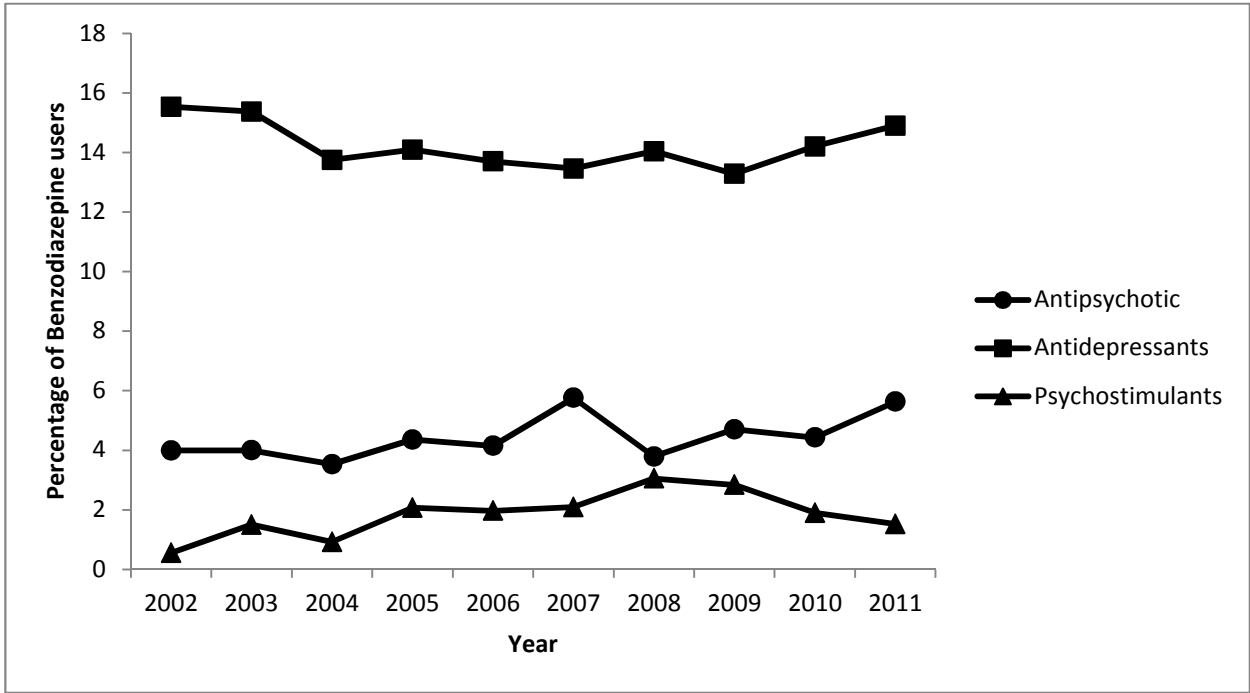
# Benzodiazepine prescribing in children

**Fig. 2** Prevalence rates of benzodiazepines per 1000 GMS population aged 0-15 years old for 2002-2011 classified by gender and age group



Benzodiazepine prescribing in children

**Fig. 3** Percentage of Benzodiazepine users aged 0-15 who are also taking antipsychotic, antidepressants and psychostimulant medications for the years 2002-2011 (excluding patients who took antiepileptics ATC N03)



# BMJ Open

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

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Benzodiazepine prescribing in children

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

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**Abstract**

## Benzodiazepine prescribing in children

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

**Setting:** Data was 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 ( $\leq$  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 (8.56/1,000 GMS population: 95% CI: 8.20-8.92) to 2011 (5.33/1,000 GMS population: 95% CI: 5.10-5.55). 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 5-11 age ranges whereas girls were higher in the 12-15 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 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 long-term. This study highlights the need for guidelines for BZD prescribing in children in terms of clinical indication and responsibility, co-prescribing, dosage and duration of treatment.

Benzodiazepine prescribing in children

Article summary

Strengths and limitations of this study

- This study to examine the prevalence and trends in benzodiazepine (BZD) prescribing in an Irish paediatric population, as well as concomitant use of antipsychotic, antidepressant and psychostimulant drugs.
- The HSE-PCRS GMS 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 over-estimation 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 are at greater risk of epilepsy and anxiety related disorders.
- The database does not contain information about the clinical indication for prescriptions or the setting in which the prescription was initiated (e.g. primary care, hospital or specialist setting).It is unclear why certain classes of BZD were prescribed, and why changes in the rates of prescribing were observed over the ten-year period.

