

change not captured in this analysis has contributed to recent favourable trends.

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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

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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 2003 the UK's Medicines and Healthcare products Regulatory Agency contraindicated paroxetine, a selective serotonin reuptake inhibitor (SSRI), in under 18s. The decision was based on trial data indicating an increased risk of suicidal thoughts and behaviour in young people receiving the drug. In December 2003 the regulatory agency concluded that the balance of risk and benefits for the use of most SSRIs in young people was unfavourable.¹

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.² Following similar regulations in the United States and the Netherlands, studies have indicated a reduction in the diagnosis and treatment of depression³ and increases in suicide rates^{4,5}; likewise some ecological data have indicated that increased SSRI prescribing in young people coincides with reductions in suicide.⁶

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 against the use of SSRIs in under 18s.

METHODS

We created three time series for relevant age groups between 1993 and 2006. Firstly, we obtained data from IMS Health for prescriptions of antidepressants to 12-19 year olds in the UK between 1993 and 2006.⁷ 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 2005.⁸ Thirdly, we used the Department of Health's Hospital Episode

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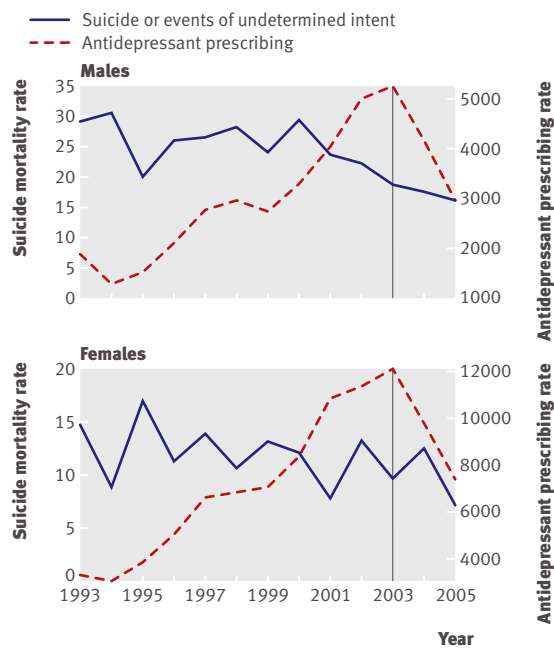


Fig 1 | Trends in rates of antidepressant prescribing in 12-19 year olds per 100 000 population in UK⁷ and mortality due to suicide or events of undetermined intent in 12-17 year olds per one million population in England and Wales,⁸ 1993 to 2005. Vertical lines indicate year in which regulatory action was taken against prescriptions for selective serotonin reuptake inhibitors in under 18s

Statistics database to obtain data on hospital admissions due to intentional self harm or events of undetermined intent among 12-17 year olds in England between January 1999 and March 2006.⁹

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.⁸ The 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 12-17 year olds. The upper age limit reflects the under 18s age group targeted by the regulatory action. 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.

We analysed trends using Joinpoint regression, which evaluates trends over time and tests for points when the trends change noticeably (“joinpoints”).¹⁰ We 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

Annual prescribing of antidepressants in young people took a sharp downturn after 2003, when regulatory action against the use of SSRIs in under 18s was taken in the UK (figures 1 and 2). The quarterly trends in prescriptions, with the modelled locations of joinpoints

(when trends change substantially) from Joinpoint regression are on bmj.com. During 1999 to 2006 an annual average of 70% (range 67%-73%) of antidepressant prescriptions were for SSRIs. Sixty five per cent of the decline in overall prescriptions for antidepressants between 2003 and 2006 resulted from a decline in SSRI prescribing.

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 fig 1). 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 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 per 100 000 in 1999 to 525 per 100 000 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%; see bmj.com). Although quarterly trends for males are not easily discerned owing to small numbers, for females 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 Food and Drug Administration resulted in reductions in prescribing of SSRIs to young people in 2003-4 followed by a reversal of 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 increased to 3.2 per 100 000 in 2004.⁵ 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.¹¹

We found an overall decrease in prescribing rates to 12-19 year olds of around 40%-50% for SSRIs and total antidepressants between 2003 and 2005, whereas in the USA the decrease for SSRI prescriptions to similar age groups was about 10%-20% over the same period.⁵ One

