

Antidepressant drug use among adolescents during 2004–2013: a population-based register linkage study

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Antidepressant drug use among adolescents during 2004–2013: a population-based register linkage study.

Objective: To study trends in use of antidepressants (ADs) by adolescents, and psychiatric morbidity and use of other psychotropic drugs as a measure of psychiatric comorbidity.

Methods: One-year prevalence of AD drug use was analyzed for 13- to 17-year-old Norwegians during 2004–2013. Use of other psychotropic drugs and specialist healthcare services was analyzed for incident AD users in 2012, using linked data from the Norwegian Prescription Database and the Norwegian Patient Register.

Results: The 1-year prevalence of AD drug use increased from 6.4/1000 to 9.1/1000 during 2004–2013, with the steepest increase from 2010, particularly among girls. The highest prevalence was found in 17-year-old girls (17.8/1000 in 2010, 27.5/1000 in 2013). Of incident AD drug users in 2012, 84.4% had been in contact with specialist health care. As the first drug, 78.4% were prescribed a selective serotonin reuptake inhibitor. The most common types of other psychotropic drugs were melatonin (24.6%), antipsychotic drugs (13.2%), stimulants (8.8%), and anxiolytics (6.0%).

Conclusions: Use of ADs among adolescents has increased over the last 3–4 years, particularly among 16- to 17-year-old girls. A total of 85% of incident users had been in contact with specialist health care, which may indicate that drug-therapy is used by adolescents with more severe symptoms.

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Key words: adolescent; antidepressant agents; Norway; pharmacoepidemiology; trend

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Accepted for publication August 4, 2016

Significant outcomes

- Antidepressant (AD) use among adolescents has increased over the last 3–4 years, particularly among 16- to 17-year-old girls. In 2013, 1.0% of 17-year-old boys and 2.8% of 17-year-old girls were dispensed an AD.
- Eighty-five per cent of incident AD users in 2012 had been referred to specialist mental health care, indicating that AD therapy is started mainly in adolescents with severe symptoms of psychiatric morbidity.
- Eighty per cent of incident users were started on a selective serotonin reuptake inhibitors, which is recommended for use in moderate-to-severe depressive illness and anxiety disorders.

Limitations

- We had no information on symptom severity or use of non-pharmacological treatment options in addition to antidepressants (ADs).
- Data on ADs used while in hospital were not available.
- Prescription data may not necessarily reflect actual drug intake because drugs may be dispensed to individuals but not used.

Background

In 2004 and 2005, regulatory medical drug agencies in Norway (1), the European Medicines Agency, and the US Food and Drug Administration (FDA) raised concerns about the elevated risk of suicidal thoughts and behaviour in children and adolescents receiving antidepressants (ADs), leading to warnings against use of ADs in youths (2, 3). These warnings led to a decline in prescribing and use of ADs among children and adolescents in many countries, at least within those with milder depression (4–6). Since then, it has been an ongoing debate on beneficial vs. harmful effects of ADs in younger people. A new meta-analysis of available clinical study reports from randomized clinical trials demonstrated a higher risk of suicidal ideation and behaviour in children and adolescents taking ADs (7). Although untreated depressive disorder is a strong risk factor for completed suicide, a recent Cochrane review questions the clinical effectiveness of ADs (8). Lessons learned from long-term follow-up studies in community populations of depressed adolescents emphasize the importance of combining pharmacological with non-pharmacological therapy (9). In Norway, selective serotonin reuptake inhibitors (SSRIs, fluoxetine and sertraline in particular) are recommended first line if drug-therapy is considered necessary in moderate-to-severe depression (fluoxetine) and obsessive-compulsive disorders (OCD; sertraline) in children and adolescents. Treatment guidelines for pediatric depression, OCD, and anxiety disorders emphasize that drug-therapy should always be given in combination with psychosocial interventions and non-pharmacological treatment, and with a close monitoring of beneficial and harmful effects (8, 10–12). In recent years, a trend of increasing use of ADs among children and adolescents has been observed in the USA, Canada, and European countries (13–18). However, large differences in prescribing prevalence of AD drugs exist between countries, with the highest use of ADs in the USA (18, 19). This may be explained partly by cultural factors and differences in clinical service delivery (18, 19). In view of the ongoing debate, and after consideration of the observed relative increase in prescribing of AD drugs in children and adolescents, more detailed information on use and users is needed.