## Benzodiazepine prescribing in children

### Introduction

The use of psychotropic medications among children and adolescents has increased markedly in the last two decades.[1-4] In the US, for example, paediatric use of psychotropic drugs increased three-fold between 1987 and 1996.[5] A similar trend was observed in 9 countries worldwide between 2000 and 2002.[6] Reports suggest 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 children<sup>1</sup>. Those that have examined BZD prescribing practices in children and adolescents report slight increases over time.[5] Despite these trends the literature supporting such increases is sparse and it remains unclear what information is guiding clinicians BZD prescribing practices.[5]

BZDs are often used to control several types of seizures in young children. Amongst the most common BZDs for this indication are diazepam, clonazepam and lorazepam. Diazepam is most frequently used in the treatment of status epileptics and cerebral convulsions.[8] Clinicians recommend caution when prescribing BZD to children and research into long term prescribing in this population advocate short term courses (6-12 weeks) because of their depressant properties and potential for tolerance and dependency.[9, 10] Furthermore, long term use can result in increased risk of cognitive deficits[11, 12] and presentation of mild withdrawal syndrome.[13]

To-date very little work has been conducted to systematically assess the role of BZDs in child and adolescent psychiatric disorders. Little is known about the efficacy of BZDs in the treatment of psychiatric symptoms in children[5, 14, 15] and there is no firmly established indication for their use with childhood psychiatric disorders.(10) Studies that have examined the efficacy of BZDs in the treatment of childhood psychiatric disorders report significant improvements in symptoms. For example, several studies have shown that alprazolam reduces anxiety in children who meet the criteria for anxiety disorder.[16-18] However, there are inconsistencies in the literature. For example, a well-controlled double-blind pilot study revealed no clinically significant effects on anxiety in a small sample of children with a diagnosis of one or more anxiety disorders.[19] Furthermore, a study of social phobia in children and adolescents did not support the use of BZD in anxiety treatment.[20] The differences

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<sup>1</sup> 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.

Benzodiazepine prescribing in children

observed in research findings may be attributed to a number of issues such as a shortage of well-designed studies with longitudinal examination of the effects, an inability to replicate the studies that do demonstrate promising results and the long term safety concerns of prescribing BZD in younger age groups. Furthermore, research to date has focused mostly on adult populations, with limited focus on paediatric prescribing of BZDs in community settings.[5] This is a common feature among many psychotropic medications whereby they are not trialled in children so little or no information is available on their effectiveness and safety.

The aim of the current study is to investigate BZD and z drug prescribing in an Irish paediatric population from a predominately low socio-economic group receiving free medical care over a ten-year period (2002-2011) and to establish long-term prescribing patterns, gender and age trends, and concomitant prescribing rates of BZD in children. An additional aim is to compare the prescribing Irish rates to European studies.

## Benzodiazepine prescribing in children

**Methods***Study population and study design*

Data was obtained from the Irish General Medical Services (GMS) scheme pharmacy claims database from the Health Service Executive (HSE) – Primary Care Reimbursement Services (PCRS). The pharmacy claims database contains basic demographic information and details on monthly dispensed medications, coded using the WHO Anatomical Therapeutic Chemical (ATC) classification system, for each individual within the scheme. The scheme is means tested and provides free health services. It represents approximately 28% of Irish children (<15 years old) but over-represents socially deprived populations. Permission was given by the data controller to use the GMS dataset if anonymised and analysed at group level. Therefore, it was unnecessary to seek specific ethical approval for this study.

Children aged 0-15 years on the HSE-PCRS database between January 2002 and December 2011 was included in this study. All BZD medication prescriptions, (ATC codes: N03AE, N05BA, N05CD and N05CF),<sup>[21]</sup> were extracted from the database. Concomitant psychotropic medication prescriptions were also extracted all antipsychotic medications (N05A), psychostimulant medications (N06B), antiepileptic medications (N03) and antidepressants (N06A).

