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RESEARCH

The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study

Benedict W Wheeler, research fellow,[1] David Gunnell, professor of epidemiology,[1] Chris Metcalfe, lecturer in medical statistics,[1] Peter Stephens, vice president, public health affairs,[2] Richard M Martin, reader in clinical epidemiology[1]

[1]Department of Social Medicine, University of Bristol, Bristol BS8 2PR

[2]IMS Health, London

Correspondence to: B W Wheeler ben.wheeler@bristol.ac.uk

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ABSTRACT

Objective To investigate the population impact on the incidence of suicide and non-fatal self harm of regulatory action in 2003 to restrict the use of selective serotonin reuptake inhibitors (SSRIs) in under 18s.

Design Ecological time series study.

Setting United Kingdom.

Populations Young people in the UK aged 12-19 years (prescribing trends), in England and Wales aged 12-17 years (mortality), and in England aged 12-17 years (hospital admissions).

Main outcome measures Deaths from suicide and hospital admissions for self harm.

Results Antidepressant prescribing doubled between 1999 and 2003 but fell to the 1999 level between 2004 and 2005. These large changes in prescribing did not seem to be associated with temporal trends in suicide or self harm. In the years 1993 to 2005 the annual percentage reduction for suicide among 12-17 year olds was −3.9% (95% confidence interval −6.2% to −1.5%) in males and −3.0% (−6.6% to 0.6%) in females, with no indication of a substantial change in this rate of decrease during that period. Similarly, hospital admission rates for self harm in the years 1999 to 2005 indicated an annual percentage increase for males of 1.1% (−0.5% to 2.7%) and for females of 5.7% (3.6% to 7.8%), again with no statistical evidence of a change in rate after the regulatory action.

Conclusions The noticeable reduction in prescribing of antidepressants since regulatory action in 2003 to restrict the use of SSRIs in under 18s does not seem to have been associated with changes in suicidal behaviour in young people. Specifically, these data for England do not indicate that reductions in antidepressant use have led to an increase in suicidal behaviour.

INTRODUCTION

In June 2003 the UK's Medicines and Healthcare products Regulatory Agency contraindicated the antidepressant paroxetine, a selective serotonin reuptake inhibitor (SSRI), in under 18s. The decision was based on a review of trial data indicating an increased risk of suicidal thoughts and behaviour in young people treated with the drug. Subsequent investigation led the regulatory agency to conclude in December 2003 that the balance of risk and benefits for the use of most SSRIs in young people, except fluoxetine, was unfavourable.[1] This advice was widely communicated to prescribers in the UK.[2] Similar actions were taken by regulatory agencies internationally.

Debate has been vigorous about the balance of risks and benefits of antidepressants in young people. The increased risk associated with SSRIs in paediatric trials was in relation to suicidal thoughts and non-fatal self harm: no suicides were reported.[3] Some mental health professionals have expressed concern that a reduction in SSRI prescribing may result in increased levels of untreated depression and an adverse impact on suicide.[4] Following similar regulations in the United States and the Netherlands, studies have indicated a reduction in the diagnosis and treatment of depression[5] and increases in suicide rates.[6 7] Some ecological data have indicated that increases in SSRI prescribing in children and young adults have coincided with reductions in suicide.[8]

We evaluated the impact of changing patterns of antidepressant use on incidence of self harm and suicide in young people in the UK following regulatory action in 2003 against the use of SSRIs in under 18s.

METHODS

Depending on the availability of data we created three separate time series for relevant age groups for the years between 1993 and 2006. Firstly, we obtained data from IMS Health's Medical Data Index for prescriptions of antidepressants to 12-19 year olds in the UK between 1993 and 2006 (quarterly for 1999-2006 and annually for 1993 to 1998).[9] Secondly, we obtained data from the Office for National Statistics on annual deaths due to intentional self harm or events of

undetermined intent among 12-17 year olds in England and Wales between 1993 and 2005.[10] Thirdly, we used the Department of Health's Hospital Episode Statistics database to obtain data on quarterly and annual hospital admissions due to intentional self harm or events of undetermined intent among 12-17 year olds in England between January 1999 and March 2006.[11]

We identified outcomes using codes from the international classification of diseases, which are those used as standard by the Office for National Statistics: intentional self harm and sequelae (E950-959, ninth revision and X60-X84 and Y87.0, 10th revision) and undetermined intent and sequelae (E980-989, ninth revision and Y10-Y34 and Y87.2, 10th revision, excluding E988.8/Y33.9 where the coroner's verdict was pending for mortality data).

