

Antidepressant prescriptions in paediatric outpatients in Europe

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Background: The evidence of antidepressant safety and efficacy in the paediatric population is scant and widely debated. In this context, monitoring the prevalence and appropriateness of antidepressant prescriptions in the paediatric population is essential.

Methods: A systematic literature search to review available knowledge concerning antidepressant use in children was performed in MEDLINE and EMBASE for studies in the outpatient European paediatric population, published between 2000 and June 2007.

Results: A total of 12 pertinent studies were found. Wide differences were observed in the prevalence rate based on the country and observation period. When taking into account the most recent data for each country, the

results showed a higher prevalence in the UK (5.7 per 1,000) and a lower one in Denmark (1.8 per 1,000). Selective serotonin reuptake inhibitors (SSRIs) were the most prescribed antidepressants in all countries, with the exception of Germany. Antidepressant prevalence increased in the 2000–2003 period and this increase was mainly due to SSRI prescriptions. A decrease in antidepressant prescriptions after 2003 was observed and was probably associated with the regulatory agencies' warnings.

Conclusion: In order to monitor antidepressant use in children and adolescents, prospective multinational collaborative pharmacoepidemiological studies aimed at collecting valid and comparable data are needed.

Paed Perinat Drug Ther 2007; 8: 103–108

Keywords: child – adolescent – antidepressive agent – general practice – drug utilisation – Europe

Introduction

The debate on the suicide risk of young people receiving antidepressants has led to increased attention on the safety and efficacy of psychotropic drugs in children over the last few years.

Since December 2003, several drug regulatory agencies have issued a warning to physicians

about an increased risk of suicidality linked to antidepressant use¹. An analysis performed by the Food and Drug Administration (FDA) of 24 placebo controlled trials evaluating the efficacy of nine antidepressants in treating major depressive disorder (MDD), obsessive compulsive disorder (OCD) and other psychiatric disorders, showed a two-fold greater risk of suicidal behaviour in patients receiving antidepressants².

On the basis of these findings the FDA asked the manufacturers to include a black box warning in the labelling of antidepressant drugs.

Because of this, monitoring the prevalence and appropriateness of psychotropic drug prescriptions in the paediatric population is essential. A systematic review of drug utilisation studies was therefore performed, with the aim to evaluate studies with original data concerning the pharmacoepidemiological evaluation of antidepressant prescriptions in the outpatient paediatric population.

Methods

A systematic literature search was performed in MEDLINE and EMBASE for studies published from 2000 to June 2007 and performed in any of the European countries. The MeSH search terms used in the search strategy were: *drug utilisation/prescription/pharmacoepidemiology; infant/child/adolescent/pediatrics; antidepressant agents*. Hand searches of bibliographies were also conducted to identify additional pertinent studies. The references retrieved were collected and analysed using the software program Reference Manager, version 11 (Institute for Scientific Information, Berkeley, California).

Prevalence rate (number of young people who received at least one antidepressant drug prescription per 1,000 individuals in the population) was used as an indicator.

Results

A total of 115 articles were retrieved from the literature databases: 60 from EMBASE and 49 from MEDLINE, and six from both. 104 papers were, however, excluded because they were not considered pertinent. One additional paper published online at the time of the bibliographic search was included³.

A total of 12 studies reported the antidepressant prevalence rate (Table 1)³⁻¹⁴. The studies involved eight countries: there were three studies in Italy^{7,9,12} and the Netherlands³⁻⁵, two in Germany^{5,11} and the UK^{6,13} and one in Denmark⁵, France⁸, Ireland¹⁰ and Spain¹⁴. One paper compared data collected in different countries⁵. Eight studies were published after 2005 and six reported data during the period 2003–2005, three of which also reported the prevalence trend over several years¹¹⁻¹³, while one compared the 2005 versus 2001 prevalence rates³.

Four studies reported data on other psychotropic drug classes^{4,7,8,12}, while one involved only selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitor (SNRI) prescriptions¹⁴. Most of the studies involved children and adolescents, even if with different upper limits of age. Five studies defined young people as less than 20 years old. One study was focused on adolescents only and was therefore not taken into account in the analysis⁸. The sample size varied widely and ranged between 37,650 and 1,500,000.

Wide differences were found in the prevalence rate depending on the country and the observation period. When taking into account the most recent data for each country, the results showed higher prevalence in the UK (5.7 per 1,000)¹³ and a lower one was reported in Denmark (1.8 per 1,000)⁵.