*Data analysis*

The prevalence of benzodiazepines per 1000 GMS population per year and associated 95% confidence intervals for children aged 0-15 years were calculated as a proportion of all eligible children (0-15 years) entitled to free health services, as identified from the annual reports produced by the PCRS. Prevalence rates are to be interpreted as the prevalence of children under the age of 15 receiving at least one benzodiazepine prescription per 1000 GMS population, as determined from the GMS database. Prevalence rates per 1000 eligible population and associated 95% confidence intervals (CIs) were also calculated across years (2002-2011). Prevalence of short term ( $\leq 90$  days) and long-term ( $> 90$  days) use among children ( $\leq 15$  years) was investigated. Additionally, age groups (0-4 years, 5-11 years and 12-15 years) and gender trends were established. Rates of concomitant prescribing of other psychotropic medication in childhood were calculated.

Benzodiazepine prescribing in children

A negative binomial regression model was used to determine trends in prescribing rates. The log of the GMS population was used as the offset term and year, age group, gender and all possible interactions between these variables were included as fixed effects in the model. The Bonferroni method was used to control for multiple comparisons, p-values were adjusted and p-values <0.01 were deemed significant.

Data analyses was performed using Stata version 11 (StataCorp, College Station, Tx, USA) and SAS version 9.3 (SAS Institute Inc. Cary, NC, USA).

*Comparison to European studies*

Comparison studies, examining overall psychotropic medication trends in paediatric populations, were identified from a search of published literature from 1980 – 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.

## Benzodiazepine prescribing in children

**Results***Population sample*

During the study period, January 2002 to December 2011, the number of children  $\leq 15$  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.

**Insert Table 1 here**

*Prescribing time-trends*

Table 1 shows the prevalence of benzodiazepines for 2002-2011. In 2002, 8.56/1,000 GMS population (95% CI: 8.20-8.92) received at least one benzodiazepine prescription and this rate decreased to 5.33/1,000 GMS population (95% CI: 5.10-5.55) 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).

**Insert figure 1 here**

During the study period diazepam was the most frequently prescribed benzodiazepine. Following the overall benzodiazepine trend, the prevalence decreased from 5.14/1,000 GMS population (95% CI: 4.86-5.42) in 2002 to 3.20/1,000 GMS population (95% CI: 3.02-3.38) in 2011. Rates of zopiclone, alprazolam, clobazam, zolpidem and clonazepam remained relatively stable over the ten 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 highest percentage of children taking benzodiazepines on a long-term basis are between 5-11 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.

**Insert Table 2 here**

Benzodiazepine prescribing in children

Gender and Age

Figure 2 shows the prevalence rates of benzodiazepines for all years for males and females and all age groups (0-4 years, 5-11 years and 12-15 years). The interactions age group  $\times$  year ( $p < 0.01$ ) and age group  $\times$  gender ( $p < 0.01$ ) were significant. This means that the effect of age group on the prevalence of benzodiazepines differed over years, and 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.

Insert Figure 2 here

Concomitant medications

An antiepileptic was co-prescribed to 28% of BZD users, an antidepressant to 11% of users, antipsychotics to 5% 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, 2006 and 2008. Rates of concomitant prescribing of psychostimulants increased from 2002 to 2009 inclusively (Table 3). Excluding patients who took antiepileptic, antipsychotic medication was prescribed to 4% of all benzodiazepine users, an antidepressant to 14% of users and psychostimulants to 2% of users (Figure 3).

Insert Figure 3 here

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. (Table 5). Two studies were identified from the Netherlands, one from France and one from Finland.

Insert Table 3 here

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

## Benzodiazepine prescribing in children

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 the data are assessed.

**Insert table 4 here**

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Benzodiazepine prescribing in children

**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 GMS children population in Ireland rate of prescribing 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 potential for addiction or other adverse events (e.g. disinhibition).[1] While trends indicate a decrease in prescribing rates in recent times, there are still a significant proportion of the GMS children population 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 [22] and that this rate was steadily increasing.[23] 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.[24]

*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. The prevalence of long-term use increased across the study period and the highest percentage of children taking BZD long-term in the 5-11 year age group. No formal studies of the long term safety of children on BZD were found. Long term use in adults has resulted in significant cognitive deficits,(18) withdrawal syndrome [25] and increased risk of dependency. [10] The current findings suggest that the proportion of children being prescribed BZD 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.[22] 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

## Benzodiazepine prescribing in children

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 the current 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 literature from Denmark[26] and France[27] with prevalence of prescription rates of BZD increasing with age. The current data shows that 12-15 year olds were prescribed more BZD. The prevalence rate, for 12-15 year olds, in the current study was slightly higher than that observed in Denmark [25]. Significant differences in gender rates of prescribing of BZD were also seen. Compared to females, males were prescribed more BZD in the 0-4 year and 5-11 year age groups. However, this pattern reversed for the 12-15 year olds 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 of adolescent boys[28]. 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[29] and gender differences in prevalence of general anxiety disorder usually emerges in early adolescence.[30]