We used annual population estimates for the UK, England, and Wales, as appropriate, from the Office for National Statistics to calculate rates of prescribing, hospital admission, and mortality.[10] Because of differences in data sources the three time series vary slightly in their geographical coverage and date and age ranges.

For the analysis of mortality trends we included annual total number of deaths in the age group 12-17 years. The upper age limit reflects the under 18s age group targeted by the Medicines and Healthcare products Regulatory Agency advice. The lower age limit considers both the age groups available in the prescribing data (12-19 years) and the low numbers of deaths with a verdict of suicide in younger children. Between 1993 and 2005 one verdict of suicide was given for the age group 0-11 years.

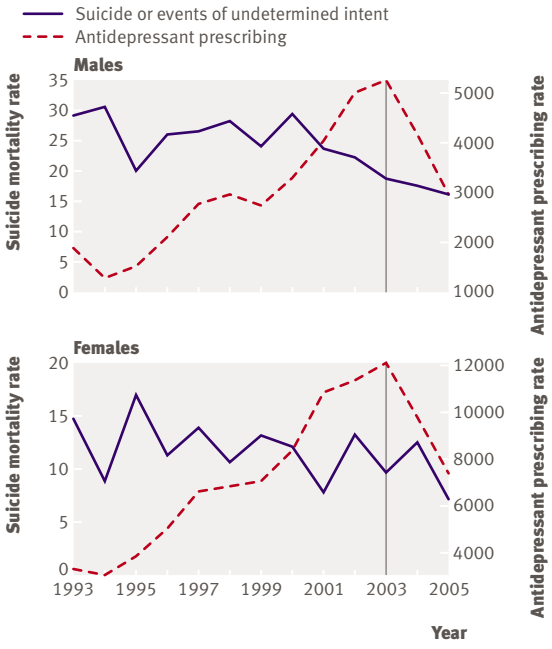

Fig 1 Trends in rates of antidepressant prescribing in 12-19 year olds per 100 000 population in UK[9] and mortality due to suicide or events of undetermined intent in 12-17 year olds per one million population in England and Wales,[10] 1993 to 2005. Vertical lines indicate year in which regulatory action was taken against prescriptions for selective serotonin reuptake inhibitors in under 18s

We analysed trends using Joinpoint regression software (http://srab.cancer.gov/joinpoint/), which evaluates trends over time and tests for points in time when the trends change noticeably ("joinpoints").[12] We

Annual counts of antidepressant prescriptions, hospital admissions for self harm, and deaths from suicide of undetermined intent in young people in the United Kingdom, England, and England and Wales

	Antidepressant prescriptions (ages 12-19, UK)*		Hospital admissions for self harm (ages 12-17, England)†		Deaths from suicide or undetermined intent (ages 12-17, England and Wales)‡	
Year	Males	Females	Males	Females	Males	Females
1993	53 000	93 000	NA	NA	54	26
1994	37 000	86 000	NA	NA	57	16
1995	43 000	112 000	NA	NA	38	31
1996	61 000	145 000	NA	NA	50	21
1997	81 000	191 000	NA	NA	52	26
1998	88 000	198 000	NA	NA	55	20
1999	82 000	207 000	2195	6597	47	25
2000	99 000	244 000	2144	7733	59	23
2001	123 000	319 000	2200	7599	48	15
2002	157 000	339 000	2088	8082	46	26
2003	170 000	369 000	2286	8918	39	19
2004	136 000	299 000	2377	9572	37	25
2005	95 000	227 000	2448	10 052	34	14

NA=not available. UK consists of England, Wales, Scotland, and Northern Ireland. England accounts for 84% of UK's 60.6 million population (2006 figures, Office for National Statistics).
*Data from IMS Health.[9]
†Data from Hospital Episode Statistics.[11]
‡Data from Office for National Statistics.[10]

compared pairs of models differing by one joinpoint to determine the model with the optimum fit to a data series, allowing a maximum of three joinpoints. An overall significance level of 0.05 was adopted for the comparisons of models applied to each data series.

