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What were the impacts of the Committee on Safety of Medicines warning and publication of the NICE guidelines on trends in child and adolescent antidepressant prescribing in primary care? A population based study

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ABSTRACT

Objectives To assess the impact of both the Committee on Safety of Medicines (CSM) warning (December 2003) and the National Institute for Health and Care Excellence (NICE) guidance (September 2005) on antidepressant prescription rates in children and adolescents within the UK primary care service.

Setting Population based study of primary care antidepressant prescribing using the Clinical Practice Research Datalink (CPRD).

Participants Under-18s presenting to primary care with a depressive disorder or related diagnostic code recorded in the CPRD.

Primary outcome measure Antidepressant prescription rates per month per 100 000 depressed 4–17 year olds.

Results Following the CSM warning, the prior trend towards increased prescribing rates for selective serotonin reuptake inhibitors (SSRIs) in children was significantly reversed (β for change in trend −12.34 (95% CI −18.67 to −6.00, p<0.001)). However, after the publication of the NICE guidelines the prior trend towards increased prescribing resumed for those SSRIs mentioned as potential treatments in the guidance (fluoxetine, citalopram and sertraline) (β for change in trend 11.52 (95% CI 5.32 to 17.73, p<0.001)). Prescribing of other SSRIs and tricyclics remained low.

Conclusions Despite a strong emphasis on psychosocial interventions for child and adolescent depression, it may be that the NICE guidelines inadvertently encouraged further antidepressant prescribing, at least for those SSRIs cited. Although the guidelines gave cautions and caveats for the use of antidepressants, practitioners may have interpreted these recommendations as endorsing their use in young people with depression and related conditions. However, more accurate prevalence trend estimates for depression in this age group, and information on the use of psychosocial interventions would be needed to rule out other reasons underlying this increase in prescribing.

Strengths and limitations of this study

- The study uses a large and representative national dataset.
- Analysing the data using an interrupted time series regression enabled estimation of the effects of two policy changes on the treatment of depression in young people in primary care.
- Imprecise diagnostic coding in the dataset meant we had to take a broad definition of 'depression' and related conditions.
- We could only observe prescriptions issued by primary care.
- For this study, we only had data up to 2010.

INTRODUCTION

Depression is a common illness affecting approximately 3%–6% of children and adolescents[1] and associated with impaired social and academic functioning[2 3] and increased suicide risk.[4] However, most depressed adolescents do not receive (specialist) treatment or support.[5 6] Within primary care settings practitioners are increasingly expected to detect child and adolescent depression at the earliest possible stage since the severity of depressive symptoms appears to correlate with serious consequences and negative behaviours.[7]

In treating childhood depression (as well as other disorders), antidepressants have been commonly prescribed.[8] During the late 1990s and early 2000s, selective serotonin reuptake inhibitors (SSRIs) became the preferred treatment for depression in children and adolescents rather than tricyclic antidepressants.[9] However in June 2003, after the reanalysis of published and unpublished data on the SSRI paroxetine, the UK Medicines and

Healthcare Products Regulatory Agency (MHRA) advised against its use in the treatment of child and adolescent depression.[10] The decision was based on the observation that the drug was neither efficacious nor safe, with an apparent increased risk for self-harm and suicide.[11] Later, in December 2003, the Committee on Safety of Medicines (CSM) reviewed the safety of all antidepressants in under 18s and advised against the initiation of venlafaxine and all other SSRIs, except fluoxetine.[12] These reviews were subsequently followed by a 'black box' warning from the US Food and Drug Administration in 2004[13] and guidelines issued by the UK National Institute for Health and Care Excellence (NICE) in 2005.[14] The NICE guidelines were produced to address the treatment and management of depression in children and young people and stated that no antidepressant should be used for mild depression. Furthermore recommendations were made so that psychological therapy should be offered for at least 3 months as a first line treatment for moderate to severe depression. For patients with inadequate response, fluoxetine could be offered in addition to psychological therapy to children aged 12–18; for children 5–11, fluoxetine could also be considered but with significant caution. In case of fluoxetine non-response or poor tolerability, further drug treatment with either sertraline or citalopram could be considered.