### *Concomitant medications*

Co-prescribing was most common with antiepileptic medication (27%), followed by antidepressants (11%), and less so, with antipsychotics (5%) and psychostimulants (2%). The comparative European data shows that antidepressants were most commonly prescribed with BZD (24%) and this was at a higher rate than the Irish population[31]; however, in one comparison study concomitant BZD prescribing was so low it was not reported[32]. When patients who were prescribed antiepileptic were excluded from the analysis the percentage of concomitant prescribing of antidepressants increased, whereas antipsychotics and psychostimulant prescribing remained similar. This may indicate that children who are being prescribed BZDs with antidepressants are doing so for psychiatric symptoms.

The efficacy of drug combinations in treating paediatric symptoms is under explored. A systematic review examined the treatment of depression with a BZD and antidepressant combination versus an antidepressant only approach. Results showed that the BZD and antidepressant combination had a significant impact on patient behaviour whereby

Benzodiazepine prescribing in children

it decreased dropout rates. However, 6-8 week follow-up revealed no differences in depression symptoms. The review did however highlight an increased risk of dependence in the combination group (1 in 3 patients) and discussed the likelihood of reduced effects of BZD in the combination group due to increased tolerance levels and drug interactions.[33] In adult clinical practice, BZD is regularly co-prescribed with antidepressants in the treatment of depression. A study in Japan found that 60% of patients who presented with major depression were prescribed a combination of BZD and antidepressant on their first psychiatric visit.[34] In spite of high rates of co-prescribing the efficacy of combined antidepressant and BZD in the treatment of psychiatric symptoms has not been established

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[34] and in one recent animal study the combination of fluoxetine and BZD actually reversed fluoxetine's anxiogenic effects.[35] 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 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 over-estimation of the true trends in BZD prescription rates, given that children from lower socioeconomic backgrounds are more likely to be prescribed a psychotropic medication[30, 36] and are at greater risk of epilepsy[37] and anxiety related disorders.[30] Direct comparison of European prescribing rates for low socioeconomic populations was not possible because of a lack of published data in this sub-population.

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 ten-year

## Benzodiazepine prescribing in children

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 BZD are often indicated to treat epilepsy. In this study, it is impossible to know whether BZD was prescribed to treat anxiety or epilepsy. To 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 to psychiatric/psychological indications. {26}

### *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 is close to the median value relative to available European countries. However, it remains that children are still being prescribed BZDs, both short 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.

Benzodiazepine prescribing in children

**Declarations:**

All authors contributed to the development of this article. T.F., K.B., N. M., & U.R., jointly conceived the study with designed and implemented the analytical model and prepared the manuscript; D.K., & F.B., created the analytic model with contributions from K. OS., and N.M. K.OS., prepared the manuscripts. K.B., T. F., F.B., & K.OS. edited the manuscript.

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## Benzodiazepine prescribing in children