RESULTS

Figures 1 and 2 show the effect of regulatory action by the Medicine and Healthcare products Regulatory Agency on annual prescribing of antidepressants in young people. A sharp downturn occurred after 2003, when the regulatory action was taken. Figure 3 shows the quarterly trends in prescriptions, with the modelled locations of joinpoints (when trends change substantially) from Joinpoint regression. During 1999 to 2006 an annual average of 70% (range 67%-73%) of antidepressant prescriptions were for selective serotonin reuptake inhibitors (SSRIs). Sixty five per cent of the decline in overall prescriptions for antidepressants between 2003 and 2006 resulted from a decline in SSRI prescribing.

Figure 1 illustrates the relation between changing antidepressant prescribing and suicide rates from 1993 to 2005. Owing to the smaller number of suicides among females from 1993 to 2005 the suicide rates for females are more variable than for males (see table). The general trend for both sexes, however, indicated steady declines in suicide rates. From 1993 to 2005 the annual percentage reduction in suicide rates among males was −3.9% (95% confidence interval −6.2% to −1.5%) and among females was −3.0% (−6.6% to 0.6%). No statistical evidence was found of any changes in trend between 1993 and 2005. These mortality trends do not seem to be temporally associated with trends in antidepressant prescribing. Analysis of trends in mortality due to suicide only—that is, excluding deaths from undetermined intent—produced similar results.

Likewise, trends in antidepressant prescribing were not associated with hospital admissions for self harm (fig 2). The rate of admissions for males remained relatively stable over the study period, at around 120 annual admissions per 100 000 population from 1999 to 2005. The admission rate for females during the same period rose steadily from 367 annual admissions per 100 000 population in 1999 to 525 per 100 000 population in 2005. Analyses of quarterly trends in hospital admissions from Joinpoint regression indicated an annual percentage change for males of 1.1% (−0.5% to 2.7%) and for females of 5.7% (3.6% to 7.8%; fig 4). Although quarterly trends for males are not easily

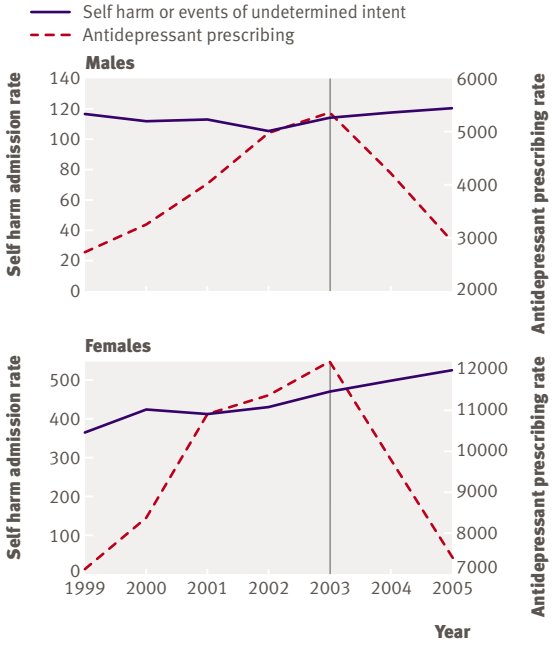

Fig 2 Trends in rates of antidepressant prescribing in 12-19 year olds per 100 000 population in UK[9] and hospital admissions with a diagnosis of self harm or events of undetermined intent in 12-17 year olds per 100 000 population in England[11], 1999 to 2005. Vertical lines indicate year in which regulatory action was taken against prescriptions for selective serotonin reuptake inhibitors in under 18s

