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Title: Antipsychotic prescribing trends among children and adolescents in Denmark: A historical cohort study based on register data

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Institute of Health Science and Technology
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Resume

Baggrund: Siden begyndelsen af 1990'erne er ordinationen af antipsykotika (AP) til børn og unge steget over hele verden, og hyppig off-label ordination af disse lægemidler har givet anledning til bekymringer om sikkerhed og effekt til patienter i denne aldersgruppe. Da der har været begrænsede studier på dette område i Danmark, havde dette studie til formål at undersøge tendenserne i brugen af AP til danske børn og unge i alderen 0-17 år som blev diagnosticeret med én eller flere psykiatriske lidelser i perioden fra 1995 til 2013.

Metode: Data om diagnoser, recepter, alder, køn og regionshospital blev udtaget fra Landspatientregistret, Lægemiddelstatistikregisteret og Det Centrale Personregister. Den mest sandsynlige indikation blev defineret ud fra den eller de diagnoser, de havde fået inden for 6 måneder før eller efter en recept. Behandlingsstop blev defineret som 280 dage uden indløsning af en ny recept. Tendenser blev rapporteret som den årlige periodeprævalens og den kumulative incidens beregnet for hvert år mellem 1995 og 2013. Prævalensestimater blev stratificeret i første- og andengenerations antipsykotika (FGA og SGA), køn, aldersgrupper og region. Incidens blev stratificeret i FGA og SGA. Joinpoint analyse blev udført for at identificere statistisk signifikante ændringer i tendenser. Logistisk regression blev anvendt til at undersøge faktorer associeret med at modtage FGA vs. SGA, behandling vs. ingen behandling og lang vs. kort behandlingsvarighed.

Resultater: Dette studie omfattede 8466 personer, hvoraf 13318 indløste mindst én recept på AP. Blandt dem, der indløste en recept, var 7374 (55,37%) mænd, mens 5944 (44,63%) var kvinder. Fra 1995 til 2013 fordobledes den årlige prævalens fra 4,20% til 8,22%, mens den årlige kumulative incidens faldt fra 4,26% til 2,74%. De hyppigste godkendte indikationer behandlet med AP var psykose (40,35%), affektive sindslidelser (28,09%) og autismespektrumforstyrrelser (18,63%), og de hyppigste ikke-godkendte indikationer var tilpasningsforstyrrelser (21,36%), ADHD (18,78%) og adfærdsforstyrrelser (8,43%). Risperidon (34,61 %) og chlorprothixen (11,07 %) var de hyppigst indløste recepter på tværs af alle indikationer.

Konklusion: Dette studie fandt en stigning af indløste recepter blandt danske børn og unge, særligt i aldersgruppen 13-17. Den kumulative forekomst viste sig at være faldende, hvilket tyder på længere behandlingsperioder. Der blev fundet stigende tendenser for SGA, hvorimod tendenserne for FGA faldt. Off-label brug var hyppig, da AP viste sig at være ordineret til ikke-godkendte indikationer og aldersgrupper.

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Abstract

Background: Since the early 1990s, the prescription of antipsychotics (APs) for children and adolescents has risen worldwide and frequent off-label prescribing of these medications raises concerns about safety and efficacy. Limited data have been available in Denmark, thus the current study aimed to investigate trends in AP use among Danish children and adolescents aged 0-17 diagnosed with a psychiatric disorder.

Methods: This historical cohort study included children and adolescents aged 0-17 who received at least one psychiatric diagnosis at departments of child and adolescent psychiatry in Denmark from January 1, 1995, to December 31, 2013. Data on diagnoses, prescriptions, age, sex, and region were extracted from the National Patient Register, the National Prescription Register, and the Civil Registration System. Indication was defined as the most likely indication, derived from diagnoses received within six months before or after a prescription. Treatment discontinuation was defined as 280 days without redeeming a new prescription. Trends were reported as the annual period prevalence and the cumulative incidence calculated for each year between 1995 and 2013. Prevalence estimates were stratified by first- and second-generation antipsychotics (SGA and FGA), sex, age groups, and region. Incidence was stratified by FGA and SGA. Joinpoint analysis was conducted to identify statistically significant changes in trends. Logistic regression was used to explore the odds for receiving SGA vs FGA, treatment vs no treatment, and longer vs shorter treatment duration.

Results: This study included 8466 individuals, of whom 13318 individuals redeemed an AP prescription. Among those redeeming an AP prescription 7374(55.37%) were males while 5944(44.63%) were females. From 1995 to 2013, the annual prevalence doubled from 4.20% to 8.22%, while the annual cumulative incidence decreased from 4.26% to 2.58%. Most common approved indications treated with APs were psychosis (40.35%), affective disorder (28.09%), and autism spectrum disorders (18.63%), and most common un-approved indications were adjustment disorder (21.36%), ADHD (18.78%), and conduct disorder (8.43%). Risperidone (34.61%) and chlorprothixene (11.07%) were the most commonly redeemed prescriptions across all indications.

Conclusion: This study found increased redeemed AP prescriptions among Danish children and adolescents, especially in ages 13-17. The cumulative incidence was found to be decreasing, suggesting longer treatment periods. Increasing trends were found for SGAs, whereas FGAs decreased. Off-label prescription was common, as APs were found to be prescribed for un-approved indications and age groups.

1. Introduction

The prescribing of antipsychotic (AP) medication in children and adolescents has increased worldwide over the past two decades, as seen across Europe, the United States (US), Australia, and New Zealand (Barczyk et al., 2020; Chen, S. et al., 2021; Chen, W. et al., 2018; Radojčić et al., 2023). A comprehensive retrospective cohort on up-to-date trends in AP prescribing for children and adolescents in the United Kingdom (UK) showed that prescriptions of AP medication doubled in the period 2000 to 2019 (Radojčić et al., 2023). A similar study found a slight rise in both first- and second-generation AP (SGAs and FGA) use in the years 2011 to 2020 in Germany (Dörks et al., 2023). In addition, a study done by Kalverdijk et al., 2017 for the calendar years 2005 to 2009 for all children and adolescents in the population aged 0-19 showed, that the prevalence of AP use increased from 0.78 to 1.03% in the Netherlands, from 0.26 to 0.48% in Denmark, from 0.23 to 0.32% in Germany, and from 0.10% to 0.14% in the United Kingdom. This rise in prescribing coincides with the introduction of SGAs in the 1990s, which is suggested to account for the overall increase in AP prescribing (Ronsley et al., 2012). It is proposed this has to do with the milder side effect profile compared to FGAs, as SGAs carry a lower risk of extrapyramidal symptoms (Campbell et al., 1999; Cortese et al., 1998). However, SGAs are associated with metabolic abnormalities such as weight gain, and risperidone and paliperidone, in particular, have been tied to heightened prolactin levels (Bostwick et al., 2009; Shirzadi & S Nassir, 1999). All current APs act on dopamine 2-receptors in the brain which reduces the intensity of psychotic episodes, thus the choice of medication is highly influenced by the patient's tolerance and sensitivity towards potential side effects (Ginovart & Kapur, 2012). In the pediatric population, APs have been approved for acute psychotic episodes and psychiatric disorders including schizophrenia, bipolar mania, irritability associated with autistic disorder, and Tourette syndrome by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Crystal et al., 2010; Pathak et al., 2010). For children and adolescents under the age of 13, aggression in mental retardation is the only approved indication in Denmark (Medicinrådet, 2022). However, results from studies (Cooper et al., ; Daviss et al., 2016a; Ronsley et al., 2012) suggest that APs are more frequently prescribed for a wider range of mental health conditions such as attention-deficit hyperkinetic disorder (ADHD), conduct disorders, depression, and anxiety which are not approved indications by the FDA or EMA. This renders the vast majority of AP prescribing for children and adolescents off-label. A Danish nation-wide register-based study (Højlund et al., 2021) identified a highly prevalent off-label use of APs among all individuals filling a prescription in 2018, as 37% did not have diagnoses approved for AP use. However, individuals in

all age groups were included, hence the results for the population of children and adolescents were unclear. In general, the lack of pediatric assessment during drug development processes raises concern about children's physical and psychological development in especially very young children, as APs are associated with severe side effects and unknown effects on the developing brain (Daviss et al., 2016b).