Prior to these warnings there was a trend towards increased prescribing for child and adolescent depression. Using data from the UK General Practice Research Database (GPRD—now renamed the Clinical Research Practice Datalink (CPRD)) to study the prevalence of overall antidepressant prescribing from 1992 to 2001, Murray and colleagues[8] found a 1.7-fold increase in prescriptions. In this period, the prevalence of tricyclic antidepressant prescriptions decreased by 30% (from 3.6 per 1000 in 1992 to 2.5 per 1000 in 2001) while SSRI use increased 10-fold from 0.5 to 4.6 per 1000 in the same time period. The diagnosis of depression in under 18s was associated with the use of SSRIs in 69% of cases. A nationally representative US-based survey reported antidepressant medication use increased from 0.3 (1987) to 1.0 (1996) per 100 children and adolescents.[15]

Several studies investigating changes in prescribing trends have been published since the issue of US and UK warnings. Using the Disease Analyzer-Mediplus database, Murray and colleagues[16] concluded that fewer children and adolescents were prescribed antidepressants in primary care (6.6 per 1000 in 2000 to 5.7 in 2004). More specifically the prevalence of CSM-contraindicated antidepressant prescriptions declined by a third (from 3.1 to 2.0 per 1000) while the prevalence of fluoxetine and non-SSRI antidepressants did not increase despite the guidance not mentioning these. The study suggests that CSM advice had a significant effect in reversing the rising prevalence of antidepressant prescribing. These findings were later replicated by Wijlaars *et al*[17] who demonstrated a significant drop in the rate of depression diagnoses and SSRI prescriptions around the time of the CSM announcement in 2003. However, rates for all antidepressants (except paroxetine and imipramine) began to rise post-2005. Studies in the Netherlands,[18] USA,[19] Australia[20] and five Western countries[21] have also shown that in general these warnings were associated with (at least temporary) reductions in the prescribing of antidepressants, especially SSRIs. In addition, Bergen and colleagues indicated that UK prescriptions of SSRIs decreased by 51% following the MHRA warning.[22] More recently, overall antidepressant prescribing in children and adolescents has been shown to have increased in Wales[23] and the wider UK.[24]

The aim of the present study was to analyse antidepressant prescribing trends, in relation to both the CSM warning and publication of NICE guidelines, for children and adolescents presenting to UK primary care services with depression between January 2000 and June 2010 using data from the CPRD. Our hypotheses, based upon previous research, were that rates of prescribing for both NICE 'approved' and 'non-NICE' SSRIs (that is those unmentioned for possible use by the guidelines) would decrease following both the CSM warning being issued and the publication of NICE guidelines in 2005, since these guidelines recommended first line use of psychological therapies where possible. In particular we expected a marked decrease in the prescription rates for antidepressants highlighted by both the CSM and NICE as those for which the potential benefits were likely to be outweighed by the risks.

METHODS

For the purposes of the study three drug groups were investigated: (1) medications named in the NICE Guidance CG28 as suitable for use in young people under the age of 18 with depressive illness (fluoxetine, citalopram and sertraline); (2) all other non-NICE approved SSRIs (paroxetine, fluvoxamine, escitalopram) and (3) tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, nortrityline, trimipramine, dosulepin, lofepramine).

Rates of primary care issued prescriptions for all medications listed under section 4.3 of the British National Formulary[25] as indicated for depressive illness were investigated. Within the UK approximately 98% of the population are registered with a general practitioner.[26] We used information from the CPRD, which is maintained by the MHRA. The CPRD contains anonymised primary care records for approximately 5.5% of the UK population with data obtained from over 460 primary care practices, providing a total of 40 million patient years of clinical data.[27]

Prescription rates

Data were abstracted from the CPRD from GP practices where data were classified as 'up-to-standard' (UTS) for at least 12 months during the study period of 1 January 2000–30 June 2010. Only data where a patient had a

relevant diagnostic code were included (see below). Prescribing rates for the three groups of antidepressants were generated by dividing the absolute number of depressed children who had a prescription issued (the numerator) by the number of under 18s with depression, as defined by the study (see below) within the dataset. This fraction was then multiplied by 100 000. Thus, the monthly rate reflected the mean number of prescriptions issued per 100 000 affected population. Prescription rates were calculated at the individual patient level; with repeat prescriptions and instances of re-prescribing subsequently removed.