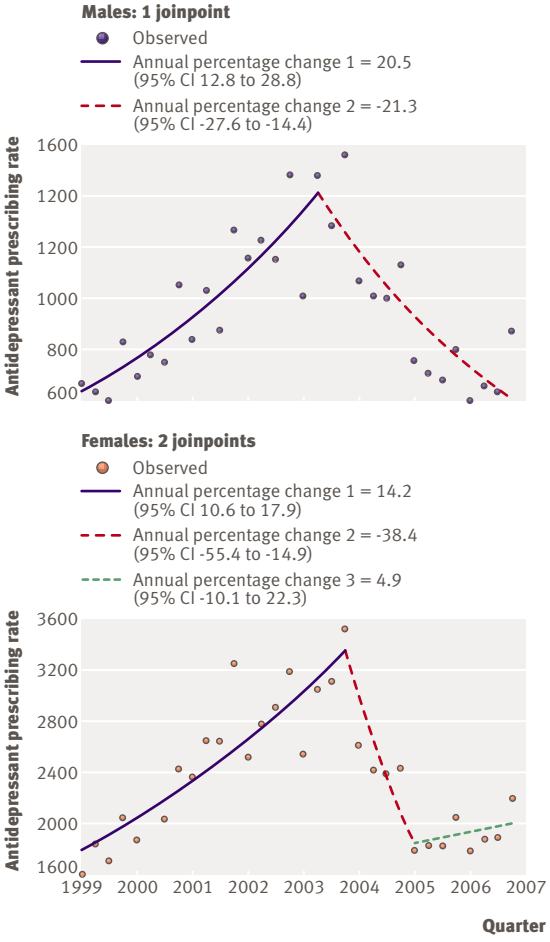

Fig 3 Joinpoint regression results: quarterly rates for antidepressant prescribing in 12-19 year olds per 100 000 population in UK[9], 1999-2006

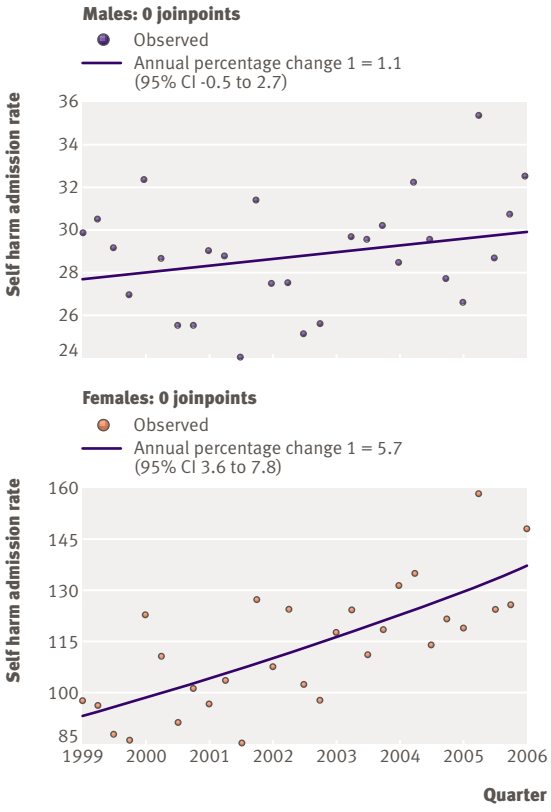

Fig 4 Joinpoint regression results: quarterly hospital admissions for self harm in 12-17 year olds per 100 000 population in England[11], 1999-2006

discerned owing to small numbers, for females it is apparent that the steady increase in admission rates was not temporally associated with the substantial changes in prescribing rates.

DISCUSSION

We found no evidence of a temporal association between trends in antidepressant prescribing and deaths from suicide or hospital admissions for self harm in young people despite a halving in levels of prescribing after the Medicines and Healthcare products Regulatory Agency's regulatory interventions in 2003.

These findings contrast with data from the USA, where regulatory action by the US Food and Drug Administration resulted in reductions in prescribing of selective serotonin reuptake inhibitors (SSRIs) to young people in 2003-4 and these were followed by a reversal of previously falling suicide rates. Between 1988 and 2003 mortality rates for suicide in 5-19 year olds in the USA fell from 4.4 to 2.8 per 100 000 population, but in 2004 they increased to 3.2 per 100 000 population.[7] That study looked at suicide rates for only one year after the regulatory action, however, and did not study rates of self harm. Preliminary analysis of data released after this study suggested that the trend from 2003 to 2004 did not continue to 2005, with a decline in number of suicides among young people despite continuing reductions in SSRI prescribing.[13]

The magnitude of changes in prescribing rates during 2003 to 2004 was larger in the UK than in the USA. We found an overall decrease in prescribing rates to 12-19 year olds of around 40%-50% for both SSRIs and total antidepressants between 2003 and 2005, whereas in the USA the decrease for SSRI prescriptions to similar age groups was in the region of 10%-20% over the same period.[7] One possible reason for any disparities between the two countries is that if young people in the UK were more likely to have been receiving psychotherapy as well as drugs, any effects of decreasing use of drugs may have been lessened. This is unlikely, however, given the relatively sparse use of psychotherapy in children and young people in the UK.[14]