To date, there is limited published data on trends for children and adolescents in Denmark, and current data is limited by small sample sizes and lack of evaluation of off-label prescribing (Aagaard & Kornø, 2018; Kaguelidou et al., 2020; Steinhausen & Bisgaard, 2013). Therefore, this study aimed to examine trends in redeemed AP prescriptions, this included treatment duration, dosage, and off-label prescribing, among children and adolescents aged 0-17 who received at least one psychiatric diagnosis in Denmark from 1995 to 2013.

2. Method

2.1 Study population and setting

This historical register-based cohort study included children and adolescents aged 0-17 who received at least one psychiatric diagnosis at the departments of child and adolescent psychiatry at the regional hospitals in Denmark between 1995-2013, according to the International Classification of Diseases, 10th Revision (ICD-10). Data on ICD-10 diagnoses, and the regional hospital where they received their first psychiatric diagnosis, were provided from the National Patient Register (NPR) (Lynge et al., 2011). In the present study, the region where the regional hospital was located was considered their place of residence. Diagnoses included F10-F19 (substance use disorders), F20-F29 (psychotic disorders), F30-F39 (affective disorders), F40 and F41 (anxiety disorders), F42 (obsessive-compulsive disorders (OCD)), F43 (adjustment disorders), F50 (eating disorders), F70 (intellectual disability), F84 (autism spectrum disorders), F90 and F98.8 (attention deficit hyperactivity disorder (ADHD)), F91 and F92 (conduct disorders), F93 (emotional disorders), and F95 (tic disorders). Transition to adult psychiatry, and thus the exiting of the cohort, occurred at age 18. Furthermore, individuals diagnosed in the psychiatric emergency department were excluded. Figure 1 illustrates the annual entry and exit of children and adolescents in the cohort at the time of initial diagnosis at the age of 18 throughout the study period (Figure 1).

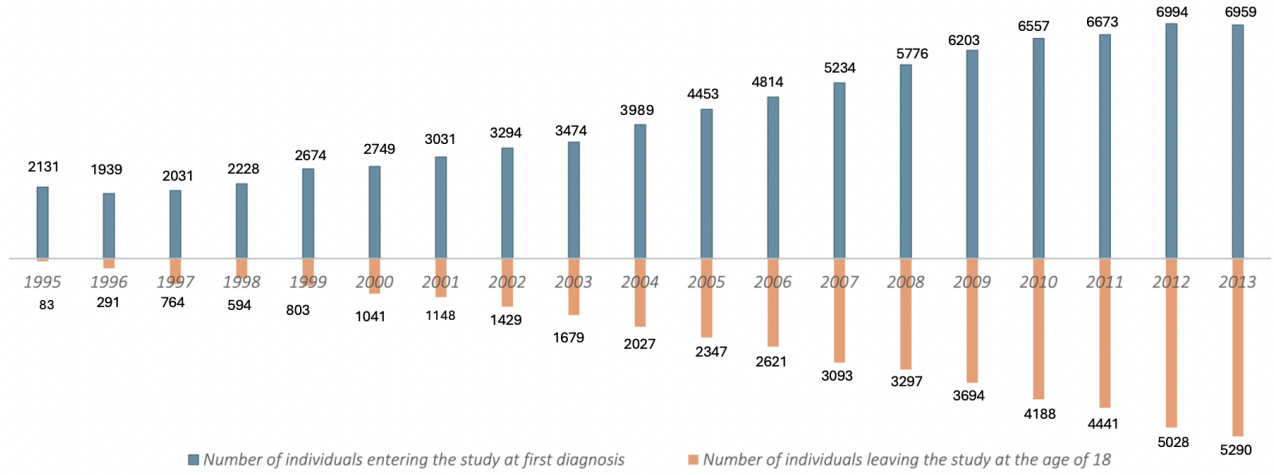

***Figure 1*: Timeline of children and adolescents aged 0-17 entering the cohort upon receiving their initial diagnosis, and exiting at the age of 18 in the period 1995-2013**

2.2 Defining antipsychotic use

Antipsychotic medications were defined in accordance with the World Health Organization classification system – the Anatomical Therapeutic Chemical Classification group N05A, except for Lithium (N05A01). Data on redeemed prescriptions from Danish pharmacies, including date of completed dispensing and product code of the product dispensed, were provided from the Danish National Prescription Register (DNPR) (Pottegård et al., 2016). Due to the absence of information on prescription duration, termination of use was defined as occurring when a patient did not redeem a new prescription within 100 days, plus an additional 180-day grace period, since patients typically receive a supply for three months at a time (Pottegård et al., 2016). All prescriptions redeemed after this period were considered the start of a new treatment period.

As the indications for prescriptions were not provided from the registries, indication was defined as the patient's most likely diagnosis associated with receiving an AP medication.
Potential diagnoses were identified in individuals' records occurring within 6 months before or after the incident prescription. If the individual had multiple approved diagnoses within this period, the indications were given following a hierarchy developed in collaboration with a psychiatrist (Appendix T1). Individuals with multiple un-approved indications were grouped together as "individuals with several un-approved diagnoses" due to challenges of determining a prioritized order for such diagnoses. Consequently, they were excluded from subsequent analyses. Individuals who had just one un-approved diagnosis within 6 months before or after the incident prescription were

assigned that diagnosis as their indication. The identification of individuals across different registries and the linking of information between them was facilitated by the Civil Personal Registration Number (CPR number), which is a unique identifier assigned to individuals at birth or immigration. The CPR-register provided information on sex and the year and month of birth (Bøcker, 2010).

2.3 Statistical analysis

Descriptive statistics were used to describe demographic and clinical information about the study population, including year of birth, sex, diagnosis at discharge, and region. The annual period prevalence of all, FGAs, and SGAs prescriptions redeemed for each calendar year from 1995 to 2013 was determined by the number of individuals receiving an AP prescription within a calendar year, divided by the total population in the cohort for that respective year. The annual period prevalence was stratified by age group (0-6, 7-12, 13-17), sex, and region. The cumulative incidence for all, FGAs, and SGAs prescriptions redeemed was calculated as the number of new individuals receiving an AP prescription within a calendar year, divided by the total population at risk in the cohort at the beginning of the year that did not have a prescription. Antipsychotic medication was described as the total number of prescriptions for each medication in the study period, and the number of individuals with a prescription divided into FGA and SGA, reported as frequencies and percentages. Most likely indications were separated into approved and un-approved indications, and for each category frequencies and percentages were reported stratified by sex and age group (0-12, 13-17).

For each indication, the four most redeemed medications were reported. For each of these medications, the number of individuals receiving the medication and the dosage summarized as the median and interquartile ranges were reported.

The duration of drug use for each medication was stratified by age group (0-6, 7-12, 13-17) and reported as number of days and the number of individuals in each age group expressed as median and interquartile ranges. Treatment duration was calculated from the time between the first and last redeemed prescriptions. If more than 280 days passed before a new prescription was redeemed, treatment was considered discontinued on the day of the last redeemed prescription. An additional 100 days were then added to account for the duration of the length of the last redeemed prescription. Individuals remained in the age group where they redeemed their first prescription, even if they aged into a different age group during the treatment period.

Trend changes in annual period prevalence and incidence of redeemed AP prescriptions from 1995 to 2013 were analyzed using joinpoint regression models. The Monte Carlo permutation test

estimated the optimal number of joinpoints, whereby statistically significant changes in (log) outcome trend were identified as well as the average annual change over a specific time frame.

For binary outcome variables, logistic regression was used to examine 1) the likelihood of receiving FGA compared to SGA 2) the likelihood of receiving treatment with APs or not, and 3) the likelihood for longer compared to shorter treatment duration with a cut off value of 595 days (calculated as the median duration of the first treatment period). Independent variables were age group (0-6, 7-12, 13-17), drug, region and most likely indication reported as non-adjusted and adjusted for the covariates age group, sex, and region. A p-value of 0.05 was considered statistically significant.