Prevalence was higher in females than in males, with a female/male ratio ranging between 1.03 and 2.00. The distribution of prevalence by age group was reported in five studies: the prevalence increased with increasing age and was higher in the adolescents, ranging from 4.5 in the Netherlands to 9.6 per 1,000 in Germany^{3,5,6,11,12}.

Only three studies reported the most prescribed antidepressants in order of prevalence: hypericum was the most prescribed drug in Germany, sertraline in Italy, and fluoxetine in Spain (Table 2)^{11,12,14}.

Table 1 Pharmacoepidemiological studies of antidepressant use in children in Europe

Reference	Country	Year	Age (years)	n	Prevalence (per 1,000)	F/M
4	Netherlands	1999	0–19	37,670	4.4	–
5	Denmark	2000	0–19	111,452	1.8	1.72
5	Germany	2000	0–19	480,680	1.1	1.16
5	Netherlands	2000	0–19	72,570	5.4	1.03
6	United Kingdom	2001	0–18	–	7.1	–
7	Italy	2001	0–18	1,500,000	2.8	1.45
8	France	2002	13–17	120,908	7.7	1.86
9	Italy	2002	0–17	568,770	2.8	–
10	Ireland	2003	0–15	250,930	4.3	–
11	Germany	2003	0–19	279,083	3.4	2.00
12	Italy	2004	0–17	1,484,770	2.4	1.20
13	United Kingdom	2004	0–18	–	5.7	–
14	Spain	2004–05	0–18	919,051	4.8	1.22
3	Netherlands	2005	0–17	62,969	2.0	–

Table 2 Most prescribed antidepressants in children and adolescents in Germany, Italy, and Spain

Germany (2003) ¹¹		Italy (2004) ¹²		Spain* (2005) ¹⁴	
Drug	Prevalence (per 1,000)	Drug	Prevalence (per 1,000)	Drug	Prevalence (per 1,000)
Hypericum	1.51	Sertraline	0.52	Fluoxetine	1.49
Opipranol	0.40	Paroxetine	0.49	Sertraline	1.23
Imipramine	0.33	Citalopram	0.38	Paroxetine	0.69
Doxepine	0.30	Fluoxetine	0.23	Citalopram	0.39
Amitriptyline	0.29	Amitriptyline	0.18	Mirtazapine	0.31
Citalopram	0.23	Trazodone	0.17	Venlafaxine	0.29
Fluoxetine	0.18	Escitalopram	0.16	Escitalopram	0.19
Sertraline	0.16	Venlafaxine	0.14	Fluvoxamine	0.16

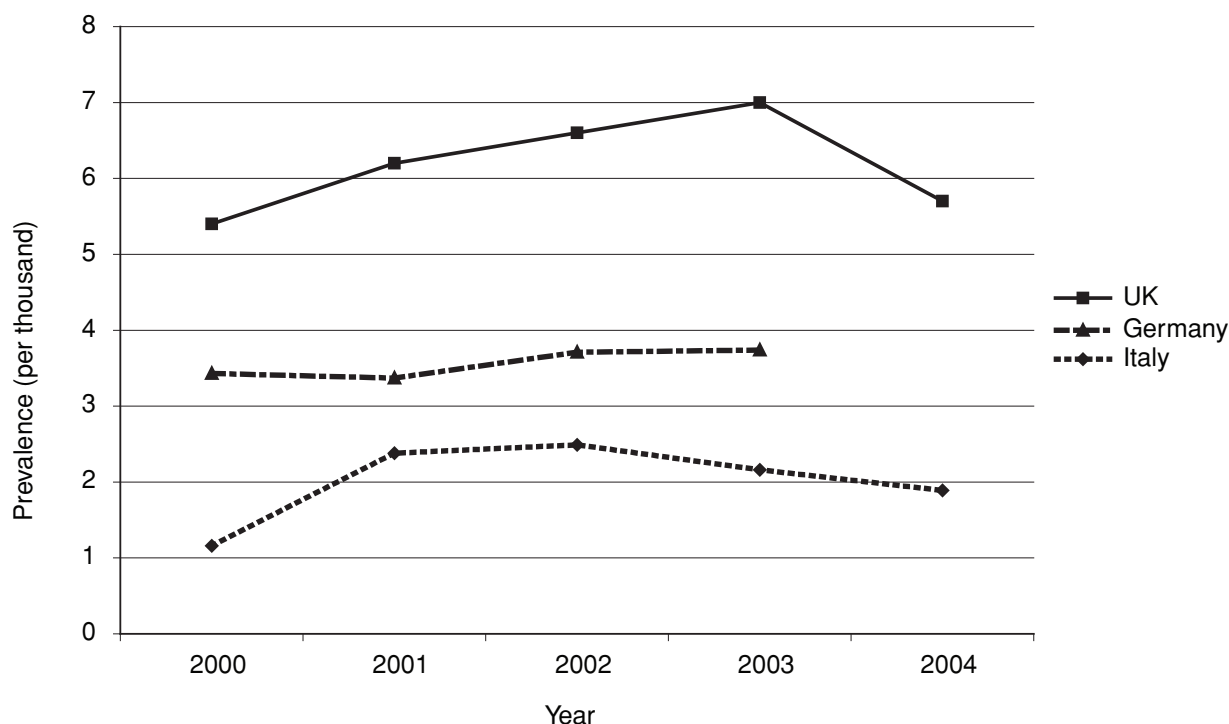
*SSRIs and SNRIs only.

