Prescribing Trends of Antidepressants and Coprescription with other Psychotropic Medications for Children and Adolescents in Primary Care in the United Kingdom, 2000-2018: A Drug Utilization Study

Thi Xuan Dai Cao

Department of Epidemiology, Biostatistics, and Occupational Health
McGill University, Montreal
August 2020

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Epidemiology

Table of Contents

Abstract

Background: An increase in antidepressant prescriptions in children and adolescents has been documented in the United Kingdom (UK) since the 2000s but no information is available on recent trends. Moreover, little is known about coprescription with other psychotropic medications, including the profile of patients with coprescription.

Objectives: To describe trends in antidepressant prescriptions and coprescription with other psychotropic medications in UK children and adolescents between 2000 and 2018.

Methods: Using the Clinical Practice Research Datalink, we defined a cohort of patients aged 5–17 years, registered with a general practitioner between 1 January 2000 and 31 December 2018. Using Poisson regression, we estimated the annual rates of patients newly prescribed an antidepressant from the following classes: selective serotonin reuptake inhibitors (SSRIs), other newer generation antidepressants, and tricyclic antidepressants (TCAs). Furthermore, we measured the prevalence of patients with antidepressant prescriptions per number of persons alive on July 1st of each calendar year. We also calculated the percentage of new and prevalent users of antidepressants with a same-day coprescription for other psychotropic medications. Finally, we reported baseline characteristics in 2007-2008 and 2017-2018 for patients newly prescribed an antidepressant and separately, for patients with a coprescription.

Results: After a brief 42% decline from 2000 to 2005, the rate of patients newly prescribed an antidepressant increased from 2006 onwards. From 2008 to 2018, the rate increased from 254.3 to 471.2 per 100,000 person-years (rate ratio 1.97, 95% confidence interval 1.96-1.99). The rate was higher for females and adolescents aged 15 to 17 years during the entire study period. SSRIs were the most commonly prescribed antidepressant class (70% of all antidepressant prescriptions), followed by TCAs (28%). The trends in prevalent antidepressant prescriptions mirrored trends in new prescriptions. Overall, 5% of patients

newly prescribed an antidepressant had at least one coprescription for another psychotropic medication. During the study period, the percentage of patients with a coprescription rose from 2.6% to 6.4% and was more frequent in males. In 2018, coprescriptions were mostly for anxiolytics and hypnotics (63%), followed by antipsychotics (26%). Patients with a coprescription in 2017-2018 were more likely to have an anxiety diagnosis and a history of prescriptions for anxiolytics and hypnotics than in 2007-2008.

Conclusion: During the last decade, antidepressant prescriptions increased steadily in UK children and adolescents, accompanied by a rise in coprescription for other psychotropic medications. Further research is needed to offer potential explanations for the trends observed.

Résumé

Contexte: Une augmentation des prescriptions d'antidépresseurs chez les enfants et les adolescents a été documentée au Royaume-Uni depuis les années 2000, mais aucune information n'est disponible sur les tendances récentes. De plus, peu d'informations existent sur la coprescription d'autres médicaments psychotropes dans cette population , et sur le profil de ces patients.

Objectifs: Décrire les tendances de prescription d'antidépresseurs et de coprescription d'autres médicaments psychotropes chez les enfants et adolescents britanniques entre 2000 et 2018.

Méthodes: À l'aide de la base de données « Clinical Practice Research Datalink », nous avons défini une cohorte de patients âgés de 5 à 17 ans, inscrits auprès d'un médecin généraliste entre le 1er janvier 2000 et le 31 décembre 2018. À l'aide d'une régression de Poisson, nous avons estimé les taux annuels de patients nouvellement traités par un antidépresseur appartenant à l'une des classes suivantes: inhibiteurs sélectifs du recaptage de la sérotonine (ISRS), autres antidépresseurs de nouvelle génération et antidépresseurs tricycliques (ATC). De plus, nous avons mesuré la prévalence de patients sous prescription d'antidépresseurs par nombre de personnes en vie au 1er juillet de chaque année civile. Nous avons également calculé le pourcentage de nouveaux utilisateurs et d'utilisateurs prévalents d'antidépresseurs ayant reçu le même jour une coprescription d'autres médicaments psychotropes. Enfin, nous avons rapporté les caractéristiques de base en 2007-2008 et 2017-2018 des patients nouvellement traités par antidépresseur et, séparément, des patients ayant reçu une coprescription.

Résultats: Après une brève diminution de 42% de 2000 à 2005, le taux de patients nouvellement traités par antidépresseur a augmenté à partir de 2006. De 2008 à 2018, le taux est passé de 254,3 à 471,2 pour 100 000 personnes-années (rapport de taux 1,97; intervalle de

confiance à 95% 1,96-1,99). Le taux était plus élevé chez les filles et chez les adolescents âgés de 15 à 17 ans durant toute la période d'étude. Les ISRS étaient la classe d'antidépresseurs la plus couramment prescrite (70% de toutes les prescriptions d'antidépresseurs), suivis des ATC (28%). Les tendances de prévalence de prescription d'antidépresseurs reflétaient les tendances observées pour les nouvelles prescriptions. Au total, 5% des patients nouvellement traités par antidépresseur ont reçu au moins une coprescription d'un autre médicament psychotrope. Au cours de la période d'étude, le pourcentage de patients avec une coprescription est passé de 2,6% à 6,4% et était plus élevé chez les garçons. En 2018, les coprescriptions concernaient principalement les anxiolytiques et les hypnotiques (63%), suivis des antipsychotiques (26%). Les patients avec une coprescription avaient plus fréquemment un diagnostic d'anxiété et des antécédents de prescriptions d'anxiolytiques et d'hypnotiques en 2017-2018 qu'en 2007-2008.

Conclusion: Au cours de la dernière décennie, les prescriptions d'antidépresseurs ont augmenté progressivement chez les enfants et les adolescents britanniques, accompagnées d'une augmentation de copréscription d'autres médicaments psychotropes. Des recherches supplémentaires sont nécessaires afin d'offrir des explications potentielles aux tendances observées.

Acknowledgements

I would like to express my gratitude to the following people:

First, my thesis advisors, Dr. Christel Renoux and Dr. Laurent Azoulay. Dr. Azoulay, for welcoming me to the world of pharmacoepidemiology. I am especially grateful to Dr. Renoux, for her help, patience and kindness at every step along the way. I could not ask for a better supervisor, one that is committed to my success, and constantly pushing me to be better.

Second, the analysts at the Lady Davis Institute, Sophie, Jonathan and Hui, for their expertise in distilling large, raw data into manageable files, and for their patience with my questions about analyses.

I would also like to thank Emily, who graciously assisted with proofreading and showing me how to use Microsoft Word to its greatest power.

Beyond the walls of an academic institution, I would like to dedicate this thesis to my grandparents and parents. My grandparents, for having the incredible vision that education is the surest path to upward mobility, and my parents, for carrying the vision forward with me and my brother.

Preface

As the MSc candidate and first author of the enclosed manuscript, I (Thi Xuan Dai Cao) was involved in all aspects of the research project. Under the supervision of my primary supervisor, Dr. Christel Renoux, I assisted with developing the study protocol submitted to the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink. I contributed to designing the study, creating variable definitions, conducting statistical analyses, interpreting the results and writing the manuscript and corresponding thesis.

Lara Fraga (research assistant) contributed to the literature review of the manuscript. Dr. Emma Fergusson and Dr. Soham Rej (collaborators) contributed clinical and research expertise in the domain of psychiatry. Jonathan Michaud, Sophie Dell'Aniello and Hui Yin (biostatisticians) contributed biostatistical expertise by extracting the data, conducting statistical analyses and providing analytical supervision.

Dr. Christel Renoux (primary supervisor) and Dr. Laurent Azoulay (co-supervisor) were instrumental in the completion of this thesis. Both supervisors aided in developing the research topic and contributed to study design, the analytic approach, and interpretation of results.

Chapter 1. Introduction

In the UK, antidepressants are indicated for pediatric use in treating depression, social anxiety disorder, obsessive-compulsive disorder and bedwetting [1-4]. Antidepressant prescriptions in children and adolescents rose steadily in the UK in the past two decades [5-8], consistent with other Western countries [9-11]. Antidepressant prescriptions briefly declined from 2000 to 2005, around the time that the Medicines and Healthcare Products Regulatory Agency (MHRA) issued a warning on the risk of suicide ideation and behaviors in pediatric antidepressant users [7, 12, 13]. However, antidepressant prescriptions increased from 2006 onwards, suggesting that the effect of the warning was short-lived [5, 6, 8]. The trends from 2015 onwards, remain unclear.

In addition to the need to continue monitoring pediatric antidepressant prescriptions, an important facet remained unexamined: the coprescription of antidepressants with other psychotropic medications. Across Western countries, very few studies investigated trends of antidepressants coprescribed with other psychotropic drugs. In particular, we only found three studies in Finland, Norway and Canada that used large administrative databases to examine trends in psychotropic coprescription among patients newly prescribed an antidepressant [14-16]. In addition, psychotropic coprescription trends have not been updated since 2014 [14-16]. Moreover, none of these studies comprehensively described the profiles of patients with psychotropic coprescription, including changes in the profiles over time [14-16]. Understanding psychotropic coprescription trends is important since the evidence for the efficacy and safety of concomitant use of antidepressants with other psychotropic medications in children and adolescents remains scarce, and existing evidence raises concerns about serious, irreversible adverse outcomes. One study indicated that concomitant

use of the antidepressant class selective serotonin reuptake inhibitors (SSRIs) with antipsychotics was associated with increased risk of type 2 diabetes in this population [17].

Given the potential adverse outcomes associated with the use of antidepressants in monotherapy and in combination with other psychotropic drugs in this vulnerable population, it is imperative to provide an updated description of longitudinal trends in antidepressants and coprescription with other psychotropic drugs in children and adolescents. This thesis will provide real-world evidence of how antidepressants are prescribed, especially in combination with other psychotropic drugs, in UK children and adolescents. The profile of patients with coprescription and changes in the profile between the last decade will also be described. Such findings can assist clinicians in refining their treatment strategies, regulators in updating drug use trends, guidelines and policies, and researchers in conducting studies on the safety of pediatric antidepressant use.

Chapter 2. Literature Review

1. Classification of Antidepressants

Antidepressants can be broadly classified based on their mechanism of action, which is derived from the prevailing hypothesis on the neurobiological etiology of depression called the monoamine hypothesis [18]. This hypothesis states that the development of depressive symptoms is caused by the depletion of monoamine neurotransmitters (serotonin, norepinephrine and dopamine) in the brain [18]. Antidepressants act to restore a balanced level of these neurotransmitters in the brain by preventing the reuptake of these neurotransmitters from synapses back into neurons [18]. Based on their primary mechanism of action, four classes of antidepressants have been distinguished: selective serotonin reuptake inhibitors (SSRIs), other newer generation antidepressants, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) (**Table 1**).

Table 1. Mechanism of action, common molecules and first approval in the United States (US) for depression of different antidepressant classes

Class	**Primary mechanism of action**	**Common drug molecules**	**First US approval for depression**
SSRIs	Bind to serotonin receptors to inhibit the reuptake of serotonin from synapses back into neurons [19]	Fluoxetine	1987 [20]
		Sertraline	1991 [21]
		Paroxetine	1992 [22]
		Fluvoxamine	1994 [23]
		Citalopram	1998 [24]
		Escitalopram	2002 [25]
		Venlafaxine	1993 [26]

Other newer generation antidepressants (SNRIs)	Bind to serotonin and norepinephrine receptors to inhibit the reuptake of serotonin and norepinephrine from synapses back into neurons [19]	Duloxetine Desvenlafaxine Milnacipran	2004 [27] 2008 [28] 2009 [29]
Other newer generation antidepressants (NRIs)	Bind to norepinephrine receptors to inhibit the reuptake of norepinephrine from synapses back into neurons [19]	Reboxetine	Not approved in the US, but approved in Europe in 1997 [30]
Other newer generation (NDRIs)	Bind to norepinephrine and dopamine receptors to inhibit the reuptake of norepinephrine and dopamine from synapses back into neurons [19]	Bupropion	1985 [31]
Other newer generation antidepressants (NDDIs)	Bind to serotonin and non-monoamine receptors to disinhibit the release of norepinephrine and dopamine in frontal cortex [19]	Agomelatine	Not approved in the US, but approved in Europe in 2009 and Australia in 2010 [32]
Other newer generation antidepressants (TeCAs)	Bind to serotonin receptors and non-monoamine receptors to increase levels of serotonin in synapses, differential effects on	Mirtazapine	1996 [33]

	norepinephrine depending on individual molecules [19]		
TCAs	Bind to serotonin, norepinephrine and non-monoamine receptors to increase levels of serotonin and norepinephrine in synapses [19]	Imipramine	1959 [34]
MAOIs	Inhibit the enzymes responsible for breaking down monoamine neurotransmitters to increase levels of monoamine neurotransmitters in synapses [19]	Phenelzine	1961 [35]

1.1. Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs specifically target the neurotransmitter serotonin by binding to the serotonin transporter protein to inhibit the reuptake of serotonin from synapses back into neurons [36, 37]. The first SSRI, fluoxetine, was approved by the Food and Drug Administration (FDA) in the United States (US) in 1987 to treat depression [20]. Since then, several other SSRIs have also been approved by the FDA to treat depression: sertraline, paroxetine, fluvoxamine, citalopram and escitalopram (**Table 1**) [21-25]. SSRIs are generally considered the safest and most efficacious antidepressant class for children and adolescents and therefore are recommended as the first-line pharmacological option for pediatric psychiatric disorders that are indicated for antidepressants in the UK by the National Institute for Health and Care Excellence (NICE) [1, 2, 4].

1.2. Other Newer Generation Antidepressants

Emerged in the 1990s, antidepressants belonging to the newer generation other than SSRIs are also reuptake inhibitors of neurotransmitters, but unlike SSRIs, they do not exclusively target serotonin [38]. These newer generation antidepressants are grouped together based on the principle that they were modified versions of antidepressants from previous generations, rather than based on the same mechanism of action [38]. Members of this newer generation include serotonin norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), norepinephrine dopamine disinhibitors (NDDIs) and tetracyclic antidepressants (TeCAs) (**Table 1**) [39]. From this newer generation class of antidepressants, the SNRI venlafaxine has been advised for cautious use in NICE guidelines involving antidepressants in children and young people due to concerns about its adverse outcome of suicide ideation and behaviors [1, 2, 4].

1.3. Tricyclic Antidepressants (TCAs)

The first TCA, imipramine, was accidentally discovered as researchers were looking to develop a drug for schizophrenia in the 1950s [18]. Imipramine was approved in the US by the FDA in 1959 to treat depression in adults, which led to the development of other molecules in the TCA class (**Table 1**) [18]. TCAs, named after their three-ring structure, act broadly by inhibiting the reuptake of serotonin and norepinephrine as well as other non-monoamine receptors [18]. The broad-acting mechanism of TCAs, however, also caused a broad range of adverse outcomes. TCAs were used for depression in children and adolescents when they first became available in the 1960s but now only certain TCAs are indicated as second-line pharmacotherapy for obsessive-compulsive disorder (OCD) (clomipramine) and bedwetting (imipramine) by NICE [3, 4, 40].

1.4. Monoamine Oxidase Inhibitors (MAOIs)

Along with TCAs, MAOIs belonged to the first generation of antidepressants. In fact, the first-ever antidepressant was a MAOI (iproniazid), which was also accidentally discovered in the 1950s [18]. Iproniazid had been used to treat tuberculosis when researchers discovered favorable side effects such as psychostimulation, increased appetite, and improved sleep [18]. Thus, iproniazid became the first successful pharmacotherapy for depression and was classified as a MAOI [18]. MAOIs work by inhibiting the enzyme monoamine oxidase responsible for metabolizing serotonin, dopamine, and norepinephrine, thus increasing the availability of these neurotransmitters in synapses [18]. Iproniazid, the first-ever antidepressant, was non-selective and irreversible [18]. Non-selectivity refers to a MAOI's equal affinity to the two subtypes of monoamine oxidase, MAO-A and MAO-B [41]. Inhibition of MAO-A will increase the level of serotonin, dopamine, and norepinephrine in the synapses, whereas inhibition of MAO-B will only increase the level of dopamine [41]. Irreversibility means that once a MAOI binds to that enzyme, that enzyme will be permanently disabled and the body will have to generate new enzymes as replacement, a process that may last for weeks [42]. Non-selective and irreversible MAOIs raised concerns about serious adverse outcomes such as hypertension, which led to the removal of iproniazid from the US market [18]. To address these concerns, newer MAOIs have been developed to be reversible and selective [18]. However, of all current antidepressants, MAOIs present the highest risk of interacting with other drugs and food since monoamine oxidase enzymes are located throughout the body, including the gastrointestinal tract [18].

2. Indication for Antidepressants in Children and Adolescents in the UK

In the UK, only a few specific antidepressants are officially approved for use in children and adolescents. Specifically, antidepressants is approved for pediatric use in treating depression, social anxiety disorder, obsessive-compulsive disorder and bedwetting, a

condition typically present in youths under the age of 19 [1-4]. Therefore, all other potential use of antidepressants in this population are off-label.

2.1. Depression

Several drugs from the SSRI class are recommended as pharmacotherapy options by the NICE for youths aged 5 to 18 with moderate to severe depression [1]. According to NICE, psychotherapy should be the first line of treatment for pediatric depression, and pharmacotherapy should only be introduced in combination with psychotherapy if a patient meets the diagnosis of moderate to severe depression, and symptoms do not improve after four to six sessions of psychotherapy [1]. Fluoxetine is recommended as the first-line pharmacotherapy, and the only SSRI considered by NICE to have enough evidence of the benefits outweighing the risks [1]. In the UK, fluoxetine is currently the only SSRI licensed for depression in children and adolescents 8 years and older [1]. If fluoxetine is not tolerated or unsuccessful, the SSRIs sertraline or citalopram are recommended as the second-line pharmacotherapy [1]. Sertraline and citalopram are currently not licensed to treat depression in youths younger than 18, and NICE advises clinicians to prescribe them with caution [1]. NICE specifically recommends against the SSRI paroxetine, the newer generation antidepressant venlafaxine, and TCAs in this population [1].

2.2. Social Anxiety Disorder (SAD)

The SSRIs escitalopram or sertraline are recommended by NICE as the first-line pharmacologic treatment for SAD in children and young people [2]. Second-line treatment options include the SSRI fluvoxamine or paroxetine, and the newer generation antidepressant venlafaxine [2]. NICE advises cautious use of paroxetine and venlafaxine, as these drugs have been reported to increase suicide-related risks [2]. The MAOIs phenelzine or moclobemide are recommended as third-line pharmacologic treatment, with caution due to

possible interactions with food and other drugs [2]. NICE recommends against using TCAs in this population [2].

2.3. Obsessive-Compulsive Disorder (OCD)

In children and young people with OCD, NICE recommends the SSRIs sertraline or fluvoxamine as the first-line pharmacologic treatment, and the TCA clomipramine as the second-line pharmacologic treatment for OCD in children and young people [4]. In the UK, sertraline is licensed for OCD in children 6 years and older [4]. Fluvoxamine is licensed for OCD in children 8 years and older [4]. NICE recommends against using other TCAs, other newer generation antidepressants and MAOIs for OCD without comorbidities in this population [4].

2.4. Bedwetting

In the NICE guideline for youths with bedwetting, behavioral interventions (such as using an alarm to establish regular toileting patterns) should be the first-line treatment [3]. If patients do not respond to behavioral interventions, desmopressin should be the first-line pharmacologic treatment [3]. The TCA imipramine should only be introduced as the second-line pharmacologic treatment if patients do not respond to previous treatments [3]. NICE does not specifically recommend against any antidepressant for this condition [3].

2.5. Off-label Use

The extent of off-label use of antidepressants in UK children and adolescents remains unknown, since no study has been done on this topic. Data from the US suggest that off-label prescribing is common, as a retrospective cohort study of 290,816 youths aged 5-24 years found that only 28% of patients had an FDA-approved diagnosis within 30 days before and after their antidepressant prescriptions [43]. In particular, FDA-approved diagnoses were even less frequent (5-10%) in children below 13 years of age in this study

[43]. Antidepressants are only approved by the FDA for depression, OCD and bedwetting in pediatric patients [43].

3. Efficacy and Safety Profiles of each Antidepressant Class

Evidence on the safety and efficacy of antidepressants indicated by NICE for pediatric use have been scarce. Only a few RCTs have been conducted in pediatric populations to compare each antidepressant against placebo for each indicated disorder [39, 52-64]. In addition, evidence from observational studies that examined long-term adverse outcomes have also been scarce [66]. This section will review the efficacy and safety results from RCTs and emerging safety results from observational studies on the risk of type 2 diabetes, a serious, lifelong adverse outcome in children and adolescents.

3.1. Evidence from Randomized Control Trials (RCTs)

3.1.1. SSRIs

SSRIs and Depression

For pediatric depression, most of the SSRIs recommended by NICE demonstrated efficacy in randomized control trials (RCTs). The most recently updated Cochrane systematic review in 2012 for the use of SSRIs and other newer generation antidepressants in pediatric depression included five trials of fluoxetine, two trials of sertraline, two trials of citalopram, two trials of escitalopram and four trials of paroxetine [39]. Analyses by individual antidepressant in this review found that fluoxetine reduced depressive symptoms (mean difference (MD) -5.63; 95% confidence interval (CI) -7.39 to -3.86), and increased remission (risk ratio (RR) 1.47; 95% CI 1.03 to 2.08) compared to placebo [39]. Sertraline also significantly reduced depressive symptoms (MD -3.52; 95% CI -6.64 to -0.40) but did not have an effect on remission (RR 1.17; 95% CI 1.00 to 1.36) compared to placebo [39]. Although recommended by NICE as a second-line pharmacotherapy for pediatric depression, the evidence for citalopram was not conclusive. Depressive symptoms were reduced but with

a wide CI that included the possibility of no difference compared to placebo (MD -2.90; 95% CI -7.77 to 1.97). Remission was improved by 16% compared to placebo but the CI included the possibility of no difference (RR 1.16; 95% CI 0.71 to 1.89) [39].

With respect to safety, common adverse outcomes reported for SSRIs in the aforementioned review were headache, nausea, diarrhea and insomnia [39]. In this review, SSRIs as a class increased adverse outcomes by 11% compared to placebo (RR 1.11; 95% CI 1.05 to 1.17), with little heterogeneity of effect (I^2 = 4%; 95% CI 0% to 55%) [39]. The pooled effect of all newer generation antidepressants, including SSRIs, indicated higher risk of suicide-related outcomes by 58% compared to placebo (RR 1.58; 95% CI 1.02 to 2.45) and there was no difference between SSRIs and other newer antidepressants [39]. However, it is worth noting that adverse outcomes were inconsistently reported in different studies, which may affect the interpretation of these safety results when comparing between individual SSRIs, or between SSRIs and other antidepressant classes.

The evidence on SSRI safety in pediatric depression has been a controversial topic that drew attention from not only researchers and clinicians but also regulatory agencies and the media, especially regarding serious adverse outcomes such as suicide ideation and behaviors [13, 44, 45]. In 2003, after a reanalysis of data on the SSRI paroxetine, the MHRA decided that this drug was not efficacious or safe, with emphasis on the increased risk of self-harm and suicide [46]. Thus, the MHRA advised against using paroxetine for child and adolescent depression [46]. Later in the same year, the MHRA reviewed the safety of all antidepressants in youths under 18 and advised against the use of all SSRIs, except fluoxetine [13]. This decision became the basis for the pharmacological options in the first NICE guideline on child and adolescent depression in 2005 [1]. However, the MHRA decision has been met with skepticism from other regulatory agencies. The editor emeritus at the official journal of the Canadian College of Neuropsychopharmacology wrote that the evidence did

not support “the hypothesis that antidepressants or, more specifically, SSRIs cause increased suicidality in patients with depression, nor do they appear to do so in patients treated with these drugs for other reasons” [47]. While Health Canada also issued its own warning, its expert panels on this matter concluded that the evidence did not support “a British-style ban, or a stronger warning” [48]. Nevertheless, by the end of 2005, regulatory agencies in the US, Canada, and Europe all conducted their own reviews of available evidence and issued warnings regarding the risk of suicide ideation and behaviors in pediatric users of antidepressants [49-51].

SSRIs and Anxiety Disorders

For several anxiety disorders, the SSRIs recommended by NICE demonstrated efficacy in RCTs. While the NICE guideline for anxiety in children and young people pertains specifically to social anxiety disorder, RCTs were often conducted for several other anxiety disorders in this population. A 9-week RCT comparing sertraline to placebo in 22 youths aged 5 to 17 years with generalized anxiety disorder (GAD) found significant improvement by the end of the study on clinical outcomes, defined as scores on the Hamilton anxiety scale ($F=18.7$, $df=1,19$, $p<0.001$) and the Clinical Global Impressions scale ($F=20.5$, $df=1,19$, $p<0.001$) [52]. Sertraline was also found to be safe since the rate of adverse outcomes did not differ between sertraline and placebo ($p>0.05$, Fisher’s exact test) [52]. In another 12-week RCT comparing sertraline and cognitive behavioral therapy to placebo for 488 youths aged 7 to 17 years with separation anxiety disorder, GAD or SAD, the percentage of patients with improved outcomes (measured by scores on the Clinical Global Impression scale) was as high for sertraline (54.9%; 95% CI 46.4 to 63.1) as for cognitive behavioral therapy (59.7%; 95% CI 51.4 to 67.5), and both were higher than placebo (23.7%; 95% CI 15.5 to 34.5) [53]. The frequency of adverse events reported did not differ between sertraline and placebo in this study ($p>0.05$, Fisher’s exact test) [53].

