

Trends in antidepressant use among children and adolescents: a Scandinavian drug utilization study

Wesselhoeft R, Jensen PB, Talati A, Reutfors J, Furu K, Strandberg-Larsen K, Damkier P, Pottegård A, Bliddal M. Trends in antidepressant use among children and adolescents: a Scandinavian drug utilization study.

Objective: To compare antidepressant utilization in individuals aged 5–19 years from the Scandinavian countries.

Methods: A population-based drug utilization study using publicly available data of antidepressant use from Denmark, Norway, and Sweden.

Results: In the study period from 2007 to 2017, the proportion of antidepressant users increased markedly in Sweden (9.3–18.0/1000) compared to Norway (5.1–7.6/1000) and Denmark (9.3–7.5/1000). In 2017, the cumulated defined daily doses (DDD) of selective serotonin reuptake inhibitors were 5611/1000 inhabitants in Sweden, 2709/1000 in Denmark, and 1848/1000 in Norway. The use of ‘other antidepressants’ (ATC code N06AX) also increased in Sweden with a higher DDD in 2017 (497/1000) compared to Denmark (225/1000) and Norway (170/1000). The use of tricyclic antidepressants was generally low in 2017 with DDDs ranging between 30–42 per 1000. The proportion of antidepressant users was highest among 15- to 19-year-old individuals. Girls were more likely to receive treatment than boys, and the treated female/male ratios per 1000 were similar in Sweden (2.39), Denmark (2.44), and Norway (2.63).

Conclusion: Even in highly comparable healthcare systems like the Scandinavian countries, variation in antidepressant use is considerable. Swedish children and adolescents have a markedly higher and still increasing use of antidepressants compared to Danish and Norwegian peers.

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Key words: drug utilization; depression; anxiety; obsessive–compulsive disorder; SSRI

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Significant outcomes

- In the year 2017, Swedish children and adolescents were more than twice as likely to fill an antidepressant prescription compared to Danish and Norwegian peers.
- Girls were more than twice as likely to be treated with antidepressants compared to boys in all three countries.

Limitations

- The analyses were based on filled prescriptions as proxies for antidepressant use.
- The study data do not include information about indications for the prescribed drugs and questions regarding the appropriateness of antidepressant use remains unanswered.

Introduction

The efficacy and safety of antidepressant use in children and adolescents has been subject to controversy and debate (1, 2). This culminated in the first decade of the 2000s, when regulatory authorities provided warnings based on reports of increased suicide-related behavior due to use of selective serotonin reuptake inhibitors (SSRIs) in youth (1, 3). The U.S. Food and Drug Administration (FDA) issued a ‘black box’ label warning in 2004 on the use of SSRIs in children and adolescents (4), which in 2007 was expanded to include young adults up to age 25 years (5). Accordingly, the European Medicines Agency recommended ‘strong warnings across the whole of the European Union to doctors and patients about these risks’ regarding antidepressant use for children and adolescents in 2005 (6).

Selective serotonin reuptake inhibitors (SSRIs) are the only antidepressants approved by the European Medicines Agency for treatment of children in Europe, with specific SSRIs holding licensed indications for childhood depressive episodes and obsessive-compulsive disorder (OCD). Tricyclic antidepressants (TCAs) are not documented effective for treatment of depression (7) or anxiety disorders (8) in children or adolescents, but are nevertheless sometimes considered second-line treatment (9). Some TCAs hold a licensed indication for nocturnal enuresis even though not considered first-line treatment (10).

Noradrenergic and specific serotonergic antidepressants (NaSSA) are approved for treatment in adults (11) but not in children and adolescents. Similarly, serotonin-norepinephrine reuptake inhibitors (SNRI) are not documented effective for treatment of depression in children or adolescents (12). However, they seem effective for treatment of anxiety disorders (13–15) and duloxetine has been approved for treatment of pediatric generalized anxiety disorders in the United States, but not in Europe.

The most recent studies of antidepressant use in children and adolescents show increasing prevalence (16–19) and incidence (18, 20, 21) rates. However, the studies are characterized by limited examination of specific drugs, only one reporting of utilization after 2013 (22), and only one study comparing antidepressant utilization between countries (16). Finally, this is the first study to compare antidepressant utilization among Scandinavian children and adolescents. The Scandinavian countries are characterized by high living standards and a fairly equal income distribution (23), and the Scandinavian healthcare systems are quite

similar and almost exclusively publicly funded through taxation (24).

