Research paper

Temporal trends in antidepressant prescribing to children in UK primary care, 2000–2015

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A R T I C L E I N F O

A B S T R A C T

Background: The prevalence of antidepressant prescribing in children and adolescents increased steadily in the United States and parts of Europe between 2005 and 2012 despite regulatory safety warnings. Little is known about the characteristics of those being prescribed antidepressants for the first time.
Methods: A longitudinal study of antidepressant prescribing in 3–17 year olds was carried out using data from the UK Clinical Practice Research Datalink (CPRD) between 2000 and 2015. Changes in the incidence of first ever antidepressant prescriptions and the characteristics of those being prescribed them was examined.
Results: Incidence of first ever prescriptions nearly doubled between 2006 and 2015 rising from 1.60 (95%CI: 1.51, 1.69) to 3.12 (3.00, 3.25) per 1000 person years. Only 21% of the 1721 patients with incident prescriptions in 2015 could be linked to a depression diagnosis, with an additional 22% of prescriptions linked to alternative indications. The incidence of prescriptions linked to a depression diagnosis increased between 2012 and 2015, with an adjusted incidence rate ratio of 1.46 (1.26, 1.70). Antidepressant prescribing for depression and other indications has been increasing most rapidly in 15 to 17 year old females.
Limitations: Diagnoses are not directly linked to prescriptions in CPRD, so linkage must be inferred by temporal proximity.
Conclusions: Antidepressant prescribing in children increased between 2006 and 2015. This is, at least in part, due to a rise in alternative uses of antidepressants, including the treatment of anxiety, chronic pain and migraines.

1. Introduction

Antidepressant prescribing rates in children and adolescents increased throughout the 1990s in the United States (US) (Chen and Toh, 2011; Skaer et al., 2009) and other parts of the Western world (Hall et al., 2003; Murray et al., 2004; Shatin and Drinkard, 2002), only to go into sharp decline between 2002 and 2006 (Chen and Toh, 2011; O'Sullivan et al., 2015; Wijlaars et al., 2012).

In 2004 the US Food and Drug Administration (FDA) directed pharmaceutical companies to add warnings about an increased risk of suicidal thoughts and behaviours associated with antidepressant use in under 18 year olds treated for depression and other psychiatric disorders to their product information (FDA, 2004), with similar warnings being issued across Europe (EMA, 2005; Weller et al., 2004).

This action was taken in response to reports by the FDA (FDA, 2004), the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK (Weller et al., 2004) and the European Medicines Agency (EMA, 2005), which extended warnings of a small increase in the risk of suicidal thoughts and behaviours in children and adolescents, initially reported for the selective serotonin reuptake inhibitor (SSRI) paroxetine in 2003 (Hammad, 2004; Le Noury et al., 2015), to other antidepressants. They also stated that only the SSRI fluoxetine had been consistently shown to be effective in the treatment of depression in under 18 year olds (FDA, 2004; EMA, 2005; Weller et al., 2004). These conclusions were primarily based on an examination of data from the limited number of short-term placebo-controlled trials of antidepressant in children and adolescent with depression and other psychiatric disorders available at the time, for the FDA report this

was 24 trials of 9 antidepressants (FDA, 2004).

These reports built on existing concerns about the use of tricyclic antidepressants (TCAs) to treat depression in this age group due to the risk of seizure and cardiovascular side-effects associated with TCA overdose and previous reports of lack of efficacy (Geller et al., 1999; Hazell and Mirzaie, 2013). In 2005, the UK National Institute for Health and Care Excellence (NICE) issued guidelines for the treatment of depression in 5 to 17 year olds that clearly stated that TCA's should not be used in this age group. They also recommend that antidepressants should only be used with caution and in conjunction with continued psychological therapy if the patient was unresponsive to psychological therapy alone (NICE, 2005a, 2005b).

However, despite these widely publicised warnings and the introduction of new guidelines, antidepressant prescribing in under 19's increased between 2005 and 2012 in the US, UK and other European countries (Bachmann et al., 2016). Additionally TCAs still accounted for approximately 20% of all antidepressants prescribed to under 19 year olds in the UK and Germany in 2012. This was nearly twice that reported for the US, but in contrast to Germany and the UK, where the use of TCAs in children appears to be decreasing the US, Denmark and the Netherlands all showed a slight increase in TCA prescribing between 2005 and 2012 (Bachmann et al., 2016).

The reasons behind this increase in antidepressant prescribing in children and adolescents are still unclear, as are the reasons for the continued high level of TCA prescribing in this age group. However the increasing number of alternative uses for antidepressants is likely to be a contributing factor (Chouinard, 2006; Stone et al., 2003). This includes licensed and well accepted uses that are part of age-appropriate treatment guidelines, such as the treatment of obsessive-compulsive disorder (OCD) (Chouinard, 2006; NICE, 2005c), anxiety (cBNF, 2015a) and neuropathic pain (cBNF, 2015b), and uses that are either not yet well supported or in some cases potentially inappropriate. Attitudes towards the use of antidepressants in children and young people with mental health conditions has also undergone changes as recent research, mainly focused on fluoxetine, suggests that the safety and efficacy of antidepressant treatment in this age group is higher than previously thought (Cox et al., 2014; Gibbons et al., 2012).

Information gained from monitoring changes in patterns of antidepressant prescribing, and the characteristics of those being prescribed them, can be used to evaluate the effectiveness of current guidelines in limiting antidepressants prescribing in specific groups (Hetrick et al., 2012). Additionally early identification of new trends in alternative uses for antidepressants can prompt the timely development of appropriate guidance and allow any gaps in the evidence base supporting current prescribing decisions to be addressed. Approximately 98% of the UK population is registered with a general practice (HSCIC, 2015). This makes longitudinal anonymised UK primary care data a powerful tool for identifying new trends in antidepressant prescribing. This study takes advantage of this to examine whether or not current trends in UK primary care antidepressant prescribing in children have continued in recent years and what proportion of this can be linked to depression diagnoses. It also examines changes in the characteristics of 3–17 year olds prescribed their first antidepressant between 2000 and 2015. The indications for which these prescriptions were issued in 2015 were examined, as was the use of TCAs in depression and for other indications.