Aims of the study

The aims of this study were to describe trends in antidepressant (AD) use among 13- to 17-year-old Norwegians in terms of prevalence and incidence

of use in the period 2004–2013, and to characterize incident users in 2012 according to AD drug of choice, psychiatric morbidity, and use of other psychotropic drugs as a measure of psychiatric comorbidity.

Material and methods

Study population

The study population consisted of all individuals aged 13–17 years in Norway who were dispensed an AD drug at least once during 2004–2013, as registered in the Norwegian Prescription Database (NorPD).

Data sources

The Norwegian Prescription Database. Data on dispensed psychotropic drugs were drawn from the NorPD, which covers the entire Norwegian population (approximately 5.2 million inhabitants) (20). Since January 2004, all Norwegian pharmacies have been obliged to send data electronically to the Norwegian Institute of Public Health on all prescribed drugs (irrespective of reimbursement or not) dispensed to individuals in ambulatory care (21). Drugs administered to patients while in hospital are not reported to the NorPD. The drugs in the NorPD are classified according to the Anatomical Therapeutic Chemical (ATC) classification system (22). In this study, we included the patients' unique identity number (encrypted), sex, age, the date of dispensing, generic drug information (ATC code), defined daily doses (DDD), and prescribers' clinical specialty.

Information was retrieved for the period 2004–2013 on dispensed drugs classified as ADs, ATC-group N06A, tricyclic antidepressants (TCA, N06AA), SSRIs (N06AB), monoamine inhibitors (MAO-I, N06AG), and other ADs (N06AX). The pediatric indications, ATC codes, and DDD definitions for SSRIs licensed for pediatric use are presented in Table 1. In addition, data on other dispensed psychotropic drugs were retrieved (ATC codes in parentheses): antipsychotics (N05A, excluding lithium, N05AN01), anxiolytics (N05B), hypnotic and sedatives (N05CD, N05CF, N05CH), centrally acting sympathomimetics referred to as stimulants (N06BA), and alimemazine (R06AD01). The systemic antihistamine alimemazine has long been used for childhood insomnia in Norway (23), and was therefore included as a hypnotic/sedative. In the following, dispensed drugs, as recorded in the NorPD, will be referred to as 'used' drugs.

Table 1. SSRIs with marketing authorization in Norway

Drug	ATC codes	DDD (mg)	Year marketed	Pediatric marketing	Approved indication in children
Fluoxetine	N0AB03	20	1995	2008	Moderate-to-severe depression (>7 years of age)
Citalopram	N0AB04	20	1995		None
Paroxetine	N0AB05	20	1993		None
Sertraline	N0AB06	50	1996	2000	Obsessive-compulsive disorder (>6 years of age)
Fluvoxamine	N0AB08	100	1990	2002	Obsessive-compulsive disorder (>8 years of age)
Escitalopram	N0AB10	10	2010		None

DDD, defined daily doses; SSRI, selective serotonin reuptake inhibitors.

The Norwegian Patient Register. The Norwegian Patient Register (NPR) is an administrative database of records reported by the specialist health care, that is, all hospitals and out-patient clinics owned or financed by the government. Thus, the NPR includes information on patients that have been referred by a general practitioner (GP) because of a need of specialist health care. All Norwegian citizens have a dedicated GP who represents the lowest level of public health care. If a patient requires treatment at a higher level, the GP may refer to a specialist healthcare facility, that is, a hospital, out-patient clinic, or private practitioner. All referrals and registered contacts with specialist health care are included in the NPR. A registered contact in the NPR may thus indicate a more severe type of illness. In Norway, government-funded mental health clinics for children and adolescents are available throughout the country, serving the entire population. Mental health care for children and adolescents is free of charge. The NPR has included unique personal identification numbers since 2008, and consequently, the register contains nationwide individual-level specialist healthcare data from 2008 and onwards (24, 25). In this study, we used data reported by the specialist health care, hospital- and out-patient clinics, and substance abuse treatment facilities in the period 2008–2012. Data on mental and behavioural disorder diagnoses [International Classification of Diseases, 10th edition (ICD-10) codes F00-F99] and registered visits in the specialist child and adolescent mental health care were obtained for all individuals in the study population.