Sensitivity analysis was conducted to assess the extent to which changes in the cut-off value altered the odd ratios when comparing shorter to longer treatment duration. This was done by calculating the mean of Q1 and Q3 for the duration of all APs in the first treatment period.

2.4 Statistical software

Stata 18.0, Joinpoint Trend Analysis Software (version 5.1.0), and Microsoft Excel (version 16.84) were used for statistical analyses.

2.5 Ethical approvals

According to Danish law, ethical review and approval of purely register-based studies are not needed (Højlund et al., 2021).

3. Results

Between January 1, 1995, and December 31., 2013, a total of 86466 children and adolescents were diagnosed with at least one psychiatric disorder according to the ICD-10 criteria, of whom 13318, accounting for 15.40% of the study population, redeemed at least one AP prescription. Median age at first diagnosis and first redeemed prescription were 12.38 years (IQR 8.36-15.45), and 15.41 years (IQR: 12.84-16.82), respectively. Of those with an AP prescription, 44.63% were females, and 55.37% were males. In total, 206150 prescriptions were identified with a median number of 7 (IQR 2-20) prescriptions per individual.

The top four diagnostic categories with the highest proportions of individuals redeeming an AP prescription were psychotic disorders (52.87%), substance use disorders (40.90%), anxiety disorders (23.11%) and OCD (22.58%). The Capital Region of Denmark had the highest proportion of children and adolescents redeeming an AP prescription at 17.64%, whereas the Central Region Denmark had the lowest proportion at 12.71% (table 1).

	Study sample [a] **(n= 86466)**	**Individuals with an antipsychotic prescription** [b] **(n= 13318)**
Year of birth		
1977-1982	4029 (4.60%)	5 563 (13.97%)
1983-1988	12397 (14.35%)	2 2077 (16.75%)
1989-1994	25575 (29.60%)	5 5118 (20%)
1995-2000	28695 (33.21%)	4 4577 (15.95%)
2001-2006	13636 (15.78%)	9 949 (6.96%)
2007-2013	2134 (2.47%)	3 34 (1.60%)
Sex		
Male	49361 (57.09%)	7374 (14.93%)
Female	37105 (42.91%)	5944 (16.01%)
Approved diagnosis at discharge [c]		
Psychotic disorders	8169 (9.45%)	4319 (52.87%)
Affective disorders	17283 (20.0%)	4326 (25.03%)
Autism spectrum disorder	22881 (26.46%)	3630 (15.86%)
Tic disorders	4264 (4.31%)	1429 (33.51%)
Substance use disorders	5518 (6.38%)	2257 (40.90%)
Un-approved diagnosis at discharge [c]		
Adjustment disorders	23016 (26.61%)	4242 (18.43%)
Attention deficit hyperactivity disorders	31966 (36.97%)	4858 (15.20%)
Conduct disorders	10227 (11.89%)	2118 (20.71%)
Eating disorders	7737 (8.95%)	1111 (14.36%)
Anxiety disorders	8521 (9.85%)	1969 (23.11%)
Obsessive-compulsive disorders	6644 (7.68%)	1500 (22.58%)
Emotional disorders	6586 (7.62%)	926 (14.06%)
Intellectual disability disorders	6413 (7.42%)	1313 (20.47%)
Regional hospital [d]		
The North Denmark Region	5260 (6.11%)	872 (16.57%)
Central Denmark Region	18416 (21.38%)	2341 (12.71%)
The region of Southern Denmark	22762 (26.42%)	3265 (14.34%)
The Region Zealand	17388 (20.18%)	2883 (16.58)
The Capital Region of Denmark	22319 (25.91%)	3936 (17.64%)

Table 1: Demographic- and clinical characteristics of children and adolescents who were diagnosed with at least one psychiatric disorder, and the proportion who dispensed an antipsychotic prescription in Denmark 1995-2013
Data shown as n (%). [a] Column percentage. [b] Row percentages. [c] Individuals who have received multiple discharge diagnoses during the study period appear in several diagnostic categories. [d] The hospital region where they received their first admission. There were 321 missing values for the hospital region among the study sample, 21 of which were for individuals with an antipsychotic prescription.

3.1 Trends in antipsychotic use in general

Prevalence estimates

The annual prevalence of individuals who filled an AP prescription increased from 4.20% in 1995 to 8.22% in 2013 (figure 2a). Between 1995 and 2009, there was one distinct trend identified by joinpoint analysis, with an average percentage change (APC) of 4.98% (appendix F1a).
The annual prevalence of individuals receiving FGAs decreased from 4.16% in 1995 to 1.22% in 2013, while it increased for SGAs from 0.03% to 5.98% (figure 2b). Joinpoint analysis identified three periods for individuals redeeming FGA prescriptions: a rise from 1995 to 1997 (APC 19.40%), a fall from 1997 to 2000 (APC -18.98%), and a fall again from 2000 to 2013 (APC -6.18%) (appendix F1c). For SGAs, joinpoint analysis identified three periods with increases from 1995 to 1997 (APC 228.83%), 1997 to 2000 (APC 65.02), and 2000 to 2005 (APC 26.87%) (appendix F1d). In 2002, there was a change in tendency, where the number of redeemed SGA prescriptions exceeded the number of redeemed FGA prescriptions (figure 2b).

Incidence estimates

Incidence rate for first-time prescriptions was one per 56 person-years. There was a decrease in the annual cumulative incidence from 4.26% in 1995 to 2.74% in 2013 (figure 2 a). Joinpoint analysis identified a fall from 1995 to 2000 (APC -11.63), followed by a rise from 2000 to 2003 (APC 14.26%), and a fall again from 2010 to 2013 (APC -9.20) (appendix F1b).
The cumulative incidence for individuals receiving SGAs increased from 0.07% in 1995 to 1.78 % in 2013, while it decreased for FGAs from 4.19% in 1995 to 0.86% in 2013 (figure 2c). Joinpoint analysis identified two distinct trends for SGAs 1995 to 1999 (APC 100.30%) and 1999 to 2003 (APC 32.20%) (appendix F1e). One distinct trend was identified for FGAs from 1995 to 2011 (APC 7.47%) (appendix F1f).

Stratification by age group showed that the increase in individuals who filled an AP prescription mainly affected individuals aged 13 to 17, whereas it remained unchanged for individuals in the age groups 0 to 6 and 7 to 12. Especially for the youngest group, it remained low at < 0.5% (Figure 2d). Generally, males consistently had a 50-100% higher annual prevalence compared to females (Figure 2e). For all regions, the trend for annual prevalence of AP prescriptions remained unchanged, except for the Region of Southern Denmark and The Capital Region where the prevalence doubled from 1995 to 2013 (figure 2f).