2. Methods

2.1. Data source

The Clinical Practice Research Datalink (CPRD; www.cprd.com) records anonymised routinely collected data from general practices across the UK. Clinical events (diagnoses and symptoms), therapies (prescriptions), referrals and tests are identified using codes. Approximately 6.9% of the UK population belong to practices participating in the CPRD, which provides a cohort of patients that are broadly representative of the UK general population in terms of age, sex and ethnicity (Herrett et al., 2015).

2.2. Study population

This consisted of all children and adolescents aged 3–17 years registered with a general practice contributing to the CPRD between the 1st of January and 31st of December who met the following inclusion criteria annually between 2000 and 2015: (i) Patients entered the cohort either at the beginning of the study window, on the 1st of January the year they turned age 3, when they had been registered at the practice for 6 months, or when the data returned by the practice was officially deemed by CPRD to be up to standard for conducting academic research. (ii) Patients remained in the cohort until the end of the study's observation period, or until they transferred out of their registered practice, reached age 18, died, or the date of the last data collection for their registered practice was reached.

2.3. Antidepressant prescribing trends, 2000–2015

The annual prevalence of 3–17 year olds prescribed one or more antidepressant and the annual incidence of first ever antidepressant prescriptions were determined for each calendar year between 2000 and 2015. A first ever antidepressant prescription was defined as the first ever recording of an antidepressant prescription in the CPRD. Prevalence and incidence by age, gender and antidepressant class (selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressant (TCA), other antidepressant) were explored. Age was measured on the 1st of January. Age bands were set at 3–5 years, 6–11 years, 12–14 years and 15–17 years old. This is in line with the child development stages set down by the Centers for Disease Control and Prevention (CDC, 2015) and the UK's educational national curriculum 'key stage' blocks (Gov.uk, 2015).

Comparisons in incidence and prevalence between specific years were made using rate ratios derived from a two-level Poisson regression model. The two-level structure allowed for practices entering and leaving the CPRD by including random effects at the practice level. Age, gender and the practice level index of multiple deprivation (IMD) 2010 quintile were included as categorical covariates. The IMD covers seven aspects of deprivation, including health deprivation and disability, education and employment (CLG, 2011). All analyses were undertaken using Stata, version 13 (Stata Corp, College Station, Texas).

2.4. Depression code lists

Codes for depression diagnoses were identified by comparing 6 publicly available code lists (Doran et al., 2011; Kendrick et al., 2015; Martinez et al., 2005; Moran et al., 2015; Rait et al., 2009; Wijlaars et al., 2012). Search terms identified during this comparison were used to identify any additional codes following a previously described protocol (Dave and Petersen, 2009). Depression codes mapping to International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) or a similar clearly defined depression diagnoses were included. Codes for depression presenting comorbidly with another psychiatric condition, for example '[X]Mixed anxiety and depressive disorder', or where depressive symptoms are a significant part of a disorder, for example 'Schizoaffective disorder, depressive type' where also included. All code lists are available via clinicalcodes.org (Springate et al., 2014). All code lists were reviewed by the study team, which included a general practitioner, a consultant in child and adolescent psychiatry, a pharmacist and epidemiologists with experience in mental health research.

2.5. Alternative uses for antidepressants

Alternative uses for antidepressants in children and adolescents were assigned to one of two levels. Level 1 groups consisted of clinical codes for a condition or group of related conditions where the uses of an antidepressant was included as a treatment option in either NICE guidelines that covered at least part of the age range under study, or the children's edition of the British national formulary (cBNF) as of December 2015. Level 2 groups consisted of i) clinical code groupings identified during this study as part of a survey of clinical codes recorded on the same day as a first ever antidepressant prescription in 2015 with a frequency of over 1%. ii) Symptom code groups; defined as codes not meeting the criteria for a depression or anxiety diagnosis. For example 'Depressed mood', 'Suspected depression', 'Low mood' and 'Anxious'.

As some of the relevant clinical codes refer to linked groups of disorders rather than a specific condition some level 1 groups were broadened or merged. For example NICE guidelines differ in their recommendations towards antidepressant use in the eating disorders between anorexia nervosa and bulima nervosa in the absence of comorbid depression but the clinical code "[X]Eating disorders" can be used for both so in this study the disorders are grouped together (NICE, 2004).

Level 1 conditions/condition groups are: 1) obsessive-compulsive disorder (OCD) (Chouinard, 2006; NICE, 2005c), 2) headache disorders (expanded from migraine) (NICE, 2012), 3) neuropathic and chronic pain (cBNF, 2015b), 4) bedwetting (NICE, 2010); 5) attention deficit hyperactivity disorder (ADHD) (NICE, 2008b); 6) eating disorders (NICE, 2004) and 7) anxiety (cBNF, 2015a) (Fig. 1). Code lists for these conditions were created using the same method as the depression code list (Dave and Petersen, 2009).

2.6. Diagnoses linked to first ever antidepressant prescriptions in 2015

The clinical codes used in CPRD are not directly linked to a specific prescription, so the association can only be made by temporal proximity. To allow for gaps between diagnosis and the start of

Fig. 1. Flow chart for assignment of 6–17 year olds with a first ever antidepressant prescription in 2015 by prescribing indication. A code recorded 12 week before to 4 weeks after the first ever prescription was considered to be contemporary. A contemporary recording of a depression diagnosis code was considered to be the primary reason for the antidepressant prescription followed by level 1, then level 2 diagnostic code groupings. Level 1 diagnostic code groups are for conditions that have antidepressant use included in age appropriated NICE guidelines or the BNF for children. Levels 2 were either identified in a survey of codes recorded on the day of the first ever prescription in 2015 or consist of symptom codes. *Less than 5 events recorded.

antidepressant treatment or delays in recording diagnoses from non-primary care settings a diagnosis was considered to be contemporary if it occurred between 12 weeks prior and 4 weeks after the recording of a first ever antidepressant prescription. Two sensitivity analyses were carried out to assess the effect of changing the size of this assessment window: First, a restricted analysis using only clinical codes recorded on the same day as the first ever antidepressant prescription and second an expanded analysis covering one year prior to the first ever prescription to 4 weeks after it.