Depression and related conditions

Cases were identified as any patient who was recorded as having received a first diagnosis of depression before the age of 17 within the study timeframe. Individuals were excluded from the study if CPRD data were not available for a period of 12 months following their 17th birthday. This approach was taken in order to reduce the risk of underestimating prescribing rates; if a young person of this age had a depression-related code they may well have had an antidepressant prescribed in the following 12 months.

The operational definition of 'depression' was constructed by consensus within the research team using CPRD diagnostic (Read/Oxford Medical Information System (OXMIS)) codes. Depression is challenging to identify and diagnose in children and adolescents presenting in a primary care setting.[28 29] In an attempt to capture the maximum number of 'true cases' a wide range of CPRD diagnostic codes related to low mood, depressive illness and self-harm were included. See the online supplementary file for the full list of the CPRD diagnostic codes used for this study. Diagnoses were carried forward for each time window so that diagnostic codes were not entered on multiple occasions.

Statistical analysis

Prescription rates (number of prescriptions per 100 000 affected population) for 4–17 year olds were calculated for each month in the study period for each drug group from the CPRD data. The denominator was the number of young people in the CPRD data, per month, with a diagnosis of depression or related diagnostic code.

Segmented linear regression analyses were performed. The magnitude of the slopes observed were formally tested in order to assess whether they significantly departed from zero. Our segmented regression followed the method described by Wagner *et al*.[30] All analyses were conducted with STATA V.14.[31]

Ethics

The data were accessed within limits set out by the Medical Research Council licence agreement for academic access with Medical Research Ethics Committee ethical approval. The proposal was approved by the Independent Scientific Advisory Committee of the GPRD (protocol number 09_075R). In addition the study was exempt from external ethical approval on the basis that the data used for this study were de-identifiable and routinely collected. This was confirmed in writing by the chair of the Durham University School of Medicine, Pharmacy and Health's Ethics Committee.

RESULTS

Overall the monthly prescription rates observed were very low, the highest observed value being for the NICE-recommended SSRIs in early 2010 at 762 prescriptions per 100 000 affected 4–18 year olds. The possible reasons for these low observed prescribing rates are outlined in the discussion section.

Interpretation of model parameters

Segmented regressions with two 'interruptions' were performed, analysing changes in trend as a result of the CSM warning in December 2003 and the publication of the NICE guidance in September 2005. The base level parameter (β_0) gives the rate of prescribing at the start of the dataset. The base trend (β_1) indicates how prescribing patterns were changing prior to the first interruption event ie, issuing of the CSM. A positive coefficient indicates an increase in prescribing rate. The post-CSM change in level (β_2) gives the altered monthly prescribing rate following this warning. The post-CSM interruption change in trend is denoted by the coefficient β_3. The post-NICE change in level (β_4) indicates the altered monthly prescribing rate following the publication of the NICE guidance. The change in trend following this second interruption is denoted by β_5.

Prescribing

Impact of CSM warning

The full results are depicted in table 1 and can also be visualised in figure 1. Prescription rates of NICE cited SSRIs significantly increased in the years leading up to the CSM warning (β_1= 5.24, 95% CI 3.43 to 7.05, p<0.001). This corresponds to a predicted prescription rate per month (ppm) per 100 000 depressed 4–18 year olds of 233 in January 2000, increasing to 474 ppm just before the CSM warning. In contrast 'non-NICE' SSRIs and tricyclic prescription trends were low and stable during this period. Following the issuing of the CSM warning only the prescribing trends for NICE cited SSRIs appeared to change, with a reduced rate (β_3= -12.34, 95% CI −18.67 to −6.00, p<0.001).

