

# Effects of the Committee on Safety of Medicines Advice on Antidepressant Prescribing to Children and Adolescents in the UK

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## Abstract

**Background:** Psychotropic medication prescribing for children and adolescents rose significantly between 2000 and 2002, including antidepressant prescribing. In 2003, the Committee on Safety of Medicines (CSM) advised against using venlafaxine or any selective serotonin receptor inhibitor (SSRI), with the exception of fluoxetine, for childhood and adolescent depression. The aim of this study was to compare the prevalence and incidence of children and adolescents who were prescribed antidepressants in UK primary care, before and after the CSM advice on antidepressant prescribing. We also compared paediatric antidepressant prescribing trends from Mediplus data with national antidepressant prescribing trends in England from the Prescription Pricing Authority (PPA).

**Methods:** The Disease Analyzer-Mediplus database contains anonymised primary care records for about 3 million patients. Eligible patients were aged ≤18 years and received ≥1 antidepressant prescription between 2000 and 2004. Antidepressants were grouped according to the CSM advice and the British National Formulary. Prevalence and incidence were calculated. The prevalences of 2000, 2002 and 2004 were compared using a Chi-squared test. PPA data on antidepressant prescribing rates were compared with paediatric antidepressant prescribing rates from Mediplus.

**Results:** 5718 children and adolescents received a total of 25 542 prescriptions between 2000 and 2004. The median number of prescriptions per patient was two (interquartile range 1–5). Common indications included depression and anxiety. Antidepressant prevalence increased from 2000 to 2002 (from 5.4 to 6.6 patients per 1000 people), with a rise in the number of patients prescribed venlafaxine and SSRIs. However, between 2002 and 2004 there was a decrease in antidepressant prevalence (from 6.6 to 5.7 per 1000). The prevalence of CSM-contraindicated antidepressants (citalopram, escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine) declined by a third (from 3.1 to 2.0 per 1000), but there was no change in fluoxetine prevalence (from 2.1 to 2.3 per 1000). The number of

patients prescribed tricyclic antidepressants dropped marginally (from 2.0 to 1.7 per 1000). Incidences followed the same trends as the prevalences, but there was a 48% reduction in the incidence of CSM-contraindicated antidepressants between 2002 and 2004. National antidepressant prescribing trends increased; paediatric prescribing trends were similar to national trends between 2000 and 2003; however, there was a 27% reduction in the paediatric prescribing rate of CSM-contraindicated antidepressants between 2002 and 2004.

**Conclusion:** Since 2003, fewer children and adolescents have been prescribed antidepressants in primary care. However, fluoxetine and non-SSRI antidepressant prevalences have not risen, implying that they are not prescribed as alternative treatments. This study shows that the CSM advice has had a significant effect in reversing the rising prevalence of antidepressant prescribing to children and adolescents in primary care.

## Background

There was a significant rise in psychotropic medication prescribing to children and adolescents between the years 2000 and 2002 in seven countries, including the UK.<sup>[1]</sup> The term 'psychotropic medications' includes antidepressants. There was a 70% increase in antidepressant use in UK primary care between 1992 and 2001, with a 10-fold rise in the use of selective serotonin reuptake inhibitors (SSRIs).<sup>[2]</sup>

The Expert Working Group of the Committee on Safety of Medicines (CSM) conducted a review of the efficacy and safety of the SSRIs and venlafaxine in paediatric depressive disorder. Consequently, in 2003 the CSM advised against their use (with the exception of fluoxetine) in children and adolescents aged <18 years, following concerns about their possible association with an increased risk of suicide and suicidal behaviour;<sup>[3]</sup> the full report is available from the Medicines and Healthcare products Regulatory Agency website.<sup>[3,4]</sup>

SSRIs are prescribed off label to this age group for a variety of conditions, such as depression, obsessive compulsive disorder, generalised anxiety disorder, other anxiety disorders and repetitive behaviours in autism spectrum disorders; studies have shown that SSRIs may be effective for these disorders.<sup>[5,6]</sup>

The consequences of this advice on clinical practice are not fully known, particularly the impact on

antidepressant prescribing and referrals to Child and Adolescent Mental Health Services (CAMHS).