Some patients could have contemporary recording of clinical codes for multiple relevant conditions. For example, it is common for children and adolescents diagnosed with depression to also have another mental health disorder, including OCD and anxiety, or a physical condition including pain and headaches (Emslie and Mayes, 2001). To account for multiple conditions, patients were assigned to a clinical code group using the following hierarchy of rules (Fig. 1):

1) A contemporary diagnosis of depression was always considered to be the primary reason for a first ever antidepressant prescription.
2) A code from a level 1 group outranked a code from a level 2 group.
3) A code recorded on the day of the first ever antidepressant prescription outrank a contemporary code.

Differences between clinical code groups in terms of gender, antidepressant class prescribed and age at time of first ever prescription were examined. Children aged 3–5 years were excluded from this analysis due to the negligible number of first ever prescriptions recorded in this age band.

2.7. Changes in depression diagnosis and symptom codes linked to incident antidepressant prescribing, 2000–2015

Changes in the incidence of 6–17 year olds receiving an antidepressant prescription with a contemporary depression diagnosis code versus those with a recording of a depression symptom code in the absence of an alternative indication between 2000 and 2015 were investigated. An alternative indication was taken to be a contemporary recording of a code from a level 1 or 2 clinical code group, excluding anxiety symptoms (Fig. 1). The impact of changes in the demographics of the study population and the effect of altering the time window used to assign patients to code groups was investigated using the same protocol described for the primary incidence and prevalence analyses.

The study protocol was approved by the Independent Scientific Advisory Committee of the MHRA (protocol number 16–071).

3. Results

3.1. Antidepressant prescribing trends

Distinct changes in the direction of prescribing frequency for both the incidence and prevalence of 3–17 year olds prescribed antidepressant were observed in 2002 and 2006. Incidence dropped from 3.16 (95% CI: 3.03, 3.30) to 1.61 (1.51, 1.69) for first ever prescriptions per 1000 person years (Fig. 2) and percent prevalence from 0.47 (0.45, 0.49) to 0.24 (0.23, 0.25) (Supplemental Figure 1). After adjusting for changes in population demographics and taking clustering within practice into account this equated to a halving of both incidence and prevalence with an incidence rate ratio of 0.48 (0.45, 0.52) and a prevalence rate ratio of 0.48 (0.46, 0.51). This reversed the increase in antidepressant prescribing in this age group seen between 2000 and 2002. However, this decreased frequency of prescribing did not persist with the observed prevalence of antidepressant prescribing in children surpassing the previous 2002 high in 2014, with a percentage prevalence of 0.49 (0.47, 0.50) in 2015. Incidence increased to 3.07 (3.93, 3.22) per 1000 person years in 2015. Adjusted rate ratios for 2015 relative to 2006 were 1.95 (1.80, 2.10) for incidence and 2.20
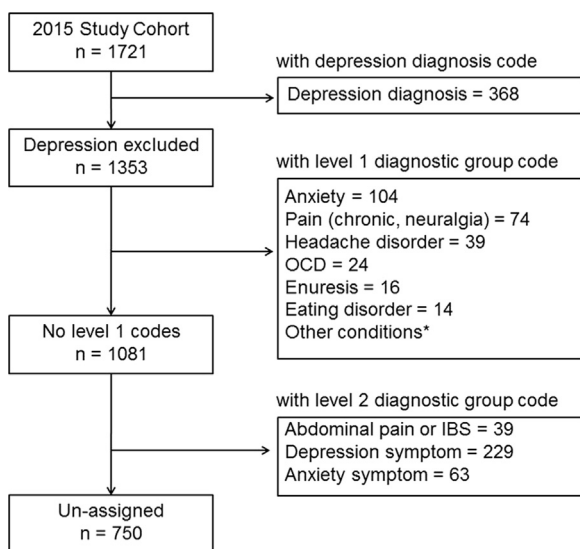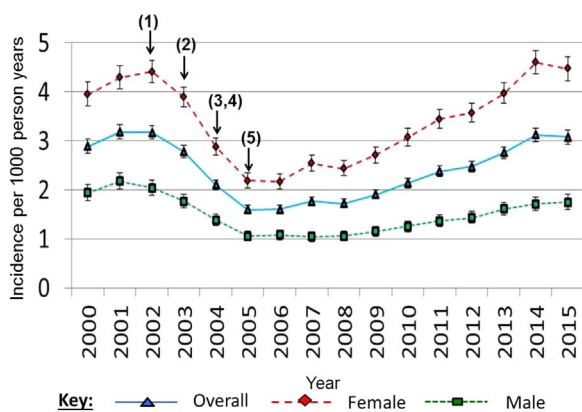
Fig. 2. Changes in rates of 3–17 year olds starting antidepressant treatment for the first time, Key: (1) The investigative program Panorama raises concerns about the use of the SSRI paroxetine in children. (2) The FDA request that GlaxoSmithKline provide clinical trial data of paroxetine in children revealing an increased risk of suicidal behaviour. (3) The FDA and MHRA complete investigations into antidepressant safety and efficacy in children. (4) The FDA requires that safety warnings be added to antidepressants. (5) NICE introduces guidelines for the treatment of depression in children which recommends limitations on antidepressant use.

(2.07, 2.35) for prevalence.

