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PHARMACO-EPIDEMIOLOGY

Rise in psychotropic drug prescribing in children and adolescents during 1992–2001: a population-based study in the UK

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Abstract *Background* The trend towards increased psychotropic drug prescribing in children and adolescents is well recognised in North America and continental Europe. However, it is unclear to what extent these studies are applicable to clinical practice in the United Kingdom (UK). This study was conducted to estimate the prevalence of psychotropic drug prescribing in children and adolescents aged <19 years in general practice in the UK from January 1992 to December 2001. *Methods* Data were obtained from the General Practice Research Database (GPRD). Annual age- and sex-specific prevalence of psychotropic drug prescribing was calculated. *Results* A total of 143,079 prescriptions were issued to 34,398 study subjects. Stimulant prescriptions rose significantly from 0.03 per 1,000 (95% confidence interval 0.02–0.04) in 1992 to 2.9 per 1,000 (2.52–3.32) in 2001; a 96-fold increase. Methylphenidate accounted for the majority of stimulant prescriptions; 2.4% (349/14,370) of stimulant prescriptions were prescribed to children aged <6 years. Increased prescribing was also noted for antidepressants (1.6-fold), hypnotics/anxiolytics (1.3-fold), antipsychotics (1.3-fold) and anticonvulsants (1.3-fold), whilst the prevalence of clonidine and lithium prescribing remained fairly stable throughout the study period. The use of antidepressant, hypnotic/anxiolytic and anticonvulsant increased with increasing age. A high proportion of boys received stimulants, whereas antidepressants and hypnotics/anxiolytics were more likely prescribed to girls. *Conclusion* There is an increased trend of psychotropic drug use in children and adolescents in the UK practice. Since most psychotropic drugs are not licensed for use in children at this time, research is needed to investigate the efficacy and long-term safety in this population.

Keywords Psychotropic drug · Children · Adolescent · Drug utilization · Prevalence

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Background

Several studies have reported a significant increase in psychotropic drug use in children and adolescents in the US and continental Europe [1–5]. This increasing trend was mainly attributable to the treatment of Attention Deficit Hyperactivity Disorder (ADHD) with stimulants, especially methylphenidate [3, 5–8]. The efficacy of methylphenidate use in children with ADHD has been extensively studies over the years [9, 10]. In contrast, data on efficacy and safety of other psychotropic drug classes in children are still limited at this time [11, 12]. A study by Wong et al. [13] which compared psychotropic drug prescribing between nine European countries during the years 2000 to 2002, showed that the increase in use was highest in the UK. Although a general increase in psychotropic drug prescribing in the UK has been demonstrated, the extent of use amongst children and adolescents in primary care settings remains unclear. In addition, many utilisation studies have been conducted in the US and it is unclear to what extent these studies are applicable to clinical practice in the UK. Therefore, we conducted a retrospective study to investigate the prevalence of psychotropic drug prescribing in children and adolescents between 1992 and 2001.

Methods

This study was carried out using the General Practice Research Database (GPRD). The GPRD contains anonymised patient records from general practices in the UK [14]. It covers approximately 5% of the UK population, and is broadly representative of the population in terms of demographic distribution [15]. In 2001, the database comprised the anonymised medical records of about 8 million people from 1987 onwards, with about 30 million person-years of observation [16]. Information held on the database includes demographic detail, clinical information, prescription details, immunisation, hospital referrals and some laboratory test results. The quality of the information has been validated in a number of studies and the completeness of medical recording was found to be high [14, 17].

The study population was drawn from the GPRD and included all children and adolescents aged <19 years registered with a GP who contributed data to the database at any time between 1 January 1992 and 31 December 2001. Study subjects were identified as those who had received at least one prescription for psychotropic drug. Psychotropic drugs were grouped according to the British National Formulary (BNF) as follows: hypnotics/anxiolytics, antipsychotics, antidepressants, stimulants and anticonvulsants. Lithium was separated from other antipsychotics as it is used mainly for manic and bipolar disorders [18]. As study from the US have suggested that the use of clonidine in children with hyperactivity problems has increased [3], we also examined its usage. Annual prevalence of prescribing was calculated from the total number of children and adolescents with at least one psychotropic drug prescription in each year and the total number of patients aged <19 years registered on the GPRD. Age and sex-specific prevalence of psychotropic drug prescribing was also calculated, stratified by the following age bands: 0–2, 3–5, 6–9, 10–12, 13–15, and 16–18 years. To investigate gender differences in prescribing patterns over time, boy–girl prevalence ratios were calculated by dividing the prevalence of prescriptions for boys by that of girls.