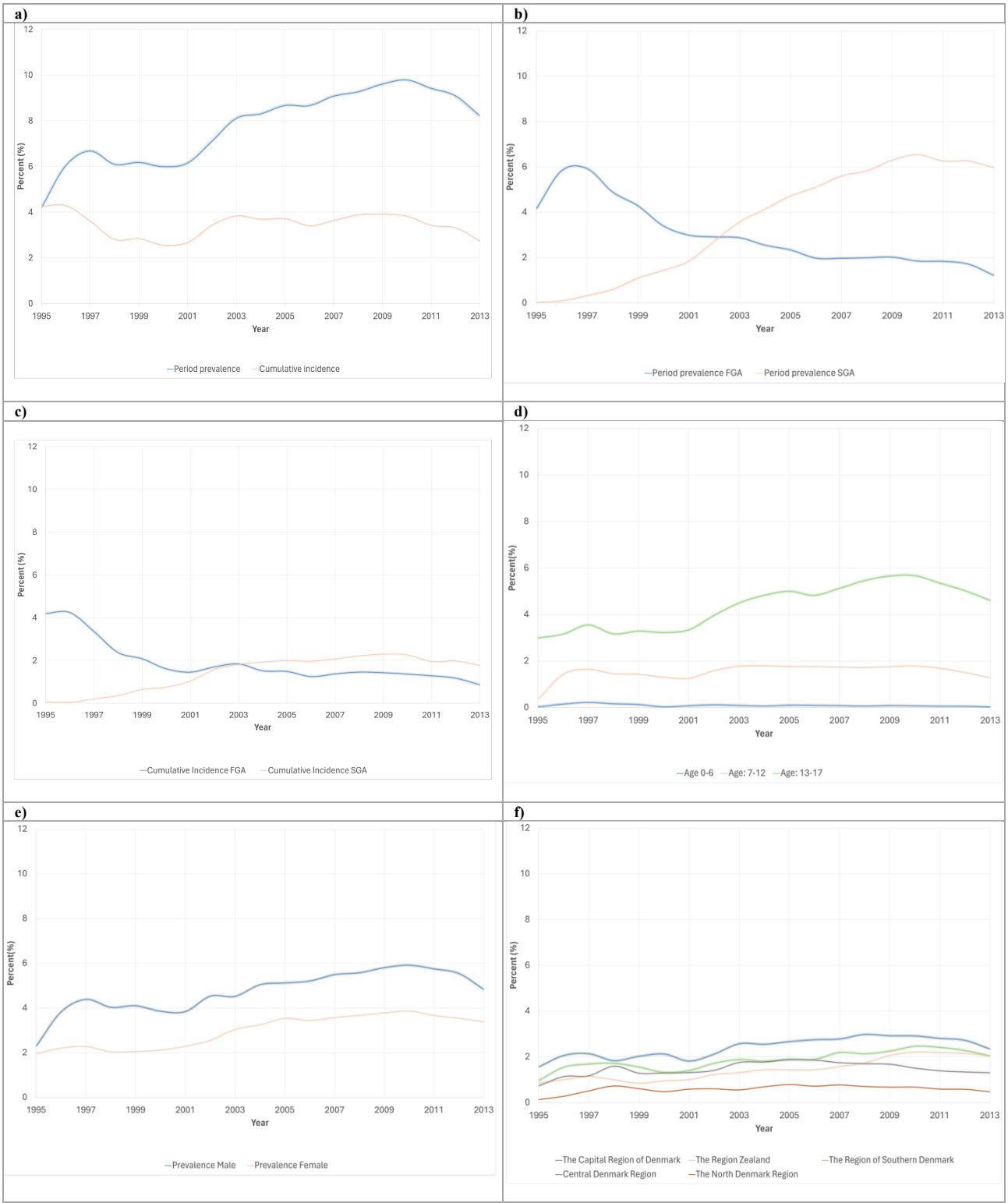

Figure 2: Trends in antipsychotic prescribing to children and adolescents in Denmark in 1995 to 2013, expressed as the annual percentage of the study population who redeemed an antipsychotic prescription

a) The annual period prevalence and cumulative incidence b) Period prevalence for FGAs and SGAs c) Cumulative incidence of FGAs and SGAs d) Period prevalences for age groups e) Period prevalences for males and females f) Period prevalences for regions

FGA = first generation antipsychotic. SGA = second generation antipsychotic.

A total of 30 different APs were identified, with 17 classified as FGAs and 13 classified as SGAs. In the study period, the four most redeemed FGAs were chlorprothixene (11.07%), pimozide (4.54%), levomepromazine (2.68%), and zuclopenthixol (1.45%). For SGAs, it was risperidone (34.61%), quetiapine (15.90%), aripiprazole (14.94%) and olanzapine (8.00%) (Table 2).

	Number of prescriptions (n= 206150)	**Number of individuals with a prescription (n= 23322)**
FGA		
Chlorprothixene	22822 (11.07%)	5981 (25.65%)
Pimozide	9362 (4.54%)	641 (2.75%)
Levomepromazine	5530 (2.68%)	912 (10.36%)
Zuclopenthixol	2994 (1.45%)	421 (1.81%)
Perphenazine	1514 (0.73%)	208 (0.89%)
Flupentixol	853 (0.41%)	252 (1.08%)
Haloperidol	716 (0.35%)	123 (0.53%)
Droperidol	28 (0.01%)	43 (0.18%)
Pipamperone	575 (0.28%)	43 (0.18%)
Periciazine	522 (0.25%)	73 (0.31%)
Thioridazine	223 (0.11%)	32 (0.14%)
Fluphenazine	127 (0.06%)	20 (0.09%)
Prochlorperazine	108 (0.05%)	17 (0.07%)
Chlorpromazine	52 (0.02%)	21 (0.09%)
Penfluridol	23 (0.01%)	8 (0.03%)
SGA		
Risperidone	71353 (34.61%)	5003 (21.45%)
Quetiapine	32783 (15.90%)	3625 (15.54%)
Aripiprazole	30805 (14.94%)	2835 (12.16%)
Olanzapine	16471 (8.00%)	1955 (8.38%)
Ziprasidone	5103 (2.48%)	437 (1.87%)
Amisulpride	479 (0.23%)	377 (1.62%)
Clozapine	1182 (0.57%)	109 (0.47%)
Paliperidone	356 (0.17%)	47 (0.20%)
Sertindole	263 (0.13%)	49 (0.21%)
Melperone	231 (0.11%)	42 (0.18%)
Sulpiride	1675 (0.81%)	377 (1.62%)
Both		
		307 (1.32%)

Table 2: Number of prescriptions per antipsychotic drug in the years between 1995 and 2013
Data shown as n (%). [a] Column percentage. Individuals with multiple prescriptions were counted more than once. 307 individuals received both FGA and SGA prescriptions. Promazine, acepromazine, asenapine, and lurasidone are not reported in the table due to low frequencies.
FGA = first generation antipsychotics. SGA = second generation antipsychotics.

3.2. Approved indications for antipsychotic use

In total, 6806 individuals received an approved indication for their first redeemed AP prescription. Psychotic disorders were the most common indication, accounting for 40.35% of cases, while tic disorders were the least frequent indication at 5.20%. The majority of individuals who received an indication in all categories were males, except for psychotic disorders and affective disorders where the majority were females at 53.51% and 64.48%, respectively. Most individuals were aged 13 to 17 when they received their initial indication, except for tic disorders and autism spectrum disorders, where most were aged 0-12 at 69.10% and 53.39% (Table 3).

	Total (n= 6806) [a]	**Sex** [b]		**Age groups** [b]	
Indication		**Females**	**Males**	**0-12 years** [c]	**13-17 years**
Psychotic disorders	2746 (40.35%)	1469 (53.51%)	1277 (46.49%)	251 (9.14%)	2495 (90.86%)
Affective disorders [d]	1912 (28.09%)	1233 (64.48%)	679 (35.52%)	150 (7.85%)	1762 (92.15%)
Autism spectrum disorders	1268 (18.63%)	293 (23.11%)	975 (76.89%)	677 (53.39%)	591 (46.61%)
Tic disorders	356 (5.20%)	60 (16.85%)	296 (83.15%)	246 (69.10%)	110 (30.90%)
Substance use disorders [d]	524 (7.70%)	193 (36.83%)	331 (63.17%)	NO	524 (100%)

Table 3: Most likely indications for first antipsychotic prescriptions (approved indications)
Data shown as n (%). [a] column percentage. [b] row percentage. [c] the age groups 0-6 and 0-12 were merged to avoid low frequencies. [d] Approved for adolescents and adults above the age of 18

3.3. Un-approved indications for antipsychotic use

In total, 2444 individuals received an un-approved diagnosis for their first redeemed AP prescription. Adjustment disorders and ADHD were the most common indications at around 20% each. Intellectual disability disorders were the least frequent indication at 1.80%. The majority who received an indication in all diagnosis categories were females, except for ADHD, conduct disorders and intellectual disability disorders, where the majority were males. Most individuals were aged 13 to 17 when they received their first un-approved indication for all un-approved indications (Table 4).