Aims of the study

We aimed to compare patterns and trends of antidepressant utilization (filled prescriptions) in the last decade among individuals aged 5–19 years in Denmark, Norway, and Sweden.

Material and methods

Study populations

This is a population-based descriptive drug utilization study including three nationwide populations using publicly available data for the study period of 1 January 2007–31 December 2017. The study population consisted of all individuals aged 5–19 years from Denmark (1 012 855 in 2017), Norway (959 237 in 2017), and Sweden (1 693 565 in 2017) (www.nordicstatistics.org). The number of individuals aged 5–19 years in each country and year was used as the denominator when calculating the proportion of antidepressant users. Children under the age of 5 years were excluded due to negligible use of antidepressants. The upper age limit of 19 years was chosen in accordance with the World Health Organization (WHO) definition of adolescence (25).

Data sources

Data were retrieved from the public authorities’ freely accessible websites that provide validated information on filled medication prescriptions; www.medstat.dk, www.socialstyrelsen.se, www.norpd.no. The prescription databases of the Scandinavian countries hold valid information on drug groups and the period prevalence of a given drug per 1000 persons per year within a given age range and sex (26).

Variables. Filled prescriptions of antidepressants were used as proxies for actual consumption of drugs. Drugs were defined according to the WHO Anatomic Therapeutic Chemical (ATC) classification system (27), and the study included prescriptions of drugs with any ATC code of N06A* (antidepressants) (* referring to inclusion of all drugs in this category). The antidepressants were further divided into three drug groups: (i) SSRIs (ATC code N06AB*), (ii) TCAs (ATC code N06AA* (Non-selective monoamine reuptake inhibitors)), and (iii) ‘other antidepressants’ (ATC codes N06AX*) including

serotonin-norepinephrine reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, melatonin agonists, serotonin agonists and antagonists, and aminoketone and norepinephrine reuptake inhibitors. Due to the hierarchical structure of ATC levels, any reporting of total antidepressant use (N06A*) also contained use of monoamine oxidase inhibitors (N06AF and N06AG). The use of these drugs was, however, extremely rare.

The quantity dispensed for each drug prescription is expressed by the defined daily dose (DDD) measure, which is defined as ‘the assumed average maintenance dose per day for a drug used for its main indication in adults’ (27). Specifications of included antidepressant drugs with and without licensed indication for use in children and adolescents (<18 years) are shown in Table 1.

Statistical analyses

In order to show trends of antidepressant use, we obtained the annual number of 5- to 19-year-olds per 1000 individuals (prevalence) in each country, who filled at least one prescription for antidepressants (by drug group and total) in the years 2007–2017. We

illustrated the annual number of antidepressant users (per 1000) in 2017, by sex, age group, and country. Finally, the total cumulated yearly amount of DDDs of the most frequently used antidepressants in 2007–2017 among 5- to 19-year-olds (per 1000 individuals) was determined. This was analyzed by country, drug group, drug, year, and age group.

All statistical analyses were performed using STATA Release 15.0 (StataCorp, College Station, TX, USA) and R (28), including the tidyverse packages (29).

Ethics

The data are publicly accessible in the three countries and approval from any ethical committee or data protection agency is therefore not required.

Results

Throughout the study period, the number of young antidepressant users increased markedly in Sweden (from 9.3 to 18/1000), whereas it increased slightly in Norway (from 5.1 to 7.6/1000) and decreased in Denmark (from 9.3 to 7.5/1000) after a peak in 2010 (13/1000) (Fig. 1,

Table 1. Licensed indication for use of antidepressants in children and adolescents (younger than 18 years) in Denmark, Norway, and Sweden