Statistical analysis

A Chi-square test (Cochran–Armitage test for trend) was used to examine the yearly trend in psychotropic drug prescribing. The boy–girl prevalence ratios of psychotropic drug use, with 95% confidence intervals, were calculated using the Taylor series method [19]. Analyses were carried out using STATA version 8.0 (Stata Corp, College Station, Texas).

Results

A total number of 143,079 prescriptions were issued to 34,398 study subjects, 44.3% (15,228/34,398) of whom were boys. The average age at first psychotropic prescription was 12.6 years (SD 5.4). The average number of prescriptions per user was 4.2 (SD 8.6). On average, study subjects were prescribed 1.2 different psychotropic drugs (SD 0.67; range 1–18); 81.3% (27,975/34,398) of study subjects received medication from only one psychotropic drug group. Over the study period, 2.4% (349/14,370) stimulant prescriptions were issued to children aged under 6 years.

Figure 1 shows the sex-specific prevalence for psychotropic drug prescribing by calendar year. There was a significant increase in stimulant, antidepressant, hypnotic/anxiolytic, antipsychotic and anticonvulsant prescriptions over time. Stimulant use increased dramatically with a 96-fold increase over time; methylphenidate accounted for the majority of these prescriptions (92%; 13,241/14,372). Antidepressant prescribing showed a 1.6-fold increase over time ($P < 0.001$), girls predominated antidepressant usage, whereas the use amongst boys remained relatively stable. Prevalence of antipsychotic, hypnotic/anxiolytics, and anticonvulsant prescribing increased 1.3-fold ($P < 0.001$). Lithium use remained relatively stable throughout the study period ($P = 0.59$).

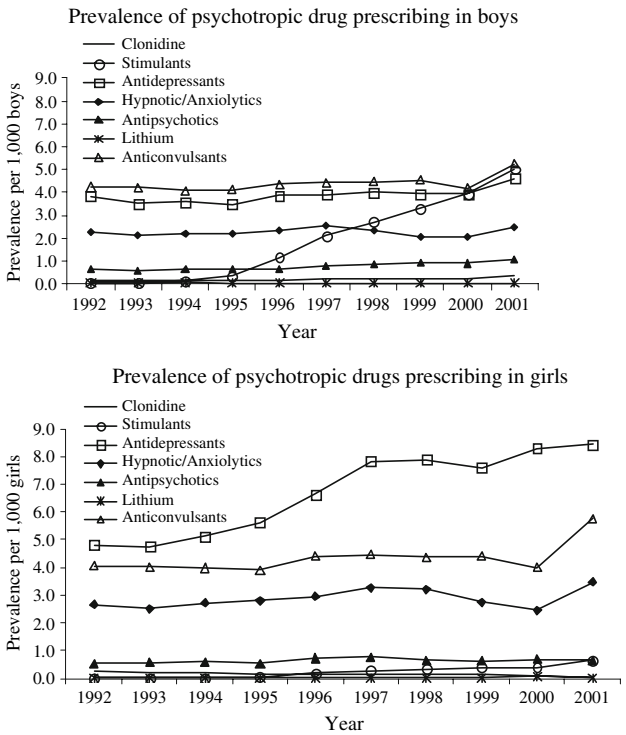

Fig. 1 Sex-specific prevalence of psychotropic drug prescribing in children and adolescents aged 0–18 years

Table 1 shows the age-specific prevalence of psychotropic drug prescribing by calendar year. Except amongst 0- to 2-year-olds, the use of stimulants increased significantly in all age groups, with the highest use amongst children aged 10–12 years. Antidepressant and anticonvulsant prescribing increased with age; the prevalence of antidepressant prescribing was highest amongst those aged 16–18 years. Antipsychotic prescribing declined in children aged <10 years, whilst an increase in use was observed amongst those aged 10–18 years.