## References:

1. Hugtenburg JG, Heerdink ER, Egberts ACG. Increased psychotropic drug consumption by children in the Netherlands during 1995–2001 is caused by increased use of methylphenidate by boys. *Eur J Clin Pharmacol* 2004; **60**(5): 377-9.
2. Chirdkiatgumchai V, Xiao H, Fredstrom BK, et al. National Trends in Psychotropic Medication Use in Young Children: 1994–2009. *Pediatrics* 2013; **132**(4): 615-23.
3. Zito J, Safer D, Berg L, et al. A three-country comparison of psychotropic medication prevalence in youth. *Child Adolesc Psychiatry Ment Health* 2008; **25**: 26 - 32.
4. Wong I, Murray M, Camilleri-Novak D, Stephens P. Increased prescribing trends of paediatric psychotropic medications. *Arch Dis Child* 2004; **89**: 1131 - 2.
5. Witek MW, Rojas V, Alonso C, Minami H, Silva RR. Review of Benzodiazepine use in Children and Adolescents. *Psychiatric Quarterly* 2005; **76**(3): 283-96.
6. Wong I, Camilleri-Novak D, Stephens P. Rise in psychotropic drug prescribing in children in the UK: an urgent public health issue. *Drug Saf* 2003; **26**: 1117 - 8.
7. Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry* 2006; **63**: 679 - 85.
8. Walkup JT, Labellarte MJ, Ginsburg GS. The pharmacological treatment of childhood anxiety disorders. *International Review of Psychiatry* 2002; **14**(2): 135-42.
9. Donoghue J, Lader M. Usage of benzodiazepines: A review. *International Journal of Psychiatry in Clinical Practice* 2010; **14**(2): 78-87.
10. Ilomäki R, Ilomäki E, Hakko H, Räsänen P. Psychotropic medication history of inpatient adolescents — Is there a rationale for benzodiazepine prescription? *Addictive Behaviors* 2011; **36**(1–2): 161-5.
11. Kutcher SP, MacKenzie S. Successful clonazepam treatment of adolescents with panic disorder. *Journal of clinical psychopharmacology* 1988; **8**(4): 299-301.
12. Simeon JG, Ferguson HB. Alprazolam effects in children with anxiety disorders. *Canadian journal of psychiatry Revue canadienne de psychiatrie* 1987; **32**(7): 570-4.
13. Simeon JG, Ferguson HB, Knott V, et al. Clinical, cognitive, and neurophysiological effects of alprazolam in children and adolescents with overanxious and avoidant disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* 1992; **31**(1): 29-33.
14. Graae F, Milner J, Rizzotto L, Klein RG. Clonazepam in childhood anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* 1994; **33**(3): 372-6.
15. Bernstein GA, Garfinkel BD, Borchardt CM. Comparative studies of pharmacotherapy for school refusal. *Journal of the American Academy of Child and Adolescent Psychiatry* 1990; **29**(5): 773-81.
16. Hsia Y, Neubert A, Sturkenboom MCJM, et al. Comparison of antiepileptic drug prescribing in children in three European countries. *Epilepsia* 2010; **51**(5): 789-96.
17. O'Brien CP. Benzodiazepine use, abuse, and dependence. *Journal of Clinical Psychiatry* 2005; **66**(SUPPL. 2): 28-33.
18. Paterniti S, Dufouil C, Alperovitch A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *Journal of clinical psychopharmacology* 2002; **22**(3): 285-93.
19. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 2004; **19**(3): 437-54.
20. Busto U, Sellers EM. Pharmacologic aspects of benzodiazepine tolerance and dependence. *Journal of substance abuse treatment* 1991; **8**(1-2): 29-33.
21. Methodology WCCfDS. Guidelines for ATC classification and DDD assignment 2012. Oslo 2011.
22. Benzodiazepine Committee. (2002) Report of the Benzodiazepine Committee, August 2002. Department of Health and Children, Dublin.
23. Galvin, Brian (2009) Use of minor tranquillisers and sedatives in the WRDTF area. Drugnet Ireland, Issue 30, Summer 2009 . pp. 10-11
24. A consensus statement on the use of benzodiazepines in specialist mental health services, College of Psychiatry (Ireland), June 2012: "Benzodiazepines are licensed for use for 4 weeks only."
25. Rickels K, Case W, Downing RW, Winokur A. Long-term diazepam therapy and clinical outcome. *JAMA* 1983; **250**(6): 767-71.

Benzodiazepine prescribing in children

26. Steinhausen HC, Bisgaard C. Nationwide time trends in dispensed prescriptions of psychotropic medication for children and adolescents in Denmark. *Acta psychiatrica Scandinavica* 2014; **129**(3): 221-31.

27. Acquaviva E, Legleye S, Auleley G, Deligne J, Carel D, Falissard B B. Psychotropic medication in the French child and adolescent population: prevalence estimation from health insurance data and national self-report survey data. *BMC Psychiatry* 2009; **9**(1): 72.

28. Madsen H, Andersen M, Hallas J. Drug prescribing among Danish children: a population-based study. *Eur J Clin Pharmacol* 2001; **57**(2): 159-65.

29. Pigott TA. Anxiety disorders in women. *The Psychiatric clinics of North America* 2003; **26**(3): 621-72, vi-vii.

30. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *The Psychiatric clinics of North America* 2009; **32**(3): 483-524.

31. Gyllenberg D, Sourander A. Psychotropic drug and polypharmacy use among adolescents and young adults: findings from the Finnish 1981 Nationwide Birth Cohort Study. *Nordic journal of psychiatry* 2012; **66**(5): 336-42.