While escitalopram is also recommended as a first line pharmacotherapy together with sertraline, no RCT on escitalopram in youths with any type of anxiety disorder has been found. In an open-label trial for escitalopram on 20 youths aged 10 to 17 years with SAD, escitalopram reduced symptom severity scores on the Clinical Global Impressions scale (MD 2.4; 95% CI 1.8 to 3.0) and increased quality of life scores (MD 11.99; 95% CI 4.9 to 18.9) in week 12 compared to baseline [54]. This study reported mild-to-moderate adverse outcomes for escitalopram, including somnolence and insomnia [54]. However, the small sample size and the lack of randomization in this study did not permit a definitive conclusion on the efficacy and safety of escitalopram over placebo in this population.

An 8-week RCT comparing fluvoxamine to placebo in 128 youths aged 6 to 17 years with either SAD, GAD, or separation anxiety disorder found an improvement on clinical outcomes (measured by scores on the Pediatric Anxiety Rating scale and Clinical Global Impressions scale) in week 8 compared to baseline (MD 7.5±2.0, $p<0.001$) [55]. With respect to safety, the fluvoxamine-treated group experienced more abdominal discomfort [55]. Notably, 10 of 63 patients (16%) in the fluvoxamine-treated group dropped out, 5 of whom due to adverse outcomes [55]. In the placebo group, 14 of 65 patients (22%) dropped out of the study, including 1 due to adverse outcomes and 5 due to lack of efficacy [55]. To address the concern of non-response, all patients from this RCT were invited to a subsequent open-label comparing fluvoxamine, fluoxetine and placebo for 6 months [56]. Patients in the original RCT who responded to fluvoxamine were continued on fluvoxamine, patients who did not respond to fluvoxamine were switched to fluoxetine, and patients who did not respond to placebo were switched to fluvoxamine [56]. In this open-label trial, 4 of 35 patients (13%) dropped out, including 1 due to adverse outcomes and 2 due to lack of efficacy. This follow-up study found that anxiety symptoms improved in 94% of fluvoxamine responders, 71% of fluvoxamine non-responders and 56% of placebo non-responders from

the original RCT [56]. Moreover, because this was an open-label study, the effect of the drug alone cannot be distinguished from potential confounders such as patient expectation of drug benefits and concurrent psychotherapies. Taken together, the result of the original RCT and the follow-up study suggests that fluvoxamine may be efficacious in treating youths with anxiety disorders. However, since anxiety disorders could be chronic, the long-term effect and the safety profile warrant further monitoring and research.

SSRIs and OCD

Efficacy for pediatric OCD from the SSRIs recommended by NICE, fluvoxamine and sertraline, was confirmed in RCTs. A 10-week RCT was conducted for fluvoxamine versus placebo in 120 youths aged 8 to 17 years with OCD, with the options for non-responders to enter the open-label phase at week 6 [57]. In this study, 19 of 57 (33%) patients in the fluvoxamine-treated group dropped out, 3 of whom due to adverse outcomes and 9 due to lack of efficacy. In the placebo group, 27 of 63 patients (43%) dropped out, 1 of whom due to adverse outcomes and 22 due to lack of efficacy [57]. The fluvoxamine-treated group saw significant reduction in symptom severity scores on the Children's Yale-Brown Obsessive Compulsive Scale compared to placebo ($F_{1,98}$= 4.69, p = 0.033) [57]. With respect to safety, 84% patients in the fluvoxamine-treated group and 76% patients in the placebo group reported at least one adverse outcome, with insomnia and asthenia more commonly reported in the fluvoxamine-treated group than placebo [57].

For sertraline, a 12-week RCT on 187 youths aged 7 to 17 years with OCD showed that sertraline reduced symptom severity scores on the Children's Yale-Brown Obsessive Compulsive Scale (95% CI of MD -5.7 to -1.1, p=0.005), the National Institute of Mental Health Global Obsessive Compulsive Scale (95% CI of MD -1.7 to -0.1, p=0.02), and the Clinical Global Impressions Scale (95% CI of MD -1.0 to -0.2, p=0.002) compared to placebo [58]. However, more patients in the sertraline-treated group dropped out during the

study than in the placebo group due to adverse outcomes, 12 of 92 (13%) patients in the sertraline-treated groups and 3 of 95 (3%) patients in the placebo group [58]. Sertraline-treated patients also experienced significantly more insomnia, nausea, agitation and tremor compared to placebo patients ($p<0.05$, Fisher's exact test) [58]. In another 12-week RCT comparing sertraline and cognitive behavioral therapy to placebo for 112 youths aged 7 to 17 years with OCD, the percentage of patients with reduced symptom severity scores measured on the Children's Yale-Brown Obsessive Compulsive Scale was as high for sertraline (21.4%; 95% CI 10% to 40%) as for cognitive behavioral therapy (39.3%; 95% CI 24% to 58%) and both were higher than placebo (3.6%; 95% CI 0% to 19%) [59]. Approximately 20% of sertraline-treated patients reported gastrointestinal adverse outcomes (nausea, diarrhea, stomachache) compared to 5% of patients on placebo in this study [59].

Taken together, the results from these RCTs suggest that fluvoxamine and sertraline are efficacious for short-term treatment in pediatric OCD and adverse outcomes are generally mild-to-moderate, which led to their license for use in this population. However, similar to anxiety, OCD is also a chronic disorder, and more research on safety and efficacy of long-term use is warranted.

3.1.2. Other Newer Generation Antidepressants

Venlafaxine was not recommended in pediatric depression by NICE due to concerns about suicide-related outcome as reported in RCTs [1]. Pooled results from two RCTs for 334 youths aged 7 to 17 years with depression indicated no difference in reducing symptom severity scores on the Children's Depression Rating Scale for venlafaxine compared to placebo (MD -1.90; 95% CI -4.79 to 0.99) [39]. One of the trials showed significantly higher risk of suicide-related outcomes in the venlaxafine-treated group compared to placebo (RR 12.93; 95% CI 1.71 to 97.82) [39]. Even though the CI was very wide, suicide-related outcomes appeared to be at least 71% higher in the venlafaxine-treated group [39].

As a second-line pharmacotherapy for SAD in children and young people, venlafaxine demonstrated efficacy in RCTs. A 16-week RCT of 293 youths aged 8 to 17 years with SAD indicated significant improvement on clinical outcomes (measured by scores on the Social Anxiety Scale, child or adolescent version and the Clinical Global Impressions scale) for venlafaxine compared to placebo ($F(2,1089) = 77.24$, $p<0.001$) [60]. With respect to safety, adverse outcomes that were reported at least twice in the venlafaxine-treated group compared to placebo included anorexia ($p<0.001$, Fisher's exact test) and weight loss ($p=0.008$, Fisher's exact test) [60]. There were no suicides or suicide attempts, but three venlafaxine-treated patients reported suicide ideation compared to no patient in placebo [60]. Suicide ideation was not considered by the investigators to be statistically different for venlafaxine-patient and placebo due to the small sample size [60].

3.1.3. TCAs

TCAs are not recommended in pediatric depression by NICE due to the lack of efficacy and increased adverse outcomes [1]. A Cochrane review of nine trials (454 patients) for using TCAs in pediatric depression found TCAs to be no more effective than placebo, with a narrow CI (RR 1.07; 95% CI 0.91 to 1.26) [40]. TCAs were also not safe for this indication, as they caused more serious adverse outcomes such as vertigo, symptoms of lowered blood pressure, tremor and dry mouth compared with placebo [40].

For the OCD indication, clomipramine-treated patients showed improved clinical symptoms (measured by mean scores on the Children's Yale-Brown Obsessive Compulsive Scale) compared to patients on placebo in an 8-week RCT of 60 youths aged 10 to 17 years with OCD ($MD = 10$, $p<0.05$) [61]. While there has been concerns about blood and cardiac problems associated with TCA use in children and adolescents, this study did not find any changes in vital signs related to the use of clomipramine [61]. Compared to patients on placebo, clomipramine-treated patients experienced more dry mouth (63% versus 16%),

somnolence (46% versus 11%), and dizziness (41% versus 14%) [61]. However, the sample size was small, and the author did not differentiate between drug-induced adverse outcomes and concomitant illnesses in reporting adverse outcomes in this study.

For the bedwetting indication, imipramine was found to significantly reduce bedwetting in an 8-week RCT of 80 children aged 5 to 13 years with a bedwetting diagnosis compared to mianserin ($\chi^2 = 10.88$, $p<0.001$) and placebo ($\chi^2 = 16.94$, $p<0.001$) [62]. Mianserin was not found to be more efficacious than placebo ($p=0.57$) [62]. Adverse outcomes were not reported in this study [62].

3.1.4. MAOIs

The NICE recommendation to use the MAOI phenelzine or moclobemide as a third-line pharmacotherapy for youths with SAD is likely based on adult studies, since no RCT was conducted on phenelzine or moclobemide that involved children with any type of anxiety disorder. A 12-week RCT for moclobemide on 390 patients aged 18-65 years with SAD, including comorbid anxiety disorders, suggested significant improvement (measured by changes in scores on the Clinical Global Impressions scale) over placebo for patients with or without other comorbid anxiety disorders ($\chi^2 = 6.24$, $p=0.01$) [63]. Adverse outcomes were similarly reported in moclobemide-treated patients (58%) and patients on placebo (52%) in this study [63]. Another 12-week RCT for phenelzine on 128 patients aged 18-65 years with SAD (excluding comorbid anxiety disorders) found that phenelzine significantly improved clinical outcomes, measured by scores on the Liebowitz Social Anxiety Scale compared to placebo (MD =-17.24, standard error = 5.52, $p<0.01$) [64]. With respect to safety, the phenelzine-treated group reported significantly more lightheadedness ($\chi^2 = 6.3$, $p=0.04$) and constipation ($\chi^2 = 10.9$, $p=0.004$) compared to placebo [64]. These results suggest that moclobemide and phenelzine are efficacious and safe in adults, with mild-to-moderate adverse outcomes.

3.2. Evidence from Observational Studies

While RCTs are instrumental for establishing efficacy against placebo, they are not designed to examine long-term adverse outcomes. Observational studies can fill in this gap, since follow-up periods in observational studies are often much longer than in RCTs. Long-term follow-up is also needed to study rare but serious adverse outcomes, which RCTs are usually not powered to detect since conducting RCTs with enough statistical power to study long-term adverse outcomes would be prohibitive in terms of cost, time and ethics.

3.2.1. Observational Studies on Long-Term Adverse Outcomes

Using an observational study design, researchers have begun to identify the risk of type 2 diabetes mellitus (T2DM) in youth users of antidepressants. T2DM is a serious, potentially chronic disease that can take a long time to develop and diagnose [65]. T2DM weakens the immune system, making the patients more susceptible to other diseases [65]. As a comorbidity to existing psychiatric disorders, T2DM can add to the burden of disease in this vulnerable population. A cohort study with 119,608 youths aged 5 to 20 years with a mean follow-up of 22.8 months found that longer duration of use is associated with T2DM in users of SSRIs or SNRIs [66]. The risk of T2DM in youths currently using SSRIs or SNRIs for 210 days or more was 2.66 times the risk of T2DM in youths currently using SSRIs or SNRIs for 90 days or fewer (RR 2.66; 95% CI 1.45 to 4.88) [66]. While further research is warranted, this piece of evidence raises concerns about the safety of SSRIs, which has been widely considered as the safest and most efficacious for this population.

3.2.2. The Need for Drug Utilization Studies to Monitor Antidepressant Trends

Given the uncertain evidence on the risk of suicide ideation and behaviors and the emerging evidence on serious long-term adverse outcomes such as T2DM, studies that monitor trends of pediatric antidepressant use are needed. Drug utilization studies have been recognized by the World Health Organization as an essential tool to understand whether

prescribing decision is rational [67]. This understanding is especially important in the face of limited evidence on safety and efficacy, as is the case of antidepressant use in children and adolescents. Drug utilization studies are also needed to compare drug use between countries or regions, as well as to determine whether prescribing decisions adhere to clinical guidelines [67]. The real-world evidence of clinical prescribing practice provided by drug utilization studies will benefit clinicians looking to refine their treatment strategies and to regulators to update drug use trends, clinical guidelines and policies. Real-world data on prescribing trends can also inform future studies on safety of pediatric antidepressant use.

4. Utilization of Antidepressants in Children and Adolescents

4.1. Trends in Prevalence of Antidepressant Prescriptions

The rise in the prevalence of antidepressant prescriptions in children and adolescents has been reported in the US, Canada and Europe since the 1980s [68-71]. While countries differed in drug approval policies and healthcare systems, broad comparison at the national level is possible given reasonable similarities in study design, patient population, measure of prevalence and sources of data. This section covers a brief literature review of studies that estimated prevalence of antidepressant prescriptions from outpatient samples in Western countries using databases of insurance claims, prescriptions and drug dispensing. As previously described, most countries in North America and Europe enacted the regulatory warning on the risks of suicide-related behaviors in pediatric antidepressant users at around the same time in 2003-2005, hence experiencing similar effects of regulation on prescription trends [49-51, 72].

4.1.1. Trends in Overall Prevalence

Before the regulatory warnings were issued, rapid rise in the overall prevalence of antidepressant prescriptions in children and adolescents was observed in North America. In the US, a study of 900,289 youths aged 2 to 19 years found that prevalence increased

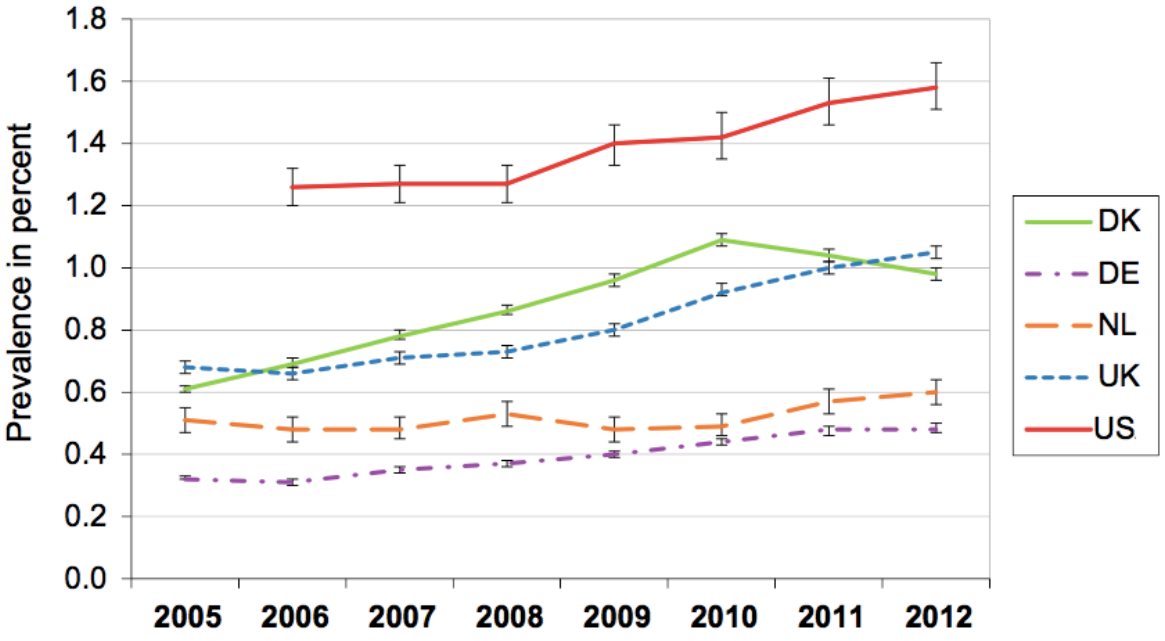
between three to five fold from 1988 to 1994 at three study sites, translating to an estimate of annual prevalence between 12.85 and 19.10 per 1,000 youths in 1994 [71]. In Canada, a study at the provincial level of youths younger than 20 years old reported that prevalence increased 75% in British Columbia and 80% in Manitoba from 1997 to 2003 [68]. In British Columbia, annual prevalence in 2003 was estimated to be 13 per 1,000 youths and 12 per 1,000 youths in Manitoba [68]. In Europe, overall prevalence increased more modestly compared to North America. From 1995 to 1999, a study in the Netherlands of 37,670 youths aged 19 years and younger reported a 16% increase from 3.8 per 1,000 youths to 4.4 per 1,000 youths [70]. A study in the UK of 24,976 youths age 18 and younger reported a 25% increase in annual prevalence (4.8 to 6.0 per 1,000 youths), also from 1995 to 1999 [69]. Thus, the average annual prevalence was roughly twice as much in North America (10 per 1,000 youths) as in Europe (5 per 1,000 youths) prior to the regulatory warning on suicide-related behaviors. Among Western countries, the US had the highest prevalence estimate and the UK had one of the lowest estimate.

After two decades of annual increase, the overall prevalence of antidepressant started to decline in the US, Canada and Europe during 2005-2007, the period immediately following the regulatory warnings regarding the risk of suicide in pediatric antidepressant users [6, 9, 73]. A time-series analysis of Canadian youths aged 18 years and younger suggested a significantly upward trend prior to the warning from 2000 to 2004 (slope = 0.0003, $p < 0.0001$), followed by a significantly downward trend right after the warning from 2005 to 2009 (slope = -0.0004, $p < 0.0001$) [73]. However, prevalence steadily rose again five years after the warning, from 2009 to 2014 (slope = 0.0002, $p = 0.0054$), suggesting that the effect of the warning was only temporary [6, 73]. In the UK, the annual prevalence in 2014 surpassed the annual prevalence prior to the warning in 2002 [6, 73]. The magnitude and rate of change in prevalence varied between countries. A study comparing prevalence of

antidepressant prescriptions in five Western countries found that prevalence was highest in the US (around 1.6%), followed by Denmark and the UK (around 1%), and lowest in the Netherlands and Germany in 2012 (around 0.5%) (**Figure 1**) [9]. Concerning the rate of change, prevalence increased more rapidly in the US, the UK and Denmark, while a slower pace of increase was observed in the Netherlands and Germany (**Figure 1**) [9]. Prevalence in Germany remained constant at about 2 per 1,000 youths from 2004 to 2012 as reported in another study [74]. Taken together, these results suggest that the UK had one of the highest estimates in magnitude and rate of change in annual prevalence of antidepressant prescriptions in Europe. In 2012, annual prevalence was roughly two-fold higher in the UK than in Germany, the country with the lowest prevalence.

Figure 1. Annual prevalence of antidepressant prescriptions in children and adolescents (0–19 years) from five Western countries, 2005–2012 (Reproduced from Bachmann et al 2012 [9], with permission from Elsevier).

Abbreviation: DE = Germany, DK = Denmark, NL = The Netherlands



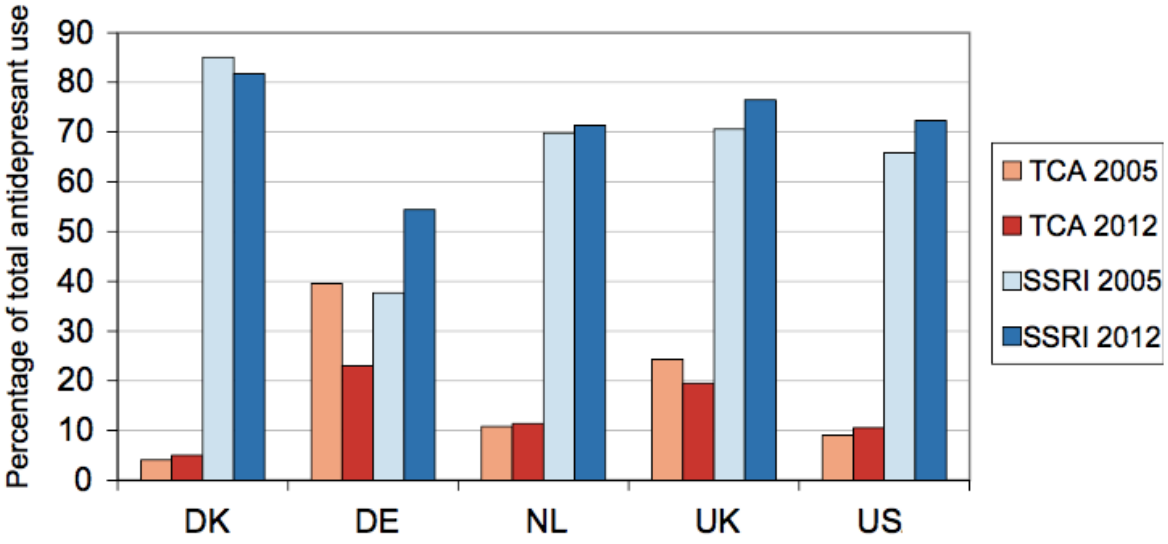
4.1.2. Trends in Prevalence by Antidepressant Class

In Western countries, the increase in overall prevalence was driven by SSRIs, which replaced TCAs as the most prescribed antidepressant class in children and adolescents since

the 1990s [5, 6, 8, 69]. From 2005 to 2012, SSRIs were the predominant antidepressant class in the US, the UK, the Netherlands, Denmark and Germany with more than 50% of total pediatric antidepressant prescriptions (**Figure 2**) [9]. In the UK, prescriptions for non-SSRIs dropped from 33% to 16% between 2006 and 2015 [6]. Interestingly, trend in TCA prevalence varied between countries. From 2005 to 2012, TCA prevalence remained at 10% or less in the US, Denmark, and the Netherlands, but was twice as much in Germany and the UK, at 20% or more [9]. In Germany, TCAs accounted for 40% of total antidepressant prevalence in 2005 and was higher than SSRI use. Although TCA prevalence in Germany dropped by half to 20% in 2012 and SSRIs became the most prevalent antidepressant class, overall TCA prevalence in Germany was still the highest among these five Western countries (**Figure 2**) [9]. After Germany, the UK had the second highest TCA prevalence among the five Western countries, with a less dramatic decline from 25% in 2005 to 20% in 2012 (**Figure 2**) [9].

Figure 2. Prevalence of use by antidepressant class in children and adolescents (0–19 years) from five Western countries, 2005–2012 (Reproduced from Bachmann et al 2012 [9], with permission from Elsevier).

Abbreviation: DE = Germany, DK = Denmark, NL = The Netherlands



4.1.3. Trends in Prevalence by Age and Sex

Differences in pediatric antidepressant prevalence based on age and sex was observed among Western countries. From 2005 to 2012, prevalence was higher in girls than in boys for the US, the UK, the Netherlands, Denmark and Germany, but specific estimates varied between countries [9]. On average, the female-to-male ratio was highest in Denmark and the UK (around 2.0), followed by Germany and the Netherlands (around 1.6) [9]. The lowest female-to-male ratio was in the US (around 1.1) [9]. In these five countries, antidepressant prevalence increased with age [9]. From 2005 to 2012, prevalence was highest in the oldest age group (15-19 years) and lowest in the youngest age group (5-9 years) [9]. Prevalence in the 0-4 years age group was negligible (below 0.05% in all years) [9]. Countries varied in how antidepressant prevalence within each age groups changed between 2005 and 2012. During this period, antidepressant prevalence in children age 5-9 years decreased in Germany, the UK and the US (-60.6%, -40.5% and -27.1%, respectively) but increased in the Netherlands and Denmark (22.8% and 4.6%, respectively) [9]. Denmark and Germany saw the highest increase in antidepressant prevalence among adolescents aged 15-19 years (71.0% and 45.1%, respectively), while the UK and the Netherlands saw the highest increase among adolescents aged 10-14 years (46.3% and 41.5%, respectively) [9]. Taken together, results stratified by age and sex suggest that female adolescents accounted for most of the rise in antidepressant prevalence over time in the UK and other Western countries.

4.2. Trends in Incidence of Antidepressant Prescriptions

This section covers a brief literature review of studies on trends in incidence of antidepressant prescriptions from outpatient samples in Western countries since the 1990s using databases of insurance claims, prescriptions and drug dispensing. These studies varied in their methodologies, especially with respect to how incidence was measured (**Table 2**). Therefore, this section will broadly compare trends between countries in terms of relative

increase and decrease in annual incidence rather than absolute measures of annual incidence rates or proportions.

4.2.1. Trends in Overall Incidence

Table 2 summarizes the results of studies on trends in the annual incidence of antidepressant prescriptions in children and adolescents in Western countries. There has been no study on longitudinal trends of incident antidepressant prescription in the US, only one regional study in Tennessee on short-term trends from 2002 to 2005 [75]. Findings from the current literature suggested that most Western countries experienced a rise in annual incidence from 1995 to 2002. A brief decline was then observed from 2002 to 2005, likely in response to the regulatory warning issued between 2003-2005 across North America and Europe by the FDA, Health Canada, the MHRA and the European Medicines Agency regarding the risk of suicide ideation and behaviors in pediatric users of antidepressants [13, 49-51]. Before the regulatory warning, annual incidence rose rapidly in Italy (60.2% from 1999 to 2004), the UK (60.7% from 1995 to 2002) and more modestly in Quebec, Canada (37.4% from 1997 to 2002) [8, 16, 76]. The pattern that emerged post-regulation, however, varied across countries. Immediately following the regulation, annual incidence decreased in Iceland (32.8% from 2004 to 2007), the US (33.0% from 2004 to 2005) and Italy (23.9% from 2006 to 2011) [75, 77, 78]. However, a return towards an increase in incident antidepressant prescriptions appeared gradually in Norway (2007-2013) and Germany (19.4% from 2005 to 2011) and more rapidly in the UK (90.7% from 2006 to 2015) [6, 15, 79]. At the same time, a slight decrease was observed in France (7.7% from 2009 to 2016) [80]. Taken together, these results suggest that annual incidence have either stabilized or increased in the five to ten years following regulatory warnings in Western countries.