The aim of this study was to compare the prevalence and incidence of children and adolescents who were prescribed antidepressants in UK primary care, before and after the CSM advice on antidepressant prescribing. We also compared paediatric antidepressant prescribing trends from the Mediplus data with national antidepressant prescribing trends in England from the Prescription Pricing Authority (PPA).

## Methods

Data were obtained on patients aged ≤18 years registered in UK primary care, who received at least one antidepressant prescription between 1 January 2000 and 31 December 2004, from the IMS Disease Analyzer-Mediplus (Mediplus) database. Mediplus contains anonymised primary care records for about 3 million patients from approximately 650 contributing UK general practitioners. Data collected include demography, medical diagnoses, prescriptions, medical tests and referrals.<sup>[7]</sup> Mediplus is subject to internal validation and quality checks at IMS. There is consistent, good agreement with other sources of UK prescription counts. The database has been shown to be of high quality and completeness, and has been commonly used in drug utilisation studies.<sup>[8,9]</sup>

Approval for the study was granted by IMS Health's Independent Scientific and Ethical Advisory Committee.

The antidepressants were grouped as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), CSM-contraindicated drugs (citalopram, escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine), fluoxetine and other antidepressants, according to the CSM advice<sup>[3]</sup> and the British National Formulary.<sup>[10]</sup>

### Calculation of Prevalence

The overall prevalence of children and adolescents receiving antidepressant prescriptions and the prevalence of each antidepressant group by calendar year were calculated. Prevalence was defined as the number of patients with one or more antidepressant prescription per 1000 people in the annual population.

Comparisons between the prevalences of 2000 and 2002 for each group were conducted using a Chi-squared test. The prevalences of 2002 and 2004 were also compared for significance using the same method. Common indications of antidepressant prescriptions were investigated, and prevalences were calculated and compared as previously specified.

### Calculation of Incidence

The first 2 years of each patient's prescribing history was used as a screening period. If the patient did not receive an antidepressant prescription during this period but did thereafter, the patient was classified as a new starter. The annual number of new starters was calculated and used to estimate incidence. Incidence is defined as the number of new starters per 1000 people in the annual population.

### Prescription Data from the Prescription Pricing Authority (PPA) and Mediplus

Data on the annual numbers of antidepressant prescriptions issued between 2000 and 2004 were obtained from the PPA.<sup>[11]</sup> The size of the population in England was obtained from the Office for National Statistics<sup>[12]</sup> and the annual numbers of

prescriptions per capita by antidepressant group were calculated as the total annual number of prescriptions divided by the population size in England.

The annual numbers of paediatric antidepressant prescriptions issued between 2000 and 2004 were obtained from Mediplus. The numbers of prescriptions per capita by antidepressant group was calculated as the total annual number of prescriptions divided by the annual population (aged 0–18 years) in the Mediplus database.

## Results

5718 children and adolescents received a total of 25 542 prescriptions between January 2000 and December 2004. The median number of prescriptions per user was two (interquartile range of 1–5). Common indications included depression ( $n = 2433$ , 42.5% of population), anxiety ( $n = 560$ , 9.8%) and nocturnal enuresis ( $n = 329$ , 5.8%). Some SSRIs were also prescribed for the treatment of other disorders such as neuropathic pain (migraine, back pain) and obsessive-compulsive disorder. Finally, some prescriptions had nonspecific indications for mental health disorders.

Figure 1 shows the prevalence of each antidepressant group by calendar year. MAOIs were rarely prescribed, so their prevalence is not shown. Antidepressant prescribing increased significantly between 2000 and 2002 ( $p < 0.001$ ), with a rise in the number of patients prescribed SSRIs and venlafaxine.