32. Schirm E, Tobi H, Zito J, de Jong-van den Berg L. Psychotropic medication in children: a study from the Netherlands. *Pediatrics* 2001; **108**: E25.

33. Furukawa TA, Streiner DL, Young LT. Antidepressant and benzodiazepine for major depression. *The Cochrane database of systematic reviews* 2002; (1): CD001026.

34. Saber-Tehrani AS, Bruce RD, Altice FL. Pharmacokinetic drug interactions and adverse consequences between psychotropic medications and pharmacotherapy for the treatment of opioid dependence. *The American Journal of Drug and Alcohol Abuse*. 2011;**37**(1):1-11. PubMed PMID: 21247284.

35. Zito J, Psychopharmacology ASoC. Pharmacoepidemiology: recent findings and challenges for child and adolescent psychopharmacology. *J Clin Psychiatry*. 2007;68:966 - 7. PubMed PMID: doi:10.4088/JCP.v68n0622.34.

36. McLaughlin KA, Costello EJ, Leblanc W, Sampson NA, Kessler RC. Socioeconomic Status and Adolescent Mental Disorders. *American Journal of Public Health* 2012; **102**(9): 1742-50.

37. Currie J, Stabile M. Socioeconomic Status and Child Health: Why Is the Relationship Stronger for Older Children? *American Economic Review* 2003; **93**(5): 1813-23.

Benzodiazepine prescribing in children

**Table 1: Prevalence rates (95% confidence intervals) of prescribing benzodiazepines to children aged 0-15 years from 2002-2011.**

Year	Prevalence rate per 1,000 GMS population (95% confidence interval)
2002	8.56 (8.20-8.92)
2003	8.64 (8.28-9.00)
2004	8.20 (7.84-8.56)
2005	8.42 (8.06-8.78)
2006	7.34 (7.01-7.67)
2007	6.88 (6.57-7.19)
2008	6.32 (6.04-6.60)
2009	5.95 (5.69-6.21)
2010	5.27 (5.03-5.50)
2011	5.33 (5.10-5.55)

Benzodiazepine prescribing in children

**Table 2: The number and percentage of children, per age group, identified as taking Benzodiazepines long-term (> 90 days).**

Males				Females		
	≤90days	>90 days	Total	≤90days	>90 days	Total
<u>2002-2006</u>						
0-4 years	1360 (95.6%)	62 (4.4%)	1422	1114 (96.0%)	46 (4.0%)	1160
5-11 years	1381 (93.7%)	93 (6.3%)	1474	1101 (91.9%)	97 (8.1%)	1198
12-15 years	1162 (93.6%)	80 (6.4%)	1242	1280 (95.0%)	67 (5.0%)	1348
<u>2007-2011</u>						
0-4 years	1166 (95.4%)	56 (4.5%)	1222	923 (94.6%)	53 (5.4%)	976
5-11 years	1325 (92.9%)	101 (7.1%)	1426	956 (91.6%)	88 (8.4%)	1044
12-15 years	1234 (94.0%)	79 (6.0%)	1313	1388 (94.3%)	84 (5.7%)	1472

## Benzodiazepine prescribing in children

**Table 3: Percentage of benzodiazepine users (aged 0-15 years) from 2002-2011 taking concomitant medications.**

Year	Benzodiazepine users (n)	Concomitant Antipsychotics n (%)	Concomitant Antiepileptics n (%)	Concomitant Antidepressants n (%)	Concomitant Psychostimulants n (%)
2002	2,127	81 (3.81)	498 (23.41)	272 (12.79)	20 (0.94)
2003	2,154	87 (4.04)	553 (25.67)	266 (12.35)	35 (1.62)
2004	1,990	84 (4.22)	572 (28.74)	215 (10.80)	21 (1.06)
2005	2,031	91 (4.48)	633 (31.17)	219 (10.78)	45 (2.22)
2006	1,928	92 (4.77)	556 (28.84)	215 (11.15)	37 (1.92)
2007	1,916	116 (6.05)	579 (30.22)	204 (10.65)	36 (1.88)
2008	1,895	91 (4.80)	549 (28.97)	213 (11.24)	51 (2.69)
2009	1,996	116 (5.81)	550 (27.56)	211 (10.57)	50 (2.51)
2010	1,951	95 (4.87)	528 (27.06)	222 (11.38)	36 (1.85)
2011	2,067	130 (6.29)	557 (26.95)	255 (12.34)	40 (1.94)

**Legend Table 2:** Percentage of benzodiazepine users aged 0-15 years who also received concomitant psychotic (column 3) or antiepileptic (column 4) or antidepressant (column 5) or psychostimulant (column 6) medication from 2002-2011.