Young people aged 15–17 showed the greatest increase in the incidence of first ever prescriptions between 2006 and 2015 (Fig. 2), with an adjusted incidence rate ratio of 2.13 (1.96, 2.32). This age group accounted for 75% of 3–17 year olds prescribed an antidepressant for the first time in 2006 and 82% in 2015. In contrast the number of 6–11 year olds prescribed an antidepressant decreased during this time period with an adjusted incidence rate ratio of 0.70 (0.52, 0.95). The number of 3–5 year olds receiving a first ever prescription was negligible at all time points, so this age group was not included in further analysis. Females were more than twice as likely as males to receive a first ever antidepressant prescription between 2006 and 2015 with an adjusted rate ratio of 2.49 (2.41, 2.57) and showed the greatest increase over time with an adjusted incidence rate ratio for 2015 compared to 2006 of 2.15 (1.97, 2.36) with males showing a smaller increase at 1.59 (1.39, 1.81).

The quantity and type of prescriptions issued also changed between 2006 and 2015, with the number of antidepressant prescriptions issued per 1000 person years rising from 9.2 (8.97, 9.39) to 24.3 (23.9, 24.71) and the proportion of prescriptions issued for non-SSRI dropping from 33–16%. The proportion of non-SSRIs prescriptions issued to those receiving their first ever antidepressant prescription dropped from 38–22%.

3.2. Diagnoses codes linked to a first ever antidepressant prescription in 2015

A total of 62.8% of recipients of a first ever antidepressant aged 6–17 were not assigned to either the depression diagnosis group or a level 1 group in 2015 (Table 1). Depression (21.4%) followed by anxiety (6.0%) were the most common assignments. The characteristics of those within each diagnostic group also differed, with those issued a first ever antidepressant prescription for enuresis being more likely to be male and aged 5–14 than members of any other demographic subgroup. In keeping with the children's version of the British national formulary (cBNF) and NICE guidelines non-SSRIs were mostly prescribed to those with enuresis (NICE, 2010), pain (cBNF, 2015b), and headache disorders (NICE, 2012). The most commonly prescribed non-SSRI was amitriptyline which accounted for 86% of all non-SSRI first ever antidepressant prescriptions in 2015.

Of the diagnostic code groups identified in the survey of codes recorded on the same day as the incident prescription only the 'irritable bowel syndrome and abdominal pain' code group could be linked to

over 1% of patients. Another category of codes identified in this survey were those indicating interaction with a mental health service, including codes indicating they had been referred to/seen by a mental health service provider or were being treated/monitored for a mental health condition. The largest level 2 code group was depression symptoms at 13.3% (Fig. 1/Table 1). A total of 43.6% of patients were not assigned to a diagnostic code group of which 28.2% (12.1% of the total) had a contemporary recording of a code indicating interaction with a mental health service (Fig. 3).

Expanding the time window within which relevant diagnostic codes were considered to be linked to the first ever antidepressant prescription to a year prior before the prescription and 4 weeks after resulted in only an additional 14% of patients being assigned to a group. This reduced the un-assigned group from 44–30%, while restricting the window to codes recorded on the same day as the prescription left 62% un-assigned (Supplemental Table 1). Additionally even using the expanded time window 34% (10.1% of the total) of un-assigned patients had a recording of a code indicating interaction with a mental health service within the expanded time window.

3.3. Changes in first ever prescriptions linked to depression diagnosis and symptom codes, 2000 – 2015

The incidence of patients assigned to both the depression diagnosis and depression symptom code groups showed an increase between 2006 and 2015. The observed incidence of first ever antidepressant prescriptions with a contemporary recording of a depression diagnosis code increased from 0.51 (0.45, 0.56) per 1000 person years in 2006 to 0.81 (0.73, 0.90) in 2015 (Fig. 4), with an adjusted incident rate ratio of 1.60 (1.37, 1.87). The majority of this increase occurred between 2012 and 2015 with an adjusted incidence rate ratio of 1.46 (1.26, 1.70). Depression symptom codes linked to a first ever prescription started to increase from 2006 rising from 0.19 (0.15, 0.22) per 1000 person years to 0.50 (0.44, 0.57) in 2015, with an adjusted incidence rate ratio of 2.75 (2.19, 3.46).

4. Discussion

4.1. Summary of the study's findings

In 2014 the prevalence of children prescribed antidepressants in the UK surpassed the level seen prior to the introduction of governmental guidelines and product warnings aimed at limiting the use of antidepressants in the treatment of depression in children and adolescents during the early 2000's (FDA, 2004; EMA, 2005; NICE, 2005b; Weller et al., 2004) (Supplemental Figure 1). Young women aged 15–17 accounted for most of this rise, accounting for 61% of all first ever prescriptions in 2015, with females in general being more than twice as likely as males to be prescribed a first ever antidepressant at all time points (Fig. 2). The proportion of first ever prescriptions that could be linked to a contemporary depression diagnosis increased sharply after 2012 (Fig. 4) but still only accounted for 21% of prescriptions in 2015, with a further 13% linked to depression symptom codes. An additional 22% were linked to other clinical code groups with 44% remaining un-assigned (Table 1), 28% of which had a contemporary recording of a code indicating interaction with a mental health service.

The majority of TCA's were prescribed to those in the pain, headache disorders or enuresis code groups in line with the appropriate NICE guidelines (cBNF, 2015b; NICE, 2012, 2010), or were un-assigned. A total of 90% of TCA prescriptions were for amitriptyline. Only 1% of those with a contemporary depression diagnosis received a non-SSRI prescription, which is in keeping with NICE guidelines which state that 'Tricyclic antidepressants should not be used for the treatment of depression in children and young people' (NICE, 2005b). A total of 43% of depression linked prescription were for

Table 1
Characteristics of patients prescribed a first ever antidepressant in 2015 by clinical code group. Groups are assigned on the basis of codes recorded contemporarily (−12weeks to +4weeks) to the first ever recorded antidepressant prescription. *Data for groups consisting of less than 5 patients is not shown. # Summary statistics for patients not assigned to depression diagnosis group or a level 1 diagnostic group.