Data from the NorPD and the NPR were linked using the unique personal identity number assigned to all individuals who are living in Norway.

Analytical approach

The 1-year prevalence of use of ADs was estimated by dividing the number of individuals aged 13–17 years who were dispensed at least one AD drug within each of the years 2004–2013 by the total number of inhabitants in Norway in the relevant age group per 1 July in each year, as registered by Statistics Norway. For SSRIs, the total amount of dispensed DDDs was calculated, specified by type of SSRI and study year (2004–2013).

Incident users in each of the years 2007–2013 were defined as people having an AD dispensed in the actual year, and no AD prescriptions during the 3 years (1095 days) preceding the first prescription in the actual year. The denominator, the population at risk, was the total number of inhabitants in Norway in the relevant age group per 1 July in the actual year, as registered by Statistics Norway, minus the number of individuals who were prevalent users in one of the previous 3 years.

For incident users in 2012, we performed a more detailed analysis of choice of type of AD at initiation, other types of psychotropic drugs dispensed in 2012, and referral to specialist mental health service during 2008–2012 (registrations in NPR). A registration in the NPR in terms of a diagnosis of mental disorders (ICD-10 F00–F99) or any registered contact with the specialist child and adolescent mental health service was classified as ‘use of specialist mental health service’. For further identification of contact with other relevant specialist health care, we used prescriber’s specialty as recorded in the NorPD to identify treatment by pediatricians, psychiatrists, and neurologists.

All analyses were performed using spss 22.0 for Windows (IBM Corp., Armonk, NY, USA).

Ethical considerations

The register linkage has been approved by the Regional Committee for Medical Research Ethics and by the Norwegian Data Protection Authority.

Results

Trends in 1-year prevalence and incidence in AD use among 13- to 17-year olds

During the years 2004–2013, there was an overall increase in the 1-year prevalence for use of ADs from 6.4/1000 to 9.1/1000, but the pattern was not linear (Fig. 1). After an initial decrease, the total prevalence increased slightly until it reached the 2004 level in 2010, and then increased markedly through 2013. The increase in prevalence was

particularly strong in girls, from 8.3/1000 in 2010 to 12.4/1000 in 2013. In boys, the prevalence increased from 5.0/1000 to 5.9/1000 in the same period. In both genders, the prevalence increased with age, with the highest proportion of users observed among 17-year olds in 2013: 10.4/1000 in boys and 27.5/1000 in girls (Fig. 2).

In general, the prevalence of AD use among the 14- to 17-year olds was higher in girls compared with boys, and the gender differences increased with increasing age: from 2009 to 2013, the relative increase in use among the 14- to 17-year olds was 57–67% among girls and 17–32% among boys respectively. The most used SSRIs in the period

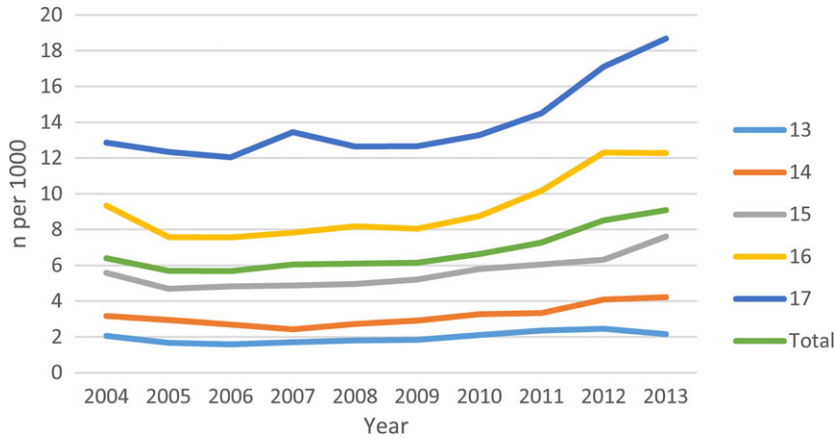


Fig. 1. The 1-year prevalence of antidepressant drug use among 13- to 17-year-old Norwegian adolescents in the period 2004–2013.