The SSRI and venlafaxine prescription prevalence in Spain was 2.8 fold higher than in Italy (4.8 versus 1.7 per 1,000). This ratio changed depending on the drug: it was highest for fluoxetine (6.5), while the prevalence of citalopram and escitalopram was nearly the same in the two countries. Figure 1 reports the trend of antidepressant prevalence in the UK, Germany and Italy. The area under the prevalence-time curve (AUC) from 2000 to 2003, calculated according to the linear trapezoidal rule, was three-fold and two-fold higher in the UK than in Italy and Germany, respectively. In spite of the different rates, between 2000 and 2003 the prevalence increased by 80% in Italy and by 30% in the United Kingdom, while a less significant increase was observed in Germany (9%). This trend was mainly related to an increase in SSRI prescriptions, consisting of 240% in Italy and 147% in Germany. A slight decrease in prevalence of antidepressant prescriptions was also reported in the Netherlands: from 2.3 per 1,000 in 2001 to 2.0 per 1,000 in 2005³.

Discussion

This is the first review of drug utilisation studies concerning antidepressant prescriptions in children and adolescents in the European countries. The finding that most of the retrieved articles were published in the last three years is consistent with the fact that the issue of antidepressant use in childhood and adolescence was widely debated after 2003. Nevertheless, relatively few comparable studies were found, regarding only eight European countries.

Substantial differences emerged in the prescription prevalence rate that may resemble different prevalence of psychiatric disorders. According to the European Health Report 2005, neuropsychiatric disorders are the fourth cause of disease in order of Disability Adjusted Life Years (DALYs) in children aged 0-14 years, but with differences between countries. In the most developed countries they represent the primary

**Figure 1** Trend of antidepressant prevalence, 2000–2004, in children and adolescents.

cause of disease, with a highest value of DALYs per 1,000 in Finland (8.3)¹⁵. However, a two-fold higher antidepressant prevalence in the UK than in Germany was found, even if the number of DALYs per 1,000 attributable to neuropsychiatric disorders is the same in the two countries (6.8). Moreover, the antidepressant prevalence in Spain ranked second, despite the value of DALYs attributable to neuropsychiatric disorders (5.4 per 1,000) being the lowest among the countries surveyed in this review¹⁵. Different socio-cultural factors, prescribing habits and healthcare system organisations therefore appear to influence antidepressant prescriptions.

Although the prevalence in Europe is substantially lower than that observed in the United States (1–2%)¹⁶, the rate of children treated with antidepressants, in particular with SSRIs, raises some concerns. To date, the available data on the safety and efficacy of these drugs in the paediatric population are limited. The benefit of SSRIs seems to be greater in general anxiety disorders, intermediate in obsessive compulsive disorder (OCD) and modest in major depressive disorder (MDD)¹⁷. A meta-analysis of 12 randomised controlled trials (RCTs), involving a total of 1,044 participants on OCD treatment with fluoxetine, fluvoxamine, paroxetine and sertraline, showed that SSRIs are more effective than placebo¹⁸. Although clomipramine was found to be more effective than SSRIs, according to the American Academy of Child and Adolescent Psychiatry, SSRIs could be considered first-line drugs because of their fewer side effects and lower toxicity with respect to clomipramine¹⁹.