|	Percent Total	Incidence per 1000 PYs (95% Confidence Intervals)	Percent Female	Percent aged 15–17	Percent prescribed SSRI
Depression diagnosis	21.4%	0.81 (0.73, 0.90)	75%	91%	99%
Level 1 diagnostic groups					
Anxiety	6.0%	0.23 (0.19, 0.28)	67%	89%	93%
Pain (chronic, neuralgia)	4.3%	0.16 (0.13, 0.20)	84%	86%	5%
Headache disorder	2.3%	0.09 (0.06, 0.12)	77%	69%	18%
OCD	1.4%	0.05 (0.03, 0.08)	54%	50%	100%
Enuresis	0.9%	0.04 (0.02, 0.06)	44%	0%	0%
Eating disorder	0.8%	0.03 (0.02, 0.05)	86%	86%	100%
ADHD*	–	–	–	–	–
Other#	62.8%	2.38 (2.24, 2.53)	70%	81%	77%
Level 2 diagnostic groups					
Abdominal pain or IBS	2.3%	0.09 (0.06, 0.12)	72%	72%	46%
Depression symptoms	13.3%	0.50 (0.44, 0.57)	78%	93%	98%
Anxiety Symptoms	3.7%	0.14 (0.11, 0.18)	68%	89%	92%
Un-assigned	43.6%	1.65 (1.54, 1.78)	68%	77%	71%
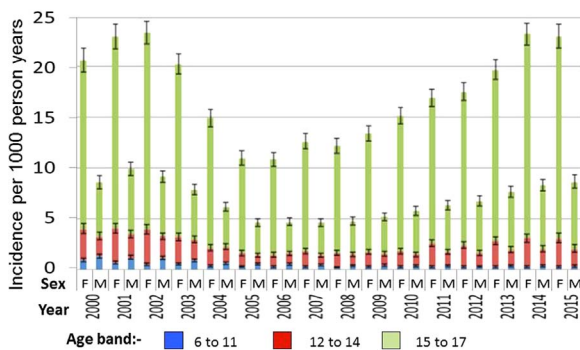
Fig. 3. Changes in incidence of first ever antidepressant prescriptions by age band and gender.
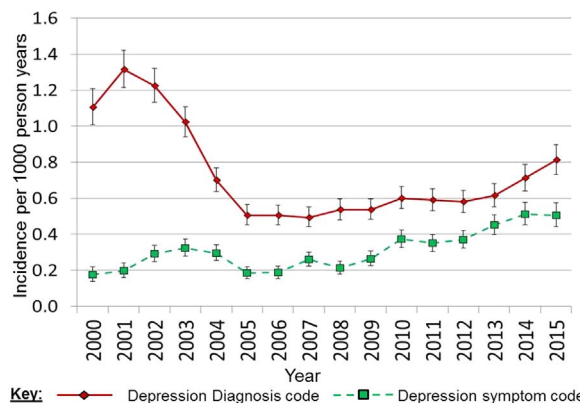

Fig. 4. Changes over time in the incidence of first ever antidepressant prescriptions assigned to depression diagnosis vs depression symptom code groups.

fluoxetine, the NICE recommended first line antidepressant treatment, and 35% for sertraline and citalopram, which are suggested as alternatives antidepressants if treatment with fluoxetine is ineffective (NICE, 2005b).

4.2. Comparison with other studies

Bachmann et al. (2016) reported that the prevalence of under 19 year olds prescribed antidepressants increased in the US and four European countries (UK, Germany, Denmark and the Netherlands)

between 2006 and 2012. This study supports the Bachmann et al. (2016) UK findings using a second anonymised primary care data set, including those for TCA prescribing levels. Additionally it shows that the prevalence of 3–17 year olds prescribed antidepressants continued to increase between 2012 and 2015 (Supplemental Figure 1). The Bachmann et al. (2016) study also reported that Germany and the UK prescribe similar levels of TCAs vs SSRIs.

The pattern of alternative uses of antidepressants for this study appears to be similar to those reported in a German study, including only 22% of children treated with antidepressant having a depression diagnosis between 2004 and 2006 (Dorks et al., 2013). Similarly a 2012 US study reported that only 28% of all subjects had a diagnosis consistent with an FDA-approved indication within 30 days pre-index and post-index antidepressant (Czaja and Valuck, 2012). In this study an increase in prescriptions linked to depression diagnoses was noted after 2012, this increase was most marked in 15–17 year old females. A recent survey of English 14 year olds reported that the mental wellbeing of teenage girls has worsened since 2005 with 37% reporting symptoms of psychological distress, over twice that reported by their male counterparts (Lessof et al., 2016), which may help to explain this gender specific rise. However, attitudes towards the use of antidepressants in children and adolescents are also shifting. The latest revision of NICE guidelines on the treatment of depression in children issued in 2015 supports the use of antidepressants as part of the initial treatment for 12–18 year olds with moderate to severe depression, whereas in the past the recommendation has been that antidepressants only be used in a child or young person who is unresponsive to an initial psychological intervention (NICE, 2005b). This change in guidance was based on a review of recent findings (NICE, 2015), including those from the treatment of adolescents with depression study which reported the highest rate of treatment response for combined fluoxetine and cognitive behavioural therapy (71%), followed by fluoxetine alone (61%). Those in the cognitive behavioural therapy alone arm of the study only achieved a response rate of 43% (March et al., 2004). This may indicate that at least part of this increase is due to an increased willingness to prescribe antidepressants to children with depression.

4.3. Strengths and Limitations

The CPRD is one of the largest longitudinal primary healthcare data set in the world. It is broadly representative of the UK population and contains a record of all prescriptions issued by participating GPs (Herrett et al., 2015) making it a powerful tool for epidemiological studies. It does however have some limitations. Population demographics may change over time as practices enter and leave the CPRD.