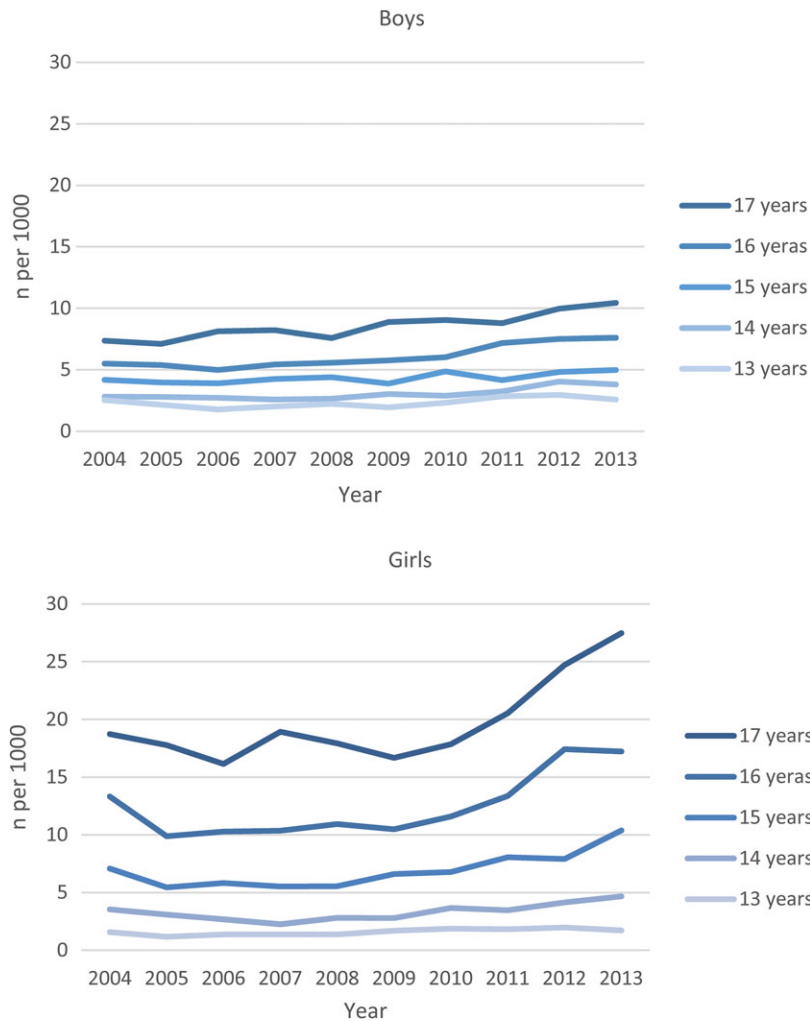


Fig. 2. The 1-year prevalence of antidepressant use among 13- to 17-year-old Norwegian adolescents in the period 2004–2013, according to age and gender.

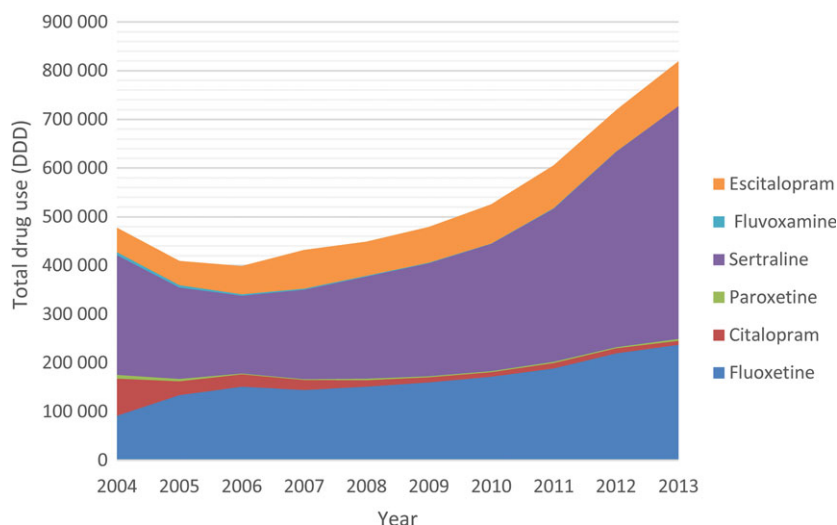


Fig. 3. Total use of selective serotonin reuptake inhibitors (SSRIs), measured in defined daily doses (DDD) and specified by drug substance and year.