	Total (n=2444)[a]	Sex[b]		Age groups[b]	
Indication		**Female**	**Males**	**0-12 years** [c]	**13-18 years**
Adjustment disorders	522 (21.36%)	352 (67.43%)	170 (32.57%)	26 (4.98%)	496 (95.02%)
Atten deficit hyperactivity disorders	459 (18.78%)	132 (28.76%)	327 (71.24%)	157 (34.20%)	302 (65.80%)
Conduct disorders	206 (8.43%)	75 (36.41%)	131 (63.59%)	63 (30.58%)	143 (69.42%)
Eating disorders	165 (6.75%)	154 (93.33%)	11 (6.67%)	13 (7.88%)	152 (92.12%)
Anxiety disorders	146 (5.97)	82 (56.16%)	64 (43.84%)	17 (11.64%)	129 (88.36%)
Obsessive compulsive disorders	138 (5.65%)	74 (53.62%)	64 (46.38%)	38 (27.54%)	100 (72.46%)
Emotional disorder	50 (2.05%)	32 (64%)	18 (36.00%)	19 (38.00%)	31 (62.00%)
Intellectual disability	44 (1.80%)	17 (38.64%)	27 (61.36%)	12 (27.27%)	32 (72.72%)
Individuals with several un-approved disorders	714 (29.21%)	-	-	-	-

Table 4: Most likely indications for first antipsychotic prescriptions (un-approved indications)
Data shown as n (%). [a] Column percentage. [b] row percentage. [c] The age groups 0-6 and 0-12 were merged to avoid low frequencies.

3.4 Median dosage for the four most redeemed antipsychotic drugs per approved indication for antipsychotic use

For all approved indications, chlorprothixene, risperidone, and quetiapine were among the top four most redeemed APs, except for individuals diagnosed with tic disorder, who did not receive quetiapine as their top four. Only for tic disorders, pimozide was among the top four. The order in which APs were redeemed most frequently varied in each diagnostic category.

Generally, the median dosage did not vary across diagnostic categories. However, median dosage for risperidone were higher for individuals who were diagnosed with psychotic- or substance use disorders at 1 mg (IQR: 0.5, 1), compared to individuals in other approved indication categories, who typically redeemed a median dosage of 0.5 mg (IQR: 0.5, 1) (appendix T2).

3.5 Median dosage for the four most redeemed antipsychotic drugs per un-approved indication for antipsychotic use

The most redeemed AP drugs across all categories for un-approved indications were risperidone, chlorprothixene and quetiapine, with the expectation of individuals with eating disorders, who did not receive quetiapine as their top four. The order in which APs were redeemed most frequently, varied within diagnostic categories, as did median dosages: individuals diagnosed with ADHD, anxiety disorders, emotional disorders, and OCD typically received a median dosage of 0.5 mg (IQR: 0.5, 1) of risperidone, whereas individuals diagnosed with adjustment disorders, conduct disorders, eating and intellectual disorders received a median dosage of 1 mg (IQR: 0.5, 1). For individuals

diagnosed with ADHD, the median dosage for aripiprazole was 5 mg (IQR: 1, 5) and for individuals diagnosed with OCD it was 1 mg (IQR: 1, 5). Levomepromazine was redeemed at a median dosage of 5 mg (IQR: 5, 5) for individuals with adjustment and anxiety disorders, 10 mg (IQR: 5, 25) for intellectual disorders, and 25 mg (IQR: 5, 25) for conduct disorders (appendix T3).

3.6 Treatment duration stratified in age group

Table 6 presents median durations for each AP drug in the first period. The median treatment duration of the top four most redeemed FGAs, stratified in age groups, was between 291 (IQR: 615.5, 1134.5) days and 2449 (IQRL: 1515, 2991) days. For SGAs it was 429.5 (IQR: 299.5, 3029) days and 2296 (IQR: 1032, 2887) days. The longest median duration was 2501 (IQR: 1383, 2793) days for haloperidol in the age group 7-12, whereas the shortest median duration was for prochlorperazine at 100 (IQR: 100, 2290) days in the 7-12 age group. Adolescents aged 13-17 had the lowest treatment duration applicable to all medications, except for pipamperone, compared to children aged 0-12.

	Age: 0-6 **Duration (days*)/Number of children)**		**Age: 7-12** **Duration(days*)/Number of children**		**Age: 13-17** **Duration(days*)/Number of children**	
Drug type	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**	**n**
FGA						
Chlorprothixene	703 (281, 2383)	85	720 (156, 2249)	943	373 (101,771)	4953
Pimozide	1410 (275.5, 2974)	40	1238 (389, 2539)	393	291 (615.5, 1134.5)	208
Levomepromazine	816 (281,2776)	42	1294 (231, 2596)	181	492 (165,932)	689
Zuclopenthixol	-	<5	2449 (1515,2991)	47	595.5 (244.5, 956)	372
Flupentixol	-	<5	664 (184, 2469)	27	322.5 (105, 721)	222
Perphenazine	NO	NO	2081 (1048, 2114)	18	573 (310, 1025)	190
Periciazine	-	<5	2223 (1448, 3100)	13	568 (219, 1050)	59
Haloperidol	195 (151. 321)	7	2501 (1383, 2793)	25	702 (214, 1401)	91
Pipamperone	-	<5	797 (445, 2606)	9	910 (177, 1318)	31
Chlorpromazine	-	<5	-	<5	141 (100, 741)	16
Thioridazine	NO	NO	-	<5	844 (524, 1103)	30
Prochlorperazine	NO	NO	100 (100, 2290)	6	357 (100, 672)	11
Fluphenazine	NO	NO	-	<5	619 (318, 1571)	19
Penfluridol	NO	NO	NO	NO	381.5 (172.5, 582)	8
SGA						
Risperidone	1111.5 (372, 2448)	238	1000 (317, 2201)	1971	561 (245, 1025)	2794

Quetiapine	1035.5 (155,2438)	30	1355 (512, 2516)	457	506 (240, 901)	3138
Aripiprazole	1272.5 (371.5,3029)	92	1151 (436,2178)	895	656 (329.5, 1115.5)	1848
Olanzapine	429.5 (299.5, 2833)	12	1533.5 (322, 2628.5)	232	576 (256, 981)	1711
Sulpiride	NO	NO	1416 (375, 2361)	37	456.5 (224.5, 846)	340
Ziprasidone	-	<5	2296 (1032, 2887)	195	760 (426.5, 1265.5)	328
Amisulpride	NO	NO	-	<5	885.5 (492.5, 1272)	80
Melperone	-	<5	-	<5	735.5 (268, 1219)	38
Clozapine	NO	NO	1817 (509, 3711)	<5	832.5 (524, 1255)	106
Paliperidone	-	<5	1141 (231, 1817)	9	857 (541, 1297)	37

Table 6: Treatment duration of antipsychotic use stratified in age groups shown as median and interquartile ranges
*An additional 100 days were added to the day of the last redeemed prescription. Promazine, acepromazine, asenapine, and lurasidone are not reported in the table due to low frequencies. NO = No observations

3.7 Multivariate logistic regression for factors associated with receiving antipsychotics

Appendix T4 presents odds ratios (OR) for receiving AP prescriptions, with sex, age group, and diagnosis as independent variables. Females had slightly higher odds for receiving an AP prescription compared to males (unadjusted OR (uOR) 1.09; 95% CI 1.05-1.13). The odds for receiving APs were over twice as high for individuals in the age group 13-17 compared to the age group 0-6 (uOR 2.30; 95% CI 1.21-2.44). Individuals in The Capital Region of Denmark had slightly higher odds compared to all other regions. Individuals with each approved diagnosis were more likely to receive treatment compared to those who had other diagnoses, especially those who were diagnosed with psychotic disorders (aOR 7.61 95 % CI 7.24-8.01), tic disorder (aOR 5.35 95 % CI 4.84-5.90), and substance use disorders (aOR 4.98 95 % CI 4.49-5.52). Similarly, individuals with each of the un-approved diagnoses were more likely to receive a prescription compared to those with other diagnoses, except for eating disorders (aOR 0.64 95% 0.56-0.74).