Table 2. Trends in incidence of antidepressant prescriptions in children and adolescents across Western countries[1]

Author, year	Country	Data source	Period	Age	Findings
Tournier, 2010 [16]	Canada	Claims from the Régie de l'assurance-maladie du Québec (RAMQ) and hospital discharge	1997-2005	2-19	Number of incident users increased by 37.4% from 1997 to 2002 (1,551 to 2,131 users), decreased 23.4% thereafter (to 1,632 users in 2005).
Kurian, 2007 [75]	US	Claims from Tennessee's Medicaid program	2002-2005	2-17	From 2002 to 2003, the mean number of incident users remained unchanged (23 per 10,000 youths per month). From 2004 to 2005, the mean number of incident users decreased 33.0% (95% CI 23.5% to 41.4%) to 15 per 10,000 youths per month.
Zoëga, 2009 [77]	Iceland	Dispensed prescriptions from the National Medicines Registry	2004-2007	0-17	Incidence proportion declined 32.8% from 11.9 incident users per 1,000 youths in 2004 to 8.0 9 incident users per 1,000 youths in 2007.
Hartz, 2016 [15]	Norway	Dispensed prescriptions from the Norwegian Prescription Database	2007-2013	13-17	Annual incidence in girls was stable from 2007 to 2009 and increased from 2010 to 2013; annual incidence in boys increased slightly during study period (data not shown).
Revet, 2018 [80]	France	Claims from the French Health Insurance Database	2009-2016	6-17	Slight overall decrease (7.7%), from 291 users in 2009 among 75,346 youths (0.39% (95% CI 0.34% to 0.43%)) to 303 users among 83,524 youths (0.36% (95% CI 0.32% to 0.41%)) in 2016.
Schröder, 2017 [79]	Germany	Claims from the German Pharmacoepidemiological Research Database	2004-2011	0-17	Annual IR increased by 19.4%, from 13.4 (95% CI 12.9 to 13.9) per 10,000 PYs in 2005 to 16.0 (95% CI 15.5 to 16.6) per 10,000 PYs in 2011.

[1] Abbreviations: IR, Incidence Ratio; PYs, Person-Years

Clavenna, 2007 [76]	Italy	Outpatient claims from a public insurance database (ARNO)	1999-2004	0-17	Annual incidence increased by 60.2%, from 0.88 per 1,000 youths in 1999 to 1.41 per 1,000 youths in 2004.
Piovani, 2016 [78]	Italy	Italian prescriptions from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance database	2006-2011	0-17	Annual incidence decreased by 23.9%, from 0.92 per 1,000 youths in 2006 to 0.70 per 1,000 youths in 2011.
Wijlaars, 2012 [8]	UK	Prescriptions from the Health Improvement Network database	1995-2009	3-18	Annual IR increased by 60.7%, from 2.8 (95% CI 2.4 to 3.1) per 1,000 PYs in 1995 to 4.5 (95% CI 4.3 to 4.6) per 1,000 PYs in 2002, then dropped to rates similar to the initial 1995 rates, but have been increasing from 2005 to 2009.
Sarginson, 2017 [6]	UK	Prescriptions from the Clinical Practice Research Datalink database	2000-2015	3-17	Annual IR dropped by 49.1%, from 3.16 (95% CI 3.03 to 3.30) per 1,000 PYs in 2002 to 1.61 (95% CI 1.51 to 1.69) per 1,000 PYs in 2006, but increased again from 2006 to 2015 (90.7%), reaching 3.07 (95% CI 3.93 to 3.22) per 1,000 PYs.
John, 2016 [5]	UK (Wales)	Prescriptions from the Secure Anonymized Information Linkage System database	2003-2013	6-18	Annual incidence declined from 5.26 to 4.36 users per 1,000 PYs from 2003 to 2005 (IR ratio 0.73; 95% CI 0.66 to 0.80), then increased from 2005 and reached 7.69 users per 1,000 PYs in 2013.

4.2.2. Trends in Incidence by Antidepressant Class

Since the 1990s, SSRIs became the most newly prescribed antidepressant class in children and adolescents in Western countries. Incident SSRI prescriptions increased from 1997 to 2016, except for a sharp decline from 2002 to 2005 due to the fact that the regulatory warnings regarding the risk of suicide ideation and behaviors in pediatric users of antidepressants targeted SSRIs [5, 6, 8, 13, 16, 20, 49, 50, 79, 80]. From 2004 to 2016, increase in incident SSRI prescriptions ranged from 1.3 fold in the UK to 2.3 fold in Germany [6, 79, 80]. By 2016, SSRIs dominated incident antidepressant prescriptions in children and adolescents across Western countries [6, 8, 15, 16, 79, 80]. SSRIs accounted for 78% of all incident antidepressant prescriptions in Norway in 2012 and also in the UK in 2015 [6, 15]. It is worth noting that during periods of declining overall incident antidepressant prescriptions, increased incident SSRI prescriptions were also observed in France (approximately 25% increase from 2009 to 2016) and the US (incident fluoxetine prescriptions increased 60% between 2004 and 2005) [75, 80]. However, at the same time that incident fluoxetine prescriptions increased in the US, incident prescriptions of non-fluoxetine SSRIs and SNRIs declined 54%, suggesting that prescribers might have switched some patients to fluoxetine since fluoxetine is considered the SSRI with the strongest efficacy and safety profile in pediatric patients [39, 75]. While incident SSRI prescriptions increased, incident TCA prescriptions steadily declined in Western countries, except in Germany where it remained between 5.3 (95% CI 4.9 to 5.6) and 6.3 (95% CI 6.0 to 6.7) per 10,000 PYs from 2004 to 2011 [8, 16, 79, 80]. With respect to other antidepressant classes, Quebec saw a rise in incident prescriptions of non-SSRI newer generation antidepressants from 1997 to 2005 (10% to 30-40% of all incident antidepressant prescriptions) [16]. Incident prescriptions of non-SSRI, non-TCA antidepressants was reported to be negligible from 1995 to 2009 in the broader UK and from 2003 to 2013 in Wales [5, 8]. Several studies in Europe also chose not

to report on incident use of non-SSRI, non-TCA antidepressants, most likely because MAOIs are not recommended in children and adolescents by clinical guidelines and the development of non-SSRI newer generation of antidepressants (such as SNRIs) has been more recent [79, 80]. In summary, SSRIs were the most newly prescribed antidepressant class in children and adolescents across Western countries in the last two decades, while new TCA prescriptions declined, and other antidepressants were not frequently prescribed in this population.

4.2.3. Trends in Incidence by Age and Sex

Older age groups experienced higher incident antidepressant prescriptions compared to younger age groups in Western countries. Incident antidepressant prescriptions in adolescents aged 12 to 17 years was 5 to 10 times higher than in children aged 6 to 11 years from 2009 to 2016 in France [80]. Incident antidepressant prescriptions in adolescents aged 12 to 17 years was approximately 1.5 times higher than in children aged 6 to 11 years and 8 times higher than in children aged 0 to 5 years from 2009 to 2016 in Iceland [77]. In the UK, the proportion of incident antidepressant prescriptions attributed to adolescents aged 15 to 17 years increased from 75% in 2006 to 82% in 2015 [6]. Across all countries, incident antidepressant prescriptions in the youngest age group (below 5 years) was rare compared to other age groups, and was considered negligible in the UK and Germany [6, 8, 15, 16, 77, 79, 80]. Across Western countries, girls received more incident antidepressant prescriptions than boys from 1995 to 2016, except in Iceland where boys accounted for slightly more incident antidepressants across age groups, with an annual female-to-male ratio between 0.88 and 0.97 from 2004 to 2007 [6, 8, 15, 16, 77, 79, 80]. The female-to-male ratio was approximately 2.5 in Norway from 2007 to 2013 and in the UK from 2006 to 2015 [6, 15, 16, 80]. In Germany, the female preponderance was slightly less pronounced, with the highest female-to-male ratio of 1.75 in 2011 [79]. However, in Quebec and France, boys received more incident antidepressant prescriptions than girls in children below age 12 [16, 80]. In Quebec, 64.8%

children aged 2 to 10 years with incident antidepressant use from 1997 to 2005 were boys [16]. In France, the female-to-male ratio in children aged 6 to 11 years declined from 0.81 in 2009 to 0.73 in 2016 [80]. Nevertheless, results stratified by age and sex suggest that incident antidepressant prescriptions were highest among female adolescents in most Western countries.

4.3. Trends in Coprescription of Antidepressants with other Psychotropic Drugs

Alongside rising prevalence and incidence of antidepressant prescriptions in the last two decades, an emerging trend of rising coprescription of antidepressants with other psychotropic drug classes in children and adolescents has also been reported [76, 77, 81-88]. However, it must be noted that there have been very few studies that examined trends in coprescription exclusively among pediatric patients prescribed an antidepressant. To date, we only found four studies, two on prevalence and two on incidence, of psychotropic coprescription among patients prescribed an antidepressant using outpatient databases of insurance claims, prescriptions and drug dispensing [11, 15, 16, 88]. Rather, most studies on coprescription examined trends in the overall coprescription among all psychotropic drug classes, including antidepressants, in patients with any psychotropic prescription (**Table 3**). In addition, most existing studies of coprescription among all psychotropic drug classes investigated only prevalence, not incidence (**Table 3**). Accordingly, the most recent review in 2012 on trends of psychotropic coprescription in children and adolescents in Western countries consisted primarily of studies on prevalence [81]. Since then, several more studies have been published, including two studies on incidence trends [10, 11, 14, 83, 85, 86, 88]. The following section provides an up-to-date review of studies on trends in psychotropic coprescription in children and adolescents from Western countries with outpatient data from surveys, insurance claims, prescriptions and drug dispensing. Since it was difficult to

distinguish the trends of only coprescriptions that involved antidepressants from the trends of overall psychotropic coprescription in these studies, this section reviews the results on the overall coprescription among all psychotropic classes and highlights specific combinations involving antidepressants where applicable. Subsequently, this section covers the few studies examining psychotropic coprescription exclusively among patients prescribed an antidepressant.

4.3.1. Trends in Coprescription in Children and Adolescents with any Psychotropic Prescription

4.3.1.1. Trends in Prevalence of Coprescription in Children and Adolescents with any Psychotropic Prescription

Table 3. Trends in prevalence of psychotropic coprescription, including the most frequent combinations with antidepressants, in children and adolescents across Western countries

Author, year	Country	Data source	Coprescription definition	Period	Findings	Most frequent combinations with AD[2]
National studies						
Olfson, 2002 [89]	US	National Medical Expenditure Survey and Medical Expenditure Panel Survey	Coprescription among different psychotropic drug classes	1987-1996	Coprescription increased eight-fold, from 0.03 per 100 youths in 1987 to 0.23 per 100 youths in 1996.	AD + Stim
Comer, 2010 [90]	US	National Ambulatory Medical Care Surveys	Multi-class visits (visits in which physicians prescribed at least two psychotropic drug classes)	1996-2007	Coprescription increased by 41%, from 14.3% (1996-1999) to 20.2% (2004-2007) of all psychiatric visits.	AD + Stim (7.3% of all visits), AD + AP (5.0% of all visits)
Saucedo, 2010 [87]	US	Medicaid pharmacy billing records, 29 states	Use of more than one psychotropic drug classes	1999-2010	Coprescription increased by 30%, from 18.8% in 1999-2000 to 24.4% in 2009-2010.	Not available
Hsia, 2009 [84]	UK	Clinical Practice Research Datalink	Prescriptions of more than one psychotropic drug class	1992-2001	Coprescription was 18.7% in patients with any psychotropic prescription during the study period.	Not available

[2] Abbreviations: Antidepressants = AD, Antipsychotics = AP, Anxiolytics = AX, Hypnotics = Hyp, Sedatives = Sed, Stimulants = Stim

Clavenna, 2007 [76]	Italy	ARNO Database	Prescriptions of more than one psychotropic drug class	2004	Coprescription was 6.1% in patients with any psychotropic prescription.	Not available
Koelch, 2009 [91]	Germany	National German Health Interview and Examination Survey for Children and Adolescents	At least two psychotropic drugs from the same or different classes	2003-2006	Prevalence of any psychotropic prescription was 4.81 per 1,000 youths during the study period; 10 youths received a coprescription.	AD + Sed (10% of all combinations), AD + AP (10% of all combinations)
Zoëga, 2009 [77]	Iceland	National Medicines Registry	Dispensing of at least two different psychotropic substances on the same day	2007	Coprescription was 17.5% in patients with any psychotropic prescription.	Not available
Kovess, 2015 [85]	France	French National Health Insurance	Prescription of multiple psychotropic drug classes	2010	Coprescription was 10.3% in patients with any psychotropic prescription.	AD + AP (12.8% of all combinations)
Regional studies						
Schirm, 2001 [70]	Netherlands	Dispensing records from the northern region	Proportion within each psychotropic drug class not used as monotherapy	1999	Coprescription ranged from 6.6% to 33.3% in 1999.	Not available
Fontanella, 2014 [83]	US	Ohio Medicaid claims	At least three psychotropic drugs from different classes combined	2002-2008	Coprescription increased by 23% (7.3% to 9.0%) in the low-income group, by 30% (17.2% to 22.3%)	AD + AP + Stim (10.2%, 15.2%, 16.8% of all combinations in the disability, low-

					in the foster care group, and by 36% (14.3% to 19.5%) in the disability group during the study period.	income and foster care group, respectively, in 2008)
Lohr, 2018 [86]	US	Kentucky Medicaid claims	At least two psychotropic drug classes used at the same time for at least 90 consecutive days	2012-2015	Coprescription was 39.5% in patients with any psychotropic prescription during the study period.	AD + Stim (12.0% of all combinations in the non-foster care group, 37.3% of all combinations in the foster care group)

Table 3 summarizes results from studies on prevalence trends of coprescription among all psychotropic drug classes in pediatric patients since the late 1980s to date, including the frequency of combinations with antidepressants. The majority of studies came from the US, which showed a sustained increase in coprescription among all psychotropic drug classes from 1987 to 2015 at the national and regional level [83, 86, 87, 89, 90]. These studies also found that combinations among all psychotropic drug classes frequently involved antidepressants [83, 86, 87, 89, 90]. According to two nationally representative surveys of 6,490 youths aged 18 years or younger, coprescription increased eight-fold between 1987 and 1996 (0.03 to 0.23 per 100 youths) [89]. A study of pharmacy billing records from 692,485 Medicaid patients from 29 states reported a 30% increase of coprescription from 18.8% of patients with any psychotropic prescription in 1999 to 24.4% in 2010 [87]. Around the same period, a nationally representative survey of 27,979 youths aged 18 years and younger found that the proportion of multi-class visits (visits in which at least two psychotropic drug classes were prescribed) rose 41%, from 14.3% of all psychiatric visits in 1996-1999 to 20.2% in 2004-2007 [90]. In this study, coprescription with antidepressants accounted for 62.6% of multi-class visits during the study period [90].

Regional studies in the US also showed an increase in coprescription. In a study of Ohio Medicaid claims data for youths aged 17 years and younger, coprescription (among three psychotropic drug classes) grew 20-30%, depending on the Medicaid eligibility group, between 2002 and 2008 [83]. Among the eligibility groups, coprescription among patients prescribed at least one psychotropic drug in 2008 was highest in the foster care group (22.3%), followed by the disability group (19.5%) and the low-income group (9.0%) [83]. In this study, three of the five most frequent combinations in 2008 involved antidepressants, accounting for 12-17% of patients prescribed at least one psychotropic drug [83]. However, it is worth noting that most combinations with antidepressants in this study declined from 2002

to 2008, except for antidepressants combined with antipsychotics and alpha-agonists, which saw an increase of 3.9% in the foster care group, 25.0% in the low-income group and 26.2% in the disability group, as well as antidepressants with stimulants and antipsychotics, which increased by 30.2% in the foster care group [83]. This decline in most combinations with antidepressants was likely a response to the 2004 FDA warning on the risk of suicide ideation and behaviors in pediatric users of antidepressants [51]. In another study on Medicaid claims for Kentucky youths aged 17 years and younger, 38% of youths prescribed at least one psychotropic drug had a coprescription for at least 90 consecutive days over the study period from 2012 to 2015 [86]. This study did not separately report the prevalence of coprescription in each year [86]. In this study, antidepressants and stimulants was the second most frequent psychotropic coprescription (approximately 130 patients per 1,000 youths from 2012 to 2015), thus suggesting a return towards frequent coprescriptions with antidepressants in the eight to ten years following the FDA warning [51, 86]. In summary, coprescription estimates in the US grew from approximately 15% of patients prescribed at least one psychotropic drug (1995-1999) to 20% (2000-2010) and 40% (2012-2015) [83, 86, 87, 89, 90]. While the definition of coprescription among all psychotropic drug classes varied substantially between studies, it is clear that coprescription increased rapidly in the last three decades [86]. It is also clear that antidepressants remained one of the most frequent coprescribed drug class, except for the brief decline corresponding to the FDA warning [51]. In particular, antidepressants were most frequently coprescribed with stimulants across US studies (**Table 3**).

The prevalence of coprescription among all psychotropic drug classes in children and adolescents appeared to be higher in the US than in several other Western countries. In a study that directly compared psychotropic coprescription in the US, the Netherlands and Germany in 2000 using insurance claims data from youths aged 0-19 years, coprescription prevalence in the US (19.2% of patients with any psychotropic prescription) was twice the

prevalence in the Netherlands (8.5%) and thrice the prevalence in Germany (5.9%) [92]. Indeed, the majority of psychotropic prescriptions did not involve coprescription in the UK (1992-2001), the Netherlands (1999), Italy (2004), Germany (2003-2006), Iceland (2007), and France (2010) [70, 76, 77, 84, 85, 91]. Among these countries, coprescription appeared highest in the Netherlands and Iceland, followed by France [70, 77, 85]. In a regional study from the Netherlands using dispensing records of 37,760 youths aged 0-19 years, coprescription ranged from 6.6% to 31.8% among patients with any psychotropic prescription in 1999 [70]. In a study of Icelandic youths aged 0-17 years using the National Medicine Registry dispensing data, coprescription in patients with any psychotropic prescription was 17.5% in 2007 [77]. In France, a study using the French National Health Insurance prescribing data of 128,298 patients aged 0-17 years reported 10.3% of coprescription in patients with any psychotropic prescription in 2010 [85]. Compared to the Netherlands, Iceland and France, coprescription appeared lower in Italy, the UK and Germany [76, 84, 91]. In a study of 1,484,770 Italian youths aged 17 years and younger, 6.1% of patients with any psychotropic prescription had a coprescription in 2004 [76]. A UK study using the Clinical Practice Research Datalink (CPRD) found that 18.7% of 34,398 youths aged 18 years and younger had a coprescription from 1992 to 2001 [84]. Coprescription was almost negligible in Germany, with only 10 of 17,450 youths aged 0 to 17 years receiving a coprescription from the same or a different psychotropic class between 2003 and 2006 [91]. Only 2 of these 10 patients had a coprescription with antidepressants [91]. In summary, the higher end of the estimates of coprescription in non-US countries (17.5-31.8%) were comparable with estimates from the US during the same period. Nevertheless, this comparison must be interpreted with caution due to the variations in methodologies between studies. In addition, since most studies outside the US only examined one-year prevalence, more longitudinal

studies, especially studies after the 2000s, are needed to understand recent evolvement in coprescription patterns and to facilitate comparison between countries.

4.3.1.2. Trends in Incidence of Coprescription in Children and Adolescents with Any Psychotropic Prescription

We found only two studies that examined incidence of coprescription among all psychotropic drug classes in the US and Finland, both reporting the cumulative incidence of coprescription following a birth cohort over time [14, 93]. The Finnish study also reported the cumulative incidence of coprescription among patients prescribed an antidepressant in the birth cohort, but the US study did not [14, 93]. In both studies, the cumulative incidence of psychotropic coprescription increased with age. In the US study using Medicaid claims data of 35,244 children born in Maryland in 2007 and followed up until 2014, the cumulative incidence of coprescription among patients with any psychotropic prescription remained close to 0% from age 0 to 4, then rapidly grew from age 5, reaching 19.7% at age 8 [93]. The most frequent combinations involving antidepressants were not reported in this study [93]. In the Finnish study using dispensing data from the National Prescription Register for 5,525 children born in 1981 and followed up until 2005, the cumulative incidence of psychotropic coprescription also increased with age (from 0.02% by age 15 to 0.9% by age 20 and 4.1% by age 25) [14]. In this study, the two most frequent combinations of psychotropic drugs overall both involved antidepressants: antidepressants with benzodiazepines (cumulative incidence 2.9%; 95% CI 2.4% to 3.4%), and antidepressants with antipsychotics (cumulative incidence 1.4%; 95% CI 1.1% to 1.8%) [14]. However, among patients prescribed an antidepressant in this study, only a minority had a coprescription, suggesting that the most frequent combinations involving antidepressants were intended for patients prescribed other psychotropic drug classes [14].

4.3.2. Trends in Psychotropic Coprescription among Children and Adolescents Prescribed an Antidepressant

As stated previously, very few studies investigated psychotropic coprescription in pediatric patients prescribed an antidepressant instead of patients with any psychotropic prescription. In total, we found two studies examining prevalence in the US and Sweden and two studies examining incidence of psychotropic coprescription in Norway and Canada among pediatric patients prescribed an antidepressant [11, 15, 16, 88].

More than half of the patients with a prevalent antidepressant prescription had a psychotropic coprescription in the two studies on prevalence in the US and Sweden [11, 88]. The US study of Medicaid patients aged 19 years and younger from one state documented a slight decline (9%) in psychotropic coprescription among patients with a prevalent antidepressant prescription from 80% in 2007 to 73% in 2014 [88]. However, it is worth noting that the baseline prevalence of psychotropic coprescription was already high in this study, and the majority of patients with a prevalent antidepressant prescription still had a coprescription after the decline. In this study, the most frequent combination was antidepressants with stimulants, similar to other US studies on coprescription among patients with any psychotropic prescription [88]. The second most frequent combination was antidepressants with antipsychotics [88]. The Swedish study using data from three national registers of all youths age 24 years and younger reported a 19% increase in the proportion of patients with a coprescription among those with a prevalent antidepressant prescription from 2006 (52.4%) to 2013 (62.1%) [94]. Anxiolytics and hypnotics were most frequently coprescribed in the Swedish study, at approximately 50% of patients with a prevalent antidepressant prescription, followed by antidepressants with stimulants at approximately 28-48% patients with a prevalent antidepressant prescription [94].

The two studies on psychotropic coprescription among patients newly prescribed an antidepressant did not describe the overall trends of coprescription over time, but rather focused on describing the most frequent combinations involving antidepressants. In the study of adolescents aged 13-17 years using data from the Norwegian Prescription Database, 62% of patients newly prescribed an antidepressant in 2012 had a coprescription [15]. In this study, the most frequently coprescribed psychotropic drug class was hypnotics (33.8%), followed by antipsychotics (13.2%), stimulants (8.8%) and anxiolytics (6.2%) [15]. The other study was a regional study in Quebec, Canada using data from the Régie de l'assurance maladie du Québec (RAMQ) of 16,215 youths aged 2-19 years who were newly prescribed an antidepressant between 1997 and 2005 [16]. This study reported that patients newly prescribed an SSRI who were aged 11-19 years were 71-74% more likely than patients newly prescribed a TCA of the same age to receive an anxiolytic coprescription, and 49-99% more likely to receive a tranquilizer coprescription [16]. This study did not report the proportion of patients with a coprescription among those newly prescribed an antidepressant [16].

4.3.3. Most Frequent Psychotropic Combinations with Antidepressants

Interestingly, the most frequent combinations involving antidepressants differed in patients with any psychotropic prescription compared to patients prescribed an antidepressant. As shown in **Table 3**, among patients with any psychotropic prescription, antidepressants with stimulants or antipsychotics were the most frequent combinations. Furthermore, the most frequent combinations involving antidepressants among patients with any psychotropic prescription differed between the US and other Western countries. In the US, antidepressants with stimulants was the most frequent combination, increasing from 7% of all combinations in 1996 to 10-40% in 2012-2015 [83, 86, 89, 90]. In studies that investigated combinations between three psychotropic drug classes, antidepressants with stimulants and antipsychotics was the most frequent combination [83, 86]. Outside the US,

antidepressants were most frequently coprescribed with antipsychotics in France (12.8% of all combinations in 2010) and Germany (10% of all combinations from 2003 to 2006) [85, 91]. In patients with any psychotropic prescription, antidepressants were rarely combined with anxiolytics and hypnotics, except in Germany where antidepressants with sedatives was also the most frequent combination (10% of all combinations) from 2003 to 2006 [91]. On the other hand, among patients with a prevalent or incident antidepressant prescription, combinations with anxiolytics or hypnotics was the most frequent, except in the US where combinations with stimulants was still the most frequent among patients with a prevalent antidepressant prescription [11, 15, 16, 88]. Across countries, antidepressants were infrequently coprescribed with mood stabilizers in patients with any psychotropic prescription and also in patients prescribed an antidepressant [11, 14, 16, 83, 85, 86, 88-91].