Benzodiazepine prescribing in children

**Table 4: Characteristics of studies included for comparative data and comparison of average prescribing rates per 1000 GMS children between 2001 and 2011, to European rates per 1000 children**

Study (publication year)	Country (year data represents)	Sample Size	Age	Rate of BZD Prescribing (per 1000)	Setting
Acquiviva (2009)	France (2003-2005)	14 070 021	0 – 18	7.8/1000	National health insurance system data
Hugtenburg (2003)	Netherlands (1995-2001)	1 000 000	0 -18	9/1000	Dispensing data from retail pharmacies
Gyllenberg (2012)	Finland (1994-2005)	60 007	0 – 24	4.4/1000	National drug prescription register
Schrim (2001)	Netherlands (1995-1999)	31 140	0 – 19	6.9/1000	Dispensing data from community pharmacy database
<b>GMS data</b>	<b>Ireland (2002 – 2011)</b>	<b>311 579</b>	<b>0 - 15</b>	<b>6.7/1000</b>	<b>Primary care reimburse ment service pharmacy claims</b>

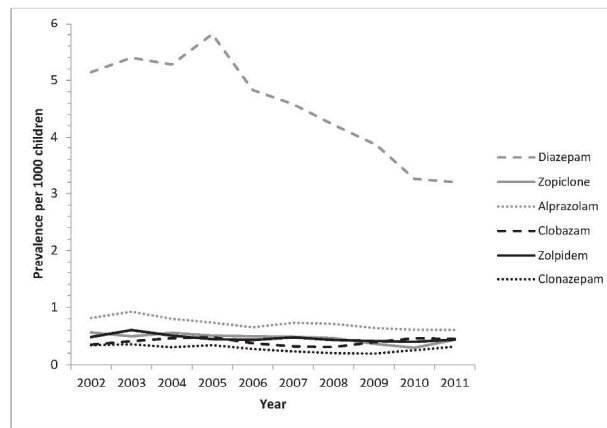


Fig. 1 Prevalence rates of the six most frequently prescribed benzodiazepines per 1000 GMS population aged 0-15 years old for 2002-2011  
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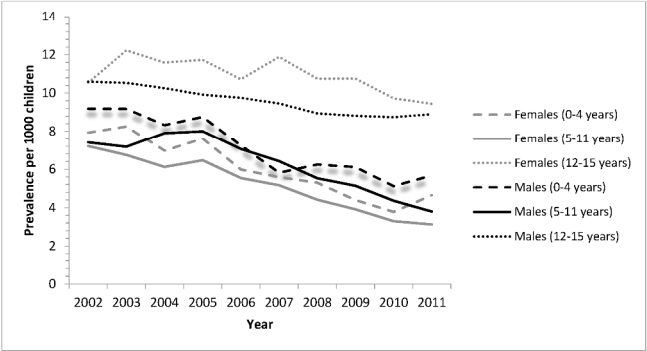


Fig. 2 Prevalence rates of benzodiazepines per 1000 GMS population aged 0-15 years old for 2002-2011  
classified by gender and age group  
210x297mm (300 x 300 DPI)

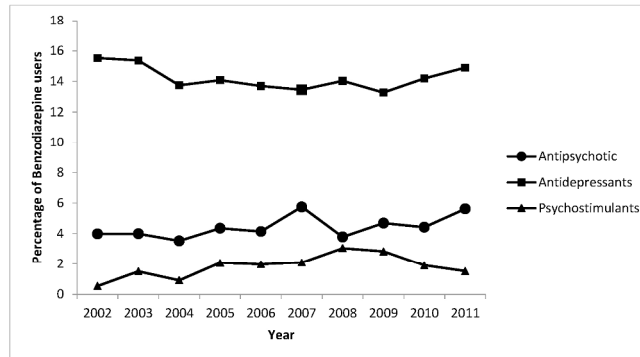


Fig. 3 Percentage of Benzodiazepine users aged 0-15 who are also taking antipsychotic, antidepressants and psychostimulant medications for the years 2002-2011 (excluding patients who took antiepileptics ATC N03)

210x297mm (300 x 300 DPI)