3.8 Multivariate logistic regression for factors associated with antipsychotic use of FGAs and SGAs

Appendix T5 presents ORs comparing individuals redeeming SGAs versus FGAs, with sex, age group, region and first indication as independent variables. Females had lower odds for receiving FGAs than SGAs compared to males (uOR 0.76 95% CI 0.71-0.82). Individuals aged 13-17 were less likely to receive FGAs than SGAs compared to those aged 0-6 (uOR 0.57 95% CI 0.45-0.72). Individuals in The Capital Region of Denmark had lower odds for receiving FGAs than SGAs compared to all other regions. For approved indications, psychotic disorder, tic disorders, and autism spectrum disorder were more likely to redeem a prescription for FGA, while individuals with substance use disorder and affective disorder were less likely to redeem a prescription with FGAs

than SGA. Approved indications did impact the likelihood for redeeming FGAs rather than SGAs but for un-approved indications, individuals were less likely to receive FGAs than SGAs compared to individuals with other diagnoses, except for conduct disorders (aOR 1.33 95 % CI 1.04-1.71).

3.9 Multivariate logistic regression for factors associated with treatment duration of antipsychotic drugs

Appendix T6 presents the ORs comparing the duration of treatment periods – either longer or shorter than 571 days – with age group, sex, diagnosis, and the seven most redeemed AP drugs as independent variables. Females had a decreased odds for being treated long term compared to males (uOR 0.80 95% CI 0.75-0.83). Individuals aged 13-17 had lower odds for being treated long term compared to those aged 0-6 (uOR 0.45 95% CI 0.35-0.57). Additionally, individuals in The Region Zealand had slightly reduced odds for being treated long term compared to those in The Capital Region of Denmark (aOR 0.90 95% CI 0.81-0.99). Among individuals with an approved diagnosis, those with psychotic disorders, tic disorder and autism spectrum disorders had higher odds for being treated long term, while individuals diagnosed with affective disorders and substance use disorders had lower odds for being treated long term. Individuals with un-approved indications had consistently reduced odds for long term treatment. For each of the 7 most redeemed APs, the odds were higher for long term treatment compared to all other APs, except for those who redeemed chlorprothixene and levomepromazine. There was no difference in aOR for quetiapine. Sensitivity analysis showed that altering the cut off value to a median of 717 days did not change the ORs (Appendix T7)

4. Discussion

This register-based study examined trends in AP prescribing to children and adolescents aged 0-17 who were diagnosed with a psychiatric disorder in Denmark in the period between 1995 and 2013. Furthermore, this study aimed to address off-label prescribing. During the study period, the prescription of APs nearly doubled with an annual prevalence of 4.20% in 1995 to 8.22% in 2013. The annual cumulative incidence decreased from 4.26% in 1995 to 2.58% in 2013. The most common approved indications managed with APs were psychosis (40.35%), affective disorder (28.09%), and autism spectrum disorders (18.63%), and the most common un-approved indications were adjustment disorder (21.36%), ADHD (18.78%), and conduct disorders (8.43%). The most frequently redeemed FGA prescriptions were chlorprothixene (11.07%), pimozide (4.54%), levomepromazine (2.68%),

and most redeemed SGA prescriptions were risperidone (34.61%), quetiapine (15.90%), and aripiprazole (14.94%).

4.1 Trends in prevalences and incidences in AP prescriptions among children and adolescents

The increase in prevalence found in this study was comparable to that reported by Radojčić et. al. who identified an annual prevalence of 6% in the UK in the year 2000, consistent with the findings of the present study. By 2013, the prevalence had risen to approximately 10% in both the UK and Denmark. However, the incidence decreased in Denmark, while it had a slight increase in the UK, indicating that the incidence did not follow the same trend as the prevalence. These findings suggest that the rise in annual prevalence was not driven by a rise in new AP prescriptions but rather point to a trend towards longer treatment durations. The results highlight the need for more comprehensive information on the long-term safety of AP use for children and adolescents, as current knowledge for these groups remained limited.

The present study found that the cumulative incidence of FGA prescriptions decreased 5-fold, while the cumulative incidence of SGA prescriptions increased 24-fold during the study period. Notably, the annual prevalence of SGAs prescriptions surpassed FGA prescriptions in 2002, reflecting trends observed by Radojčić et. al, where SGA prevalence exceeded FGA prevalence in 2000. The emergence of SGAs in the 1990s is suggested to account for the overall increase in AP prescribing (Ronsley et al., 2012). This trend is attributed to the perceived milder side effect profile of SGAs compared to FGAs, as SGAs carry a lower risk of extrapyramidal symptoms. Consequently, it is suggested that the prescribing physicians may be more likely to prescribe the SGAs due to their perceived favorable risk-benefit profile. However, as mentioned, it is important to note that SGAs are associated with endocrine and metabolic changes (Bostwick et al., 2009; Shirzadi & S Nassir, 1999).

As for sex, the present study, largely consistent with international studies (Barczyk et al., 2020; Chen, S. et al., 2021; Chen, W. et al., 2018; Radojčić et al., 2023), showed that more males redeemed APs with approximately a difference of 50-100% for the whole study period. However, females were found to be slightly more likely to receive treatment compared to males (uOR 1.09 95% CI 1.05-1.13). Studies (Bor et al., 2014; Potrebny et al., 2023) have noted a rising trend in AP use among female adolescents aged 15-19, which was attributed to increasing mental health problems. Particularly, female adolescents receiving quetiapine treatment were frequently diagnosed with depression, anxiety, and emotional disorders, which suggests that quetiapine has been used to treat

internalizing symptoms (ibid). Although not investigated, this may potentially have contributed to the higher likelihood of females receiving AP treatment in the present study. In addition, studies (Gould, 2017; Young et al., 2020) have shown that a large number of females with approved and un-approved indications commonly associated with AP use, such as autism and ADHD, often go unidentified and untreated. Raising awareness of clinical symptoms in females could increase the likelihood of receiving a diagnosis and consequently, appropriate treatment with APs (Gould, 2017; Young et al., 2020). A study by Edelsohn et al. 2016, examining the trends of AP prescription in children and adolescents from 2008 to 2013 in the US, found that males received APs more frequently across all age groups (Edelsohn et al., 2016). The higher prescription rate was attributed to a greater number of males being diagnosed with autism, ADHD, and disruptive behavior disorders. However, this was not investigated in the present study. The overall increase in AP use was primarily attributed to an increased use in the oldest age group 13-18 years, in line with the findings from (Bachmann et al., 2014; Radojčić et al., 2023)

4.2 Approved and un-approved indications for AP use

In the present study, AP medication was used across all diagnostic categories, resulting in a relatively high proportion of off-label prescriptions since only 3 out of 13 diagnostic categories were approved for such treatment for children and adolescents aged under 18 (Medicinrådet, 2022). However, only 15.40% of children and adolescents in the study cohort filled an AP prescription, indicating that the majority of individuals with a diagnosis did not receive this type of medication. Despite this, the increasing trend in AP use identified in the study raises concerns about whether this pattern will continue to grow, as seen in recent studies (Barczyk et al., 2020; Kalverdijk et al., 2017; Radojčić et al., 2023).

Consistent with the findings in the present study, risperidone and quetiapine were frequently redeemed for a variety of psychiatric disorders not approved for AP use in children and adolescents, as reported in several studies (Alessi-Severini et al., ; Bachmann et al., 2014; Ronsley et al., 2012). From 2005 to 2012, Bachman et al. found risperidone as the most common prescribed AP for ADHD, conduct disorders, intellectual disability disorders, emotional disorders, and depressive disorders in Germany. Similarly, Ronsley et al. observed that risperidone, quetiapine, and olanzapine, were among the most common prescribed APs in British Columbia from 1996 to 2011, with depressive disorders and ADHD being the most common diagnoses associated with these prescriptions. However, these

studies did not specify the indications for AP use beyond the diagnosis at the time of prescription, suggesting that the AP might have been prescribed for a different indication.