(amount of DDDs) were sertraline followed by fluoxetine (Fig. 3).

The incidence was stable until 2009 in girls, and then, it increased during 2010–2013; for boys, a weak increase was observed over the whole period (Fig. 4). The proportion of incident users among prevalent users was stable throughout the period (data not shown).

Detailed characteristics of incident AD users in 2012

The great majority (78.4%) of the incident AD users were started on an SSRI, and fluoxetine (33.1%), sertraline (27.5%), and escitalopram (16.0%) were the most prevalent drugs (Table 2). The TCA amitriptyline was prescribed as the first drug to 8.7% of all new users.

A total of 33.8% of the incident AD users were also dispensed at least on hypnotic drug in 2012. The most common was melatonin (used by 24.6% of the incident users) followed by alimemazine (11.7%) (Table 3).

A total of 78.7% of the incident users had been referred to a specialist/hospital by their GP and were registered in the NPR during 2008–2012 as users of specialist mental health service, thus a marker of more severe mental health problems. Of the remaining, 26.7% had been prescribed ADs by a psychiatrist, neurologist, or pediatrician. In total, 84.4% of all incident AD users had been in contact with the specialist healthcare services, and the remaining 15.6% of incident users were treated by GPs only.

Discussion

The results of this study demonstrate a marked increase in ADs use by Norwegian adolescents

during 2010–2013. This pattern was most prominent in girls, for whom a 50% relative increase in prevalence was observed from 2010 to 2013. The gender difference in AD use varied with age and time, from similar prevalence in girls and boys at age 13 and 14 throughout the period to almost three times higher prevalence in girls than in boys at age 17 in 2013. Among incident AD users in 2012, SSRIs were the first drug in about 80%, one-third was also prescribed a hypnotic drug, and nearly 85% had been in contact with relevant specialist healthcare services as a marker of severity of symptoms.

The development in Norway differs somewhat from that in Denmark, where a practically linear five-fold increase in AD use has been observed from 2000 to 2011, with a minor drop in 2005 (16). In both Denmark and Norway, the increase in use of SSRIs over time has been driven by increased use in adolescents, among girls in particular (15, 16). Levels of use in boys and girls were comparable in the two countries. For example, around 10/1000 and 20/1000 of all 17-year-old boys and girls, respectively, had ADs dispensed in 2011. A parallel trend in increasing AD use among adolescents have been observed in the USA and other European countries in the period 2005–2012 (18), and in Canada in the period 2005–2009 (14). It is interesting that an opposite trend has been observed in Iceland, where AD use decreased from 28.3 to 23.4 per 1000 among 0- to 17-year olds in the period 2003–2007, but with the strongest decrease from 2004 to 2005 (26). The level of AD use has, however, been consistently higher in Iceland than in the other Nordic countries, for example, in 2007 1.8/1000 of all boys and 2.6/1000 of all girls aged <18 years were prescribed ADs in Norway; thus, the level in