The boy–girl prevalence ratio of stimulant use widened during the years 1992–2001, from 3.00 (1.20–7.50) to 9.52 (6.69–13.6), suggesting an increased use in boys (Table 2). Although there was no overall increase in clonidine prescribing ($P = 0.63$), the prevalence ratio revealed that clonidine use increased in boys. The prevalence ratio of antipsychotic drug was comparable in both sexes.

Discussion

This study indicates that the prescribing of antidepressants (aged 13–15 years), hypnotics/anxiolytics (aged 13–18 years), antipsychotics (aged 10–18 years), anticonvulsants (aged 6–18), and in particular, stimulants amongst some children and adolescents (aged 3–18) has statistically increased in the UK between 1992 and 2001. The level of clonidine and lithium prescribing remained relatively stable. The majority of study subjects received only one psychotropic drug class.

There are several limitations need to note. Firstly, the indications for prescribing, dosage, switching of medications, and duration of use are not presented in this study. Those data are crucial to evaluate the rationality of prescribing from a clinical perspective. However, the aim of this study was to provide the overall trend of use of these drugs in primary care settings. This finding will enable us to prioritize further research on paediatric psychiatry. Secondly, the prescribing of methylphenidate should be initiated by specialists in the UK. Although referral data are recorded in the GPRD, which specialists involved in assessing cases and initiating stimulant prescribing is unrecorded. Hence, we were unable to evaluate those specialists' attitudes toward prescribing. Thirdly, the GPRD does not contain information on socio-economic status (SES) and ethnicity so we were not able to examine how these factors might be associated with the prevalence of psychotropic drug prescribing.

Comparison with other studies

In our study, the increased use of stimulant prescribing is in line with that seen in other countries. However, the overall prevalence of stimulant prescribing was lower in our study population. According to the National Institute for Clinical Excellence (NICE) guideline, about 1% of children aged 6–16 (69,000 in England and 4,200 in Wales) meet the diagnostic criteria for hyperkinetic disorder, of which approximately 48,000 of these children are not receiving treatment with methylphenidate in the UK [20]. It has been suggested that under-diagnosis of ADHD is of greater concern than over-diagnosis in the UK [21]. A GPRD-based study estimated the prevalence of stimulant-treated attention deficit disorder in boys aged 5–14 years. The findings indicated a lower incidence rate of stimulant treatment for attention deficit disorder compared with that of other countries [22]. Despite the use of stimulants being lower than other countries, usage has increased dramatically during 1992 and 2001. This trend may be attributed in part to a change in the licensing status of methylphenidate. As a controlled drug, methylphenidate used to be available from the license holder on a named patient basis. In 1995, the drug licence changed to make it generally available through wholesaler, which would be one of plausible explanations for this growth [23, 24]. In addition, ADHD is becoming a more recognised disorder. The 'hyperkinetic disorder' is more clearly defined in the ICD-10 than in the previous version, this change could possibly make ADHD more readily diagnosed [21, 24, 25].

Based on data from one Health Maintenance Organization (HMO) database and two state Medicaid databases, Zito et al. [2, 3] observed a steep increase in the use of α-agonists, antidepressants, anticonvulsants, lithium, neuroleptics, and stimulants in youths aged <20 years. In the Netherlands, the prevalence of stimulant, antipsychotic, and hypnotic/anxiolytic prescribing was shown to significantly increase, during 1995 and 1999, whilst clonidine and lithium prescribing remained stable [5]. The level of antidepressant prescribing in our study is similar to that reported by Murray et al. using the GPRD data [26]. In contrast to Zito et al. [1] girls were more likely to be prescribed antidepressants than boys in the US. Antipsychotics were more likely to prescribe to adolescents aged 16–18 years in our study. This may probably due to adolescent-onset schizophrenia (before aged 18 years) [27]. In contrast to US studies, the use of clonidine and lithium remained relatively stable in our study. A study by Zito et al. [28] comparing one year prevalence of psychotropic drug prescribing in youths (aged 0–19) in US, the Netherlands, and Germany has shown a variation of prescribing between countries. Authors stated that several factors such as government regulatory restriction, reimbursement policy, diagnostic guidance and cultural belief may be attributable for this variation. The difference of concomitant use of psychotropic drugs also been observed in our study. A review article by Safer et al. noted that the rate of concomitant prescribing of psychotropic drugs has increased, particularly in