Impact of NICE guidelines publication

As can be seen from table 1 and figure 1, following release of the NICE Guidelines, there was a trend for an increase in the prescribing rate for NICE cited SSRIs (β_5=11.52, 95% CI 5.32 to 17.73, p<0.001). This equates to a modelled rise from 229 ppm at publication of the NICE guidance to 531 ppm at the end of the dataset. As can be seen from table 1, all three NICE cited SSRIs contributed to this

Table 1 Results from segmented regression analyses of rate of prescribing in the UK in 4–18 year olds

	Base level (β_0) (95% CI)	P value	Base trend (β_1) (95% CI)	P value	Post-CSM intervention (β_2) (95% CI)	P value	Post-CSM change in trend (β3) (95% CI)	P value	Post-NICE intervention (β_4) (95% CI)	P value	Post-NICE change in trend (β_5) (95% CI)	P value
NICE cited SSRIs	232.70 (184.33 to 281.07)	<0.001	5.24 (3.43 to 7.05)	<0.001	−107.94 (−194.72 to −21.15)	0.02	−12.34 (−18.67 to −6.00)	<0.001	52.72 (−34.95, 140.40)	0.24	11.52 (5.32 to 17.73)	<0.001
Fluoxetine	144.26 (112.62 to 175.90)	<0.001	2.10 (0.92 to 3.29)	0.001	58.71 (1.94 to 115.48)	0.04	−8.69 (−12.83 to −4.54)	<0.001	60.06 (2.71 to 117.41)	0.04	7.97 (3.91 to 12.03)	<0.001
Citalopram	75.61 (47.99 to 103.22)	<0.001	2.89 (1.85 to 3.92)	<0.001	−84.94 (−134.49 to −35.40)	0.001	−4.65 (−8.27 to −1.03)	0.01	44.40 (−5.56, 94.35)	0.08	5.52 (1.98 to 9.06)	0.002
Sertraline	13.31 (−3.67 to 30.29)	0.12	2.30 (1.67 to 2.93)	<0.001	−62.57 (−92.24 to −32.90)	<0.001	−3.26 (−5.43 to −1.09)	0.003	−16.02 (−45.84, 13.80)	0.29	2.51 (0.39 to 4.62)	0.02
Non-NICE SSRIs	116.40 (100.89 to 131.91)	<0.001	−0.25 (−0.83, 0.34)	0.41	−37.78 (−65.61 to −9.95)	0.01	−0.16 (−2.19, 1.88)	0.88	−21.12 (−49.24, 7.00)	0.14	0.61 (−1.38, 2.60)	0.54
Tricyclics	78.65 (59.44 to 97.85)	<0.001	0.55 (−0.17, 1.27)	0.14	−0.96 (−35.41 to 33.49)	0.96	−1.68 (−4.20, 0.84)	0.19	−4.73 (−39.54, 30.08)	0.79	1.89 (−0.58, 4.35)	0.13

NICE, National Institute for Health and Care Excellence; SSRI, selective serotonin reuptake inhibitor.

trend, with significant increases in their prescribing rates. Non-NICE and tricyclic antidepressant prescribing rates appeared unaffected and consistently relatively low.

DISCUSSION

This is, to our knowledge, the first study evaluating the impact of both the CSM warning and NICE guidance on antidepressant prescribing trends in young people. The findings of this study contradict our hypothesis that the publication of the NICE guidelines would result in a decrease in both NICE cited and non-cited SSRIs prescription rates. Rather, we observed a trend towards increased prescription rates. More specifically, prior to the CSM warning there was a trend towards increased SSRI prescribing, at least for those medications destined to be cited by NICE as possible treatments for under 18s. Following the warning this trend was reversed, but appears to have resumed following publication of the NICE Guidelines. Our findings, at least in relation to the CSM warning, are in line with previous reports, highlighting a temporary reduction in prescription rates for antidepressants for under 18s following such official cautions.[16–22]