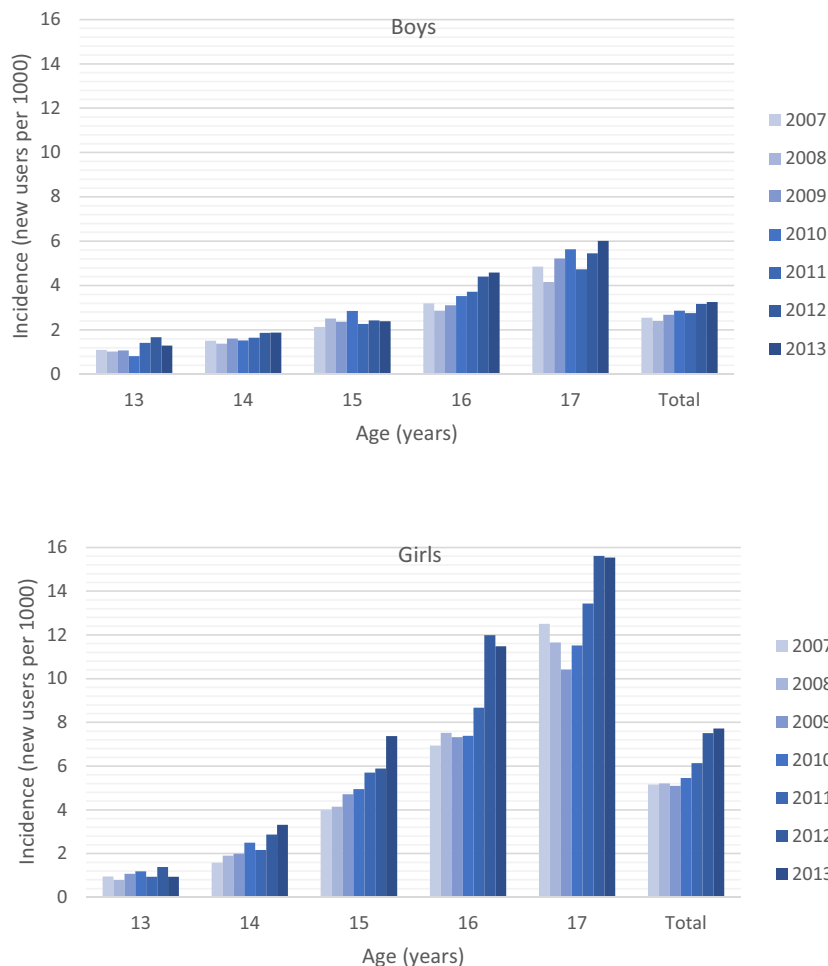


Fig. 4. The 1-year incidence¹ of antidepressant (AD) use in 13- to 17-year olds in the period 2007–2013 in Norway, according to age and gender. ¹Incident use was defined as no ADs dispensed during the 3-year period before the first dispensing in the actual year.

Norway is only about 10% of the level in Iceland (26, 15).

The increase in AD use among adolescents may be attributed to several factors. In 2000 and 2009, the SSRIs sertraline and fluoxetine were approved for use in children and adolescents in Norway, and since then, they have been marketed and included in guidelines for treatment of severe cases of depressive disorders (fluoxetine) and OCD (sertraline). This development paralleled the increase of AD use among the adolescent population observed in the present study.

Since warnings were issued by the regulatory agencies in 2004–2005 (2, 3), new risk–benefit evaluations of pediatric use of SSRIs for depression, OCD, and anxiety disorders have been published. A recent meta-analysis concludes that use of SSRIs in children and adolescents doubles the risk of suicidality and aggression (7). When used in pediatric depressive disorders, a Cochrane review of randomized controlled trials (RCTs) concludes that while the overall reduction in depressive symptoms and relapse is statistically significant, the effects are small and there are still questions about the clinical

effectiveness in children and adolescents (8, 27). Further, because of strict inclusion and exclusion criteria, patients recruited to RCTs may not be representative for all patients presenting for treatment. This makes it difficult to draw any firm conclusions. Even though untreated depression is a strong risk factor for completed suicide and severely impacts on functioning (8), a careful consideration of potential benefits and risk should precede initiation of AD drug-therapy in children and adolescents. AD prescriptions should always be combined with non-pharmacological treatment options, and close follow-up and monitoring of effects and side-effects (8, 11).

In pediatric OCD, both international and national guidelines (10, 12) recommend cognitive behaviour therapy (CBT) as a first-line treatment, with SSRIs (sertraline is licensed and thus recommended as first choice) being an endorsed treatment option where CBT fails or in severe cases (10, 12, 28). Currently published evidence suggests that SSRIs are effective in treating children and young people with severe OCD (28). It is not known whether the same risk of suicidality occurs with

Table 2. Antidepressant (AD) of choice among 13- to 17-year-old incident* users in 2012 in Norway