Table 1 Age-specific prevalence of psychotropic drug prescriptions in children and adolescents aged 0–18 years, 1992–2001

Prevalence	1992	1995	1998	1999	2001
Clonidine					
0–2	0.01 (0.0003–0.06)	NA	NA	NA	NA
3–5	NA	0.01 (0.002–0.04)	0.02 (0.003–0.08)	0.02 (0.005–0.11)	NA
6–9[a]	0.05 (0.02–0.09)	0.04 (0.01–0.08)	0.15 (0.08–0.25)	0.14 (0.07–0.25)	0.12 (0.01–0.44)
10–12	0.20 (0.11–0.25)	0.10 (0.06–0.17)	0.21 (0.12–0.34)	0.18 (0.09–0.33)	0.23 (0.05–0.66)
13–15	0.39 (0.29–0.52)	0.23 (0.15–0.32)	0.27 (0.16–0.42)	0.34 (0.20–0.54)	0.30 (0.08–0.77)
16–18	0.52 (0.41–0.66)	0.40 (0.29–0.53)	0.24 (0.14–0.39)	0.26 (0.14–0.44)	0.24 (0.05–0.69)
Stimulants					
0–2	0.01 (0.0003–0.06)	NA	NA	NA	NA
3–5[a]	NA	0.02 (0.004–0.06)	0.22 (0.12–0.36)	0.12 (0.04–0.26)	0.18 (0.02–0.64)
6–9[a]	0.06 (0.03–0.10)	0.34 (0.26–0.43)	2.02 (1.75–2.32)	2.53 (2.18–2.93)	2.78 (2.04–3.71)
10–12[a]	0.06 (0.02–0.11)	0.40 (0.30–0.52)	3.20 (2.80–3.63)	3.72 (3.22–4.27)	6.14 (4.88–7.64)
13–15[a]	0.03 (0.008–0.08)	0.26 (0.17–0.36)	2.34 (1.99–2.72)	2.76 (2.33–3.25)	4.69 (3.59–6.01)
16–18[a]	0.008 (0.0002–0.04)	0.05 (0.02–0.11)	0.50 (0.35–0.70)	0.80 (0.57–1.08)	1.65 (1.02–2.53)
Antidepressants					
0–2	0.15 (0.09–0.25)	0.11 (0.05–0.20)	0.07 (0.02–0.22)	0.23 (0.09–0.48)	NA
3–5	1.10 (0.91–1.25)	0.60 (0.48–0.74)	0.40 (0.26–0.58)	0.32 (0.18–0.52)	0.35 (0.10–0.90)
6–9	4.72 (4.42–5.04)	3.25 (3.00–3.52)	2.45 (2.15–2.78)	2.16 (1.83–2.53)	2.12 (1.48–2.95)
10–12	4.15 (3.83–4.50)	3.32 (3.02–3.64)	2.99 (2.61–3.41)	2.89 (2.47–3.39)	2.12 (1.41–3.07)
13–15[a]	4.14 (3.80–4.51)	3.65 (3.32–3.99)	4.77 (4.28–5.31)	4.56 (4.00–5.18)	6.13 (4.86–7.61)
16–18[a]	8.52 (8.03–9.04)	13.7 (13.1–14.4)	20.1 (19.1–21.2)	20.2 (19.1–21.6)	23.9 (21.3–26.8)
Hypnotics/Anxiolytics					
0–2	3.92 (3.54–4.34)	3.17 (2.80–3.58)	2.56 (2.09–3.10)	2.05 (1.57–2.63)	2.15 (1.14–3.67)
3–5	1.89 (1.68–2.12)	1.79 (1.58–2.02)	1.33 (1.07–1.64)	1.14 (0.86–1.48)	1.50 (0.87–2.40)