Specifically, for children diagnosed with ADHD, concerns have been raised regarding the extent of AP use (Findling et al., 2011). Findling et al. conducted a study on children diagnosed with only ADHD, where the results showed an ADHD diagnosis alone was not a predictive factor for SGA use, and for those who did receive APs, it was not used as first-line pharmacotherapy. In the present study, 4858 children with ADHD received at least one AP prescription during the study period, but only 734 had ADHD as their most likely indication. These findings emphasize the importance of distinguishing between ADHD as a diagnosis and as an indication for receiving AP medication when conducting studies to minimize the likelihood of misclassification and information bias.

4.3 AP use according to Danish Recommendations based on EMA and/or FDA approved indications

In the present study, any approved indication for AP use for children and adolescents under the age of 18 was determined based on the most recent guidelines (2022) from The Danish Medicines Council (DMC) (Medicinrådet, 2022). Guidelines from DMC are based on FDA and/or EMA approved criteria for AP use. However, during the study period, there were limited guidelines and evidence available regarding AP use in Denmark, as the first concrete guidelines for AP use in children and adolescents were endorsed on June 2013, by the Council for the Use of Expensive Hospital Medicine, *Rådet for Anvendelse af Dyr Sygehusmedicin* (RADS, 2013). During the study period, prior to the endorsement of the first guidelines, risperidone, and quetiapine were among the most common redeemed APs for all indications, which is in line with the later guidelines from RADS and DMC, as risperidone and quetiapine are recommended as first-choice medication. Quetiapine was, however, not recommended as the initial option for children under the age of 13 by DMC or RADS. The only indication approved for risperidone was schizophrenia in children aged 13 and above, and for children as young as 5 who have aggression associated with mental retardation. In the present study, chlorprothixene was the only FGA among the top four most redeemed APs in each diagnosis category, despite the availability of approved SGAs for children and adolescents at the time. One potential explanation could be that Truxal (chlorprothixene) was one of the first APs in the world launched by the Danish pharmaceutical company Lundbeck, and it became their top selling product during the 1960's and beyond (Lundbeck, 2024). Chlorprothixene was not identified as one of the most frequently used AP in none of the mentioned studies. Furthermore, it has not been recommended by RADS and DMC. However, multiple regression showed that the odds for receiving long term treatment with chlorprothixene was approximately 50% lower compared to other APs (aOR 0.58 95%

CI 0.54-0.63), suggesting chlorprothixene not being the first choice in cases of long-term AP treatment.

In general, the median dosages corresponded to the recommendations from RADS and DMC (Table7 & 8). However, median dosages in the present study represent the dose for the redeemed package, and not the actual dose issued by the psychiatrist, thus the actual doses are unknown. Typically, the packages redeemed were those with the smallest mg amounts, except for risperidone which was most often redeemed as 1 mg dose packages. This aligns with the recommendations of 1-6 mg for risperidone as maintenance dose interval by RADS and dose by DMC. It is important to note that the dose recommendations are primarily for individuals diagnosed with psychotic disorders.

2013 recommendations from RADS

	Age: < 13	Age: 13-17	Initial dose (mg)[a]	Maintenance dose interval (mg)
First choice	Risperidone	Risperidone	0.5 mg	1-6 mg
		Paliperidone	3 mg	3-12 mg[b]
		Quetiapine	50 mg (2*25)	400-800 mg
		Aripiprazole	2 mg	10-30 mg

Table 7: First choice recommendations for AP use in children and adolescents diagnosed with psychotic disorders from Rådet for Dyr Sygehusmedicin (RADS) in 2013

[a]Approved by FDA for children and adolescents aged 13-17 diagnosed with schizophrenia. [b]Weight <51 kg max dose is 6 mg

Guidelines adopted from RADS, 2013.

2022 recommendations from DMC for children and adolescents who meet the criteria for psychotic conditions (ICD-10 diagnosis F20-F29)

	Age: < 13	Age: 13-14	Age: 15-17	Dose (mg)
First choice	Risperidone[a]	Risperidone[a]	-	1-6 mg (FDA 13-17)
	-	Paliperidone	Paliperidone	1-6 mg (EMA 15-17)[d]
	-	Quetiapine[c]	-	400-800 mg (FDA 13-17)
	Aripiprazole[b]	Aripiprazole	Aripiprazole[b]	10-30 mg (EMA 15-17)
		Lurasidone		40-80 mg (FDA 13-17)

Table 8: First choice recommendations for AP use in children and adolescents who meet the criteria for psychotic conditions (ICD-10 diagnosis F20-F29)

[a]Approved for children aged 5 and above for the indication aggression in mental retardation in Denmark. [b]Approved by the FDA for children aged 6 and above with the indications Tourette's syndrome and irritibility in autism spectrum disorders. Overall associated with the lowest side effects. [c]Approved for mani for children and adolescents aged 10-17. [d]Weight < 51 kg: 3-6 mg Weight >51 kg: max 12 mg

Guidelines adopted from Medicinådet, 2022.

4.4 Treatment duration of AP use

Children and adolescents were treated with APs for several months, and in some cases, several years, despite their very young age. Notably, children in the two youngest age groups received pimozide, risperidone, quetiapine, and aripiprazole, each medication for a median duration of three years. However, multiple logistic regression showed that quetiapine in general was not associated with longer treatment compared to other medications as it was found to be not significant ($p>0.05$). As pimozide was among the most redeemed APs by individuals diagnosed with tic disorders, it could be argued if the longer treatment of this medication had to do with pimozide being considered as an effective treatment for individuals with tics, despite of pimozide being an FGA (Pringsheim & Marras, 2009). In general, the youngest age group, 0-6 years, had the longest treatment durations for most medications. One possible explanation for the shorter treatment durations in the oldest age group in this study was that individuals were no longer followed in the cohort once they turned 18, thus shortening their observed treatment duration. A Canadian study (Pringsheim et al., 2011) examined treatment durations for olanzapine, quetiapine, and risperidone in children and adolescents and found much shorter durations for individuals in all age groups. While individuals in the present study were treated with the same medication for around three years, the Canadian study reported a median duration of 1-3 months (Pringsheim et al., 2011). Given that children in that age were on medication for extended periods, it is crucial to closely monitor them for adverse events, as studies have shown significant weight gain and higher risk of extrapyramidal side effects with long term treatment in children (Luby et al., 2006; Reyes et al., 2006). Individuals with each approved indication for AP use, except for affective disorders and substance use disorder, were more likely to receive longer treatment durations compared to those with other diagnoses, while those without an approved indication, AP use consistently had a lower risk for longer treatment durations compared to those with other diagnoses. These findings are noteworthy, as shorter treatment duration for individuals with un-approved indications reduce the extent of prolonged off-label use.

4.5 Limitations

There were several limitations in this study. One major limitation was the lack of data on intended treatment duration and prescribed dosage in the DNPR. As a result, researchers must rely on guidelines, pill strengths, package size and the quantity of packages to make assumptions on these factors (Kilde). We identified the most likely indications for AP use if an individual was diagnosed with one or more diagnoses within 6 months before or after a redeemed prescription, assuming that

the prescription was issued by the physician around the time of redemption, as the DNPR relies on redeemed prescriptions rather than issued prescriptions. This suggests that the identified most likely indications might not always be directly related to the prescription being filled, which could potentially lead to differential information bias in cases where the correct intended treatment was for another diagnosis than the one specified. This could lead to an overestimation of the number of individuals who were prescribed APs for a diagnosis they were not intended for. Also, the established hierarchy for approved diagnoses may result in differential information bias, because we assumed that the approved indications listed in the hierarchy always took the precedence over other indications, potentially leading to an overestimation (and an underestimation of others) of these diagnosis as the primary reason for AP use, even if the true intended use was for a different indication. In addition, individuals who were labeled as ‘’individuals with several non-approved diagnoses’ were not given any indication for AP use, thus it underestimates the number of individuals in one or more of the non-approved indication categories. In addition, due to lack of this information, it was difficult to accurately determine the correct number of issued AP prescriptions. Furthermore, APs administered during hospital admission, as well as APs given to children and adolescents with psychiatric disorders in institutional settings, are not registered in the NPR, which may give misleading impression on the actual AP use. Regarding planned length of time of treatment, we assumed that one prescription could last at least 100 days, which could potentially lead to an overestimate of the duration of the treatment period, as it was most likely that the treatment duration could be shorter than 100 days, especially for individuals who received only 1 prescription in a treatment period. Package sizes and mg varied between and among APs, thus it was difficult to make assumptions regarding intended use, thus the duration for one prescription.