One interpretation of these findings is that despite a strong emphasis in the NICE guidelines upon using psychosocial interventions for child and adolescent depression, it may be that this publication inadvertently encouraged further antidepressant prescribing. Although the guidelines gave cautions and caveats to their use, practitioners may have interpreted these recommendations as approval and validation for their widespread use. This 'approval' interpretation may also have been adopted by patients and their carers' willingness to be prescribed these medications. Another factor underlying these trends may have been an increased pressure for primary care-based clinicians to prescribe SSRIs for young people affected by depression, anxiety or other mental health indications for the medications, such as Obsessive Compulsive Disorder. This could have occurred due to challenges with accessing secondary care located within Child and Adolescent Mental Health Services (CAMHS), for example, with the presence of increasingly long waiting lists during that period. Certainly, there are indications from 'CAMHS Benchmarking' reports that waiting lists for such secondary care services have increased over time and that, roughly, half of all referrals were not accepted by such teams.[32] It also may have been that young people were presenting with more severe depressive or anxiety symptoms, adding to the pressure to prescribe promptly in primary care. It is well established that depression, while relatively common in adolescents, often presents to primary care under the guise of physical medical symptoms.[33] An increased awareness, and changing attitudes towards mental health issues in the UK population may also have led to a higher proportion of affected young people labelling their difficulties as

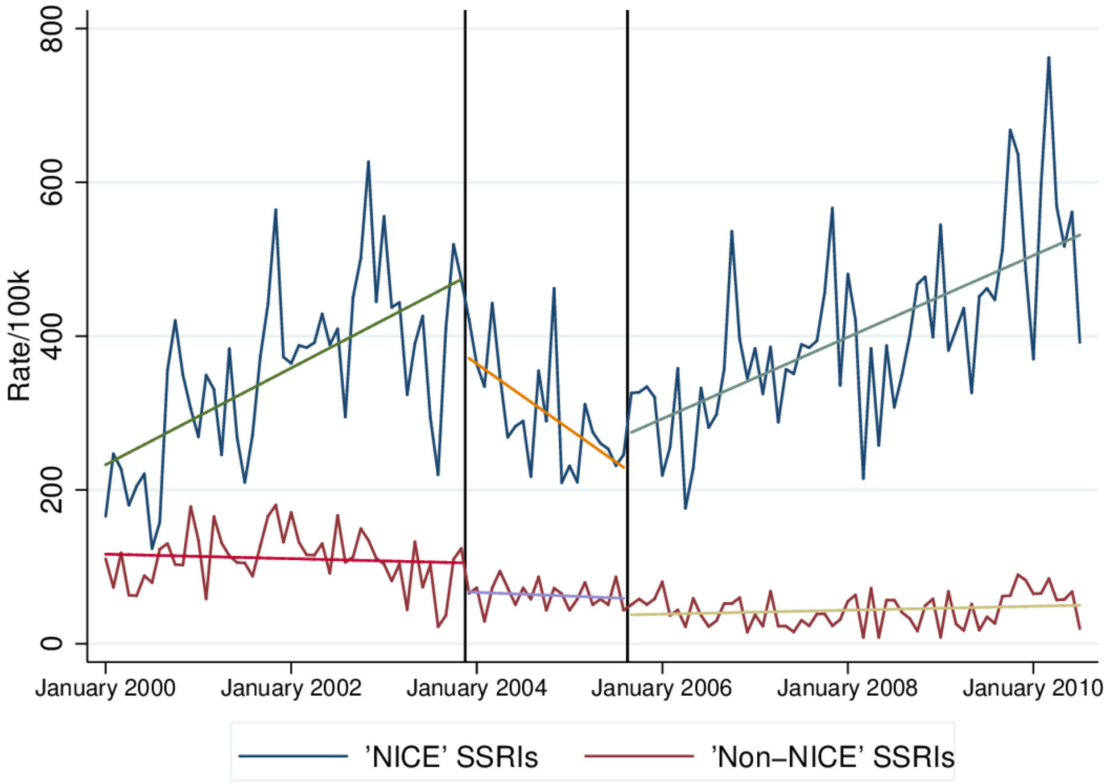

Figure 1 Prescribing rates for NICE cited SSRIs and non-NICE cited SSRIs. Also shown are the intercepts (vertical lines) and slopes for the associated segmented regression analyses. NICE, National Institute for Health and Care Excellence;SSRI, selective serotonin reuptake inhibitor.

being primarily psychological in nature, and thus receive a primary care antidepressant prescription.[34]

Strengths and limitations

The study uses a large and representative dataset to estimate the effect of policy changes on the treatment of depression in young people in primary care. Our method of using an interrupted time series regression has also been adopted and highlighted as a strength by others analysing prescribing trends.[22] This study builds on previous research into antidepressant prescribing rates in under 18s[8 16 21–24] by classifying SSRIs into those mentioned in the NICE guidance and those not cited. Additionally, by modelling an interruption at the time of the release of the guidance, we have been able to show trends which are consistent with the guidance inadvertently increasing the prescribing rates of citalopram and sertraline in particular. This study thus highlights the potential for clinical guidelines to have unintended consequences.