6–9	0.90 (0.77–1.05)	0.93 (0.80–1.08)	1.01 (0.82–1.22)	0.85 (0.65–1.09)	1.40 (0.88–2.09)
10–12	0.97 (0.82–1.15)	1.04 (0.87–1.22)	1.12 (0.89–1.40)	1.04 (0.79–1.35)	1.37 (0.81–2.16)
13–15[a]	1.71 (1.50–1.95)	1.99 (1.76–2.24)	2.02 (1.70–2.39)	2.04 (1.68–2.47)	2.95 (2.10–4.03)
16–18[a]	5.17 (4.79–5.57)	5.87 (5.44–6.32)	7.36 (6.73–8.04)	6.39 (5.71–7.13)	8.33 (6.83–10.1)
Anticonvulsants					
0–2	4.41 (4.01–4.85)	4.21 (3.79–4.68)	3.08 (2.56–3.67)	2.74 (2.19–3.40)	3.97 (2.54–5.90)
3–5	3.85 (3.55–4.18)	3.47 (3.17–3.78)	3.76 (3.32–4.25)	3.50 (3.00–4.06)	4.31 (3.19–5.70)
6–9[a]	3.81 (3.55–4.09)	3.71 (3.44–3.99)	4.49 (4.08–4.93)	4.60 (4.12–5.12)	5.26 (4.22–6.50)
10–12[a]	4.55 (4.21–4.91)	4.46 (4.12–4.83)	4.94 (4.44–5.47)	5.56 (4.96–6.23)	6.14 (4.88–7.64)
13–15[a]	5.62 (5.22–6.03)	5.13 (4.76–5.52)	6.06 (5.50–6.60)	6.06 (5.45–6.76)	7.34 (5.95–8.95)
16–18[a]	7.58 (7.12–8.07)	8.31 (7.80–8.84)	9.29 (8.58–10.0)	8.58 (7.79–9.43)	9.05 (7.47–10.9)
Antipsychotics					
0–2	0.11 (0.05–0.20)	0.12 (0.06–0.22)	0.07 (0.02–0.22)	NA	NA
3–5	0.07 (0.04–0.13)	0.07 (0.03–0.13)	0.07 (0.02–0.17)	0.08 (0.02–0.20)	NA
6–9	0.15 (0.01–0.21)	0.20 (0.14–0.28)	0.24 (0.16–0.36)	0.15 (0.07–0.27)	0.18 (0.04–0.53)
10–12[a]	0.28 (0.20–0.39)	0.27 (0.19–0.38)	0.48 (0.33–0.67)	0.53 (0.35–0.76)	0.53 (0.21–1.09)
13–15[a]	0.65 (0.52–0.81)	0.54 (0.42–0.68)	0.71 (0.53–0.94)	0.91 (0.67–1.20)	0.83 (0.42–1.49)
16–18[a]	2.09 (1.85–2.36)	2.07 (1.83–2.35)	2.39 (2.03–2.78)	2.49 (2.07–2.96)	3.15 (2.25–4.29)
Lithium					
0–2	NA	NA	NA	NA	0.06 (0.002–0.36)
3–5	NA	NA	NA	NA	NA
6–9	NA	0.01 (0.001–0.04)	NA	NA	NA
10–12	NA	NA	NA	NA	NA

Table 1 continued

Prevalence	1992	1995	1998	1999	2001
13–15	0.02 (0.002–0.05)	0.02 (0.005–0.07)	0.03 (0.003–0.10)	0.02 (0.0005–0.11)	NA
16–18	0.10 (0.05–0.17)	0.10 (0.05–0.17)	0.05 (0.01–0.17)	0.06 (0.01–0.17)	0.08 (0.002–0.44)