Drug group/ATC code	ATC Class	Drug	DDD (mg)	Denmark Year of licensed indication	Norway Year of licensed indication	Sweden Year of licensed indication
TCA						
N06AA	N06AA02	Imipramin	100	Before 1995 (nocturnal enuresis ≥ 6 years)	None	None
	N06AA03	Imipraminoxid	100	None	None	None
	N06AA04	Clomipramin	100	None	None	None
	N06AA09	Amitriptylin	75	2017 (nocturnal enuresis ≥ 6 years)	1976 (nocturnal enuresis ≥ 6 years)	2017 (nocturnal enuresis ≥ 6 years)
	N06AA10	Nortriptylin	75	None	None	None
SSRI						
N06AB	N06AB03	Fluoxetine	20	2006 (Depression† ≥ 8 years)	2008 (Depression† ≥ 8 years)	2006 (Depression† ≥ 8 years)
	N06AB04	Citalopram	20	None	None	None
	N06AB05	Paroxetine	20	None	None	None
	N06AB06	Sertraline	50	2001 (OCD ≥ 6 years)	2000 (OCD ≥ 6 years)	1999 (OCD ≥ 6 years)
	N06AB08	Fluvoxamine	100	2006 (OCD ≥ 8 years)	2002 (OCD > 8 years)	2002 (OCD > 8 years)
	N06AB10	Escitalopram	10	None	None	None
Other antidepressants						
N06AX	N06AX16	Venlafaxine	100	None	None	None
	N06AX21	Duloxetine	60	None	None	None
	N06AX11	Mirtazapine	30	None	None	None
	N06AX03	Mianserin	60	None	None	None
	N06AX12	Bupropion	300	None	None	None
	N06AX18	Reboxetine	8	None	None	None
	N06AX26	Vortioxetine	10	None	None	None
	N06AX22	Agomelatine	25	None	None	None
	N06AX06	Nefazodone	400	None	None	None
	N06AF	N06AF01	Isocarboxazid	15	None	None
N06AG	N06AG2	Moclobemid	300	None	None	None

TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; OCD, obsessive-compulsive disorder; DDD, defined daily dose, defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.

†Moderate to severe depression if no remission after 4–6 weeks of psychological treatment.

Table S1). Thus, Swedish children and adolescents were more than twice as likely to fill an antidepressant prescription in 2017 (1.8%) compared to Danish (0.75%) and Norwegian (0.76%) peers. The increase in Swedish use was accounted for by SSRIs and ‘other antidepressants’, whereas the number of TCA users in 2017 was larger in Norway (0.9/1000) than in Denmark (0.5/1000) and Sweden (0.5/1000).

The extensive antidepressant treatment of Swedish individuals compared to Danish and Norwegian peers applied across age groups (Fig. 2, Table S2). It was, however, most pronounced for 5- to 9-year-olds, who were four times more likely to receive treatment in Sweden (0.69/1000) than Danish (0.17/1000) and Norwegian (0.18/1000) children, although the overall use was low. As expected, antidepressant use increased in late adolescence (15–19 years), but the age-related increase (from 10 to 14 years) was almost twice as high in Norway for both males (Norway, 6.4, Denmark 3.9, Sweden 3.3.) and females (Norway 17, Denmark 8.9, Sweden 7.2).

Female antidepressant users (per 1000) were more than twice as frequent as male users (Denmark 10 vs. 4.8, Norway 11 vs. 4.6, Sweden 24 vs.

12) (Fig. 2). The preponderance of female antidepressant users per 1000 was markedly higher in the age group 15–19 years (Sweden 68 vs. 28, Denmark 27 vs. 11, Norway 30 vs. 12).

SSRIs were the most commonly used antidepressants in all three countries, with a total cumulated DDD of 5611/1000 in Sweden, 2709/1000 in Denmark and 1848/1000 in Norway in 2017 (Fig. 3, Table S3). Sertraline was most frequently used in 2017 followed by fluoxetine and in Norway by escitalopram to the same extent. The total DDD of ‘other antidepressants’ in 2017 was 497/1000 in Sweden, 225/1000 in Denmark, and 170/1000 in Norway. Venlafaxine and mirtazapine were most commonly used, and there was a trend of increasing use of various ‘other antidepressants’ in Sweden. The total use of TCAs was generally low, with DDD of 30/1000 in Sweden, 38/1000 in Denmark, and 42/1000 in Norway.