We did not find any temporal association between antidepressant prescribing rates and hospital admissions for deliberate self harm. This is contrary to evidence from a meta-analysis of randomised trials, which indicated around a 1.7-fold increased risk of suicidal thoughts or behaviour in children and adolescents taking an SSRI compared with those taking placebo.[15] The data presented here indicate a steadily increasing trend in admissions of females and a relatively flat trend for males, with neither responding to the dramatic increase and decrease in prescribing rates occurring between 1999 and 2006, a pattern primarily driven by SSRI prescriptions. The data on hospital admissions lend additional weight to our assessment of a lack of association between trends in antidepressant prescribing and deaths from suicide, especially given that they are based on greater numbers.

Interpretation of these data must take into account the limitations of this study. Firstly, as our study was an ecological one we were limited to analysis of population trends in prescribing and self harm and suicide. Adverse or beneficial impacts of changing levels of antidepressant use may be masked by changing levels of other influences on suicide and non-fatal self harm.[16] Secondly, the prescribing and outcome datasets are for different groups of UK countries, and age groups differ. The potential errors introduced by comparing data for different geographical areas are negligible; on the basis of population estimates in mid-2006 from the Office for National Statistics, the population of England made up 84% of the UK population. Trends that include other UK countries will therefore be dominated by those for England. Additionally, regulations by the Medicines and Healthcare products Regulatory Agency cover the entire UK simultaneously, and any impacts on trends in prescribing in England will likely be similar to those elsewhere within the UK. Similarly, in using prescribing rates for 12-19 year olds to infer those for 12-17 year olds, we are unlikely to be introducing any important bias. It is unlikely that changes in prescribing to 18-19 year olds compensate for changes in the under 18s age group affected by the regulatory action. Thirdly, our prescribing data are restricted to

WHAT IS ALREADY KNOWN ON THIS TOPIC

Prescription of SSRIs to young people has been restricted in the UK and elsewhere owing to a potential increased risk of suicidal behaviour

Studies in other countries suggest that the downturn in prescribing has been associated with an increase in suicide mortality owing to untreated depression

WHAT THIS STUDY ADDS

No change was apparent in trends of suicide mortality and hospital admissions for self harm in the UK following the regulatory action against SSRI use in under 18s

These findings do not suggest that reduced access to SSRIs in young people has had an adverse impact on population health in the UK

prescribing by general practitioners—it is possible that some of the downturn in primary care prescribing was taken up by increased use of antidepressants in secondary care. Analysis of data on antidepressants from hospital and retail pharmacies (prescribed in primary care), however, indicates that hospital prescribing accounts for about only 4% of all antidepressant prescribing, and that this percentage did not vary substantially over the period 2001-6 (all ages) (unpublished results). It is therefore unlikely that our analysis is biased by unmeasured changes in prescribing in secondary care. Finally, our analysis of beneficial and adverse effects of recent advice on antidepressant prescribing are limited to its impact on suicidal behaviour; there might be other adverse or beneficial long term and short term impacts on the mental health and quality of life of young people whose management has changed.

The noticeable change in antidepressant prescribing to young people after the introduction of SSRIs and subsequent regulatory action limiting their use in under 18s in the UK does not seem to have impacted on the incidence of self harm or suicide at the population level. These findings are important because they do not suggest that reduced access to SSRIs in young people has had an adverse impact on suicidal behaviour among adolescents in the UK, as has been suggested. Longer term impacts on population health of recent changes in antidepressant prescribing requires careful assessment.

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Contributors: RMM, DG, and CM had the original idea for the study and obtained funding. BWW collected and analysed data, and drafted the methods, results, and discussion. He is the guarantor. CM advised and assisted with statistical analysis. PS supplied prescribing data and assisted with analysis and interpretation. All authors contributed to various drafts and approved the final draft.

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Competing interests: DG was a member of the Medicines and Healthcare products Regulatory Agency expert working group on the safety of SSRIs. He acted as an independent adviser, receiving travel expenses and a small fee for attending meetings and reading materials in preparation for the meeting. Data from IMS Health are used by both the pharmaceutical industry and the Medicines and Healthcare products Regulatory Agency.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

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