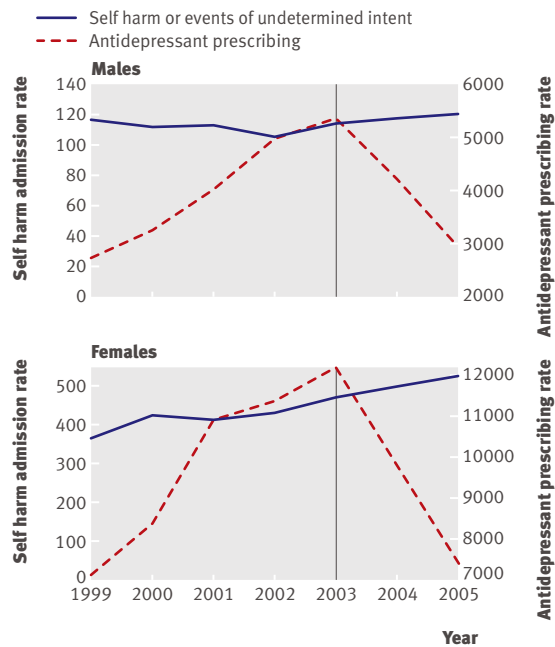


Fig 2 | Trends in rates of antidepressant prescribing in 12-19 year olds per 1000 000 population in UK⁷ and hospital admissions with a diagnosis of self harm or events of undetermined intent in 12-17 year olds per 100 000 population in England,⁹ 1999 to 2005. Vertical lines indicate year in which regulatory action was taken against prescriptions for selective serotonin reuptake inhibitors in under 18s

possible reason for the disparities between the two countries is if young people in the UK were receiving psychotherapy as well as drugs. This is unlikely, however, given the sparse use of psychotherapy in young people in the UK.¹²

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.¹³ 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 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.¹⁴ Secondly, the prescribing and outcome datasets are for different groups of UK countries, and age groups differ. The potential errors introduced by comparing 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, 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 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, however, indicates that hospital prescribing accounts for about only 4% of all antidepressant prescribing, and that this percentage did not vary substantially from 2001-6 (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 long term and short term impacts on the mental health and quality of life of young people.

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.

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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.

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 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

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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Effects of acupuncture on rates of pregnancy and live birth among women undergoing in vitro fertilisation: systematic review and meta-analysis

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ABSTRACT

Objective To evaluate whether acupuncture improves rates of pregnancy and live birth when used as an adjuvant treatment to embryo transfer in women undergoing in vitro fertilisation.

Design Systematic review and meta-analysis.

Data sources Medline, Cochrane Central, Embase, Chinese Biomedical Database, hand searched abstracts, and reference lists.

Review methods Eligible studies were randomised controlled trials that compared needle acupuncture administered within one day of embryo transfer with sham acupuncture or no adjuvant treatment, with reported outcomes of at least one of clinical pregnancy, ongoing pregnancy, or live birth. Two reviewers independently agreed on eligibility; assessed methodological quality; and extracted outcome data. For all trials, investigators contributed additional data not included in the original publication (such as live births). Meta-analyses included all randomised patients.

Data synthesis Seven trials with 1366 women undergoing in vitro fertilisation were included in the meta-analyses. There was little clinical heterogeneity. Trials with sham acupuncture and no adjuvant treatment as controls were pooled for the primary analysis. Complementing the embryo transfer process with acupuncture was associated with significant and clinically relevant improvements in clinical pregnancy (odds ratio 1.65, 95% confidence interval 1.27 to 2.14; number needed to treat (NNT) 10 (7 to 17); seven

trials), ongoing pregnancy (1.87, 1.40 to 2.49; NNT 9 (6 to 15); five trials), and live birth (1.91, 1.39 to 2.64; NNT 9 (6 to 17); four trials). Because we were unable to obtain outcome data on live births for three of the included trials, the pooled odds ratio for clinical pregnancy more accurately represents the true combined effect from these trials rather than the odds ratio for live birth. The results were robust to sensitivity analyses on study validity variables. A prespecified subgroup analysis restricted to the three trials with the higher rates of clinical pregnancy in the control group, however, suggested a smaller non-significant benefit of acupuncture (odds ratio 1.24, 0.86 to 1.77).

Conclusions Current preliminary evidence suggests that acupuncture given with embryo transfer improves rates of pregnancy and live birth among women undergoing in vitro fertilisation.

INTRODUCTION

In vitro fertilisation is expensive, lengthy, and stressful, and new drugs and technologies have been developed to improve success rates. Although some procedures have been shown to improve pregnancy rates in women with a poorer prognosis because of specific conditions, few adjuvant procedures have been shown to be effective for women in general. One exception is luteal phase support, which has been shown to increase pregnancy rates¹ and is routinely used.

Acupuncture has been used in China for centuries to regulate the female reproductive system.² Three