Sertraline and fluoxetine were also the most commonly used SSRIs, when looking at age groups separately in each country (Figure S1). ‘Other antidepressants’ were rarely used for 5- to 14-year-olds but a general increasing trend in use was observed for all age groups in Sweden (Figure S2). TCAs were rarely used under the age of

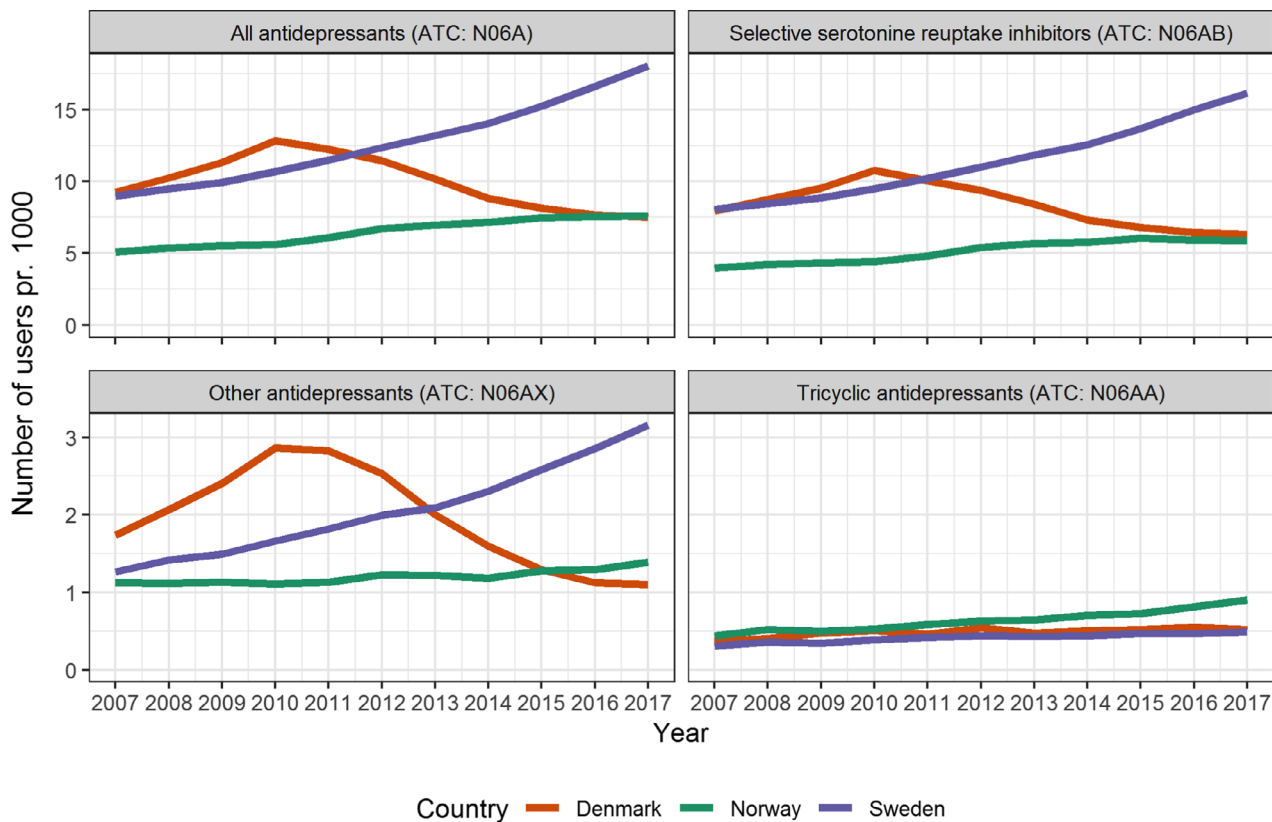


Fig. 1. Number of annual antidepressant users (per 1000) aged 5–19 years by country (note: variation in y-axes). ATC, Anatomical Therapeutic Chemical.