NA not available; no case was being given drug

[a] A significant trend for an increasing of psychotropic drugs prescribing

Table 2 The boy–girl prevalence ratios for psychotropic drug use in children and adolescents aged 0–18 years

	Clonidine	Stimulant	Antidepressants	Hypnotic/Anxiolytics	Antipsychotics	Anticonvulsants	Lithium
1992	0.54 (0.39–0.75)	3.00 (1.20–7.50)	0.87 (0.81–0.93)	0.89 (0.82–0.98)	1.29 (1.07–1.56)	1.04 (0.98–1.11)	1.58 (0.57–4.34)
1993	0.61 (0.43–0.88)	2.94 (1.39–6.24)	0.80 (0.74–0.86)	0.89 (0.81–0.98)	1.07 (0.88–1.29)	1.04 (0.97–1.11)	0.35 (0.09–1.34)
1994	0.65 (0.45–0.94)	7.16 (3.25–15.7)	0.76 (0.71–0.81)	0.85 (0.77–0.93)	1.11 (0.92–1.34)	1.02 (0.95–1.09)	1.35 (0.51–3.55)
1995	0.74 (0.50–1.10)	5.94 (3.79–9.32)	0.66 (0.61–0.71)	0.79 (0.72–0.87)	1.23 (1.01–1.50)	1.05 (0.98–1.13)	0.44 (0.17–1.15)
1996	1.19 (0.80–1.78)	6.53 (4.92–8.66)	0.61 (0.57–0.66)	0.83 (0.75–0.92)	1.02 (0.83–1.25)	0.99 (0.92–1.07)	0.83 (0.30–2.29)
1997	1.50 (0.97–2.32)	7.85 (6.08–10.1)	0.53 (0.49–0.58)	0.79 (0.71–0.88)	1.07 (0.87–1.32)	1.00 (0.92–1.08)	0.41 (0.11–1.58)
1998	1.56 (0.95–2.57)	8.72 (6.63–11.5)	0.53 (0.48–0.58)	0.74 (0.66–0.84)	1.25 (0.99–1.59)	1.02 (0.93–1.12)	NA
1999	1.52 (0.89–2.58)	8.72 (6.63–11.5)	0.55 (0.50–0.61)	0.75 (0.65–0.88)	1.40 (1.07–1.83)	1.03 (0.93–1.15)	0.48 (0.09–2.60)
2000	3.19 (1.28–7.95)	9.52 (6.69–13.6)	0.50 (0.43–0.57)	0.86 (0.69–1.07)	1.32 (0.92–1.90)	1.04 (0.90–1.21)	NA
2001	5.60 (1.25–25.0)	7.64 (4.96–11.8)	0.56 (0.46–0.68)	0.71 (0.54–0.92)	1.54 (0.92–2.59)	1.00 (0.75–1.10)	NA

NA not available; no case was being given drug

the US [29]. However approximately 80% of our study subjects received only one psychotropic drug during study period; this prescribing pattern is similar to that of the Netherlands [5]. The above comparison must be interpreted with caution. In addition to those factors noted by Zito et al. [28], other factors such as data sources, sampling, ethnicity and socio-economic status could also lead to variation in prevalence estimate [2, 3, 30, 31].

Many psychotropic drugs have not yet been fully test in children and adolescents to date, as a result, many young people receive psychotropic drug for treatment as off-license use in clinical practice. Several initiatives have been proposed to improve the current practice. In 2002, the European Union (EU) proposed the "Better Medicines for Children" regulation and developed research strategy to improve paediatric research in order to increase the availability of licensed drugs use in children [32]. The European Medicines Agency (EMEA) and the Paediatric Working Party made an attempt to establish paediatric medication needs [33]. All these initiatives aim to increase the availability of drug use for children, ensuring drugs are properly authorised to use in paediatric population.

Conclusion

There was a significant increase in the prescribing of psychotropic drugs to children and adolescents in the UK from 1992 to 2001. To date, many of these drugs are not licensed for use in this population. Given the limited information available to date, our findings illustrate that future research into the efficacy and long-term safety in this population is needed.

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