Prescriptions are not directly linked to a diagnosis, so temporal proximity must be used to infer that link. Additionally diagnosis codes may be missing, ambiguous or inaccurate, potentially leading to misclassification. NICE recommends that depression in children is diagnosed and treated by a multidisciplinary team (NICE, 2005b, 2015) so the first antidepressant prescription recorded in CPRD may not be the first ever prescription issued to the patient. This may explain why 35% of the first ever prescriptions recorded in CPRD for patients with a contemporary depression diagnosis were for sertraline or citalopram, which are recommended in NICE guidelines for use in patients who have not responded to treatment with fluoxetine (NICE, 2005b).

To account for changes in population demographics over time adjusted rate ratios were calculated using a Poisson model. A conservative approach to the inclusion of potentially ambiguous codes was used to improve the accuracy of diagnostic code group assignment, although this may in turn lead to group sizes being underestimated. For example, 28% of those not assigned to a diagnostic code group had a contemporary recording of a code indicating that they were interacting with a mental health service, including evidence of depression monitoring. This, along with the relatively frequent use of depression symptom codes, may also reflect clinician's unwillingness to 'label' a child with a probably transitory depressive condition as having a serious mental health disorder (Dowrick et al., 2009; Joling et al., 2011; Mitchell et al., 2011). Two additional time windows in which clinical codes were considered to be linked to the first ever antidepressant prescription were also assessed, one restricted and the other expanded from that used in the study (Supplemental Figure 1) confirming that the time window used is reasonable for capturing relevant codes recorded by GPs.

4.4. Implications for clinicians and policymakers

There are an increasing number of alternative uses for antidepressants and up to date age appropriate evidence based guidelines are not always available. In this study irritable bowel syndrome (IBS) and abdominal pain were linked to a first ever prescription in 2% of case. The use of antidepressants in the treatment of IBS is supported in adults (NICE, 2008a) but no guidelines are available for children. Humans can react differently to specific drugs at different developmental stages (de Wildt, 2011; Pichini et al., 2009), so it may not always be appropriate to extrapolate finding in adult populations to children and adolescents. Part of the reason for this lack of appropriate guidance may be the limited number of studies looking at antidepressant use in children and adolescents. Randomised controlled trials (RCT), which provide some of the best evidence on the efficacy and safety of specific drug, are also often short term. In 2011 the FDA issued a warning regarding a potential elevated risk of abnormal heart rhythms with high doses of citalopram, which account for 17% of the 2015 prescriptions in this study. The only age-specific guidance given in this warning was for adults aged over 60 (FDA, 2011). At the time only 2 randomised clinical trials of citalopram had been carried out in children (Carandang et al., 2011). More research is needed into the long-term safety and clinical effectiveness of antidepressant use in children, including the use of large scale pharmacoepidemiological studies to monitor trends in antidepressant prescribing.

The incidence of first ever antidepressant prescriptions linked to depression or a depression symptom code is increasing (Fig. 4). In part this is likely to be a response to changing guidance on the treatment of children with depression (Cox et al., 2014; NICE, 2015; Gibbons et al., 2012) but also occurs at a time when child and adolescent mental health services, which account for only 0.7% of the National health service budget, are under increasing pressure in terms of budget cuts and increased referrals (Barr et al., 2015; Frith, 2016). Antidepressants, like fluoxetine, are relatively inexpensive (BNF, 2016) particularly in comparison to psychological therapies, with

medication accounting of only 1% of spending on depression in the UK (McCrone et al., 2008). Additionally the majority of first ever mental health related antidepressants were prescribed to 15–17 year olds in this study. The transition between children and adolescent mental health services and adult services most often occurs between 16 and 18 (NICE, 2016), presenting issues in gaining access to mental health services for these young people. It is also an age range that is important for academic and social development. In a recent UK study a total of 24% of students aged 18–24 surveyed reported a mental health problem, most commonly depression or anxiety, with nearly half indicating that their mental health condition interfered with their ability to complete daily task (YouGov.uk, 2016). This would seem to suggest that additional resources should be targeted at this age group.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jad.2016.12.047.

References

Bachmann, C.J., Aagaard, L., Burcu, M., Glaeske, G., Kalverdijk, L.J., Petersen, I., Schuiling-Veninga, C.C., Wijlaars, L., Zito, J.M., Hoffmann, F., 2016. Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005–2012. Eur. Neuropsychopharmacol. 26, 411–419.

Barr, B., Kinderman, P., Whitehead, M., 2015. Trends in mental health inequalities in England during a period of recession, austerity and welfare reform 2004 to 2013. Soc. Sci. Med. 147, 324–331.

British National Formulary for Children (cBNF), 2015a. 4.3 Antidepressant drugs. ⟨https://www.evidence.nhs.uk/formulary/bnfc/current/4-central-nervous-system/43-antidepressant-drugs⟩ (accessed 15.12.15)

British National Formulary for Children (cBNF), 2015b. 4.7.3 Neuropathic pain. ⟨https://www.evidence.nhs.uk/formulary/bnfc/current/4-central-nervous-system/47-analgesics/473-neuropathic-pain⟩ (accessed 15.12.15)

British National Formulary, 2016. Fluoxetine. ⟨http://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/43-antidepressant-drugs/433-selective-serotonin-re-uptake-inhibitors/fluoxetine⟩ (accessed 02/09/16)

Carandang, C., Jabbal, R., Macbride, A., Elbe, D., 2011. A review of escitalopram and citalopram in child and adolescent depression. J. Can. Acad. Child Adolesc. Psychiatry 20, 315–324.

Centers for Disease Control (CDC), 2015. Child Development stages. ⟨http://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/adolescence2.html⟩ (accessed 12.10.15.)

Chen, S.Y., Toh, S., 2011. National trends in prescribing antidepressants before and after an FDA advisory on suicidality risk in youths. Psychiatr. Serv. 62, 727–733.

Chouinard, G., 2006. The search for new off-label indications for antidepressant, antianxiety, antipsychotic and anticonvulsant drugs. J. Psychiatry Neurosci.: JPN 31, 168–176.