Antidepressant use in children and adolescents

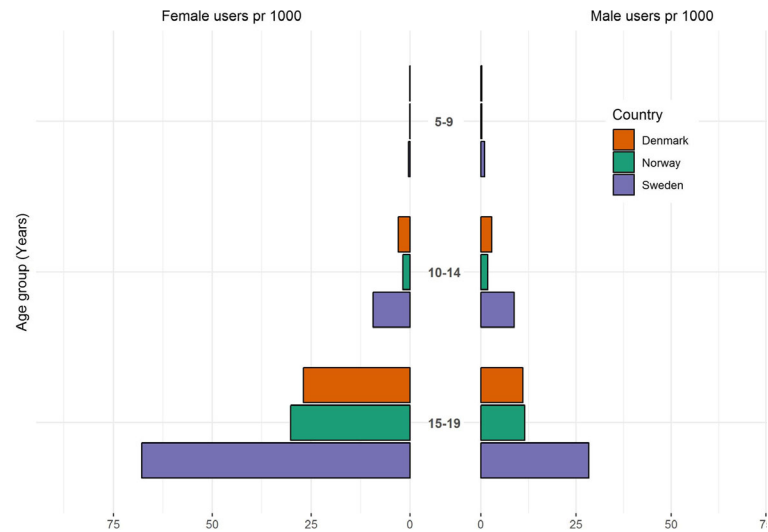


Fig. 2. Number of antidepressant users (per 1000) by sex and age group in Denmark, Norway, and Sweden in 2017.

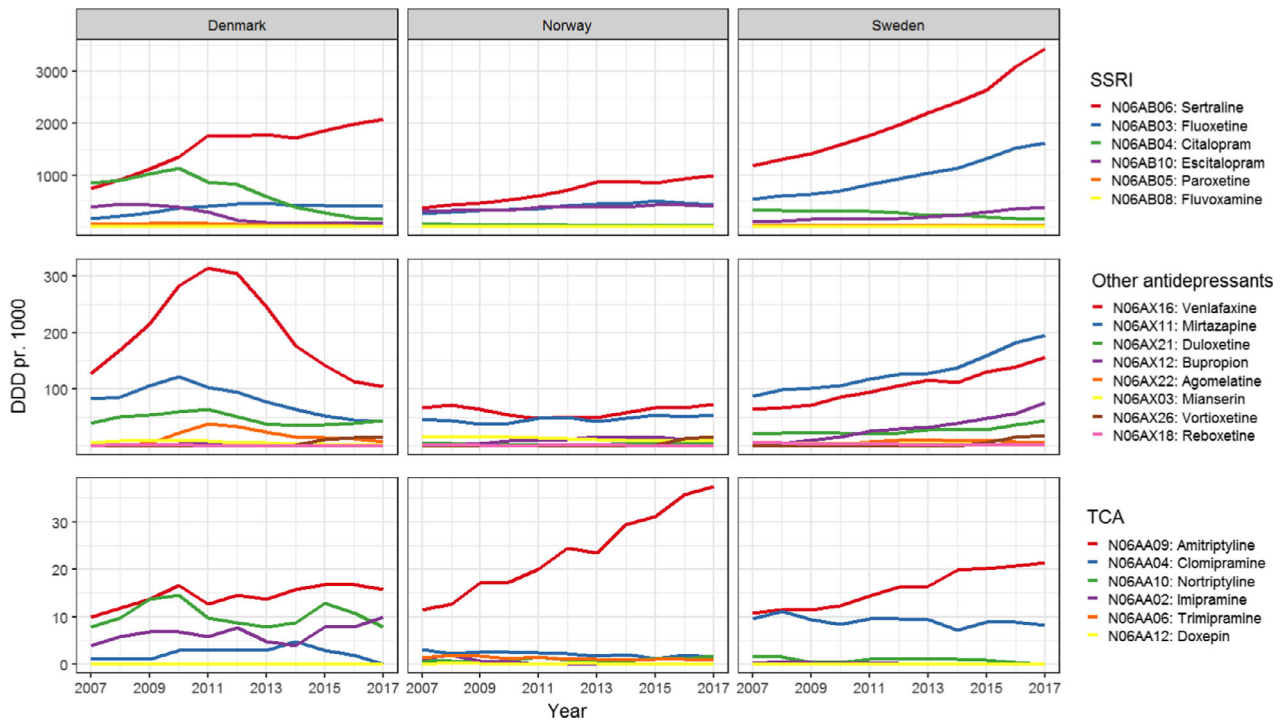


Fig. 3. Cumulated annual defined daily dose (DDD) of antidepressants by drug group per 1000 inhabitants (aged 5–19 years) in Denmark, Norway, and Sweden (note variation in y-axes).

ten (Figure S3). Amitriptyline and imipramine were the most commonly used TCAs for 5- to 14-year-olds. Amitriptyline was most frequently used in 15- to 19-year-olds with some use of clomipramine in Sweden and nortriptyline in Denmark.