4.3.4. Profile of Patients with Psychotropic Coprescription

The profile of patients with coprescription among those with any psychotropic prescription has been described in several studies, whereas little is known about the profile of patients with coprescription among those prescribed an antidepressant. Most of what is known about the profile of patients with coprescription among those with any psychotropic prescription came from studies in the US [86, 90]. From 1996 to 2015, 60% of US patients with coprescription among all psychotropic classes were male, and approximately 50% were diagnosed with a mood disorder [86, 90]. From 1996 to 2007, 92% of US patients with coprescription among all psychotropic classes also had repeated visits to physicians [90]. The youngest patients (0-5 years) received the fewest coprescriptions [86, 90]. However, it was unclear whether coprescription was higher in patients aged 6-12 years or 13-17 years. One study observed higher coprescription in patients aged 13-17 years compared to patients aged 6-12 years (55% versus 45% of all patients with coprescription, respectively) from 1996 to 2007 [90]. Yet, another study showed the opposite trend of higher coprescription in patients

aged 12-17 years from 2012 to 2015 (47% of all patients with coprescription who were aged 6-11 years compared to 40% of all patients with coprescriptions who were aged 12-17 years [86]. Outside of the US, the Finnish birth cohort study reported an interesting sex difference in which girls were more likely than boys to receive a coprescription for antidepressants with benzodiazepines, the most frequent of all psychotropic combinations in this study (female-to-male ratio 1.5; 95% CI 1.1 to 2.1) [14]. Also, girls were significantly more likely than boys to receive a coprescription for antidepressants with mood stabilizers in this study (female-to-male ratio 5.0; 95% CI 1.7 to 14.8) [14]. However, as previously noted, antidepressants with mood stabilizers were infrequently coprescribed (cumulative incidence 0.5%, 95% CI 0.2% to 0.8%) [14]. There were no sex difference with respect to other combinations with antidepressants in this study [14].

Most studies that examined psychotropic coprescription among those prescribed an antidepressants did not describe the profile of patients with coprescription [11, 15, 16, 88]. One study briefly reported on age difference in Swedish patients with a prevalent antidepressant prescription [11]. In this study, coprescription increased more rapidly in adolescents (aged 12-17 years), from 48.8% of patients with a prevalent antidepressant prescription in 2006 to 69.9% in 2013, than in children aged 11 years and younger [11]. The proportion of patients with coprescription in children aged 11 years and younger was not reported [11].

4.3.5. The Need for More Studies on the Coprescription of Antidepressants with other Psychotropic Drug Classes in Children and Adolescents

The high proportion of coprescription among patients with any psychotropic prescription and among patients prescribed an antidepressant observed in several Western countries is concerning due to the lack of evidence on the efficacy and safety of combining psychotropic drugs. Psychotropic combinations involving antidepressants comes with

numerous safety concerns, from increased risk of adverse events and drug-drug interactions to complex drug regimens and nonadherence to such regimens, which may be especially difficult for children. As previously described, an increased risk in type 2 diabetes has been associated with the use of antidepressants combined with antipsychotics [17]. As shown in **Table 3**, antidepressants with antipsychotics was one of the most frequent combinations in patients with any psychotropic prescription. In addition, studies in young animals showed that antidepressant monotherapy may interfere with normal brain development [95]. The risk of antidepressant monotherapy interfering with brain development in human is currently unknown, let alone in combination with other psychotropic drugs. Thus, it is important to continue monitoring the use of antidepressants combined with other psychotropic drugs, together with the use of antidepressants, in this vulnerable population.

Further research is also required to address several other gaps in the literature. First, since most studies have been cross-sectional or with a period of five years or fewer, studies with longer periods are needed to describe long-term trends, rather than short-term fluctuations of psychotropic coprescription involving antidepressants, especially to understand the long-term effect of the regulatory warning on the risk of suicide ideation and behaviors for pediatric users of antidepressants in North America and Europe [49-51]. Second, as most studies on coprescription focused only on prevalence trends, studies on incidence trends are also needed. Third, since most studies on psychotropic coprescription originated from the US, studies from other countries are needed. The US had an exceptionally high prevalence and incidence of psychotropic coprescription involving antidepressants, as well as a health system dissimilar to most other Western countries [83, 86-90]. Yet, most of what is known about psychotropic coprescription came from the US [83, 86-90]. Most studies outside the US only captured overall trends and not stratified by age, sex or psychotropic drug classes [15, 76, 77, 84, 85]. In particular, we only found one study in the

UK on the overall prevalence of coprescription among patients with any psychotropic prescription [84]. In this study, the observational period ended in 2001 and thus did not cover the effect of the 2003 regulatory warning on the risk of suicide ideation and behaviors for pediatric users of antidepressants in the UK [84]. We also did not find any study that examined psychotropic coprescription specifically among patients prescribed an antidepressants in the UK. Thus, more recent studies are needed to understand the effect of the regulatory warning and the practice of psychotropic coprescription specifically among patients prescribed an antidepressant in the UK.

Finally, among studies that examined psychotropic coprescription specifically among patients prescribed an antidepressant, no studies have comprehensively characterized the profile of these patients, including their demographics, comorbid conditions, use of other medications, and patterns of health utilization. As previously stated, only one study briefly discussed the difference in coprescription between age groups [11]. Since so little is known about the profile of these patients, a more detailed description of the profile of these patients, including changes in the profiles over time, is needed to advance the understanding of patients with coprescription among those prescribed an antidepressant.

Chapter 3. Objectives

1. Overall Objective

The overall objective of this thesis is to describe time trends in antidepressant prescriptions and coprescription with other psychotropic medications in children and adolescents in UK primary care between 2000 and 2018.

2. Primary Objectives

This thesis has two primary objectives:

2.1. To estimate the annual rates of patients newly prescribed an antidepressant (incidence rates), both overall and stratified by age, sex, antidepressant class and UK nations between 2000 and 2018.

2.2. To estimate the proportion of patients with a coprescription for other psychotropic drugs among patients newly prescribed an antidepressant, stratified by age, sex, psychotropic drug class and UK nations.

3. Secondary Objectives

This thesis has three secondary objectives:

3.1. To estimate the annual prevalence of patients with an antidepressant prescription, both overall and stratified by age, sex, antidepressant class and UK nations between 2000 and 2018.

3.2. To estimate the proportion of patients with a coprescription for other psychotropic drugs among patients with a prevalent antidepressant prescription, stratified by age, sex, psychotropic drug class and UK nations.

3.3. To describe changes in baseline characteristics (age, sex, obesity, psychiatric diseases, other comorbidities, and measures of health utilization) between 2007-2008 and 2017-2018 for patients newly prescribed an antidepressant and separately, for patients with a coprescription.

Chapter 4. Supplemental Methods

The following chapter will provide preliminary information to the manuscript's Methods section. More details on the data source will be included, as well as its suitability for drug utilization studies. The operational definitions of exposures and covariates will also be described.

1. Data Source

The Clinical Practice Research Datalink (CPRD), an electronic medical records primary care database in the UK, was chosen as the data source for the study in this thesis. The CPRD contains more than 15 million patient records from approximately 700 practices in the UK, with data available since 1987, effectively making it one of the largest longitudinal primary care databases in the world [96]. Patients in the CPRD have been shown to be broadly representative of the UK population in terms of age and sex when compared against UK census data [96]. Participating GPs are trained to routinely provide information on demographics, laboratory test results, clinical measures, lifestyle factors such as obesity status, smoking status and substance abuse, clinical symptoms, diagnoses and prescriptions, as well as referrals and feedbacks from secondary care visits [96]. Clinical symptoms and diagnoses are recorded using Read codes, a universal classification system developed in the UK, and prescriptions are recorded using the UK Prescription Pricing Authority [96, 97]. All prescriptions issued by general practitioners (GPs) are automatically recorded in the CPRD, ensuring a complete and accurate history of prescriptions for every patient [96]. In addition, practices are required to meet data quality standards before they can contribute data to the CPRD ('up to standard date') [96].

The CPRD is ideal for longitudinal drug utilization studies considering the structure of the UK healthcare system. The UK employs a universal healthcare system with more than 98% of the population registered with a GP [96]. GPs are designated the role of gatekeeper in

the UK healthcare system, serving as the first point of contact for non-emergency care and referring patients to secondary care as needed [98]. After consultations with secondary care specialists, patients are referred back to their GPs for follow-up care [98]. Therefore, despite being a primary care database, CPRD captures all of the patient's contacts with the UK healthcare system. In fact, part of the data quality standards requires practices to record all referrals to specialists as well as feedback from these referral visits [98]. As such, the CPRD is better suited than other databases from hospitals or specialists care to estimate prevalence and incidence of drug utilization in the population thanks to its representativeness, large sample size, and comprehensive data collection. Indeed, the CPRD has been used in at least three drug utilization studies of antidepressants in UK children and adolescents in the past two decades [6, 69, 84].

2. Exposures and Covariates

Exposures of interest were operationalized based on the British National Formulary (BNF) classification system, Section 4 (Central Nervous System) [99]. A list of product codes was compiled for antidepressants (our main exposure) and other psychotropic drug classes (anxiolytics and hypnotics, antipsychotics, stimulants and mood stabilizers). To ensure that no codes are missed, a thorough search in the CPRD drug dictionary was conducted using BNF codes, followed by searches for drug substance names and product names (generic and brand names of drug substances available in the UK). The codes were then checked to remove duplicates, and categorized according to the appropriate psychotropic drug class.

Relevant baseline characteristics (age, sex, lifestyle factors, psychiatric and other comorbidities, history of psychotropic medications and other medications, and measures of health utilization) were pre-selected as covariates based on a review of the literature. Age was categorized into three groups: 5-10 years, 11-14 years and 15-17 years. Obesity status in

children and adolescents was calculated using body mass index (BMI) percentiles, taking into account age and sex [100]. The absence of relevant codes in patients' medical records was assumed to imply an absence of the specific risk factor or comorbidity. Missing data were expected for lifestyle factors (obesity status, smoking status, substance abuse), and was classified as a separate category. Similar to psychotropic drugs, prescriptions for other drugs were classified using BNF and searched in the drug dictionary. Medical diagnoses (psychiatric disorders and other comorbidities) were thoroughly searched using Read codes in the CPRD medical dictionary and checked to remove duplicates. GP and psychiatric consultations were categorized based on the quartiles of their respective distributions. Specifically, GP consultations were classified into four categories: 0-3, 4-6, 7-12 and 13 or more. We expected fewer psychiatric consultations, which were also classified into four categories: 0, 1, 2, and 3 or more. All baseline characteristics were measured in the year before the first antidepressant prescription.

Chapter 5. Manuscript

This chapter will present a manuscript on the trends of antidepressants and coprescription with other psychotropic drugs in children and adolescents in UK primary care from 2000 to 2018. The manuscript is intended for submission to a journal in the UK, and thus the spelling of several words in the manuscript may differ from the rest of the thesis, which has been formatted according to American spelling conventions. To facilitate ease of reference, the figures and tables in the manuscript and supplementary materials are not presented in this chapter, but are included in a separate chapter (Chapter 7) together with the figures and tables from the chapter on additional results (Chapter 6) since the chapter on additional results also refer to figures and tables in the supplementary materials.

Prescribing Trends of Antidepressants and Coprescription with other Psychotropic Medications for Children and Adolescents in Primary Care in the United Kingdom, 2000-2018

D. Cao[1,2], L. Fraga[3], E. Fergusson[4], J. Michaud[2], S. Dell'Aniello[2], H. Yin[2], S. Rej[5], L. Azoulay[1,2,6], C. Renoux[1,2,7]

1. Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montréal, Québec, Canada
2. Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montréal, Québec, Canada
3. Universidade Nove de Julho (UNINOVE), Sao Paulo, Brazil
4. Oxford Health NHS Trust, Department of Psychiatry, Oxford University, Oxford, United Kingdom
5. Department of Psychiatry, McGill University, Montréal, Québec, Canada
6. Gerald Bronfman Department of Oncology, McGill University, Montréal, Québec, Canada
7. Department of Neurology and Neurosurgery, McGill University, Montréal, Québec, Canada

Address for correspondence:

Dr. Christel Renoux

Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital

3755 Cote Sainte-Catherine Road, H416.1

Montréal, Québec, Canada H3T 1E2

Telephone: (514) 340-27593

Fax: (514) 340-7564

Email: christel.renoux@mcgill.ca

Word count (Abstract; limit 300): 299

Word count (Text; limit 4,000): 4,000

Keywords: antidepressants, coprescription, polypharmacy, trends, CPRD, UK

Abstract

Background

No recent information is available on trends in paediatric antidepressant prescriptions in the United Kingdom (UK). Moreover, little is known about the coprescription with other psychotropic medications.

Aims

To describe trends in antidepressant prescriptions and coprescription with other psychotropic medications in UK children and adolescents between 2000 and 2018.

Method

Using the Clinical Practice Research Datalink, we defined a cohort of patients aged 5–17 years, registered with a general practitioner between 2000 and 2018. Using Poisson regression, we estimated the annual rates of patients newly prescribed an antidepressant (selective serotonin reuptake inhibitors (SSRIs), other newer generation antidepressants, and tricyclic antidepressants (TCAs)). We also measured the prevalence of patients with antidepressant prescriptions per number of persons alive on July 1st each year. Finally, we calculated the percentage of new and prevalent users of antidepressants with a same-day coprescription for other psychotropic medications.

Results

After a 42% decline from 2000 to 2005, the rate of patients newly prescribed an antidepressant increased from 2006 onwards. From 2008 to 2018, the rate increased from 254.3 to 471.2 per 100,000 person-years (rate ratio 1.97, 95% confidence interval 1.96-1.99). The rate was higher in females and adolescents aged 15 to 17. SSRIs were most commonly prescribed (70% of all antidepressant prescriptions), followed by TCAs (28%). Overall, 5% of patients newly prescribed an antidepressant had at least one coprescription for another psychotropic medication. During the study period, the percentage of patients with a coprescription rose from 2.6% to 6.4% and was more frequent in males. In 2018, most coprescriptions were anxiolytics and hypnotics (63%) and antipsychotics (26%).Trends in prevalent antidepressant prescriptions mirrored trends in new prescriptions.

Conclusions

During the last decade, antidepressant prescriptions and psychotropic coprescription increased in UK children and adolescents. Further research is needed to offer potential explanations for the trends observed.

INTRODUCTION

Antidepressant prescriptions in children and adolescents rose steadily for more than a decade in the UK and in other Western countries [5-9, 11, 15, 79]. A brief decline was observed from 2000 to 2005, likely due to the 2003 warning from the Medicines and Healthcare Products Regulatory Agency (MHRA) on the risk of suicide ideation and behaviors associated with antidepressant use in youths [7, 13]. However, the rate of children and adolescents newly prescribed an antidepressant increased from 2006 onwards and, in 2014, surpassed the rate in 2002 before the warning was issued [6]. The trends from 2015 onward remain unknown.

The coprescription of antidepressants with other psychotropic medications is another potential concern. A recent review reported an increase in coprescription involving antidepressants in some Western countries during the past decade [81]. According to this review, psychotropic coprescription among antidepressant users ranged between 16-34% [81]. However, patterns of coprescription with antidepressants in children and adolescents has not been described in the UK. Currently, clinical guidelines in children and adolescents on combining antidepressants with other psychotropic medications, including specific combinations of medications, are limited. The UK National Institute for Health and Care Excellence (NICE) guidelines for combination therapy only specifies augmenting antidepressants with antipsychotics for depression, bipolar disorder, obsessive-compulsive disorder and body dysmorphic disorder [1, 4, 101]. Moreover, evidence for the efficacy and safety of concomitant use of antidepressants with other psychotropic medications in this population remains scarce. A recent study suggested that selective serotonin reuptake inhibitors (SSRIs), the most frequently prescribed antidepressant class in children and adolescents, was associated with an increased risk of type 2 diabetes in this population [66].

Moreover, concomitant use of SSRIs with atypical antipsychotics has been shown to carry an additive risk of type 2 diabetes in this population [17].

Given these safety concerns, more research is needed to inform clinicians and regulators on the evolution of prescription patterns of antidepressants in this population. Therefore, the objective of our study was to describe time trends in prescription of antidepressants and coprescription with other psychotropic medications in children and adolescents in UK primary care between 2000 and 2018.

METHOD

Data source

We used the UK Clinical Practice Research Datalink (CPRD), one of the world's largest primary care databases, with approximately 15 million patients from 700 practices [96]. CPRD data are broadly representative of the UK population in age and sex [96]. The CPRD contains anonymized information on patient demographics, lifestyle factors, medical diagnoses, laboratory tests, prescriptions, and referrals to specialists and hospitals [96]. Prescriptions by general practitioners (GPs) are automatically recorded in the CPRD [96]. Data completeness and quality have been validated [102].

Study cohort

We defined a cohort of patients aged of 5 to 17 years old, registered with a GP for at least one day between 1 January 2000 and 31 December 2018. Patients with an unknown month of birth were assigned the first of July of their birth year as their birthday. Follow-up began on 1 January 2000, one year after the patients' registration date with the practice or one year after the date that the practice started contributing valid data to CPRD ('up to standard date'), whichever occurred later. Children below age 5 were excluded, as the NICE guidelines for paediatric depression only apply to youths aged 5 to 18 years old [103]. Moreover, previous studies reported few prescriptions in children below age 5 [5, 6]. Follow-up ended at the patient's 18th birthday, transfer out of the practice, death or the end of the study period (31 December 2018), whichever occurred first.

Exposure definition

We identified patients with a prescription for one of the following antidepressant classes during follow-up: SSRIs, other newer generation antidepressants, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Among patients with an

antidepressant prescription, we identified prescriptions on the same day for one or more of the following psychotropic medications: antipsychotics, mood stabilizers, anxiolytics and hypnotics, and stimulants.

Statistical analysis

1. Trends of antidepressant prescription from 2000 to 2018

1.1. Rate of patients newly prescribed an antidepressant

We estimated the annual rate with 95% confidence intervals (CIs) of patients newly prescribed an antidepressant based on a Poisson distribution. For this analysis, the cohort was limited to patients with no record of an antidepressant prescription at any time before cohort entry. The numerator was the number of patients with a first-ever antidepressant prescription, and the denominator was the total person-years of follow-up for all cohort members up to the first prescription within that year. Rates were stratified by age (5-10, 11-14, and 15-17 years), sex, UK nation (England, Northern Ireland, Scotland, and Wales) and antidepressant class. Patients changed age categories on the day they completed the last year of a given category. We also estimated rate ratios (RRs) and 95% CIs using Poisson regression, adjusted for age and sex, comparing annual rates of patients newly prescribed an antidepressant to the year 2008 (indicating changes in the last decade) and to the preceding year. All models included an overdispersion parameter to account for potential extra-Poisson variation. We also calculated the proportion of prescriptions attributable to each antidepressant class for each calendar year.

1.2. Annual prevalence of patients prescribed an antidepressant

Annual prevalence was defined as the number of individuals with a prescription for an antidepressant divided by the total number of persons alive the first of July of the calendar year. We also estimated annual period prevalence stratified by age, sex, UK nation, and antidepressant class.

2. Trends of coprescription of antidepressants with other psychotropic medications from 2000 to 2018

2.1. Proportion of coprescription in patients newly prescribed an antidepressant

Among patients with a first-ever antidepressant prescription, for each calendar year, we calculated the proportion of patients with a same-day prescription for another psychotropic medication. The proportion of patients with a coprescription was stratified by age, sex, UK nation and psychotropic medication class. The most frequently coprescribed psychotropic medications were also identified.

Among patients with no record of psychotropic prescriptions before the first antidepressant prescription, we also calculated the proportion of patients with a coprescription for a psychotropic medication in the three months and six months following the first antidepressant prescription by calendar year.

2.2. Proportion of coprescription in patients with a prevalent antidepressant prescription

For each calendar year, we calculated the proportion of coprescription among patients with a prevalent antidepressant prescription, overall and stratified by age, sex, UK nation and psychotropic medication class.

3. Baseline characteristics in 2007-2008 and 2017-2018

We described the baseline characteristics of patients newly prescribed an antidepressant, and separately for patients with a psychotropic coprescription in 2007-2008 and 2017-2018. Baseline characteristics, measured in the year before the first antidepressant prescription, included age, sex; obesity, smoking status, alcohol abuse, substance abuse; history of psychiatric diagnoses (attention-deficit hyperactivity disorder, autism spectrum disorder, anxiety disorder, bipolar disorder, depression, personality disorder, obsessive-compulsive disorder, schizophrenia); history of psychotropic medication prescription

(antipsychotics, anxiolytics and hypnotics, stimulants, mood stabilizers); prescription of other medications (antidiabetic medications, lipid-lowering drugs, nonsteroidal anti-inflammatory drugs), and measures of health utilization (number of GP consultations, number of psychiatric consultations). GP and psychiatric consultations were categorized based on the quartiles of their respective distributions.

All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). The study protocol (No. 19_163R) was approved by the independent scientific advisory committee of the CPRD, and the research ethics committee of the Jewish General Hospital (Montreal, Canada).

RESULTS

After applying selection criteria, the cohort included 2,319,957 patients, contributing 11,860,375 person-years of follow-up. In this cohort, 41,537 patients (1.8%) were newly prescribed an antidepressant during the study period. Females accounted for 68.9% of patients newly prescribed an antidepressants and the majority of patients were aged 15-17 years (78.1%), followed by patients aged 11-14 years (16.8%) and patients aged 5-10 years (5.1%).

Trends in incident antidepressant prescription and coprescription with other psychotropic medications

After a brief 42% decline from 2000 to 2005, the rate of children and adolescents newly prescribed an antidepressant increased from 2006 onwards (**Figure 1, eTable1**). From 2006 to 2018, the rate more than doubled (RR 2.13, 95% CI 2.12-2.15). Specifically, in the last decade (2008-2018), the rate of patients newly prescribed an antidepressant increased from 254.3 (95% CI 242.7-265.4) to 471.2 (95% CI 450.5-493.6) per 100,000 person-years (RR 1.97, 95% CI 1.96-1.99) (**eTable 1**). The rate difference in the last decade was 216.9 (95% CI 193.4-242.1) per 100,000 person-years. Females were newly prescribed an antidepressant more frequently than males, with a rate of 502.4 (95% CI 496.6-508.3) and 209.7 (95% CI 206.1-213.3) per 100,000 person-years, respectively (RR 2.40, 95% CI 2.35-2.45) **(Figure 1**). The rise in patients newly prescribed an antidepressant was driven by patients aged 15-17 years as the rate in those aged 11-14 years remained largely stable during the study period and declined four-fold in those aged 5-7 years (**eFigure 1**). Similar to the overall rate, after an initial decline from 2000 to 2005, the rate in patients aged 15-17 years approximately doubled between 2006 and 2018, from 792.1 (95% CI 751.3-836.2) to 1,842.3 (95% CI 1,752.4-1,939.4) per 100,000 person-years (RR 2.33, 95% CI 2.16-2.50) (**eFigure**

1). Similar trends were observed in all four UK nations (England, Wales, Scotland and Northern Ireland) (**eFigure 2**).

SSRIs were the antidepressant class most commonly prescribed to children and adolescents initiating an antidepressant during the entire study period (**Figure 2**). Similar to the overall rate, the rate of patients newly prescribed an SSRI initially declined from 2000 to 2005, and increased from 2006 to 2018 (151.8 to 380.1 per 100,000 person-years; RR 2.50 (95% CI 2.32-2.71)). Conversely, the rate of patients newly prescribed a TCA declined steadily during the study period, from 158.3 per 100,000 person-years in 2000 to 80.4 per 100,000 person-years in 2018, and the rate of patients newly prescribed other newer antidepressants remained below 14 per 100,000 person-years. Moreover, the proportion of new prescriptions attributable to SSRIs rose from 57.8% of all new antidepressant prescriptions in 2000 to 80.6% ($p<0.0001$) in 2018. The most frequently prescribed SSRIs in the last ten years (2008-2018) were fluoxetine, citalopram and sertraline. Fluoxetine remained the most newly prescribed SSRI, but sertraline overtook citalopram as the second most newly prescribed antidepressant, increasing five-fold from 7.2% of all new SSRI prescriptions in 2008 to 34.0% in 2018 (**eFigure 3**). On the other hand, the proportion of new prescriptions attributable to TCAs decreased two-fold, from 39.7% in 2000 to 17.0% in 2018. New prescriptions for other newer generation antidepressants represented 2.3% of all new antidepressant prescriptions over the study period. MAOIs were excluded from analyses since only one new MAOI prescription was issued during the study period.

Among 41,537 patients newly prescribed an antidepressant, 1,950 (4.7%) received at least one same-day coprescription for another psychotropic drug, most of whom (93.6%) received only one same-day coprescription. The proportion of patients with a coprescription steadily increased during the study period, from 2.6% in 2000 to 6.4% in 2018 and was higher in males (6.5%) than in females (3.9%) ($p<0.0001$) (**Figure 3**). Patients aged 15-17

years accounted for the majority of coprescription (74.6%), followed by patients aged 11-14 years (20.7%) and patients aged 5-10 years (4.7%). However, unlike in patients newly prescribed an antidepressant, the increase in coprescription was not driven by any age group in particular (**eFigure 4)**.

Coprescription trends among UK nations are presented in **eFigure 5**. Coprescription in Northern Ireland started as the lowest among nations, and ended as the highest (six-fold increase from 2.1% in 2000 to 11.9% in 2018). Over the study period, coprescription increased more modestly in Scotland and England, and declined slightly in Wales.