Communities and local government (CLG), 2011. The English Indices of Deprivation 2007: technical report. ⟨http://geoconvert.mimas.ac.uk/help/imd-2007-manual.pdf⟩ (accessed 22.07.15.)

Cox, G.R., Callahan, P., Churchill, R., Hunot, V., Merry, S.N., Parker, A.G., Hetrick, S.E., 2014. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database Syst. Rev., CD008324.

Czaja, A.S., Valuck, R., 2012. Off-label antidepressant use in children and adolescents compared with young adults: extent and level of evidence. Pharmacoepidemiol. Drug Saf. 21, 997–1004.

Dave, S., Petersen, I., 2009. Creating medical and drug code lists to identify cases in primary care databases. Pharmacoepidemiol. Drug Saf. 18, 704–707.

de Wildt, S.N., 2011. Profound changes in drug metabolism enzymes and possible effects on drug therapy in neonates and children. Expert Opin. Drug Metab. Toxicol. 7, 935–948.

Doran, T., Kontopantelis, E., Valderas, J.M., Campbell, S., Roland, M., Salisbury, C., Reeves, D., 2011. Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework. Bmj 342, d3590.

Dorks, M., Langner, I., Dittmann, U., Timmer, A., Garbe, E., 2013. Antidepressant drug use and off-label prescribing in children and adolescents in Germany: results from a large population-based cohort study. Eur. Child Adolesc. Psychiatry 22, 511–518.

Dowrick, C., Leydon, G.M., McBride, A., Howe, A., Burgess, H., Clarke, P., Maisey, S., Kendrick, T., 2009. Patients' and doctors' views on depression severity questionnaires incentivised in UK quality and outcomes framework: qualitative study. Bmj 338, b663.

Emslie, G.J., Mayes, T.L., 2001. Mood disorders in children and adolescents: psychopharmacological treatment. Biol. Psychiatry 49, 1082–1090.

European Medicines Agency (EMA), 2005. European Medicines Agency finalises review of antidepressants in children and adolescents. London.

Food and Drug Administration (FDA), 2004. Suicidality in Children and Adolescents

Being Treated With Antidepressant Medications. USA. ⟨http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161679.htm⟩ (accessed 06/06/16)

Food and Drug Administration (FDA), 2011. FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. ⟨http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm#safety⟩ (accessed 08/07/16)

Frith, E., 2016. CentreForum Commission on Children and Young People's Mental Health: state of the Nation. CentreForum Commission, London.

Geller, B., Reising, D., Leonard, H.L., Riddle, M.A., Walsh, B.T., 1999. Critical review of tricyclic antidepressant use in children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry 38, 513–516.

Gibbons, R.D., Brown, C.H., Hur, K., Davis, J., Mann, J.J., 2012. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Arch. Gen. Psychiatry 69, 580–587.

Gov.uk, 2015. The National Curriculum. ⟨https://www.gov.uk/national-curriculum/overview⟩ (accessed 18.07.15.)

Hall, W.D., Mant, A., Mitchell, P.B., Rendle, V.A., Hickie, I.B., McManus, P., 2003. Association between antidepressant prescribing and suicide in Australia, 1991–2000: trend analysis. Bmj 326, 1008.

Hammad, T.A., 2004. Review and Evaluation of Clinical Data.

Hazell, P., Mirzaie, M., 2013. Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst. Rev. 6, CD002317.

Health and Social Care Information Centre (HSCIC), 2015. Prescriptions dispensed in the community. Statistics for England, 2004–2014. ⟨http://www.hscic.gov.uk/catalogue/PUB17644/pres-disp-com-eng-2004-14-rep.pdf⟩ (accessed 13.07.16.)

Herrett, E., Gallagher, A.M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T., Smeeth, L., 2015. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J. Epidemiol. 44, 827–836, (doi: 810.1093/ije/dyv1098. Epub 2015 Jun 1096).

Hetrick, S.E., Thompson, A., Yuen, K., Finch, S., Parker, A.G., 2012. Is there a gap between recommended and 'real world' practice in the management of depression in young people? A medical file audit of practice. BMC Health Serv. Res. 12, 178. http://dx.doi.org/10.1186/1472-6963-1112-1178.

Joling, K.J., van Marwijk, H.W., Piek, E., van der Horst, H.E., Penninx, B.W., Verhaak, P., van Hout, H.P., 2011. Do GPs' medical records demonstrate a good recognition of depression? A new perspective on case extraction. J. Affect Disord. 133, 522–527.

Kendrick, T., Stuart, B., Newell, C., Geraghty, A.W., Moore, M., 2015. Changes in rates of recorded depression in English primary care 2003–2013: time trend analyses of effects of the economic recession, and the GP contract quality outcomes framework (QOF). J. Affect Disord. 180, 68–78.

Le Noury, J., Nardo, J.M., Healy, D., Jureidini, J., Raven, M., Tufanaru, C., Abi-Jaoude, E., 2015. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ (Clin. Res. Ed.) 351, h4320.

Lessof, C., R.A, Brind, R., Bell, E., N.S, 2016. Longitudinal Study of Young People in England cohort 2: health and wellbeing at wave 2. Department of Education, London, UK.

March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., Burns, B., Domino, M., McNulty, S., Vitiello, B., Severe, J., 2004. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for Adolescents with Depression study (TADS) randomized controlled trial. JAMA 292, 807–820.

Martinez, C., Rietbrock, S., Wise, L., Ashby, D., Chick, J., Moseley, J., Evans, S., Gunnell, D., 2005. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ (Clin. Res. Ed.) 330, 389.

McCrone, P., Patel, D.S., Knapp, A., Lawton-Smith S, M., 2008. In: fund, Ks (Ed.), PAYING THE PRICE: The cost of mental health care in England to 2026. King's fund, London.

Mitchell, C., Dwyer, R., Hagan, T., Mathers, N., 2011. Impact of the QOF and the NICE guideline in the diagnosis and management of depression: a qualitative study. Br. J. Gen. Pract. 61, e279–e289, (doi: 210.3399/bjgp3311×572472).