Discussion

This study demonstrates that trends of antidepressant utilization in children and adolescents differed markedly between the Scandinavian countries from 2007 through 2017. There was an increasing

use of SSRIs and ‘other antidepressants’ in Sweden, while Norway and Denmark appeared to move toward a stable and lower use. In 2017, Swedish children and adolescents were more than twice as likely to fill an antidepressant prescription (1.8%) compared to Danish (0.75%) and Norwegian (0.76%) peers. Hence, two out of three Scandinavian countries did not display an increasing trend in antidepressant use as opposed to earlier findings in young Scandinavian samples (17–20) and samples from other countries (16, 21). However, the study periods of those studies ended no

later than 2013. A French study examining antidepressant use until 2016 showed a decrease in use at age 6–11 years and just a minor increase at age 12–17 years (22), similar to our findings.

The marked drop in antidepressant use in Denmark from 2010 could reflect a delayed dissemination of the FDA black box warning leading to a reluctance in prescription of antidepressants for children and adolescents. A large US study showed that there were significant reductions of antidepressant utilization rates within two years after the FDA warning and that these continuously remained lower than the rates of 2004 (30). The drop could, however, also illustrate a ‘spillover effect’ because studies showed that the antidepressant regulatory warnings actually led to a reduction in the numbers of youths (31–33) and adults (33, 34) diagnosed with depression and treated for the disorder. Still, this does not explain the trend of an increasing use in Sweden, where the licensed indications for antidepressants are similar to those of Denmark and Norway. Our results showed that Swedish children and adolescents were two-four times more likely to receive treatment with SSRIs and ‘other antidepressants’ than their Norwegian and Danish peers in 2017, depending on age group.

The use of TCAs was limited and stable throughout the last decade except that there was an increasing trend in Norway. Amitriptylin (and in Denmark also imipramin) holds a licensed indication for nocturnal enuresis in all three countries, which probably explains the main part of use (10). Amitriptyline and imipramine are occasionally used for treatment of pediatric chronic pain (35, 36), and amitriptyline also for migraine prevention (37, 38) and pain-related functional gastrointestinal disorders (39). However, neither drug holds licensed indications for these purposes in children and adolescents. Clomipramine and nortriptyline were also used for the age group of 15- to 19-year-olds, likely due to second-line treatment.

The Global Burden of Disease study provides online data (<https://gbd2016.healthdata.org/gbd-search/>) showing that the Scandinavian countries have comparable frequencies of depression and anxiety disorders for individuals aged 10–19 years. However, the Swedish prevalence rates of childhood depressive episodes seem to be somewhat higher than those of Denmark and Norway, a finding supported by studies examining the three countries separately (40–42). The prevalence of anxiety disorders in children and adolescents, on the other hand, appears to be slightly higher in Norway compared to Denmark and Sweden, whereas similar prevalence proportions (approximately 5%) were reported in a Danish (43) and Norwegian (44)

study. A study comparing OCD prevalence rates between countries (not including Norway) showed that the age-specific prevalence rates were markedly lower in Sweden compared to Denmark (45). Hence, there is a lack of studies that compare the frequencies of childhood depression and anxiety disorders between the Scandinavian countries using comparable outcome measures and age groups. Variation in disease frequency could be a plausible explanation for the different patterns of antidepressant use in between Scandinavian countries. It is also possible that access to National clinical guidelines may influence prescription patterns. Currently, Sweden is the only Scandinavian country where up-to-date National clinical guidelines are available for the treatment of all three conditions (depression, anxiety, and OCD) that are most commonly associated with antidepressant use in children and adolescents (46).