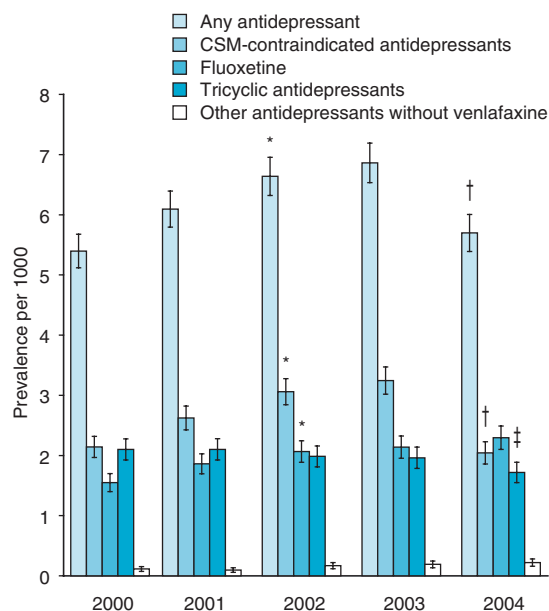
However, between 2002 and 2004 there was a significant decrease in antidepressant prevalence ( $p < 0.001$ ). The number of patients prescribed the CSM-contraindicated antidepressants decreased by a third ( $p < 0.001$ ), but there was a nonsignificant increase in the prevalence of fluoxetine use ( $p = 0.09$ ). The prevalence of TCAs dropped, although this was only marginally statistically significant ( $p = 0.03$ ).

The number of patients prescribed CSM-contraindicated antidepressants for depression rose from 2000 to 2002, but dropped between 2002 and 2004 (prevalences with 95% CI: 2000, 1.15 per 1000 [1.02, 1.28]; 2002, 1.61 per 1000 [1.45, 1.76]; 2004,

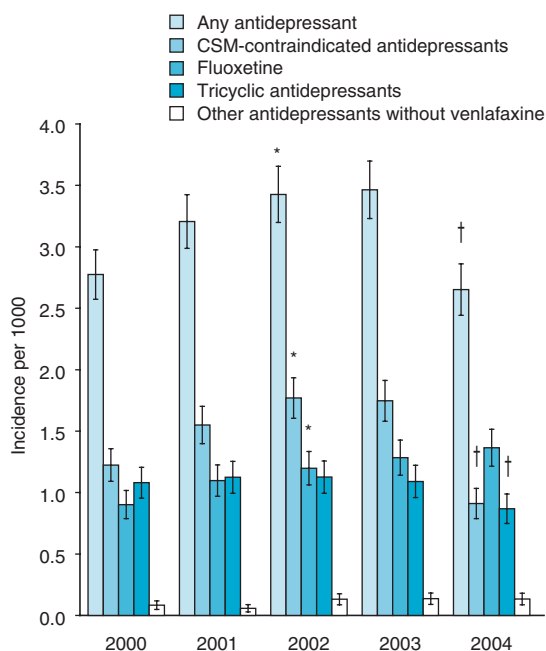
0.98 per 1000 [0.86, 1.11]). Their prevalence for anxiety also rose from 2000 to 2002, but there was a nonstatistically significant reduction from 2002 to 2004 (2000, 0.23 per 1000 [0.18, 0.29]; 2002, 0.41 per 1000 [0.33, 0.49]; 2004, 0.32 per 1000 [0.25 to 0.39]).

The incidences of antidepressant prescribing followed the same trends as the prevalences (figure 2); noticeably, there was a 48% reduction in the incidence of children and adolescents receiving CSM-contraindicated antidepressants between 2002 and 2004.