Moran, G.M., Calvert, M., Feltham, M.G., Ryan, R., Marshall, T., 2015. A retrospective cohort study to investigate fatigue, psychological or cognitive impairment after TIA: protocol paper. BMJ Open. 5, e008149, (doi: 008110.001136/bmjopen-002015-008149).

Murray, M.L., de Vries, C.S., Wong, I.C., 2004. A drug utilisation study of antidepressants in children and adolescents using the general practice Research database. Arch. Dis. Child. 89, 1098–1102.

National Institute for Health and Care Excellence (NICE), 2004. NICE guidelines [CG9] Eating disorders in over 8s: management. ⟨http://www.nice.org.uk/guidance/cg9/chapter/1-recommendations⟩ (accessed 12.08.16)

National Institute for Health and Care Excellence (NICE), 2005a. Depression in Children: identification and management of depression in children and young people in primary, community and secondary care ⟨https://www.nice.org.uk/guidance/CG28/documents/depression-in-children-clinical-guideline-second-consultation-full-guideline2⟩ (accessed 11.08.16.)

National Institute for Health and Care Excellence (NICE), 2005b. NICE guidelines [CG28] Depression in children and young people: identification and management. ⟨https://www.nice.org.uk/guidance/cg28/chapter/1-guidance#ftn.footnote_4⟩ (accessed 06.09.15.)

National Institute for Health and Care Excellence (NICE), 2005c. NICE guidelines [CG31] Obsessive-compulsive disorder and body dysmorphic disorder: treatment. ⟨https://www.nice.org.uk/guidance/cg31/chapter/guidance#ftn.footnote_7⟩ (accessed 11.08.16.)

National Institute for Health and Care Excellence (NICE), 2008a. NICE Guidelines [CG61] Irritable bowel syndrome in adults: diagnosis and management. ⟨https://www.nice.org.uk/guidance/cg61/chapter/1-Recommendations⟩ (accessed 01.07.16.)

National Institute for Health and Care Excellence (NICE), 2008b. NICE guidelines [CG72] Attention deficit hyperactivity disorder: diagnosis and management. ⟨https://www.nice.org.uk/guidance/cg72/chapter/Recommendations⟩ (accessed 12.08.16.)

National Institute for Health and Care Excellence (NICE), 2010. NICE guidelines [CG111] Bedwetting in under 19s. ⟨http://www.nice.org.uk/guidance/cg111/chapter/1-recommendations⟩ (accessed 12.08.16.)

National Institute for Health and Care Excellence (NICE), 2012. NICE guidelines [CG150] Headaches in over 12s: diagnosis and management. ⟨http://www.nice.org.uk/guidance/CG150/chapter/1-Guidance#ftn.footnote_13⟩ (accessed 14.08.16.)

National Institute for Health and Care Excellence (NICE), 2015. Addendum to clinical guideline 28, depression in children and young people. ⟨https://www.nice.org.uk/guidance/cg28/resources/cg28-depression-in-children-and-young-people-full-guideline-2⟩ (accessed 08.08.16.)

National Institute for Health and Care Excellence (NICE), 2016. NICE guidelines [NG43]: Transition from children's to adults' services for young people using health or social care services. ⟨https://www.nice.org.uk/guidance/ng43/chapter/Recommendations⟩ (accessed 18.09.16.)

O'Sullivan, K., Boland, F., Reulbach, U., Motterlini, N., Kelly, D., Bennett, K., Fahey, T., 2015. Antidepressant prescribing in Irish children: secular trends and international comparison in the context of a safety warning. BMC Pediatr. 15, 119.

Pichini, S., Papaseit, E., Joya, X., Vall, O., Farre, M., Garcia-Algar, O., de laTorre, R., 2009. Pharmacokinetics and therapeutic drug monitoring of psychotropic drugs in pediatrics. Ther. Drug Monit. 31, 283–318.

Rait, G., Walters, K., Griffin, M., Buszewicz, M., Petersen, I., Nazareth, I., 2009. Recent trends in the incidence of recorded depression in primary care. Br. J. Psychiatry 195, 520–524, (doi: 510.1192/bjp.bp.1108.058636).

Shatin, D., Drinkard, C.R., 2002. Ambulatory use of psychotropics by employer-insured children and adolescents in a national managed care organization. Ambul. Pediatr. 2, 111–119.

Skaer, T.L., Sclar, D.A., Robison, L.M., 2009. Trends in prescriptions for antidepressant pharmacotherapy among US children and adolescents diagnosed with depression, 1990 through 2001: an assessment of accordance with treatment recommendations from the American Academy of child and adolescent Psychiatry. Clin. Ther. 31, 1478–1487, (doi: 1410.1016/j.clinthera.2009.1407.1002).

Springate, D.A., Kontopantelis, E., Ashcroft, D.M., Olier, I., Parisi, R., Chamapiwa, E., Reeves, D., 2014. ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. PLoS One 9, e99825, (doi: 99810.91371/journal.pone.0099825. eCollection 0092014).

Stone, K.J., Viera, A.J., Parman, C.L., 2003. Off-label applications for SSRIs. Am. Fam. Physician 68, 498–504.

Weller, I.V.D., Ashby, D., Brook, R., Chambers, M.G.A., Chick, J.D., Drummond, C., Ebmeier, K.P., Gunnell, D.J., Hawking, H., Mukaetova-Ladinska, E., O'Tierney, E., Taylor, R.J., York, A., Zwi, M., 2004. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. Medicines and Healthcare products Regulatory Agency, London, UK.

Wijlaars, L.P., Nazareth, I., Petersen, I., 2012. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). PloS One 7, e33181.

YouGov.uk, 2016. One in Four Students Suffer from Mental Health Problems. ⟨https://yougov.co.uk/news/2016/08/09/quarter-britains-students-are-afflicted-mental-hea/⟩ (accessed 12.08.16.)