On the contrary, the efficacy of pharmacological therapies for MDD in children and adolescents is controversial²⁰. A systematic review of the literature did not find a statistically significant difference between tricyclic antidepressants and placebo²¹. Moreover, taking SSRIs into account, the risk–benefit profile appears favourable only for fluoxetine^{22–24}.

The safety of antidepressant use in children is also a matter of debate, not only in terms of the risk of suicide. The incidence of some adverse events may differ with age: an analysis of adverse events reported in the RCTs comparing SSRIs and placebo found that activation and vomiting were more prevalent in children than in adolescents, and that their rate was lowest in adults. On the contrary, somnolence was an uncommon adverse event in children²⁵. Furthermore, the trials performed lasted between eight and 12 weeks, so scant data are available concerning the long-term safety and little is known about the effects on neurological and behavioural development.

In this regard, findings from some exploratory animal and human studies suggest that early life exposure to antidepressants may affect motor, cognitive, and effective development^{26–28}.

The SSRIs licensed for use in children in European countries are sertraline and fluvoxamine for OCD respectively, in children ≥ 6 years and ≥ 8 years, and fluoxetine for the treatment of depression in children ≥ 8 years. Despite this, only sertraline was among the most prescribed antidepressants. Fluoxetine was the most prescribed drug in Spain only, while fluvoxamine was infrequently prescribed in all countries.

On the contrary, paroxetine was one of the most prescribed antidepressants even though it is contraindicated in patients under 18 years of age in all European countries. The data concerning its efficacy in paediatric depression are scant. Three randomised placebo controlled trials were performed. Two negative trials were published in 2006^{29,30} after the company was accused of withholding data in order to overestimate the efficacy of the drug³¹. In the third trial, the authors suggested a greater efficacy of paroxetine even though no statistically significant differences were found on the primary outcome measure³². Furthermore, the safety of this drug raises some concerns. Paroxetine was the first SSRI for which a link with an increased risk of suicide was suspected, and during the summer of 2003, several drug regulatory agencies (Medicines and Healthcare Regulatory Agency [MHRA] and FDA first) warned health professionals about the risk of suicidal ideation linked to paroxetine^{33,34}.

Citalopram is also widely prescribed, even though only one RCT was published in 2004 and did not provide sound evidence of efficacy³⁵. Its enantiomer, escitalopram, was among the most prescribed antidepressants in Italy and Spain, despite the fact that the only existing RCT, which had negative results, was published in 2006³⁶. In this regard, it is interesting to note that, despite a nearly three-fold higher SSRI prevalence in Spain compared to Italy, the prevalence of citalopram and escitalopram was similar. This is likely due to the influence of companies' marketing strategies.

Germany represents an exception among the countries surveyed in this review. In this country, the most prescribed drug was hypericum, which is not reimbursed by the health service in other countries. Despite this, tricyclic agents were the most prescribed antidepressants, covering 40% of antidepressant users, while only 21% of antidepressant users received SSRIs. This figure is different from the other European countries, but is similar to that observed in the German adult population¹¹.

On the other hand, in the period 2000–2003 the SSRI prevalence increased in Germany, as well as in Italy and the UK. The prevalence trend in Italy and the UK shows a decrease after 2003, a fact that could have been influenced by the regulatory agencies' resolutions and the debate held in the medical journals. A decrease in antidepressant prevalence rate following the regulatory warnings was also observed in the United States³⁷. However, a longer period of time is necessary to evaluate the real impact of the regulatory agencies' warnings in terms of changes in prevalence and appropriateness of prescriptions.

In order to monitor antidepressant use in children and adolescents, prospective multinational collaborative pharmacoepidemiological studies aimed at collecting valid and comparable data are needed. A substantial lack of systematic attention to the epidemiology of drug use in children, as observed more than 10 years ago³⁸, still seems to be a problem. Despite the increased attention to the issue of antidepressant use in children and adolescents and the number of drug utilisation studies on this topic published in the last few years, the heterogeneity is high, e.g. few studies reported the distribution of prevalence by gender and age group or details of the most prescribed drugs.

Furthermore, even if 18 years is considered the upper limit of the paediatric age group, at least in performing clinical trials³⁹, five out of the 12 studies involved children and adolescents aged up to 19 years and the results of these studies could not give a reliable figure of the paediatric population exposed to antidepressants. The epidemiological evaluation of drug use in children should therefore be improved, both in the number and quality of the studies performed.

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Paper PPDT-0194_3, Accepted for publication: 25 September 2007
Published Online: 2 November 2007
doi:10.1185/146300907X199911