Trends in coprescription by psychotropic medication class are presented in **Figure 4**. The most commonly coprescribed psychotropic medication class over the study period was anxiolytics and hypnotics, followed by antipsychotics. Prescriptions for anxiolytics and hypnotics increased three-fold from 1.5% of patients newly prescribed an antidepressant in 2000 to 4.3% in 2018. Prescriptions for antipsychotics also increased three-fold from 0.6% in 2000 to 1.8% in 2018. Stimulants and mood stabilizers were the least prescribed, with coprescriptions remaining below 1.0% throughout the study period. In 2018, most coprescriptions were anxiolytics and hypnotics (63.0%), followed by antipsychotics (26.0%). Across all psychotropic medication classes, coprescription with SSRIs was most common, in particular in combination with anxiolytics and hypnotics (55.5% of all combinations). The most frequent combinations over the study period were between the SSRIs fluoxetine, citalopram, or sertraline and the anxiolytics or hypnotics melatonin, zopiclone or diazepam.

Using our extended definition of coprescription for patients with no record of psychotropic prescriptions before the first antidepressant prescription, we also observed a gradual rise in coprescription over the study period that applied to coprescription issued on the same day, three months and six months after the first antidepressant prescription (**Figure 5**). From 2000 to 2018, the proportion of patients with a coprescription rose from 2.0% to

3.8% for coprescription on the same day, from 4.2% to 6.0% for coprescription within three months after the first antidepressant prescription, and from 5.6% to 7.5% for coprescription within six months after the first antidepressant prescription.

Trends in prevalent antidepressant prescription and coprescription with other psychotropic medications

Trends in annual prevalence of patients prescribed an antidepressant mirrored trends in the rate of patients newly prescribed an antidepressant, overall and stratified by age, sex, UK nation and antidepressant class. The annual prevalence also briefly decreased from 2000 to 2006, then rose steadily from 283 per 100,000 youths in 2007 to 591 per 100,000 youths in 2018 (**eFigure 6**). Prevalence was consistently higher in females than males (**eFigure 6)** and in adolescents aged 15-17 years (**eFigure 7**). In addition, all four UK nations followed the same trend as the overall prevalence (**eFigure 8**). Overall, the prevalence of children and adolescents prescribed an SSRI increased, meanwhile TCA prevalence gradually declined, and prevalence for other newer antidepressants remained low over the study period (**eFigure 9**). We excluded MAOIs from analyses since there were only three patients with prevalent MAOI prescriptions found during the study period.

Similarly, coprescription trends among patients with a prevalent antidepressant prescription mirrored coprescription trends among those newly prescribed an antidepressant. Overall, the proportion of patients with a coprescription tripled from 6.9% in 2000 to 21.3% in 2018 (**eFigure 10**). Males received more coprescriptions (17.3%) than females (10.2%) ($p<0.0001$) (**eFigure 10**). Coprescription was not driven by any particular age group (**eFigure 11**). Coprescriptions for anxiolytics and hypnotics were consistently highest, followed by antipsychotics (**eFigure 12**). From 2000 to 2018, the proportion of coprescriptions for anxiolytics and hypnotics increased four-fold, from 3.5% to 15.7%, and coprescriptions for antipsychotics increased two-fold, from 2.1% to 4.0% (**eFigure 12**).

Coprescriptions for mood stabilizers and stimulants remained low, at less than 2.0% over the study period (**eFigure 12**). Coprescription increased in all UK nations, with the highest proportion distinctively observed in Northern Ireland over the study period (**eFigure 13)**.

Changes in patients' baseline characteristics between 2007-2008 and 2017-2018

Baseline characteristics of patients newly prescribed an antidepressant between 2007-2008 and 2017-2018 were largely similar in demographic and lifestyle factors, but differed with respect to the history of psychiatric diagnoses and medications (**eTable 2**). Patients newly prescribed an antidepressant in 2017-2018 were more likely to have had an anxiety disorder and prescriptions for anxiolytics and hypnotics, and less likely to have had depression and antipsychotic prescriptions than in 2007-2008.

Baseline characteristics of patients with a coprescription among those newly prescribed an antidepressant were also largely similar in demographic and lifestyle factors between 2007-2008 and 2017-2018 but differed with respect to the history of psychiatric diagnoses, medications and health utilization (**Table 1**). Patients with a coprescription were more likely to have had an anxiety disorder and prescriptions for anxiolytics and hypnotics, and less likely to have depression and antipsychotic prescriptions in 2017-2018 than in 2007-2008.-Patients with a coprescription in 2017-2018 were also more likely to have had stimulant prescriptions and less likely to have had mood stabilizer prescriptions than in 2007-2008. Furthermore, patterns of health utilization diverged. In 2017-2018, patients with a coprescription were more likely to have had more consultations with GPs and psychiatrists. The proportion of patients with at least thirteen GP consultations doubled from 25.8% in 2007-2008 to 41.5% in 2017-2018. The proportion of at least one psychiatric consultation increased from 35.9% in 2007-2008 to 49.6% in 2017-2018.

DISCUSSION

After a brief decline from 2000 to 2005-2006, new and prevalent antidepressant prescriptions for children and adolescents in UK primary care steadily increased thereafter. Overall, the rate of patients newly prescribed an antidepressant nearly doubled from 2008 to 2018. SSRIs were the most commonly prescribed antidepressant class whereas TCAs became less prescribed over the study period. Coprescription with other psychotropic medications rose steadily throughout the study period. The most commonly coprescribed medications were anxiolytics and hypnotics, followed by antipsychotics. In addition, patients with a coprescription were more likely to have had an anxiety diagnosis and prescriptions for anxiolytics and hypnotics in 2017-2018 than in 2007-2008.

Our results on new and prevalent antidepressant prescriptions are consistent with the few previous UK studies reporting trends in the last two decades [5-8]. Similar to our findings, a study using the CPRD from 2000 to 2015 documented an initial decline in new and prevalent antidepressant prescriptions from 2000 to 2005-2006, followed by an increase thereafter [6]. However, it was unclear whether new and prevalent antidepressant prescriptions would plateau after the end of this study [6]. Our study shows that prescriptions continued to increase until 2018, with no signs of slowing down. The initial decline in antidepressant prescriptions was likely in response to the MHRA warning in 2003 on the risk of suicide ideation and behaviors in paediatric users [7, 13]. Yet, we found that new antidepressant prescriptions nearly doubled from 2008 onwards, suggesting that the effect of the warning was short-lived. Similarly, after the regulatory warning was adopted in North America and Europe, a return towards increased antidepressant prescriptions was reported in several other countries, with substantial variations [49, 51]. Immediately following the warning, new antidepressant prescriptions decreased in Iceland (32.8% during 2004-2007), the US (33.0% during 2004-2005) and Italy (23.9% during 2006-2011) [75, 77, 78]. New

antidepressant prescriptions then increased slowly in Norway (2007-2013) and Germany (19.4% from 2005 to 2011), but decreased slightly in France (7.7% from 2009 to 2016) [15, 79, 80]. These results suggest that new antidepressant prescriptions have either stabilized or increased in the five to ten years following regulatory warnings in Western countries.

Similar to our findings, SSRIs accounted for the majority of new antidepressant prescriptions across other Western countries, while new TCA prescriptions declined over time [6, 8, 15, 16, 75, 79, 80]. The rise in SSRIs and decline in TCAs also varied by country, likely due to differences in drug approval policies, clinical guidelines and healthcare systems. In the UK, increased SSRI prescriptions likely resulted from multiple factors. NICE recommends SSRIs as the first-line pharmacologic treatment following initiation of psychotherapy for moderate to severe depression, social anxiety disorder, and obsessive-compulsive disorder [1, 2, 4]. Interestingly, our findings show that from 2008 to 2018, sertraline overtook citalopram as the second most newly prescribed SSRI after fluoxetine, possibly related to the more favorable efficacy and safety profile of sertraline in paediatric use. Indeed, in a review of SSRI efficacy for paediatric depression, sertraline significantly reduced depressive symptoms compared to placebo, but the placebo effect could not be ruled out for citalopram [39]. Increased new antidepressant prescriptions could also be partly due to the rise in the number of children and adolescents diagnosed with mental health disorders. We found that the number of patients diagnosed with anxiety nearly doubled in the last decade but the number of patients diagnosed with depression and obsessive-compulsive disorder declined. Also, we do not have information on the indication for the issued antidepressant prescriptions in our database. Therefore, the contribution of changing diagnoses to the observed trends in antidepressant prescriptions is uncertain from our data. Finally, since only a few specific antidepressants are approved for use in youths in the UK, off-label prescribing might be another factor for the observed increase, as suggested by

previous studies [5, 6]. While the extent of off-label prescribing in the UK is unknown, approximately 70% of paediatric antidepressant prescriptions in the US have been considered off-label [43].

Our study found that fewer than 8% of patients newly prescribed an antidepressant each year received a coprescription, suggesting that coprescribing is not widely practiced in UK primary care. When extending the definition of coprescription up to six months following the first antidepressant, coprescription remained below 9% each year in patients with no record of psychotropic prescriptions before initiating an antidepressant. Three other studies from Western countries used administrative databases to investigate psychotropic coprescription among paediatric patients newly prescribed an antidepressant from Finland, Norway and Canada [14-16]. Two studies reported a much higher proportion of coprescribing among patients newly prescribed an antidepressant, including 33% in a Finnish birth cohort (1994-2005) and 62% in Norwegian adolescents aged 13-17 years (2012) [14, 15]. The proportion of patients with a coprescription was not reported in the Canadian study [16]. Similar to our findings, combinations with anxiolytics and hypnotics were also the most common in these three studies [14-16]. Nevertheless, these comparisons must be interpreted with caution due to the varied methodologies among studies.

Although antidepressants were most commonly coprescribed with anxiolytics and hypnotics, evidence on the efficacy and safety of combining these medication classes in children and adolescents is lacking. In our study, SSRIs with melatonin, zopiclone and diazepam were the three most frequent combinations during the study period. However, zopiclone is not indicated for use in UK patients under 18 years old [104]. Also, NICE does not recommend combining SSRIs with anxiolytics or hypnotics in guidelines for paediatric psychiatric disorders [1, 2, 4, 101]. The rationale for coprescribing these medications may be

extrapolated from adult studies, yet the evidence for combining antidepressants with anxiolytics and hypnotics in adults is not well-established. A Cochrane systematic review showed that antidepressants combined with benzodiazepines (including hypnotics) was more efficacious in the early phase of adult depression than antidepressant monotherapy, but this advantage disappeared after four weeks [105]. Combined treatment reduced drop-out rates due to adverse effects, but raised the risk of developing tolerance to benzodiazepines [105].

Our study has a number of strengths. We presented the most recent update on antidepressant prescriptions in UK paediatric patients, and the first description of trends in coprescription with other psychotropic medications in this population. Our 19-year study period is one of the longest, which allowed us to examine long-term trends following the regulatory warning, rather than short-term fluctuations. Among studies on coprescription in patients newly prescribed an antidepressant, we provided the most comprehensive description of trends over time, and examined changes in patients' profile over time. We used the CPRD, a large, representative primary care database used extensively in research. The CPRD includes information on lifestyle factors, such as obesity, smoking status and substance abuse, which allowed us to comprehensively characterize patient profiles.

Several limitations inherent to our data must also be noted. The CPRD only captures data on prescribing, not dispensing. However, dispensing data, while available in some databases, does not guarantee that patients consume the medications. Also, the CPRD does not include prescriptions from specialists or during hospitalizations. However, since GPs are central to the UK health system, we assumed that prescriptions initiated by specialists would be maintained by GPs, thus mitigating the risk of underestimating the number of patients prescribed these medications. Since diagnoses are not systematically recorded along with prescriptions in the CPRD, we expect some degree of misclassification or missing information on indication. Due to incomplete records of diagnosis and psychotherapy, we

could not verify whether the prescribed antidepressants and associated psychotropic medications were following NICE recommendations [1, 2, 4]. Nevertheless, since only a few antidepressants were approved for paediatric use, our decision to study the prescription of antidepressants and associated psychotropic medications in all patients rather than patients with an approved diagnosis helped us capture off-label prescriptions, which accurately reflected the real-world practice of prescribing these medications.

In summary, antidepressant prescriptions in UK children and adolescents increased steadily in the last decade, accompanied by a rise in coprescription for other psychotropic medications. Over the study period, anxiolytics and hypnotics were most commonly coprescribed, followed by antipsychotics. Further studies are needed to offer explanations for these trends, and investigate the safety and efficacy of antidepressants combined with other psychotropic medications in this population.

REFERENCES

1. Sarginson J, Webb RT, Jill Stocks S, Esmail A, Garg S, Ashcroft DM. Temporal trends in antidepressant prescribing to children in UK primary care, 2000–2015. Journal of Affective Disorders. 2017;210:312-8.
2. Wijlaars LP, Nazareth I, Petersen I. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). PLoS One. 2012;7(3):e33181.
3. John A, Marchant AL, Fone DL, McGregor JI, Dennis MS, Tan JOA, et al. Recent trends in primary-care antidepressant prescribing to children and young people: an e-cohort study. Psychol Med. 2016;46(16):3315-27.
4. Bachmann CJ, Aagaard L, Burcu M, Glaeske G, Kalverdijk LJ, Petersen I, et al. Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005-2012. Eur Neuropsychopharmacol. 2016;26(3):411-9.
5. Tiffin PA, Mediavilla JL, Close H, Kasim AS, Welsh P, Paton LW, et al. 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. BMJ Open. 2019;9(8):e028201.
6. Hartz I, Skurtveit S, Hjellvik V, Furu K, Nesvag R, Handal M. Antidepressant drug use among adolescents during 2004-2013: a population-based register linkage study. Acta Psychiatr Scand. 2016;134(5):420-9.
7. Lagerberg T, Molero Y, D'Onofrio BM, Fernandez de la Cruz L, Lichtenstein P, Mataix-Cols D, et al. Antidepressant prescription patterns and CNS polypharmacy with antidepressants among children, adolescents, and young adults: a population-based study in Sweden. Eur Child Adolesc Psychiatry. 2019.
8. Schröder C, Dörks M, Kollhorst B, Blenk T, Dittmann RW, Garbe E, et al. Outpatient antidepressant drug use in children and adolescents in Germany between 2004 and 2011. Pharmacoepidemiol Drug Saf. 2017;26(2):170-9.
9. Medicines and Healthcare Products Regulatory Authority. Selective Serotonin Reuptake Inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents including a summary of available safety and efficacy data. 2003 [updated 06-12-2014. Available from: https://webarchive.nationalarchives.gov.uk/20141206082100/http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON019494.
10. Diaz-Caneja CM, Espliego A, Parellada M, Arango C, Moreno C. Polypharmacy with antidepressants in children and adolescents. Int J Neuropsychopharmacol. 2014;17(7):1063-82.
11. National Institute for Health and Care Excellence. Depression in children and young people: identification and management. 2019.
12. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. 2020.
13. National Institute for Health and Care Excellence. Obsessive-compulsive disorder and body dysmorphic disorder: treatment. 2005.
14. Burcu M, Zito JM, Safer DJ, Magder LS, dosReis S, Shaya FT, et al. Association of antidepressant medications with incident type 2 diabetes among Medicaid-insured youths. JAMA Pediatr. 2017;171(12):1200-7.

15. Burcu M, Zito JM, Safer DJ, Magder LS, dosReis S, Shaya FT, et al. Concomitant use of atypical antipsychotics with other psychotropic medication classes and the risk of type 2 diabetes mellitus. J Am Acad Child Adolesc Psychiatry. 2017;56(8):642-51.
16. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.
17. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4-14.
18. National Institute for Health and Care Excellence. Depression in children and young people: identification and management. 2017.
19. US Food and Drug Administration. Suicidality in children and adolescents being treated with antidepressant medications 2018 [updated 02/05/2018. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications.
20. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents. 2005 [Available from: https://www.ema.europa.eu/en/documents/referral/european-medicines-agency-finalises-review-antidepressants-children-adolescents_en.pdf.
21. Zoëga H, Baldursson G, Hrafnkelsson B, Almarsdottir AB, Valdimarsdottir U, Halldorsson M. Psychotropic drug use among Icelandic children: a nationwide population-based study. J Child Adolesc Psychopharmacol. 2009;19(6):757-64.
22. Piovani D, Clavenna A, Cartabia M, Bonati M. Psychotropic medicine prescriptions in Italian youths: a multiregional study. Eur Child Adolesc Psychiatry. 2016;25(3):235-45.
23. Kurian BT, Ray WA, Arbogast PG, Fuchs DC, Dudley JA, Cooper WO. Effect of regulatory warnings on antidepressant prescribing for children and adolescents. Arch Pediatr Adolesc Med. 2007;161(7):690-6.
24. Revet A, Montastruc F, Raynaud JP, Baricault B, Montastruc JL, Lapeyre-Mestre M. Trends and Patterns of Antidepressant Use in French Children and Adolescents From 2009 to 2016: A Population-Based Study in the French Health Insurance Database. J Clin Psychopharmacol. 2018;38(4):327-35.
25. Tournier M, Greenfield B, Galbaud du Fort G, Ducruet T, Zito JM, Cloutier AM, et al. Patterns of antidepressant use in Quebec children and adolescents: trends and predictors. Psychiatry Res. 2010;179(1):57-63.
26. National Institute for Health and Care Excellence. Social anxiety disorder: recognition, assessment and treatment. 2013.
27. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev. 2012;11:CD004851.
28. Czaja AS, Valuck R. Off-label antidepressant use in children and adolescents compared with young adults: extent and level of evidence. Pharmacoepidemiol Drug Saf. 2012;21(9):997-1004.
29. Gyllenberg D, Sourander A. Psychotropic drug and polypharmacy use among adolescents and young adults: findings from the Finnish 1981 Nationwide Birth Cohort Study. Nord J Psychiatry. 2012;66(5):336-42.
30. National Health Service. Medicines A to Z - Zopiclone [Available from: https://www.nhs.uk/medicines/zopiclone/.
31. Ogawa Y, Takeshima N, Hayasaka Y, Tajika A, Watanabe N, Streiner D, et al. Antidepressants plus benzodiazepines for adults with major depression. Cochrane Database Syst Rev. 2019;6:CD001026.

Chapter 6. Additional Results

This section will elaborate upon results from the Supplementary Materials and provide relevant results that have not been presented in the manuscript. Specifically, this section will describe the complete results on time trends of patients with a prevalent antidepressant prescription since the manuscript discussed time trends of patients newly prescribed an antidepressant in great details. Additionally, results of the most frequent combinations of antidepressants with other psychotropic drugs at the class and molecule level among patients newly prescribed an antidepressant will also be discussed. Finally, the baseline characteristics of patients newly prescribed an antidepressant in 2007-2008 and 2017-2018, which has been briefly described in the manuscript, will be reported in greater detail here.

Time trends of patients with a prevalent antidepressant prescription between 2000 and 2018

After a brief 45% decline from 2000 to 2006, the overall annual prevalence of patients prescribed an antidepressant increased from 2007 onwards. In 2018, the prevalence reached 591 per 100,000 youths. Females were consistently prescribed more prevalent antidepressants during the study period than males (**eFigure 6**). The rise in the annual prevalence of patients prescribed an antidepressant was driven by the rise in the annual prevalence of patients aged 15-17 years, as annual prevalence of those aged 5-7 years declined five-fold, and of those aged 11-14 years remained largely stable during the study period (**eFigure 7**). Between 2008 and 2018, annual prevalence of those aged 15-17 years doubled from 933 to 2,232 per 100,000 youths. In addition, the annual prevalence of patients aged 15-17 years far exceeded that of younger age groups. Each year, annual prevalence in patients aged 15-17 years was 5 to 8 times the annual prevalence in the next highest age group (11-14 years). Across all four UK nations, similar trends to the overall annual prevalence were observed with an initial

decline from 2000 to 2006, followed by a steady increase from 2007 until the end of the study period (**eFigure 8**). England maintained the highest annual prevalence from 2000 to 2013, which was surpassed by Scotland and Northern Ireland from 2014 to 2018 (**eFigure 8**). Annual prevalence in Wales remained the lowest of all UK nations during the study period (**eFigure 8**).

Annual prevalence stratified by antidepressant class is presented in **eFigure 9**. The rise in the annual prevalence of patients prescribed an antidepressant was driven by the rise in SSRI prevalence, as TCA prevalence declined and the prevalence of other antidepressants remained fairly stable during the study period. Similar to the overall annual prevalence, SSRIs experienced an initial decline from 2000 to 2006-2007, and steadily increased three-fold from 184 per 100,000 youths in 2008 to 483 per 100,000 youths in 2018. From 2000 to 2018, annual TCA prevalence declined two-fold from 215 per 100,000 youths to 107 per 100,000 youths and annual prevalence of other antidepressants remained consistently below 33 per 100,000 youths.

Time trends of patients coprescribed other psychotropic drugs among those with a prevalent antidepressant prescription between 2000 and 2018

Among patients with a prevalent antidepressant prescription, the proportion with a coprescription tripled from 6.9% (127 patients with a coprescription per 1,828 patients with a prevalent antidepressant prescription) in 2000 to 21.3% (491 patients with a coprescription per 2,306 patients with a prevalent antidepressant prescription) in 2018 (**eFigure 10**). While annual prevalence of antidepressant prescriptions experienced an initial decline from 2000 to 2006, the proportion with a coprescription steadily increased from 2000 to 2018. Females consistently had more prevalent antidepressant prescriptions, while males consistently had more coprescriptions (**eFigure 10**). The increase in coprescription was not driven by any age group in particular unlike in annual prevalence of antidepressant prescriptions (**eFigure 11**).

Trends in coprescription among those with a prevalent antidepressant prescription across UK nations are presented in **eFigure 13**. Each UK nation displayed a unique trend in coprescription. During the study period, coprescription among those with a prevalent antidepressant prescription in Northern Ireland was the highest, but coprescription increased the fastest in England (increased by a factor of 3.4), followed by Northern Ireland and Scotland (three-fold increase). Coprescription in Wales increased three-fold from 2000 to 2008 and decreased by 25% from 2009 to 2015. Coprescription in Wales appeared to slowly increase from 2016 to 2018, with some fluctuations by year.

Similar to patients newly prescribed an antidepressant, coprescription for anxiolytics and hypnotics was consistently highest in patients with a prevalent antidepressant prescription, followed by antipsychotics (**eFigure 12**). From 2000 to 2018, the proportion of patients with a coprescription for anxiolytics and hypnotics among those with a prevalent antidepressant prescription increased four-fold from 3.5% to 15.7% and coprescription for antipsychotics increased two-fold from 2.1% to 4.0% (**eFigure 12**). Coprescription for mood stabilizers and stimulants remained stable and was the least frequently co-prescribed with less than 2.0% over the study period (**eFigure 12**).

Most frequent combinations of antidepressants and other psychotropic classes among patients newly prescribed an antidepressant

Among patients newly prescribed an antidepressant, the five most frequent combinations of antidepressants and other psychotropic drugs over the entire study period were the same as the five most frequent combinations at the end of the study period in 2017-2018 (**eTable 3**). The most frequent combination was SSRIs with anxiolytics and hypnotics at 55.5% over the entire study period and 58.6% in 2017-2018, followed by SSRIs with antipsychotics at 25.6% over the entire study period and 28.9% in 2017-2018. The rest of the combinations (SSRIs with stimulants, TCAs with anxiolytics and hypnotics, TCAs with

antipsychotics) each accounted for less than 10% of all combinations over the entire study period as well as in 2017-2018.

Further details of the most common SSRIs combined with individual anxiolytics and hypnotics are presented in **eTable 4** and **eTable 5**. While the combination of fluoxetine and melatonin remained the most frequent among all combinations of SSRIs with anxiolytics and hypnotics during the study period (16%) and in 2017-2018 (25%), sertraline became more frequently prescribed in combination over time, while citalopram became less frequently prescribed in combination in 2017-2018. As shown in **eTable 4**, among the five most frequent combinations, which accounted for 51.3% of all combinations of SSRIs with anxiolytics and hypnotics, were two combinations involving citalopram. However, in 2017-2018, among the five most frequent combinations, which accounted for 74.3% of all combinations of SSRIs with anxiolytics and hypnotics, were two fluoxetine combinations and three sertraline combinations. In fact, in 2017-2018, sertraline was more frequently coprescribed with anxiolytics or hypnotics (42.2%) than fluoxetine (32.1%) (**eTable 5**).

Baseline characteristics of patients newly prescribed an antidepressant in 2007-2008 and 2017-2018

As shown in **eTable 2**, baseline characteristics of patients newly prescribed an antidepressant were largely similar in terms of demographic and lifestyle factors between 2007-2008 and 2017-2018. Most of the patients were female (over 67%). The age distribution was similar between 2007-2008 and 2017-2018, with the majority of patients aged 15-17 years (approximately 80%), followed by patients aged 11-14 years (approximately 16%). Among patients with available data for lifestyle factors, the majority of patients did not smoke or abuse alcohol and substance. Approximately 30% of patients were overweight or obese.

As described in the manuscript, baseline characteristics differed with respect to the history of psychiatric diagnoses, medications and health utilization between 2007-2008 and 2017-2018. In addition to changes in the most frequent diagnoses (anxiety and depression) noted in the manuscript, patients newly prescribed an antidepressant in 2017-2018 were more likely to have had an autism spectrum disorder diagnosis and less likely to have had an OCD diagnosis. All other psychiatric diagnoses were present in less than 1% of patients. In addition to changes in the most frequently prescribed psychotropic drugs at baseline (anxiolytics and hypnotics, followed by antipsychotics) noted in the manuscript, patients newly prescribed an antidepressant in 2017-2018 were more likely to have had a prescription for stimulants and less likely to have had a prescription for mood stabilizers. However, it must be noted that very few patients had a prescription for mood stabilizers (less than 1% of patients in 2007-2008 and in 2017-2018). With respect to non-psychiatric drugs, patients newly prescribed an antidepressant in 2017-2018 were less likely to have had a prescription for nonsteroidal anti-inflammatory drugs (13.6%) compared to 2007-2008 (21.5%). Furthermore, patterns of health utilization diverged. In 2017-2018, patients newly prescribed an antidepressant were more likely to have had more consultations with GPs and psychiatrists. The largest increase was seen in the group with the highest number of consultations (13 or more GP consultations and three or more psychiatric consultations). From 2007-2008 to 2017-2018, the proportion of patients with 13 or more GP consultations increased from 19.0% to 30.9%, and the proportion of patients with three or more psychiatric consultations increased from 3.3% to 7.9%.