Substances (ATC code)	First prescription, n (%)
SSRI	
Fluoxetine (N06AB03)	551 (33.1)
Sertraline (N06AB06)	458 (27.5)
Escitalopram (N06AB10)	266 (16.0)
Citalopram (N06AB04)	21 (1.3)
Paroxetine (N06AB05)	10 (0.6)
TCA	
Amitriptyline (N06AA09)	145 (8.7)
Trimipramine (N06AA06)	27 (1.6)
Clomipramine (N06AA04)	6 (0.4)
Nortriptyline (N06AA10)	5 (0.3)
Doxepin (N06AA12)	1 (0.1)
MAO-I	
Moclobemide (N06AG02)	1 (0.1)
Other substances	
Mianserin (N06AX03)	76 (4.6)
Mirtazapine (N06AX11)	69 (4.1)
Venlafaxine (N06AX16)	15 (0.9)
Bupropion (N06AX12)	9 (0.5)
Oxatriptan (N06AX01)	3 (0.2)
Reboxetine (N06AX18)	2 (0.1)
Total	1665 (100)

SSRI, selective serotonin reuptake inhibitor; MAO-I, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

Only the first ADs dispensed in 2012 are included in the table.

*Incident use defined as: no ADs dispensed during the 3-year period before the first dispensing in the actual year.

Table 3. Use of other psychotropic drugs among 13- to 17-year-old incident* antidepressant (AD) users in Norway in 2012 (n = 1665)

Type of psychotropic drug†	Users in 2012, n (%)
Antipsychotics (N05A)	219 (13.2)
Anxiolytics (N05B)	103 (6.2)
Hypnotics/sedatives‡	563 (33.8)
Benzodiazepines (N05CD)	7 (0.4)
z-Hypnotics (N05CF)	98 (5.9)
Melatonin agonists (N05CH)	410 (24.6)
Alimemazine (R06AD01)	194 (11.7)
Stimulants (N06BA)	146 (8.8)

*Incident use: no ADs dispensed during the 3-year period before the first dispensing in the actual year.

†One psychotropic drug dispensed at least once in 2012.

‡Sum of all hypnotics/sedatives >33.8% because of retrieval of more than one group of hypnotic/sedative by same individual.

their use in OCD, but similar adverse reactions cannot be ruled out, and appropriate caution should be observed, especially in the presence of comorbid depression (10, 12).

In Norway, use of SSRIs is approved for use in children and adolescents with moderate/severe depressive illness or OCD, but not anxiety disorders (10). However, in severe cases, an SSRI (sertraline first choice) may be initiated, always in combination with psychosocial interventions. Evidence supports the efficacy of newer ADs in

treating pediatric anxiety disorders, but with a moderate effect size (29).

So, does the observed increase in AD drug use reflect increasing prevalence of indications for their use: moderate/severe depression, anxiety, and OCD? Self-reported mental distress has increased among adolescents in Norway: about 15% of 15- to 16-year olds in one county in Norway reported mental distress in 2001, increasing to 25% in 2009 (30). Still, we do not know whether there has been an increase in severity of depression, OCD, and anxiety in the adolescent population in Norway over time, corresponding to the observed increase in AD use. A recent meta-analysis of studies using standardized diagnostic interviews for DSM-IV disorders among children and adolescents revealed prevalence estimates of any anxiety disorder and any depressive disorder at 6.5% and 2.6% respectively (31). In the interview-based National Comorbidity Survey Replication in the US, lifetime prevalence of severe anxiety disorders and mood disorders were 8.3% and 11.2%, respectively, among 13- to 18-year-old respondents (32). A previous questionnaire-based study of depressive disorders in two counties in Norway found that 2.6% of adolescents reported symptoms that fulfilled diagnostic criteria for a current major depressive disorder and 23% met criteria for lifetime depression (33). Despite an observed increase in AD use, our study shows that <1% of 13- to 17-year-old girls and boys in Norway had an AD dispensed in 2013. Thus, only a small proportion of those assumed to have a disorder with a possible indication for use seems to receive AD drug treatment.