National antidepressant prescribing trends in England increased between 2000 and 2004 (figure 3). The paediatric prescribing trends followed similar patterns to the national trends between 2000 and 2003; however, between 2002 and 2004 there was a



**Fig. 1.** Prevalence of antidepressants by calendar year. Committee on Safety of Medicines (CSM)-contraindicated antidepressants are citalopram, escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine. Other antidepressants without venlafaxine are flupentixol, mirtazapine, nefazodone and reboxetine. It should be noted that some antidepressants were prescribed for non-mental health related indications. For example, the use of tricyclic antidepressants for the treatment of nocturnal enuresis. \* = significant increase from 2000 to 2002 ( $p < 0.001$ ); † = significant decrease from 2002 to 2004 ( $p < 0.001$ ); ‡ = marginally significant decrease from 2002 to 2004 ( $p < 0.05$ ).



**Fig. 2.** Incidence of antidepressants by calendar year. Committee on Safety of Medicines (CSM)-contraindicated antidepressants are citalopram, escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine. Other antidepressants without venlafaxine are flupentixol, mirtazapine, nefazodone and reboxetine. \* = significant increase from 2000 to 2002 ( $p < 0.01$ ); † = significant decrease from 2002 to 2004 ( $p < 0.01$ ).

27% reduction in the prescribing rate of CSM-contraindicated antidepressants in children and adolescents.

## Discussion

### Reduction in Number of Children and Adolescents Taking Antidepressants

Since 2003, fewer children and adolescents have been prescribed antidepressants in primary care, particularly the CSM-contraindicated drugs. Unexpectedly, the prevalence of fluoxetine and non-SSRI antidepressants has not risen significantly, suggesting that they are not prescribed as alternative treatments to the CSM-contraindicated antidepressants.

Based on our data, we estimated that approximately 13 000 fewer patients have been prescribed

one of the contraindicated antidepressants since the CSM guidance was published. The incidence data showed a 48% reduction between 2002 and 2004, which is greater than that seen in the prevalence (39%) for the same period. The results suggest that clinicians, patients and/or their parents were less willing to start such antidepressant treatment.

Furthermore, SSRIs seem to be less frequently prescribed for conditions other than depression; however, our results only show a nonstatistically significant reduction.

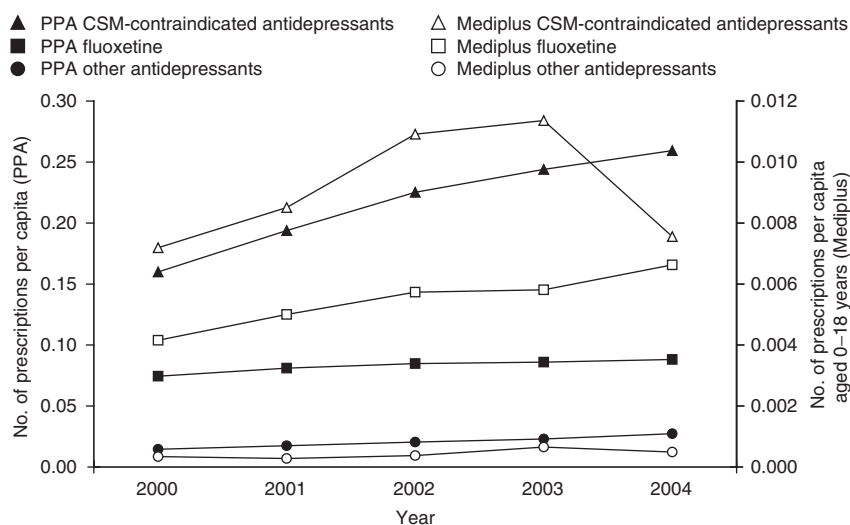
#### Comparison with Prescription Data from the PPA

The number of SSRI prescriptions issued to children and adolescents aged  $\leq 18$  years between 1999 and 2003 in England were presented in Annex A of the report by the Expert Working Group of the CSM on the safety of SSRI antidepressants.<sup>[13]</sup> Analysis of this data showed that there was a 52% reduction in paroxetine prescriptions between 2001 and 2003,<sup>[13]</sup> which is very similar to our data: a 49% reduction in paroxetine prescriptions over the same period. These findings can serve as an external validation of our results.