Chapter 7. Figures and Tables

For ease of reference, this chapter will present all the figures and tables that have been referred to in the preceding chapters on the manuscript (Chapter 5) and on additional results (Chapter 6).

Manuscript:

Supplementary Materials:

<u>Additional Results:</u>

Manuscript

Figure 1. Rate of patients newly prescribed an antidepressant overall and stratified by sex

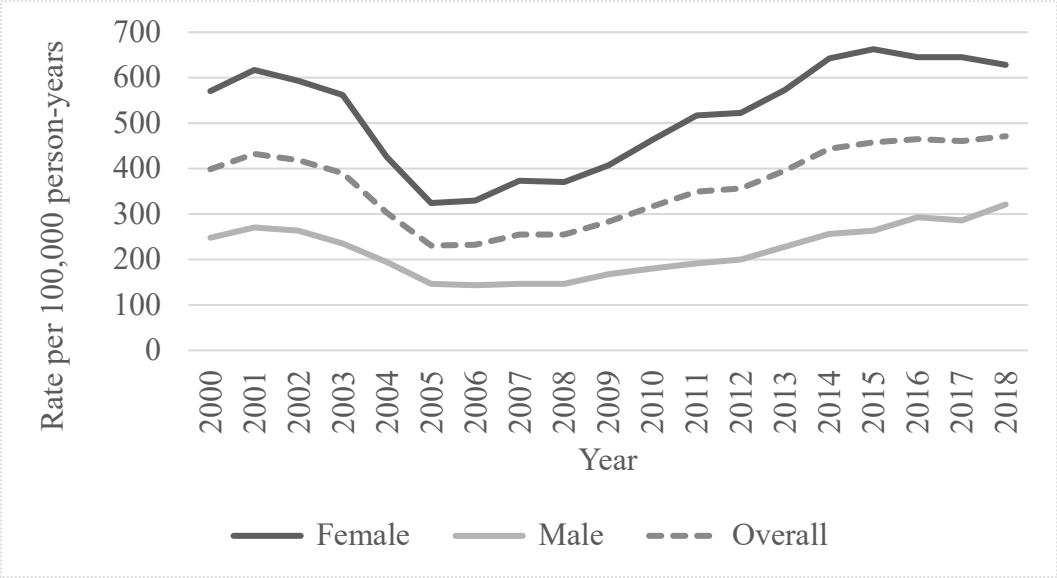


Figure 2. Rate of patients newly prescribed an antidepressant stratified by class

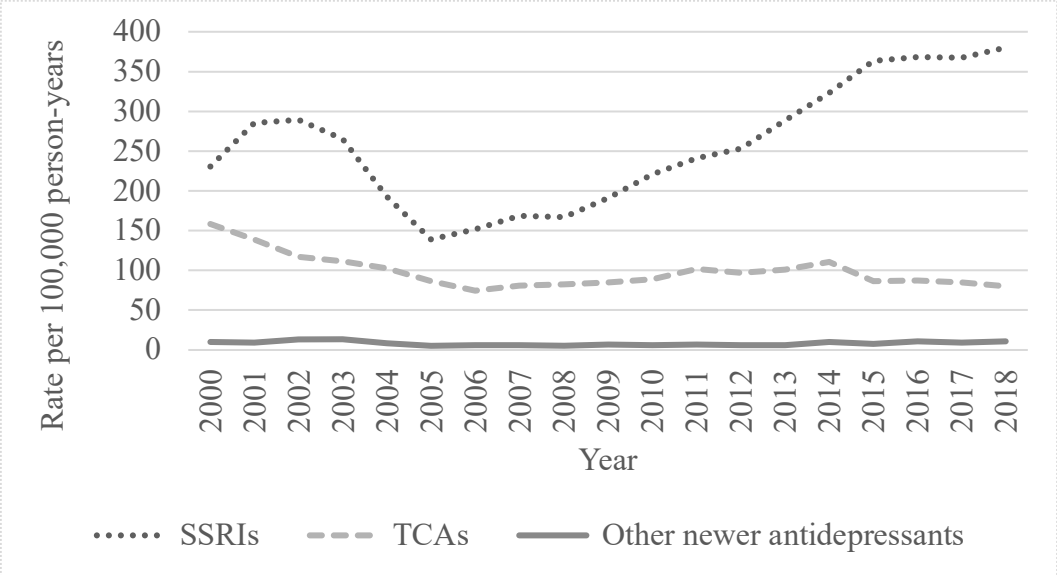


Figure 3. Proportion of coprescription in patients newly prescribed an antidepressant overall and stratified by sex

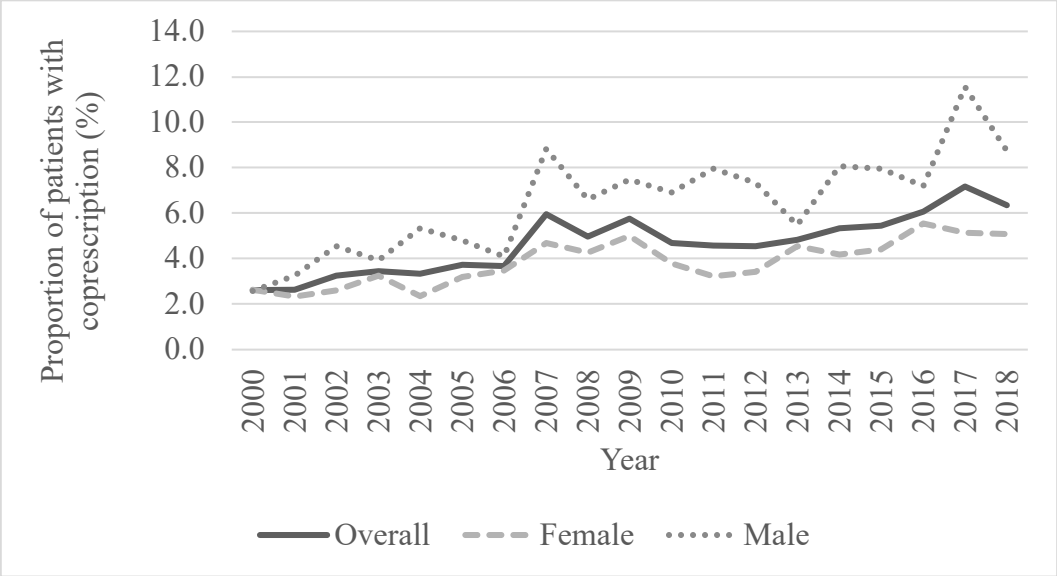


Figure 4. Proportion of coprescription in patients newly prescribed an antidepressant stratified by psychotropic medication class

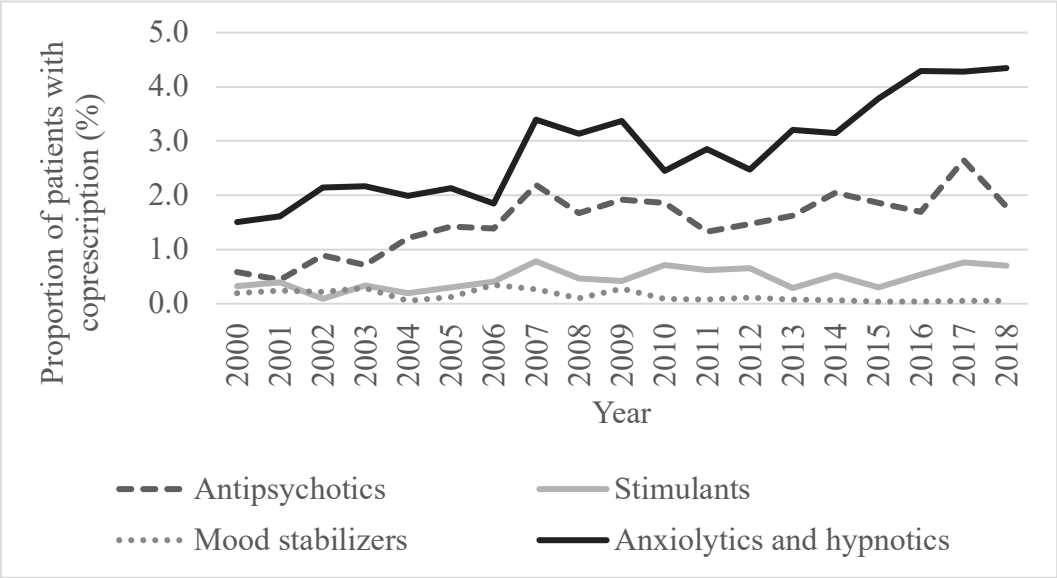


Figure 5. Proportion of coprescription in patients newly prescribed an antidepressant three months and six months following the first antidepressant prescription

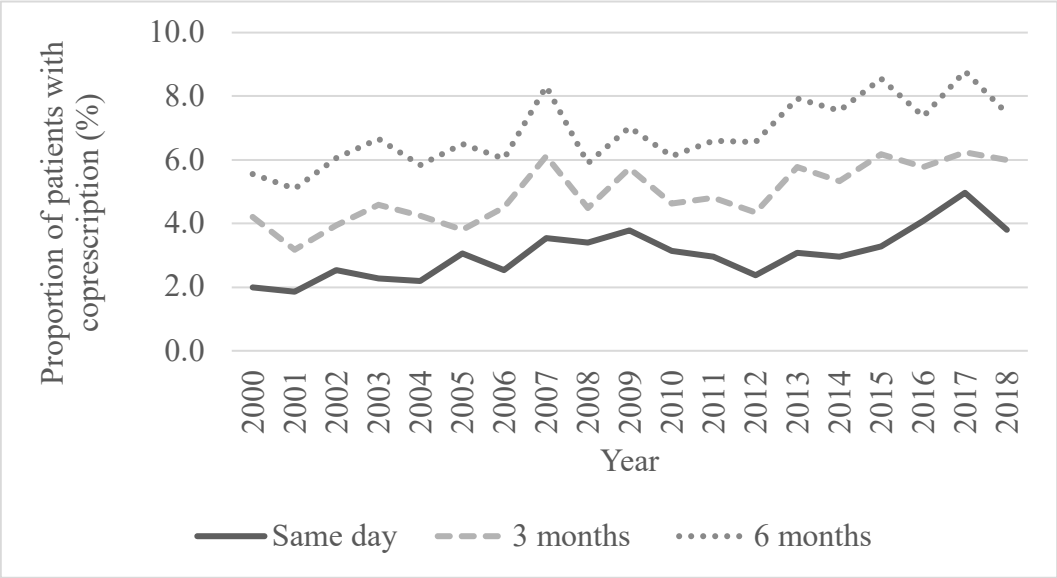


Table 1. Baseline characteristics of patients with a coprescription overall, in 2007-2008 and 2017-2018

	2000-2018	2007-2008	2017-2018
Number of patients	1,950	209	258
Age			
Median (IQR)	16 (14-17)	16 (15-17)	16 (14-17)
Mean (SD)	15.2 (2.2)	15.4 (2.3)	15.0 (2.1)
5-10 (%)	92 (4.7)	13 (6.2)	12 (4.6)
11-14 (%)	403 (20.7)	29 (13.9)	67 (26.0)
15-17 (%)	1,455 (74.6)	167 (79.9)	179 (69.4)
Sex (%)			
Female	1,109 (56.9)	120 (57.4)	130 (50.4)
Male	841 (43.1)	89 (42.6)	128 (49.6)
Psychiatric and related diagnoses (%)			
Attention-deficit hyperactivity disorder	71 (3.6)	10 (4.8)	12 (4.7)
Autism spectrum disorder	79 (4.1)	9 (4.3)	13 (5.0)
Anxiety disorder	271 (13.9)	28 (13.4)	39 (15.1)
Bipolar disorder	11 (0.6)	-	1 (0.4)
Depression	520 (26.7)	69 (33.0)	48 (18.6)
Personality disorder	8 (0.4)	1 (0.5)	1 (0.4)
Obsessive-compulsive disorder	55 (2.8)	6 (2.9)	5 (1.9)
Schizophrenia	62 (3.2)	9 (4.3)	11 (4.3)
Sleep disorders	145 (7.4)	19 (9.1)	11 (4.3)
Obesity (%)*			
Normal weight	472 (24.2)	57 (27.3)	74 (28.7)
Overweight	95 (4.9)	12 (5.7)	12 (4.7)
Obesity	121 (6.2)	12 (5.7)	21 (8.1)
Unknown	1,262 (64.7)	128 (61.3)	151 (58.5)
Smoking (%)			
Yes	378 (19.4)	46 (22.0)	29 (11.2)
No	554 (28.4)	74 (35.4)	58 (22.5)
Unknown	1,018 (52.2)	89 (42.6)	171 (66.3)
Alcohol abuse (%)	21 (1.1)	2 (0.8)	2 (1.0)
Substance abuse (%)	36 (1.9)	2 (1.0)	9 (3.5)
Medications (%)			
Any psychotropic medication	768 (39.4)	81 (38.8)	103 (39.9)
Antipsychotics	274 (14.1)	39 (18.7)	26 (10.1)
Anxiolytics and hypnotics	445 (22.8)	43 (20.6)	64 (24.8)
Stimulants	178 (9.1)	16 (7.7)	33 (12.8)
Mood stabilizers	61 (3.1)	10 (4.8)	3 (1.2)
Antidiabetic medications	11 (0.6)	3 (1.4)	1 (0.4)
Lipid-lowering drugs	2 (0.1)	-	-

Nonsteroidal anti-inflammatory drugs	296 (15.2)	29 (13.9)	29 (11.2)
Number of GP consultations (%)			
0-3	311 (15.9)	53 (25.4)	23 (8.9)
4-6	337 (17.3)	41 (19.6)	32 (12.4)
7-12	616 (31.6)	61 (29.2)	96 (37.2)
13+	686 (35.2)	54 (25.8)	107 (41.5)
Number of psychiatric consultations (%)			
0	1,148 (58.9)	134 (64.1)	130 (50.4)
1	361 (18.5)	37 (17.7)	49 (19.0)
2	153 (7.8)	11 (5.3)	38 (14.7)
3+	288 (14.8)	27 (12.9)	41 (15.9)

Abbreviations: IQR = interquartile range, SD = standard deviation, GP = general practitioner
* When using only patients with available data as the denominator, the percentages of overweight and obese patients were 31.4% (2000-2018), 29.6% (2007-2008) and 30.8% (2017-2018).

Supplementary Materials

eTable 1. Rate of patients newly prescribed an antidepressant with 95% confidence interval (CI) and rate ratio (RR) for each calendar year compared to 2008 and the preceding year

Year	Rate per 100,000 (95% CI)	Crude RR compared with 2008	Adjusted RR* compared with 2008 (95% CI)	Adjusted RR* versus preceding year (95% CI)
2000	399.3 (379.0-418.9)	1.57	1.70 (1.68-1.72)	1.00 (Ref for 2001 only)
2001	432.7 (414.6-452.2)	1.71	1.84 (1.82-1.85)	1.08 (1.07-1.09)
2002	419.0 (402.3-437.0)	1.65	1.76 (1.74-1.78)	0.96 (0.95-0.97)
2003	389.7 (374.7-405.9)	1.54	1.62 (1.60-1.63)	0.92 (0.91-0.93)
2004	303.3 (289.9-316.0)	1.19	1.24 (1.23-1.26)	0.77 (0.76-0.78)
2005	230.7 (220.1-242.2)	0.91	0.93 (0.93-0.94)	0.75 (0.74-0.76)
2006	232.3 (221.8-243.7)	0.92	0.93 (0.92-0.94)	0.99 (0.98-1.00)
2007	255.4 (244.4-267.3)	1.01	1.01 (1.00-1.02)	1.09 (1.08-1.10)
2008	254.3 (242.7-265.4)	Reference	Reference	0.99 (0.98-1.00)
2009	282.5 (270.9-294.9)	1.11	1.11 (1.10-1.12)	1.12 (1.11-1.13)
2010	316.4 (304.1-329.7)	1.25	1.25 (1.24-1.26)	1.12 (1.11-1.13)
2011	349.4 (336.4-363.5)	1.38	1.38 (1.37-1.39)	1.11 (1.10-1.12)
2012	356.2 (342.1-369.4)	1.40	1.41 (1.39-1.42)	1.02 (1.01-1.03)
2013	395.2 (381.0-410.4)	1.56	1.56 (1.55-1.58)	1.11 (1.10-1.12)
2014	443.9 (428.3-460.7)	1.75	1.77 (1.75-1.78)	1.13 (1.12-1.14)
2015	457.7 (440.9-475.8)	1.80	1.83 (1.82-1.85)	1.04 (1.03-1.05)
2016	465.2 (445.4-483.9)	1.83	1.89 (1.87-1.90)	1.03 (1.02-1.04)
2017	461.1 (441.5-482.3)	1.82	1.91 (1.89-1.93)	1.01 (1.00-1.02)
2018	471.2 (450.5-493.6)	1.86	1.97 (1.96-1.99)	1.04 (1.03-1.05)

*Adjusted for age and sex

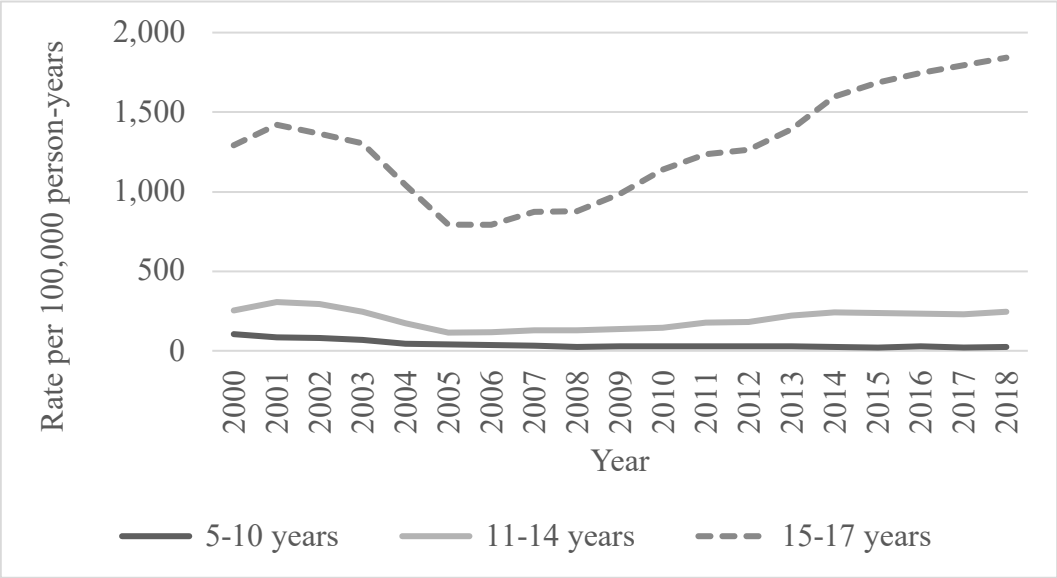
eTable 2. Baseline characteristics of patients newly prescribed an antidepressant overall, in 2007-2008 and 2017-2018

	2000-2018	2007-2008	2017-2018
Number of patients	41,537	3,829	3,806
Age			
Median (IQR)	16 (15-17)	16 (15-17)	16 (15-17)
Mean (SD)	15.4 (2.2)	15.4 (2.2)	15.7 (1.8)
5-10 (%)	2,136 (5.1)	200 (5.2)	89 (2.3)
11-14 (%)	6,970 (16.8)	605 (15.8)	599 (15.7)
15-17 (%)	32,431 (78.1)	3,024 (79.0)	3,118 (81.9)
Sex (%)			
Female	28,606 (68.9)	2,677 (69.9)	2,542 (66.8)
Male	12,931 (31.1)	1,152 (30.1)	1,264 (33.2)
Psychiatric and related diagnoses (%)			
Attention-deficit hyperactivity disorder	274 (0.7)	22 (0.6)	34 (0.9)
Autism spectrum disorder	445 (1.1)	32 (0.8)	83 (2.2)
Anxiety disorder	4,775 (11.5)	375 (9.8)	679 (17.8)
Bipolar disorder	48 (0.1)	2 (0.1)	3 (0.1)
Depression	12,202 (29.4)	1,181 (30.8)	883 (23.2)
Personality disorder	82 (0.2)	6 (0.2)	5 (0.1)
Obsessive-compulsive disorder	633 (1.5)	79 (2.1)	71 (1.9)
Schizophrenia	134 (0.3)	13 (0.3)	19 (0.5)
Sleep disorders	2,152 (5.2)	215 (5.6)	172 (4.5)
Obesity (%)			
Normal weight	9,056 (21.8)	1,019 (26.6)	812 (21.3)
Overweight	1,977 (4.8)	229 (6.0)	176 (4.6)
Obesity	2,169 (5.2)	231 (6.0)	230 (6.1)
Unknown	28,335 (68.2)	2,350 (61.4)	2,588 (68.0)
Smoking (%)			
Yes	8,183 (19.7)	989 (25.8)	354 (9.3)
No	13,295 (32.0)	1,450 (37.9)	1,016 (26.7)
Unknown	20,059 (48.3)	1,390 (36.3)	2,436 (64.0)
Alcohol abuse (%)	195 (0.5)	21 (0.6)	9 (0.2)
Substance abuse (%)	276 (0.7)	26 (0.7)	34 (0.9)
Medications (%)			
Any psychotropic medication	4,571 (10.7)	410 (10.7)	502 (13.2)
Antipsychotics	1,415 (3.4)	157 (4.1)	121 (3.2)
Anxiolytics and hypnotics	2,881 (6.9)	244 (6.4)	354 (9.3)
Stimulants	649 (1.6)	46 (1.2)	102 (2.7)
Mood stabilizers	248 (0.6)	23 (0.6)	12 (0.3)
Antidiabetic medications	318 (0.8)	25 (0.7)	40 (1.1)
Lipid-lowering drugs	32 (0.1)	4 (0.1)	3 (0.1)

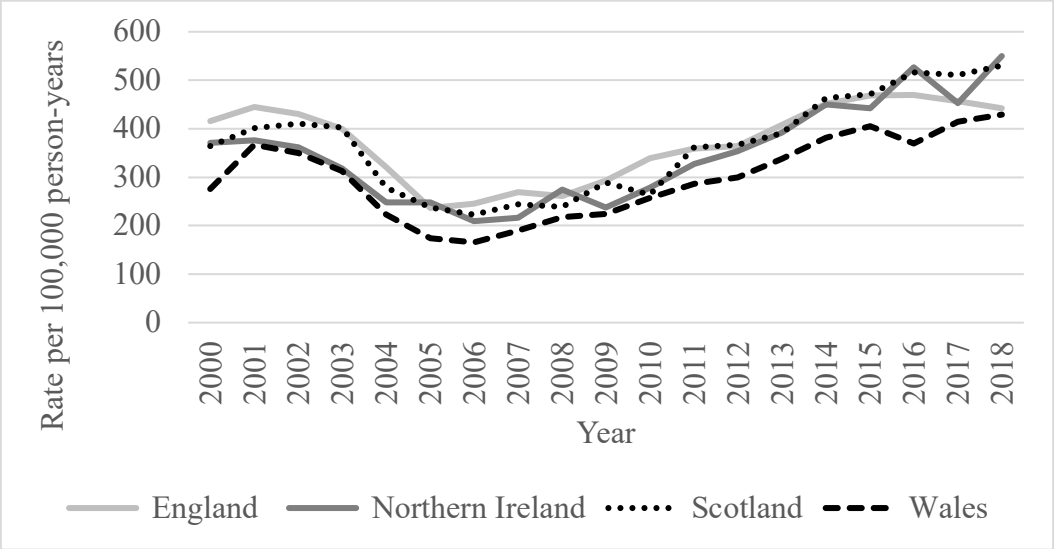
Nonsteroidal anti-inflammatory drugs	8,053 (19.4)	824 (21.5)	518 (13.6)
Number of GP consultations (%)			
0-3	9,027 (21.7)	952 (24.9)	652 (17.1)
4-6	9,765 (23.5)	972 (25.4)	758 (19.9)
7-12	12,759 (30.7)	1,175 (30.7)	1,219 (32.1)
13+	9,986 (24.1)	730 (19.0)	1,177 (30.9)
Number of psychiatric consultations (%)			
0	31,811 (76.6)	3,093 (80.8)	2,558 (67.2)
1	5,625 (13.5)	482 (12.6)	693 (18.2)
2	1,875 (4.5)	126 (3.3)	253 (6.7)
3+	2,226 (5.4)	128 (3.3)	302 (7.9)

Abbreviations: IQR = interquartile range, SD = standard deviation, GP = general practitioner
* When using only patients with available data as the denominator, the percentages of overweight and obese patients were 31.4% (2000-2018), 31.1% (2007-2008) and 33.3% (2017-2018).