The Scandinavian countries have given rise to the term ‘the Scandinavian welfare model’ and provide very comparable healthcare systems (24) although minor differences exist (23). The licensed indications for antidepressant use for children and adolescents are also similar in the three countries (as illustrated in our Table 1). Still, Scandinavian differences in treatment patterns have previously been observed regarding attention deficit hyperactivity disorder (47). A comparison of 28 EU countries showed that Sweden had the highest availability of child and adolescent psychiatrists per 100 000 young people (23.4) compared to all countries, including Denmark (10.3) (48). The rates of Scandinavian children diagnosed with depression and OCD diagnoses seem to be rising (42, 45, 49). Our findings could reflect that Swedish children and adolescents are treated more extensively pharmacologically for these disorders due to higher availability of mental health services (48).

The most significant strengths of our study are the use of three nationwide study populations and validated exposure data sets that eliminate selection and recall bias. The analyses of our study were based on filled prescriptions as proxies for antidepressant use. Although filled prescriptions are considered superior to information collected from medical records or questionnaires (26) and are more indicative of use than prescriptions alone (50), they may not reflect consumption exactly. However, the agreement between filled prescription data and self-reported antidepressant medication is reported to be good in a large population-based study (51). Furthermore, our study holds the limitations that the data sources used did not provide information on indications for antidepressant use nor did they allow us to differentiate between incident and prevalent antidepressant users.

Finally, drugs dispensed in hospital were not included in the databases.

Concluding remarks

In this comprehensive drug utilization study, we found that Swedish children and adolescents were more than twice as likely to receive treatment with an SSRI than their Danish and Norwegian peers. Most distinctly, Swedish 5- to 9-year-olds had a four-fold likelihood of receiving antidepressant treatment compared to other Scandinavian children. The healthcare systems in the Scandinavian countries are considered quite comparable. However, the availability of child and adolescent psychiatrists is markedly higher in Sweden compared to other EU countries and the access to national clinical guidelines for treatment of depression and anxiety disorders differs between the three countries. The Global Burden of Disease study provides data indicating that the prevalence rates of depression and anxiety disorders are comparable in the Scandinavian countries but the literature is sparse. We recommend that future studies examine these healthcare differences further in order to find possible explanations for the variation of antidepressant use in Scandinavian children and adolescents.

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Conflicts of interest

Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. Johan Reutfors is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organisations) for performance of drug safety and drug utilization studies, with no relation to the work reported in this paper. Kari Furu, Ardesheer Talati, Rikke Wesselhoeft, Peter Bjørdstrup Jensen, Mette Bliddal, Katrine Strandberg-Larsen, and Per Damkier report no conflicts of interest.

Data availability statement

The data that support the findings of this study are openly available in Zenodo.org at [<https://zenodo.org/doi/10.5281/zenodo.3366068>]. The data were derived from the following resources in the public domain:

Drug statistics data:

https://sdb.socialstyrelsen.se/if_lak/val.aspx (download date: 2018.10.24).

<http://www.norpd.no/> (download date: 2018.10.24).

<http://www.medstat.dk/> (download date: 2018.01.10).

Census data:

<http://www.statistikdatabasen.scb.se> (download date: 2018.10.24).

<https://www.ssb.no/> (download date: 2018.10.24).

<https://statistikbanken.dk> (download date: 2018.01.10).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Cumulated annual defined daily dose (DDD) of selective serotonin reuptake inhibitors (SSRI) (ATC code N06AB) per 1000 inhabitants (by country, age group, and drug) in Denmark, Norway, and Sweden (*note variation in y-axes*).

Figure S2. Cumulated annual defined daily dose (DDD) of ‘other antidepressants’ (ATC code N06AX) per 1000 inhabitants (by country, age group and drug) in Denmark, Norway, and Sweden (*note variation in y-axes*).

Figure S3. Cumulated annual defined daily dose (DDD) of tricyclic antidepressants (TCA) (ATC code N06AA) per 1000 inhabitants (by country, age group, and drug) in Denmark, Norway, and Sweden (*note variation in y-axes*).

Table S1. Number of antidepressant users (per 1000) aged 5–19 years by country, year, and drug group.

Table S2. Number of antidepressant users (per 1000) by country, sex, and age group in 2017.

Table S3. Defined daily dose (DDD) of antidepressants by country, year, and drug per 1000 inhabitants (aged 5–19 years).