The paediatric antidepressant prescribing trends follow similar patterns to the national trends between 2000 and 2003; however, there was a 27% reduction in the number of prescriptions per capita of CSM-contraindicated antidepressants between 2002 and 2004, suggesting that the CSM advice had a very specific effect on antidepressant prescribing practice for children and adolescents. In our previous study,<sup>[14]</sup> we demonstrated a 68% increase in the number of paediatric psychotropic drug prescriptions between 2000 and 2002 in the UK; a similar trend was also observed in the adult population of the UK (49%). It suggests that, in general, British society was more willing to use psychotropic medications in both adults and children prior to publication of the CSM guidance. However, our current study shows that the CSM advice has made a significant effect in reversing the antidepressant prescribing trend for children and adolescents.

#### Usefulness of Suicide Data in the Paediatric Population of England and Wales

Analysis of secular trends has demonstrated that the increase in antidepressant prescribing coincides with the reduction in suicidal mortality rates.<sup>[4]</sup> We



**Fig. 3.** Paediatric antidepressant prescribing trends from Mediplus data and national antidepressant prescribing trends in England from the Prescription Pricing Authority (PPA). Committee on Safety of Medicines (CSM)-contraindicated antidepressants are citalopram, escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine. Other antidepressants without venlafaxine are flupentixol, mirtazapine, nefazodone and reboxetine.

obtained mortality data from the UK Office for National Statistics to investigate this aspect (Office for National Statistics, personal communication). However, the occurrence of reported successful suicides in children and adolescents were rare in the UK (average mortality rate between 2000 and 2004 is 4.6 per million children [aged 0–18 years]), these figures were too small to make a meaningful interpretation.

#### Possible Implications of the Committee on Safety of Medicines Advice on the Healthcare System

The CSM advice recommends psychotherapies, such as cognitive-behavioural therapy, as first-line treatment for children and adolescents with depression; therefore, it may be a logical assumption that general practitioners are choosing to refer more patients for psychotherapies. However, this raises difficulties in real-life practice. According to a report published in 2004, there are only 469 qualified child and adolescent psychotherapists in the UK and some 159 in training. The majority of child psychotherapists (75% of the total number) are employed in the London region.<sup>[15]</sup> This highlights the disparity in the provision of psychotherapy between regions of the country and that long waiting lists exist. The shortage of trained psychotherapists in Child and Adolescent Mental Health Services (CAMHS) teams may have helped to increase SSRI prescribing in the first place, as a stopgap in general practice, paediatric and child mental health settings.

If this assumption is correct, the net result may now be that patients have to wait much longer for treatment of a range of disorders where SSRIs were previously used. This will have implications regarding resource availability and the funding of nonpharmacological interventions in CAMHS teams dealing with these distressing conditions. Unfortunately, data on referrals to CAMHS have not been collected systematically in a way that would allow detailed analysis to confirm or refute this assumption. Further research is urgently required to understand the integration between various management strategies

of depression, so that adequate infrastructure and resources can be provided. Finally, no doubt the government will have to invest more resources in order to provide the best treatment for children and adolescents with depressive illness.

## Conclusion

Since 2003, fewer children and adolescents have been prescribed antidepressants in primary care. However, fluoxetine and non-SSRI antidepressant prevalences have not risen significantly, implying that they are not prescribed as alternative treatments. This study shows that the CSM advice has had a significant effect in reversing the rising prevalence of antidepressant prescribing to children and adolescents in primary care.

Psychotherapies may now be preferred over antidepressants for depression and other disorders, but the shortage of psychotherapists raises difficulties. Further research into the integration between various management strategies of depression may help to provide infrastructure and resources to address this issue.

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I.C.K. Wong conceived the research idea and is the guarantor. I.C.K. Wong and M.L. Murray developed the study design. M. Thompson abstracted the data and provided the denominator estimates, M.L. Murray conducted the analysis. All authors contributed to the interpretation of the data and the writing of the paper.

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