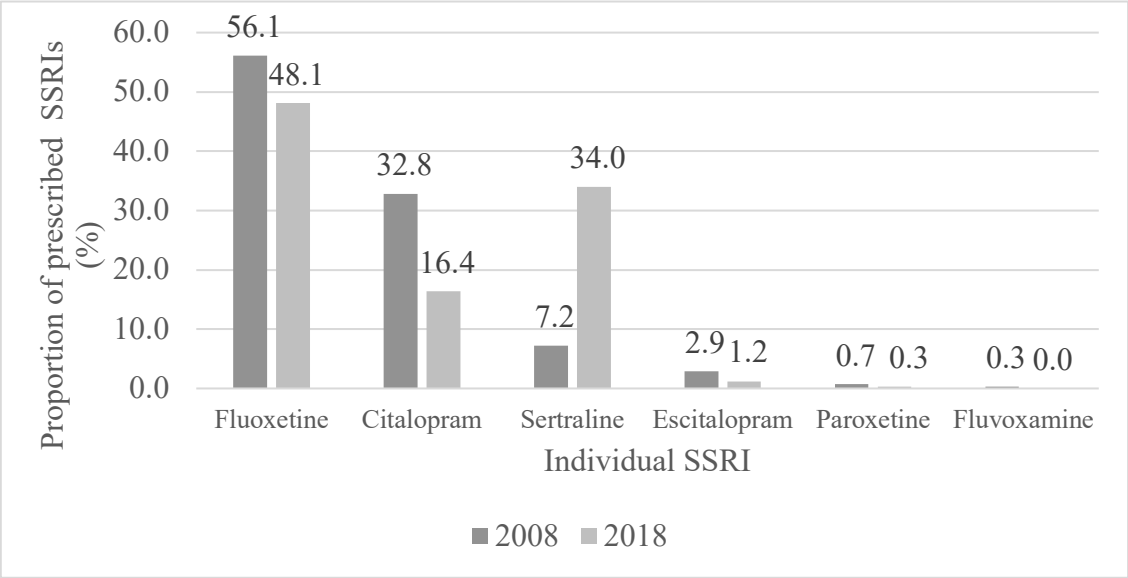
eFigure 1. Rate of patients newly prescribed an antidepressant stratified by age



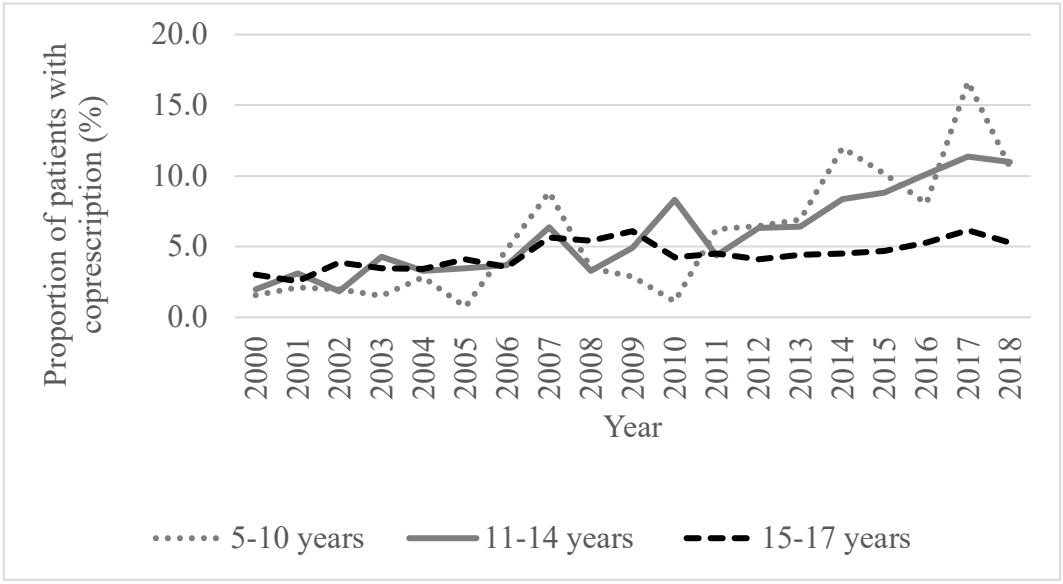
eFigure 2. Rate of patients newly prescribed an antidepressant stratified by UK nation



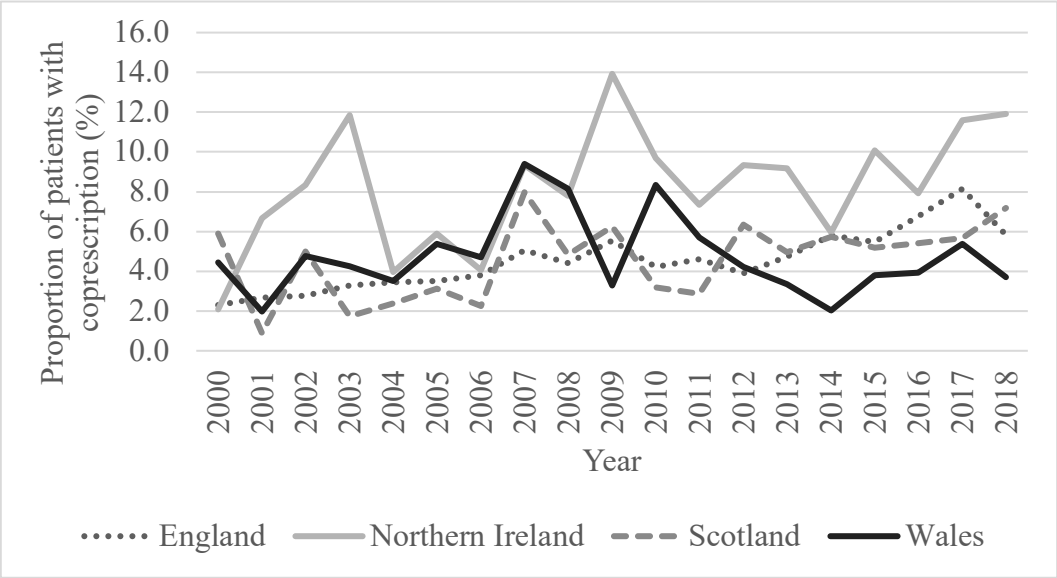
eFigure 3. Proportion of individual selective serotonin reuptake inhibitor (SSRI) molecules prescribed between 2008-2018



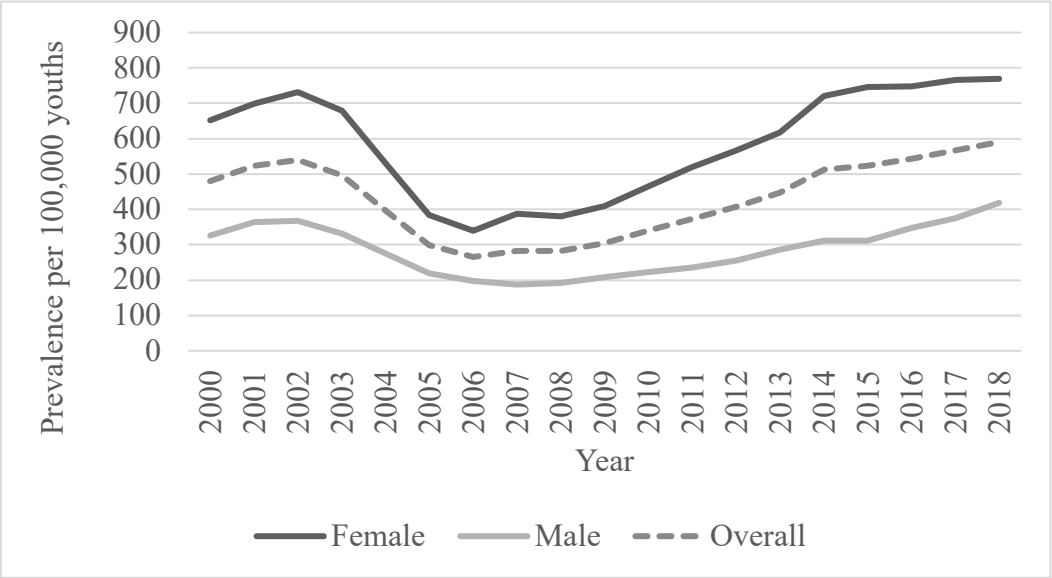
eFigure 4. Proportion of coprescription in patients newly prescribed an antidepressant stratified by age



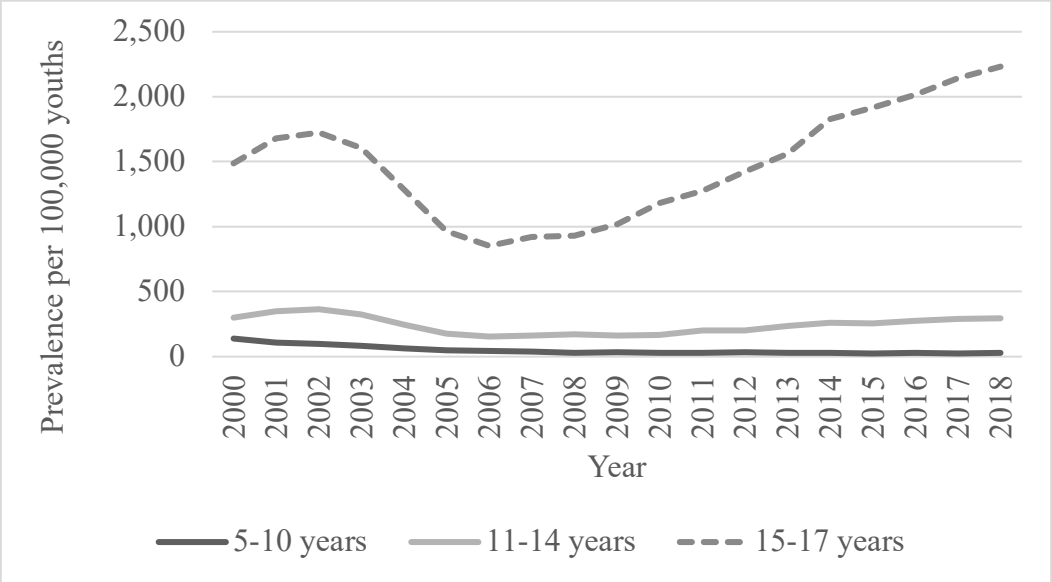
eFigure 5. Proportion of coprescription in patients newly prescribed an antidepressant stratified by UK nation



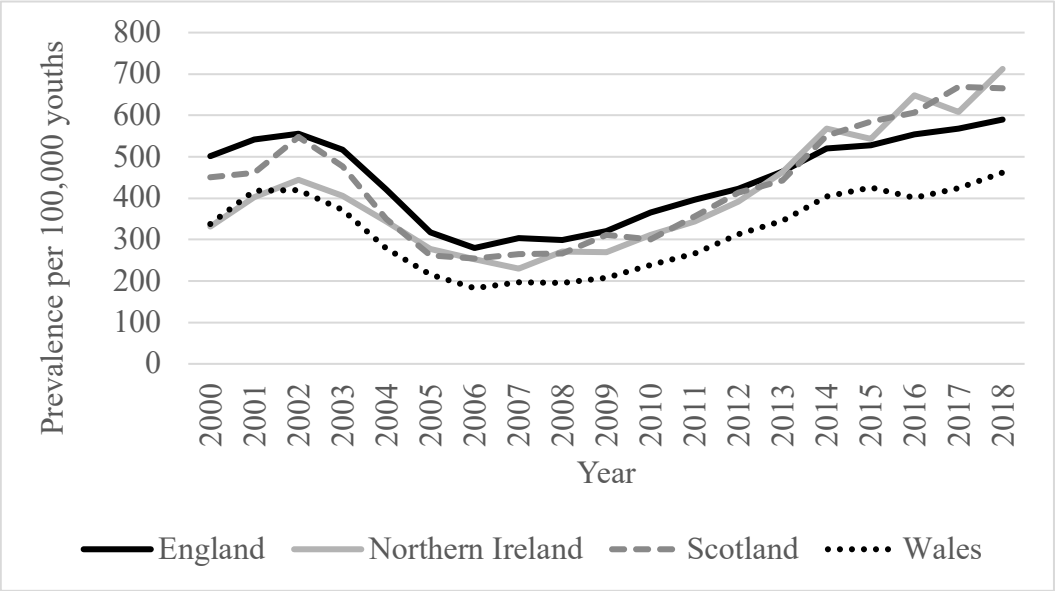
eFigure 6. Annual prevalence of patients prescribed an antidepressant overall and stratified by sex



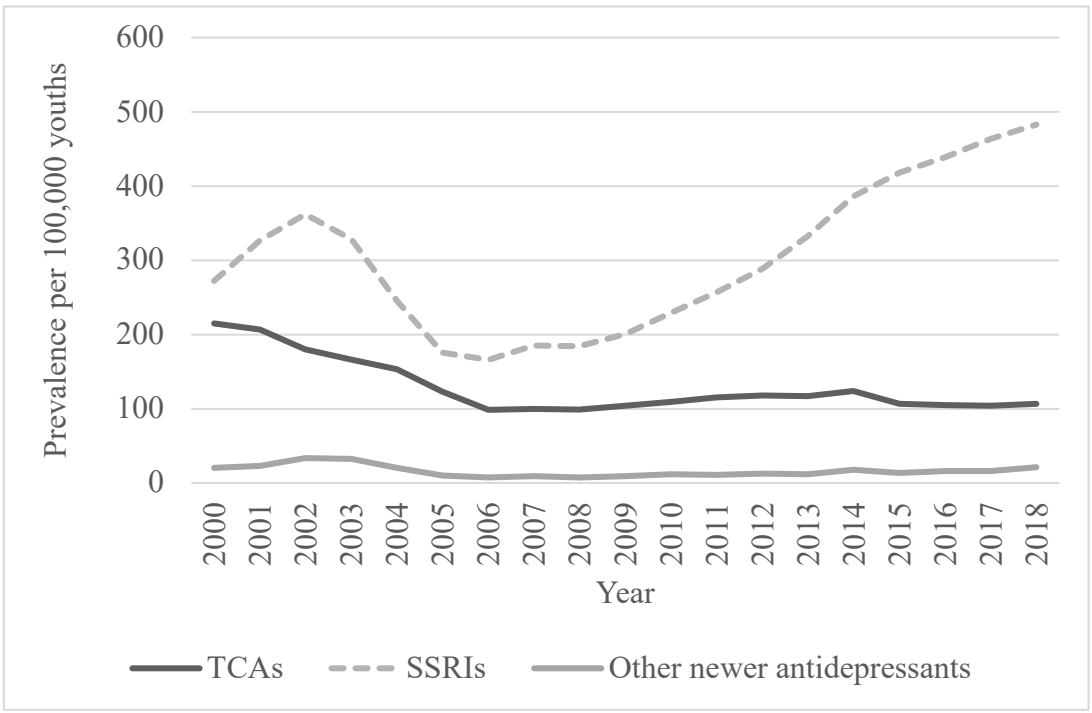
eFigure 7. Annual prevalence of patients prescribed an antidepressant stratified by age



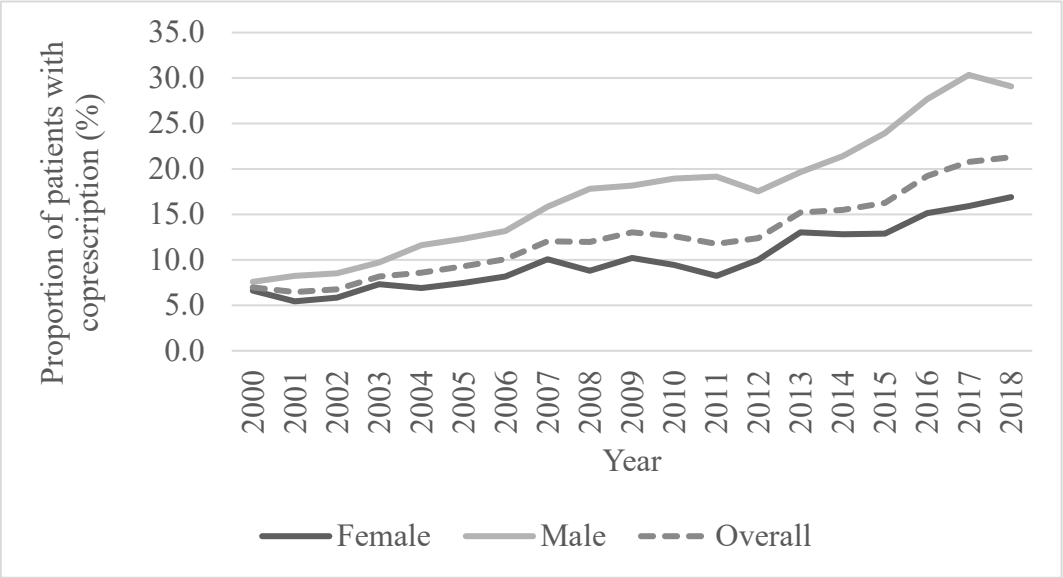
eFigure 8. Annual prevalence of patients prescribed an antidepressant stratified by UK nation



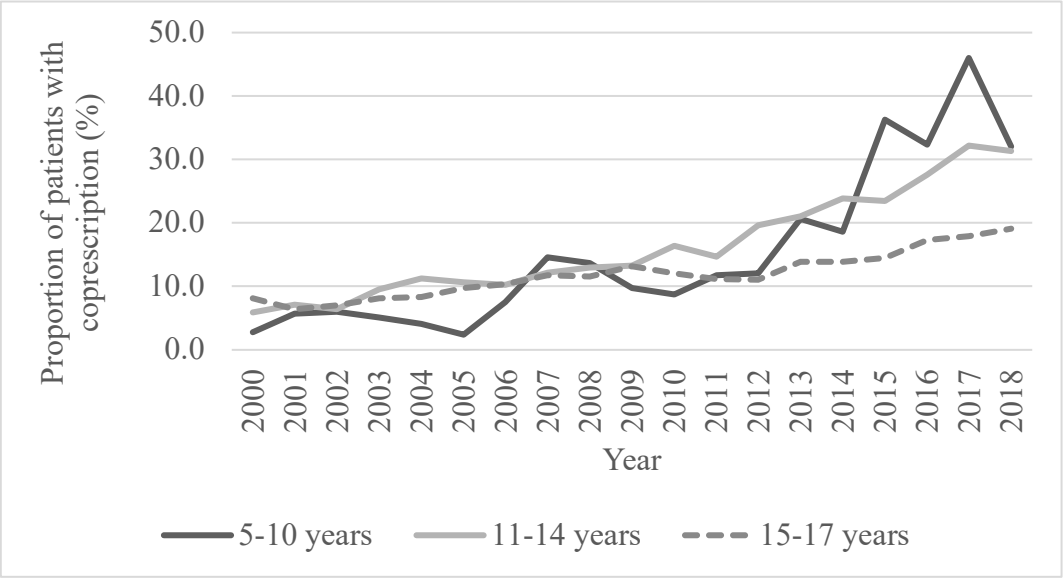
eFigure 9. Annual prevalence of patients prescribed an antidepressant stratified by class



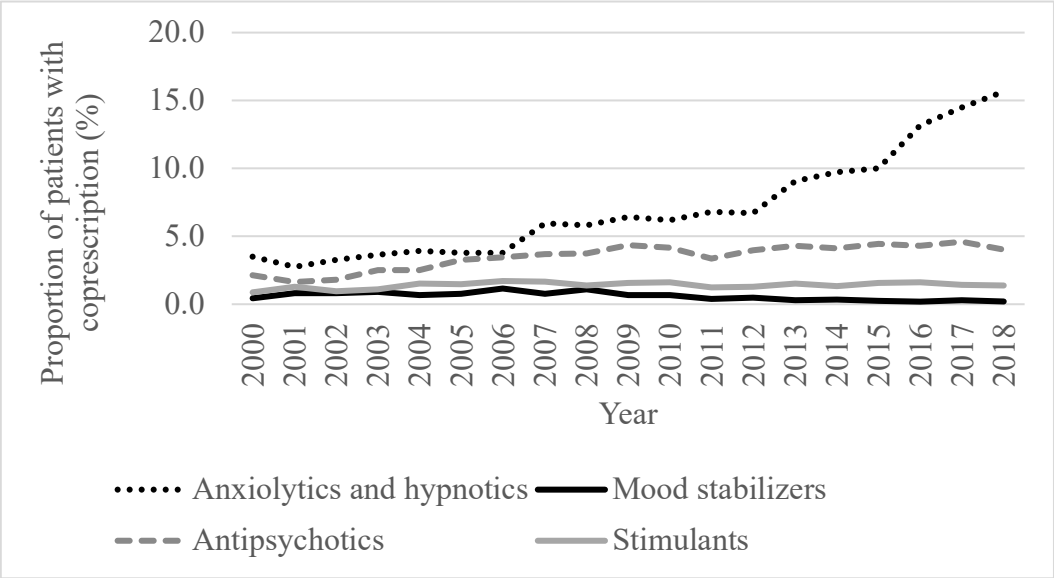
eFigure 10. Proportion of coprescription in patients with a prevalent antidepressant prescription overall and stratified by sex



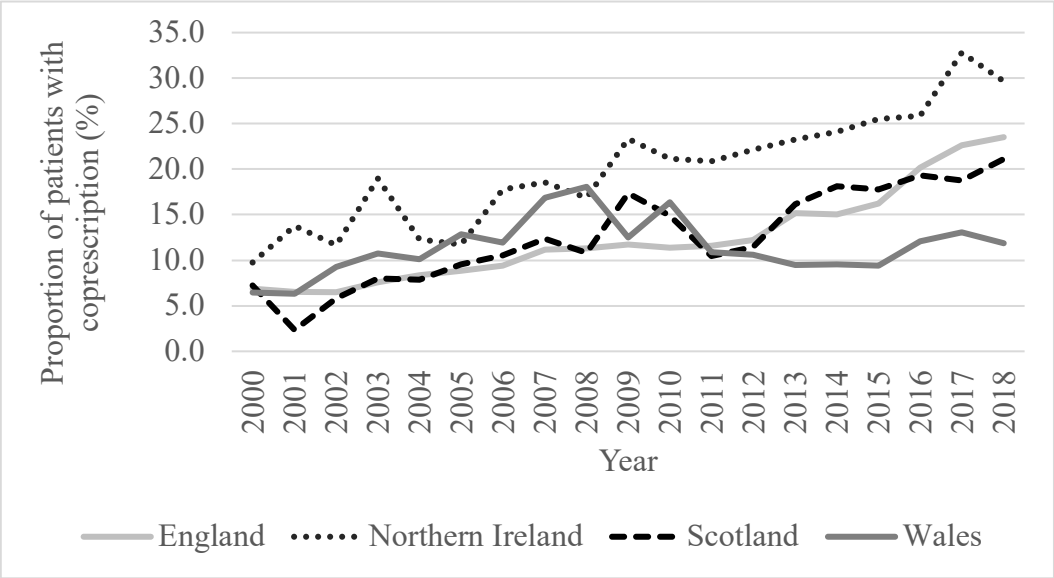
eFigure 11. Proportion of coprescription in patients with a prevalent antidepressant prescription stratified by age



eFigure 12. Proportion of coprescription in patients with a prevalent antidepressant prescription stratified by psychotropic medication class



eFigure 13. Proportion of coprescription in patients with a prevalent antidepressant prescription stratified by UK nation



Additional Results

eTable 3. Most frequent combinations of antidepressants and other psychotropic classes among patients newly prescribed an antidepressant with one other psychotropic class in 2000-2018 and 2017-2018

Combinations	N (2000-2018)	% (2000-2018)	N (2017-2018)	% (2017-2018)
SSRIs x Anxiolytics	1,013	55.5	140	58.6
SSRIs x Antipsychotics	467	25.6	69	28.9
SSRIs x Stimulants	102	5.6	14	5.9
TCAs x Anxiolytics	67	3.7	8	3.4
TCAs x Antipsychotics	49	2.7	4	1.7

eTable 4. Most frequent combinations of SSRIs with anxiolytics and hypnotics among patients newly prescribed an SSRI with an anxiolytic or an hypnotic in 2000-2018

SSRIs	Anxiolytics/Hypnotics	N (2000-2018)	% (2000-2018)
Fluoxetine	Melatonin	165	16.3
Fluoxetine	Zopiclone	105	10.4
Sertraline	Melatonin	99	9.8
Citalopram	Zopiclone	78	7.7
Citalopram	Diazepam	73	7.2
Fluoxetine	Diazepam	67	6.6
Fluoxetine	Promethazine	52	5.1
Sertraline	Zopiclone	42	4.2
Sertraline	Diazepam	40	4.0
Fluoxetine	Temazepam	36	3.6

eTable 5. Most frequent combinations of SSRIs with anxiolytics and hypnotics among patients newly prescribed an SSRI with an anxiolytic or an hypnotic in 2017-2018

SSRIs	Anxiolytics/Hypnotics	N (2000-2018)	% (2000-2018)
Fluoxetine	Melatonin	35	25.0
Sertraline	Melatonin	35	25.0
Sertraline	Promethazine	13	9.3
Sertraline	Diazepam	11	7.9
Fluoxetine	Promethazine	10	7.1
Fluoxetine	Diazepam	5	3.6
Sertraline	Zopiclone	5	3.6
Fluoxetine	Zopiclone	4	2.9

Chapter 8. Discussion

1. Summary of Objectives and Results

As described in Chapter 2, studies on antidepressant prescriptions in UK children and adolescents did not examine coprescription with other psychotropic drugs, including how the profile of patients with coprescription changed over time. To address these gaps, the primary objective of this thesis was to describe time trends in new and prevalent antidepressant prescriptions and coprescription with other psychotropic medications in UK children and adolescents in primary care between 2000 and 2018. Additionally, the secondary objective of this thesis aimed to describe changes in baseline characteristics of patients newly prescribed an antidepressant, as well as patients with coprescription among those newly prescribed an antidepressant.