More than four of five new AD users in our study had been referred by their GP to specialist mental healthcare service and were recorded with a diagnosis of mental or behavioural disorders. This supports the assumption that those who are most severely burdened are the ones treated with ADs. In accordance with this, we found that a third of the incident AD users had also been prescribed a hypnotic drug, 13% had been prescribed an antipsychotic, 6% an anxiolytic drug, and 9% a stimulant, a marker of psychiatric comorbidity. Unpublished data from the NPR shows that there has also been an increase in 1-year prevalence of diagnosed depressive disorders among 14- to 18-year olds in the period 2008–2013: from 6.2/1000 to 7.1/1000 of all boys and from 16.5/1000 to 23.0/1000 of all girls (L. J. Hauge, personal communication). Thus, one explanation to the increase in observed AD drug use may be that more adolescents are being referred to specialist mental health care. In parallel, the proportion of adolescents

reporting to seek help for mental health problems has increased (30).

There are only minor gender differences in psychiatric symptoms among preschool children (34). Between 6 and 12 years, two of three children with a diagnosed psychiatric symptoms are boys (35). While the girl : boy ratio increases for symptoms of depression and OCD postpuberty (35). This is reflected in our results which show increasing gender differences in AD use during adolescence, with an overall girl : boy ratio of about one among 13-year olds, increasing to almost three in 17-year olds. Similar gender differences have also been documented in prescription data from Denmark (16).

The type of AD substances used by the adolescents in this study did correspond with the recommendations for AD drug treatment in 9 of 10 new AD users. When drug treatment of depression, OCD, and anxiety is indicated, SSRIs should be considered as first-line treatment (8, 10–12). In the present study, SSRIs were started in almost 80% of all new users. Fluoxetine and sertraline, which are approved and recommended as first choice in depression and OCD, were the first-line choice in 33% and 27%, respectively, of the new users in 2012. Guidelines also suggest that sertraline may be prescribed for severe anxiety disorders in children, which may contribute to its high prevalence of use. If treatment fails, guidelines recommend a switch to another type of SSRI as the first step, and if there is still no response, switch to another class of AD (e.g. venlafaxine) (8, 10–12). Certain symptoms or patterns of comorbidity with the depressive illness may guide the choice of another AD. If there is need for quick response, for example, because of frequent suicidal ideations, citalopram or escitalopram may be the best choice (10). There have, however, been warnings on an increased risk for QT interval prolongation on an ECG with citalopram (36, 37) which may explain the preference for escitalopram observed in the present study. Hence, escitalopram and citalopram were started in 16% and 1% of all new AD users respectively. The SSRI paroxetine was initiated in <1% of new AD users, in agreement with specific warnings directed at this agent and limited evidence supporting its efficacy (38). For severe sleeping difficulties, mirtazapine or mianserin may be tried (10), tentatively, together with other AD treatment. In our study, these substances were started in almost 10% of all new users. Thus, up to 90% of substances of choice in new AD users seem to agree with the recommendations in the guidelines (10, 38). The remaining 10% of first-choice AD substances were TCAs. In parallel, 5–23% of all

0- to 19-year-old AD users were prescribed TCAs in a recent study from five western countries, with variations between the countries (18). According to a recent systematic review from the Cochrane Collaboration, TCAs are of no use in treating depression in young children. There is, however, some evidence to support the use of TCAs in the treatment of severe treatment-resistant depression in adolescents (13–20 years) (39). The percentage using the TCA amitriptyline (8.7%) in the present study may seem high. The drug is also indicated for the use for chronic pain and enuresis nocturna, which also might contribute some to the high percentage.

Strengths and limitations

The NorPD provides age- and gender-specific information on all dispensed ADs prescribed by all practising physicians and covers the whole population of adolescents living in Norway. This approach eliminates the possibility of selection and recall bias, which may be a problem with estimates based on prescribing in general practice only or among selected parts of the population, or on surveys with self-reported drug use. However, there are also some limitations. A major limitation with this study is that beyond the extent to which new AD users have been referred to and diagnosed by the specialist mental health care, no information was available to further assess and conclude on the appropriateness of AD use. Important information in this context would be information on the severity of disease, the extent to which AD drugs are given in combination with non-pharmacological treatment options, and follow-up, which is emphasized by guidelines and thus important in order to assess the appropriateness of drug-therapy.

Further, we do not know whether the dispensed drugs reflect actual drug use and we have no information about drugs administered to hospitalized adolescents. However, in Norway, very few adolescents are in institutions for long periods, and we do not expect this lack of information to substantially influence the estimates of prevalence and incidence.

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