The main limitation to our study was that we observed that absolute monthly prescription rates were lower than might be anticipated from previous, unrelated studies. This raises issues with the precision of either prescribing information and/or diagnostic problem category coding in our CPRD extract. However, in order to mitigate against imprecise diagnostic coding we took a broad definition of 'depression' and related conditions, including acts of self-harm. Nevertheless, we cannot exclude the possibility that some cases were missed. However, assuming the 'measurement error' was uniform and identically distributed throughout the study period the trends we elicited should remain valid, even if absolute prescribing rates themselves were systematically underestimated. It should also be noted that only monthly crude prescription rates were used in the trend analysis. Therefore, the influence of the same individual being switched from one antidepressant to another would not have been captured. However, these effects would have been subtle and likely to have been swamped by other sources of noise in the data, such as reporting accuracy.

It is likely that most psychotropic prescribing occurs in secondary care. Thus, our findings may not generalise to CAMHS prescribers. Moreover, it was not possible to discriminate between prescriptions initiated within primary care, and those taken over by practitioners within general practice, under the supervision, or at the request of CAMHS prescribers. From the data used it was also not possible to estimate the role of possible confounders in such trends, such as access to psychological therapies within the NHS (in spite of the NICE recommendations) and possible selection bias of compliance with NICE guidance among CPRD registered practices. It should also be noted that some of the tricyclic antidepressants have indications other than mental health problems such as enuresis (wetting) and neuropathic pain, and may have been prescribed for these reasons.

Research and clinical implications

In due course it would be important to analyse data post 2010 to see if the upward trend in approved SSRI prescriptions has continued and whether this increase is associated with improved clinical outcomes and suicide rates. It would also be useful to complement this analysis with referral rates over time for psychological therapies. Qualitative research might provide a rich narrative of how the guidance was received and interpreted and views about the balance of psychotherapeutic and drug intervention.

In terms of clinical implications, previous studies have found evidence that the publication of warnings have been associated with significant reductions in aggregated rates of diagnosis and treatment of paediatric depression.[35] However there may be limitations in continuing to extrapolate the CPRD dataset backward or forward in time due to changes in GP coding, CPRD diagnostic criteria and other contemporaneous clinical and policy influences.

Finally, NICE specifically recommends varying the approach to treatment according to the severity of depression. Further more in-depth analysis might consider whether the publication of NICE guidance influenced prescription rates according to depression severity (mild, moderate or severe) and whether certain medications were preferred depending upon severity. Unfortunately subcategorisation of child and adolescent depression is not possible using the CPRD diagnostic codes. We also note that, while the changes to the original NICE guidelines were minimal, in relation to the update conducted in 2017, additional footnotes emphasised that fluoxetine was only licensed for the treatment of adolescents with depression if a previous trial of a psychological therapy had been unsuccessful. Moreover, the absence of specific licences for both sertraline and citalopram for the treatment of those under 18 was stressed.[36]

CONCLUSION

Prescription of NICE cited antidepressants in the UK increased significantly between 2005 and 2010, following the publication of guidance for children and adolescents with depression, following an initial decrease after the CSM was issued. The rate of non-NICE recommended SSRIs and tricyclics prescriptions before and after publication remained low. Despite the guidelines strongly emphasising the role of psychosocial interventions for child and adolescent depression, it may be that the release of the NICE publication inadvertently encouraged higher rates of antidepressant prescribing, and in particular that of sertraline and citalopram. Thus, practitioners possibly interpreted these cautious recommendations as endorsements for their use with young people presenting with distressing psychological symptoms.

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