After a brief decline from 2000 to 2005-2006, new and prevalent antidepressant prescriptions for children and adolescents in the UK primary care increased steadily. Over the study period, SSRIs were the most commonly prescribed antidepressant class. Meanwhile, TCA prescriptions declined gradually. Antidepressant prescriptions were highest in girls aged 15-17 years. Coprescription steadily increased throughout the study period, and was higher in boys. The most commonly coprescribed psychotropic class was anxiolytics and hypnotics, followed by antipsychotics. Baseline characteristics between 2007-2008 and 2017-2018 were overall similar for patients newly prescribed an antidepressant and for patients with coprescription. However, patients newly prescribed an antidepressant and patients with coprescription in 2017-2018 were more likely to have an anxiety diagnosis and a history of prescriptions for anxiolytics and hypnotics than in 2007-2008.

2. Strengths and Limitations

In addition to the strengths and limitations noted in the manuscript, this section will discuss further advantages and disadvantages of using an electronic medical records primary

care database. Central to this discussion are the risks of potential biases, a common issue in epidemiological research, as well as the steps we have taken to minimize these risks.

Thanks to its advantages, the CPRD has been used in at least three previous drug utilization studies of antidepressants in UK children and adolescents in the past two decades [6, 69, 84]. Using the CPRD helps to minimize the risk of selection bias since the CPRD has been shown to be broadly representative of the UK population in terms of age and sex [96]. While the CPRD does not capture information from a portion of the population, such as privately insured patients, more than 98% of the UK population is registered with a GP and therefore the exclusion of these patients is unlikely to distort our results in any significant way [96]. Moreover, GPs are gatekeepers in the UK healthcare system, serving as the first point of contact for non-emergency care and referring patients to secondary care as needed. After consultations with secondary care specialists, patients are referred back to their GPs for follow-up care [98]. Thus, despite being a primary care database, CPRD captures all of the patient's contacts within the UK healthcare system. CPRD data have also been validated for completeness and quality [102, 106]. The other main advantage of the CPRD lies in its large sample size of patients, which reduces sampling errors, resulting in precise estimates with narrow CIs. As antidepressant prescriptions have shown to be uncommon in children below the age of ten in the UK, the large sample size also allows us to capture this rare exposure with sufficient statistical power [4, 6, 7]. Given the advantages of CPRD, the real-world evidence offered by this thesis is directly applicable to clinicians looking to refine their treatment strategies and to regulators looking to update drug use trends, clinical guidelines and policies.

While data completeness and quality are ensured for our main exposures (antidepressant prescriptions and coprescriptions with other psychotropic drugs) in the CPRD, the accuracy of diagnosis data and missing data in several covariates are potential

concerns. In particular, data on psychiatric diagnoses are prone to misclassification due to the heterogeneity of symptom presentation and changing trends in recording diagnoses over time. For example, in the past two decades, GPs have increasingly favored recording depressive symptoms in place of recording depression diagnoses [5, 6, 8]. However, since depression is a condition with heterogeneity of symptoms, GPs may record different symptoms for the same diagnosis [107]. Alternatively, as depression shares several symptoms with other psychiatric disorders, the same codes for symptoms may be misinterpreted, leading to misclassification. Currently, there is no consensus on how to code psychiatric diagnoses among existing studies. In our study, we chose to exclude unspecified symptom codes, such as low mood. Our decision may have reduced the proportion of patients with a psychiatric diagnosis, but ensured a lower chance of misclassified diagnoses. Finally, while the CPRD included information on lifestyle factors, a benefit uncommon to computerized databases, it must be noted that data on obesity were missing for more than 60% of patients and data on smoking status were missing for more than 40% of patients. In order to avoid the risk of selection bias, our sample included some patients with missing data as patients with fully recorded data may differ systematically from those patients with missing data [96].

3. Implications and Future Directions

This thesis offers an in-depth description of trends in antidepressant prescriptions and coprescriptions with other psychotropic drugs in UK children and adolescents in primary care over a study period of 19 years. Findings from this thesis reflect how antidepressants are prescribed in an everyday primary care setting and provide a springboard for future research on the efficacy and safety of antidepressant use in monotherapy and combined therapy with other psychotropic drugs. These findings are especially important since they apply to children and adolescents, a vulnerable population whose use of psychotropic drugs remains under-studied.

Given the sustained increase in antidepressant prescriptions shortly after the MHRA warning, more research on factors that influence antidepressant prescribing in children and adolescents in the UK is needed. In particular, research on whether specific diagnoses are associated with higher antidepressant prescriptions is of interest, since our data did not permit conclusive results of diagnoses to verify against approved diagnoses in clinical guidelines. Research on diagnosis could also reveal the sex differences in antidepressant prescriptions, since girls have been shown to experience more psychological distress than boys in the UK, Canada and globally [108-110]. Off-label prescribing is also another factor to further examine since off-label prescriptions likely accounted for part of the rise in antidepressant prescriptions and no description of off-label pediatric antidepressant use in the UK existed to date. In the US, off-label antidepressant prescriptions has been estimated at 82% in children aged 5 to 12 years and 58% for adolescents aged 13 to 18 years [43]. Therefore, future research should quantify the extent of off-label antidepressant prescriptions in UK pediatrics, as well as the most common diagnoses associated with off-label prescribing.

Another important area of inquiry is the safety of antidepressant use alone and in combination with other psychotropic drugs, especially in long-term use. In our study, antidepressants were most often coprescribed with anxiolytics and hypnotics, followed by antipsychotics. As described in the manuscript, the rationale for coprescribing these medications was likely extrapolated from studies in adults, as there are virtually no RCTs on the efficacy and safety profiles of these combinations in children and adolescents. Existing evidence raises serious concerns about long-term adverse outcomes, especially given the dearth of research on this topic. As discussed in Chapter 2, one study showed that SSRIs, the most commonly prescribed antidepressant class in children and adolescents, were associated with an increased risk of type 2 diabetes, and that the risk increased with duration of use in this population [66]. Another study reported an increased risk of type 2 diabetes in children

and adolescents for SSRIs used concomitantly with antipsychotics, the second most frequent combinations observed in our study [17]. Given the dearth of evidence, the need for more studies on the safety of long-term pediatric use of antidepressants alone and in combination with other psychotropic drugs is warranted. The results of these future studies, in conjunction with the results of this thesis, will provide clinicians and regulators with the much needed evidence to plan future treatment strategies, guidelines and policies for psychotropic prescriptions involving antidepressants in children and adolescents.

Chapter 9. Conclusion

This thesis examined longitudinal trends of antidepressant prescriptions and coprescription with other psychotropic medications in children and adolescents in UK primary care from 2000 to 2018. Antidepressant prescriptions in UK children and adolescents increased steadily in the last decade, accompanied by a rise in coprescription for other psychotropic drugs. Over the study period, the most commonly prescribed antidepressant class was SSRIs, whereas TCA prescriptions decreased. The most frequent coprescribed psychotropic drugs with antidepressants were consistently anxiolytics and hypnotics, followed by antipsychotics. We hope that the results of this thesis will be of practical use for clinicians to refine future treatment strategies and for regulators to update drug use trends, guidelines and policies. We also hope to inspire further research on the safety of antidepressants in children and adolescents, especially when combined with other psychotropic drugs. While further research is warranted, given the emerging evidence on the risk of type 2 diabetes in pediatric use of antidepressants alone and in combination with antipsychotics, it is imperative to continue monitoring the prescribing trends of these drugs in children and adolescents. In addition, clinicians should exercise caution in prescribing antidepressants, either alone or with other psychotropic drugs in their pediatric patients.

References

1. National Institute for Health and Care Excellence. Depression in children and young people: identification and management. 2019.
2. National Institute for Health and Care Excellence. Social anxiety disorder: recognition, assessment and treatment. 2013.
3. National Institute for Health and Care Excellence. Bedwetting in under 19s. 2010.
4. National Institute for Health and Care Excellence. Obsessive-compulsive disorder and body dysmorphic disorder: treatment. 2005.
5. John A, Marchant AL, Fone DL, McGregor JI, Dennis MS, Tan JOA, et al. Recent trends in primary-care antidepressant prescribing to children and young people: an e-cohort study. Psychol Med. 2016;46(16):3315-27.
6. Sarginson J, Webb RT, Jill Stocks S, Esmail A, Garg S, Ashcroft DM. Temporal trends in antidepressant prescribing to children in UK primary care, 2000–2015. Journal of Affective Disorders. 2017;210:312-8.
7. Tiffin PA, Mediavilla JL, Close H, Kasim AS, Welsh P, Paton LW, et al. 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. BMJ Open. 2019;9(8):e028201.
8. Wijlaars LP, Nazareth I, Petersen I. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). PLoS One. 2012;7(3):e33181.
9. Bachmann CJ, Aagaard L, Burcu M, Glaeske G, Kalverdijk LJ, Petersen I, et al. Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005-2012. Eur Neuropsychopharmacol. 2016;26(3):411-9.
10. Hartz I, Skurtveit S, Steffenak AK, Karlstad O, Handal M. Psychotropic drug use among 0-17 year olds during 2004-2014: a nationwide prescription database study. BMC Psychiatry. 2016;16:12.
11. Lagerberg T, Molero Y, D'Onofrio BM, Fernandez de la Cruz L, Lichtenstein P, Mataix-Cols D, et al. Antidepressant prescription patterns and CNS polypharmacy with antidepressants among children, adolescents, and young adults: a population-based study in Sweden. Eur Child Adolesc Psychiatry. 2019.
12. Murray ML, Thompson M, Santosh PJ, Wong IC. Effects of the Committee on Safety of Medicines advice on antidepressant prescribing to children and adolescents in the UK. Drug Saf. 2005;28(12):1151-7.
13. Medicines and Healthcare Products Regulatory Authority. Selective Serotonin Reuptake Inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents including a summary of available safety and efficacy data. 2003 [updated 06-12-2014. Available from: https://webarchive.nationalarchives.gov.uk/20141206082100/http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON019494.
14. Gyllenberg D, Sourander A. Psychotropic drug and polypharmacy use among adolescents and young adults: findings from the Finnish 1981 Nationwide Birth Cohort Study. Nord J Psychiatry. 2012;66(5):336-42.
15. Hartz I, Skurtveit S, Hjellvik V, Furu K, Nesvag R, Handal M. Antidepressant drug use among adolescents during 2004-2013: a population-based register linkage study. Acta Psychiatr Scand. 2016;134(5):420-9.

16. Tournier M, Greenfield B, Galbaud du Fort G, Ducruet T, Zito JM, Cloutier AM, et al. Patterns of antidepressant use in Quebec children and adolescents: trends and predictors. Psychiatry Res. 2010;179(1):57-63.
17. Burcu M, Zito JM, Safer DJ, Magder LS, dosReis S, Shaya FT, et al. Concomitant use of atypical antipsychotics with other psychotropic medication classes and the risk of type 2 diabetes mellitus. J Am Acad Child Adolesc Psychiatry. 2017;56(8):642-51.
18. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol. 2015;23(1):1-21.
19. Owens MJ, Morgan WN, Plott SJ, Nemeroff CB. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. J Pharmacol Exp Ther. 1997;283(3):1305-22.
20. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs - Prozac - Fluoxetine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018936.
21. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs - Zoloft - Sertraline [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019839.
22. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs - Paxil - Paroxetine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020031.
23. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs - Luvox - Fluvoxamine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020243.
24. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs - Celexa - Citalopram [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020822.
25. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs - Lexapro - Escitalopram [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021323.
26. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs Effexor - Venlafaxine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021427.
27. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs Effexor - Cymbata - Duloxetine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021427.
28. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs Effexor - Pristiq - Desvenlafaxine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021992.
29. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs Effexor - Savella - Milnacipran [Available from:

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022256.
30. Eyding D, Lelgemann M, Grouven U, Harter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ. 2010;341:c4737.
31. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs Effexor - Wellbutrin - Bupropion [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018644.
32. Norman TR, Olver JS. Agomelatine for depression: expanding the horizons? Expert Opin Pharmacother. 2019;20(6):647-56.
33. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs Effexor - Remeron - Mirtazapine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020415.
34. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs Effexor - Tofranil - Imipramine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=011838.
35. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs Effexor - Nardil - Phenelzine [Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=011909.
36. Baldessarini RJ. Drug therapy of depression and anxiety disorders. In: Brunton LL, Lazoskip JS, Parker KL, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. Columbus, OH: McGraw-Hill; 2005.
37. Chang AS, Chang SM, Starnes DM, Schroeter S, Bauman AL, Blakely RD. Cloning and expression of the mouse serotonin transporter. Brain Res Mol Brain Res. 1996;43(1-2):185-92.
38. Olver JS, Burrows GD, Norman TR. Third-generation antidepressants: do they offer advantages over the SSRIs? CNS Drugs. 2001;15(12):941-54.
39. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev. 2012;11:CD004851.
40. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst Rev. 2013(6):CD002317.
41. Nowakowska E, Chodera A. [Inhibitory monoamine oxidases of the new generation]. Pol Merkur Lekarski. 1997;3(13):1-4.
42. Fiedorowicz JG, Swartz KL. The role of monoamine oxidase inhibitors in current psychiatric practice. J Psychiatr Pract. 2004;10(4):239-48.
43. Czaja AS, Valuck R. Off-label antidepressant use in children and adolescents compared with young adults: extent and level of evidence. Pharmacoepidemiol Drug Saf. 2012;21(9):997-1004.
44. Marsh S, Greenfield P. Children under 10 among those given strong antidepressants in UK The Guardian. 2018.
45. Newlan O. Antidepressant prescriptions for children on the rise. BBC. 2018.
46. Waechter F. Paroxetine must not be given to patients under 18. BMJ. 2003;326(7402):1282.

47. Lapierre YD. Suicidality with selective serotonin reuptake inhibitors: Valid claim? J Psychiatry Neurosci. 2003;28(5):340-7.
48. Kondro W. UK bans, Health Canada warns about antidepressants. CMAJ. 2004;171(1):23.
49. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents. 2005 [Available from: https://www.ema.europa.eu/en/documents/referral/european-medicines-agency-finalises-review-antidepressants-children-adolescents_en.pdf.
50. Government of Canada. Archived - Important drug warning - Paxil® - Until further information is available, Paxil® (paroxetine hydrochloride) should not be used in children and adolescents under 18 years of age - GlaxoSmithKline. 2003.
51. US Food and Drug Administration. Suicidality in children and adolescents being treated with antidepressant medications 2018 [updated 02/05/2018. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications.
52. Rynn MA, Siqueland L, Rickels K. Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. Am J Psychiatry. 2001;158(12):2008-14.
53. Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med. 2008;359(26):2753-66.
54. Isolan L, Pheula G, Salum GA, Jr., Oswald S, Rohde LA, Manfro GG. An open-label trial of escitalopram in children and adolescents with social anxiety disorder. J Child Adolesc Psychopharmacol. 2007;17(6):751-60.
55. Walkup JT, Labellarte MJ, Riddle MA, Pine DS, Greenhill L, Klein R, et al. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. N Engl J Med. 2001;344(17):1279-85.
56. Walkup J, Labellarte M, Riddle MA, Pine DS, Greenhill L, Fairbanks J, et al. Treatment of pediatric anxiety disorders: an open-label extension of the research units on pediatric psychopharmacology anxiety study. J Child Adolesc Psychopharmacol. 2002;12(3):175-88.
57. Riddle MA, Reeve EA, Yaryura-Tobias JA, Yang HM, Claghorn JL, Gaffney G, et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. J Am Acad Child Adolesc Psychiatry. 2001;40(2):222-9.
58. March JS, Biederman J, Wolkow R, Safferman A, Mardekian J, Cook EH, et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. JAMA. 1998;280(20):1752-6.
59. Pediatric OCDTST. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA. 2004;292(16):1969-76.
60. March JS, Entusah AR, Rynn M, Albano AM, Tourian KA. A Randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. Biol Psychiatry. 2007;62(10):1149-54.
61. DeVeaugh-Geiss J, Moroz G, Biederman J, Cantwell D, Fontaine R, Greist JH, et al. Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder--a multicenter trial. J Am Acad Child Adolesc Psychiatry. 1992;31(1):45-9.
62. Smellie JM, McGrigor VS, Meadow SR, Rose SJ, Douglas MF. Nocturnal enuresis: a placebo controlled trial of two antidepressant drugs. Arch Dis Child. 1996;75(1):62-6.

63. Stein DJ, Cameron A, Amrein R, Montgomery SA, Moclobemide Social Phobia Clinical Study G. Moclobemide is effective and well tolerated in the long-term pharmacotherapy of social anxiety disorder with or without comorbid anxiety disorder. Int Clin Psychopharmacol. 2002;17(4):161-70.
64. Blanco C, Heimberg RG, Schneier FR, Fresco DM, Chen H, Turk CL, et al. A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. Arch Gen Psychiatry. 2010;67(3):286-95.
65. Berbudi A, Rahmadika N, Cahyadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. Curr Diabetes Rev. 2019.
66. Burcu M, Zito JM, Safer DJ, Magder LS, dosReis S, Shaya FT, et al. Association of antidepressant medications with incident type 2 diabetes among Medicaid-insured youths. JAMA Pediatr. 2017;171(12):1200-7.
67. World Health Organization. Introduction to drug utilization research Oslo, Norway: World Health Organization 2003 [Available from: https://apps.who.int/iris/handle/10665/42627.
68. Mitchell B, Carleton B, Smith A, Prosser R, Brownell M, Kozyrskyj A. Trends in psychostimulant and antidepressant use by children in 2 Canadian provinces. Can J Psychiatry. 2008;53(3):152-9.
69. Murray ML, de Vries CS, Wong IC. A drug utilisation study of antidepressants in children and adolescents using the General Practice Research Database. Arch Dis Child. 2004;89(12):1098-102.
70. Schirm E, Tobi H, Zito JM, de Jong-van den Berg LT. Psychotropic medication in children: a study from the Netherlands. Pediatrics. 2001;108(2):E25.
71. Zito JM, Safer DJ, DosReis S, Gardner JF, Soeken K, Boles M, et al. Rising prevalence of antidepressants among US youths. Pediatrics. 2002;109(5):721-7.
72. Weller IVD, Ashby D, Brook R, Chambers MGA, Chick JD, Drummond C, et al. Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants. 2005.
73. Morkem R, Williamson T, Patten S, Queenan JA, Wong ST, Manca D, et al. Trends in antidepressant prescribing to children and adolescents in Canadian primary care: A time-series analysis. Pharmacoepidemiol Drug Saf. 2017;26(9):1093-9.
74. Abbas S, Ihle P, Adler JB, Engel S, Gunster C, Linder R, et al. Psychopharmacological Prescriptions in Children and Adolescents in Germany. Dtsch Arztebl Int. 2016;113(22-23):396-403.
75. Kurian BT, Ray WA, Arbogast PG, Fuchs DC, Dudley JA, Cooper WO. Effect of regulatory warnings on antidepressant prescribing for children and adolescents. Arch Pediatr Adolesc Med. 2007;161(7):690-6.
76. Clavenna A, Rossi E, Derosa M, Bonati M. Use of psychotropic medications in Italian children and adolescents. Eur J Pediatr. 2007;166(4):339-47.
77. Zoëga H, Baldursson G, Hrafnkelsson B, Almarsdottir AB, Valdimarsdottir U, Halldorsson M. Psychotropic drug use among Icelandic children: a nationwide population-based study. J Child Adolesc Psychopharmacol. 2009;19(6):757-64.
78. Piovani D, Clavenna A, Cartabia M, Bonati M. Psychotropic medicine prescriptions in Italian youths: a multiregional study. Eur Child Adolesc Psychiatry. 2016;25(3):235-45.
79. Schröder C, Dörks M, Kollhorst B, Blenk T, Dittmann RW, Garbe E, et al. Outpatient antidepressant drug use in children and adolescents in Germany between 2004 and 2011. Pharmacoepidemiol Drug Saf. 2017;26(2):170-9.
80. Revet A, Montastruc F, Raynaud JP, Baricault B, Montastruc JL, Lapeyre-Mestre M. Trends and Patterns of Antidepressant Use in French Children and Adolescents From 2009 to

2016: A Population-Based Study in the French Health Insurance Database. J Clin Psychopharmacol. 2018;38(4):327-35.
81. Diaz-Caneja CM, Espliego A, Parellada M, Arango C, Moreno C. Polypharmacy with antidepressants in children and adolescents. Int J Neuropsychopharmacol. 2014;17(7):1063-82.
82. Chen H, Patel A, Sherer J, Aparasu R. The definition and prevalence of pediatric psychotropic polypharmacy. Psychiatr Serv. 2011;62(12):1450-5.
83. Fontanella CA, Warner LA, Phillips GS, Bridge JA, Campo JV. Trends in psychotropic polypharmacy among youths enrolled in Ohio Medicaid, 2002-2008. Psychiatr Serv. 2014;65(11):1332-40.
84. Hsia Y, Maclennan K. Rise in psychotropic drug prescribing in children and adolescents during 1992-2001: a population-based study in the UK. Eur J Epidemiol. 2009;24(4):211-6.
85. Kovess V, Choppin S, Gao F, Pivette M, Husky M, Leray E. Psychotropic medication use in French children and adolescents. J Child Adolesc Psychopharmacol. 2015;25(2):168-75.
86. Lohr WD, Creel L, Feygin Y, Stevenson M, Smith MJ, Myers J, et al. Psychotropic Polypharmacy Among Children and Youth Receiving Medicaid, 2012-2015. J Manag Care Spec Pharm. 2018;24(8):736-44.
87. Saucedo RS, Liu X, Hincapie-Castillo JM, Zambrano D, Bussing R, Winterstein AG. Prevalence, Time Trends, and Utilization Patterns of Psychotropic Polypharmacy Among Pediatric Medicaid Beneficiaries, 1999-2010. Psychiatr Serv. 2018;69(8):919-26.
88. Zito JM, Pennap D, Safer DJ. Antidepressant Use in Medicaid-Insured Youth: Trends, Covariates, and Future Research Needs. Front Psychiatry. 2020;11:113.
89. Olfson M, Marcus SC, Weissman MM, Jensen PS. National trends in the use of psychotropic medications by children. J Am Acad Child Adolesc Psychiatry. 2002;41(5):514-21.
90. Comer JS, Olfson M, Mojtabai R. National trends in child and adolescent psychotropic polypharmacy in office-based practice, 1996-2007. J Am Acad Child Adolesc Psychiatry. 2010;49(10):1001-10.
91. Koelch M, Prestel A, Singer H, Keller F, Fegert JM, Schlack R, et al. Psychotropic medication in children and adolescents in Germany: prevalence, indications, and psychopathological patterns. J Child Adolesc Psychopharmacol. 2009;19(6):765-70.
92. Zito JM, Safer DJ, de Jong-van den Berg LT, Janhsen K, Fegert JM, Gardner JF, et al. A three-country comparison of psychotropic medication prevalence in youth. Child Adolesc Psychiatry Ment Health. 2008;2(1):26.
93. Pennap D, Zito JM, Santosh PJ, Tom SE, Onukwugha E, Magder LS. Patterns of Early Mental Health Diagnosis and Medication Treatment in a Medicaid-Insured Birth Cohort. JAMA Pediatr. 2018;172(6):576-84.
94. Lagerberg T, Molero Y, D'Onofrio BM, Fernandez de la Cruz L, Lichtenstein P, Mataix-Cols D, et al. Antidepressant prescription patterns and CNS polypharmacy with antidepressants among children, adolescents, and young adults: a population-based study in Sweden. Eur Child Adolesc Psychiatry. 2019;28(8):1137-45.
95. Cousins L, Goodyer IM. Antidepressants and the adolescent brain. J Psychopharmacol. 2015;29(5):545-55.
96. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.
97. Chisholm J. The Read clinical classification. BMJ. 1990;300(6732):1092.

98. Garcia Rodriguez LA, Perez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol. 1998;45(5):419-25.
99. Joint Formulary Committee. British National Formulary 2020 [Available from: http://www.medicinescomplete.com
100. National Health Service. BMI healthy weight calculator [Available from: https://www.nhs.uk/live-well/healthy-weight/bmi-calculator/.
101. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. 2020.
102. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4-14.
103. National Institute for Health and Care Excellence. Depression in children and young people: identification and management. 2017.
104. National Health Service. Medicines A to Z - Zopiclone [Available from: https://www.nhs.uk/medicines/zopiclone/.
105. Ogawa Y, Takeshima N, Hayasaka Y, Tajika A, Watanabe N, Streiner D, et al. Antidepressants plus benzodiazepines for adults with major depression. Cochrane Database Syst Rev. 2019;6:CD001026.
106. Jick SS, Kaye JA, Vasilakis-Scaramozza C, Garcia Rodriguez LA, Ruigomez A, Meier CR, et al. Validity of the general practice research database. Pharmacotherapy. 2003;23(5):686-9.
107. Goldberg D. The heterogeneity of "major depression". World Psychiatry. 2011;10(3):226-8.
108. Lessof CR, A.; Brind, R.; Bell, E.; Newton, S.,. Longitudinal Study of Young People in England cohort 2: health and wellbeing at wave 2. Department for Education; 2016.
109. Pearson C, Janz T, Ali J. Mental and substance use disorders in Canada 2013 [Available from: https://www150.statcan.gc.ca/n1/pub/82-624-x/2013001/article/11855-eng.htm.
110. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013;382(9904):1575-86.