As for the NPR there were some limitations, as it only provides information on psychiatric diagnoses if the individuals have been admitted to a psychiatric hospital, thus information on those who were diagnosed at a general practitioner were not included. However, it was likely that it was only in cases where the mental disorders were mild to moderate (Momen et al., 2022; Mors et al., 2011). Additionally, individuals were included in the cohort only if they received a diagnosis after 1995. Consequently, there was no data on individuals diagnosed before this year unless they received another diagnosis after 1995, which could potentially introduce sampling error. Regarding regions, we assumed that the region where they were initially diagnosed was their place of residence. However, it was possible that some may have moved or could have been referred to a more specialized psychiatric hospital in another region.

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4.6 Strengths

The major strength is that the data sets contain details on every individual and every AP prescription dispensed in Denmark. This comprehensive coverage ensures a complete count rather than a sample, thereby avoiding sampling error and selection bias, and ensuring representativeness, which allows for the generalization of results. This is in contrast to other studies as they only included data from subpopulations, such as a single hospital setting or members from a specific insurance plan (Aagaard & Kornø, 2018; Chen, S. et al., 2021; Pringsheim et al., 2011). The lack of representativeness and short data collection periods in most studies hindered comparisons with other studies. Furthermore, utilizing data sets offers a non-invasive approach to studying children. Another strength is the stable and homogeneous demographic population in Denmark. Additionally, since most hospitals in Denmark are public and there are only a few private ones, this minimizes selection bias related to economic status and age groups (Lynge et al., 2011).

5. Conclusion

This study showed an increasing trend in the annual prevalence of AP use among children and adolescents in Denmark, consistent with trends observed in other countries. The increase was greatest in the 13–17-year-olds. Additionally, there was a rising trend of SGA use, and a decreasing trend of FGA use. Risperidone, chlorprothixene and quetiapine were among the most frequently prescribed drugs for almost all indications. However, the annual cumulative incidence of APs was found to be decreasing, suggesting that increase in prevalence might be due to longer treatment durations. Furthermore, this study found that individuals across all diagnostic categories redeemed a

prescription, often for off-label uses, as most indications, such as ADHD, conduct disorders and adjustment disorders, were not approved for such treatments. Guidelines at the time were limited, however, recommendations from the Danish Medicines Councils were introduced in 2013, thus making it interesting to follow how the trends in prescribing, and how off-label use have developed since.

Abbreviations

ADHD Attention deficit hyperactivity disorder

aOR Adjusted odds ratio

AP Antipsychotic

APC Average percentage change

CI Confidence interval estimate

DMC The Danish Medicines Council

DNPR The Danish National Prescription Register

EMA The European Medicines Agency

FDA The Food and Drug Administration

FGA First generation antipsychotic

ICD-10 The International Classification of Diseases, 10th Revision

IQR Interquartile range

KG Kilogram

MG Milligram

NO No observations

NPR The Danish National Patient Register

OCD Obsessive compulsive disorder

RADS Rådet for Anvendelse af Dyr Sygehusmedicin

SGA Second generation antipsychotic

UK United Kingdom

uOR Unadjusted odds ratio

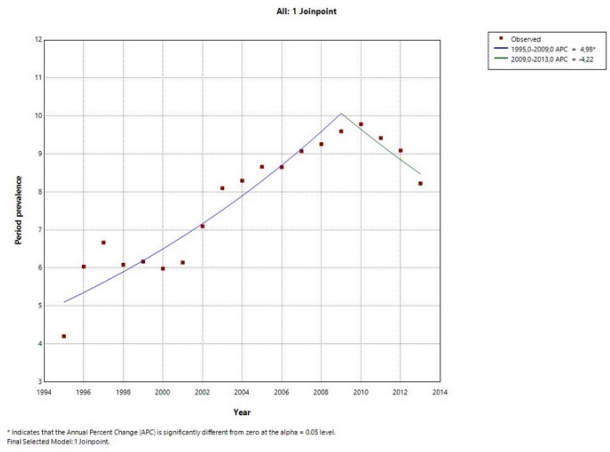
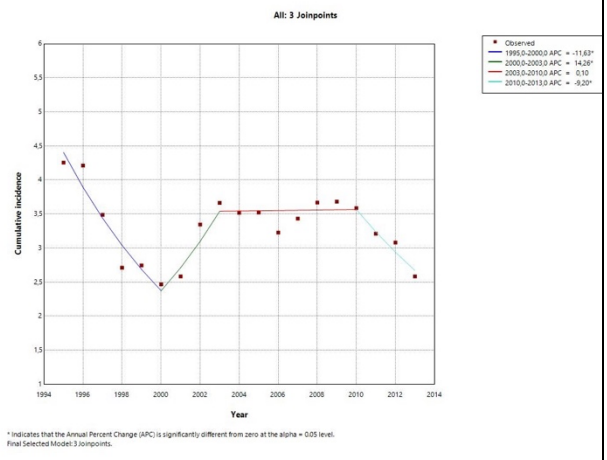
US United States

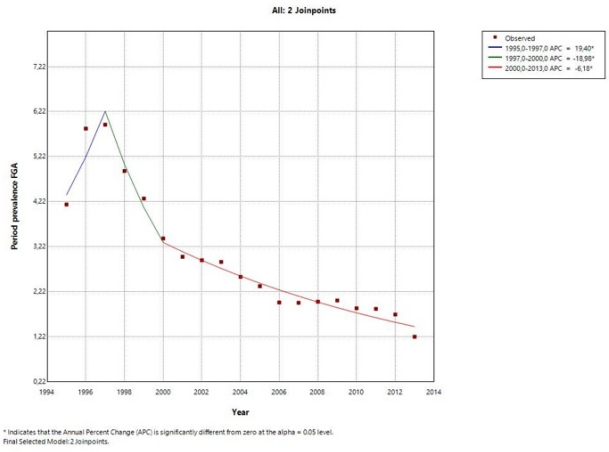
6. Appendix

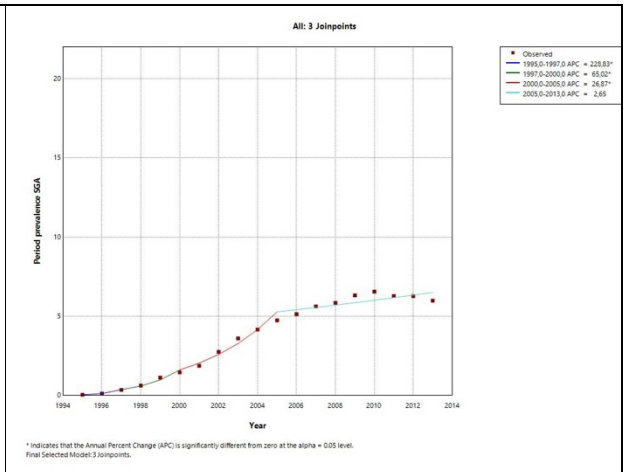
6.1. Figures

Steps for identifying the most likely indication	
1. step	Identify all psychiatric diagnoses given within 6 months before or after the incident prescription
2. step	If multiple approved diagnoses for AP use were found, prioritize based on the following hierarchy[a] to determine the most likely indication: 1. Psychotic disorders 2.. Depression with psychotic symptoms 3.. Autism spectrum disorders 4.. Tic disorders 5.. Substance use disorders
3. step[b]	For individuals with only one un-approved diagnosis 6 months before or after a prescription, assign this diagnosis as their most likely indication. Exclude individuals with multiple un-approved diagnoses.

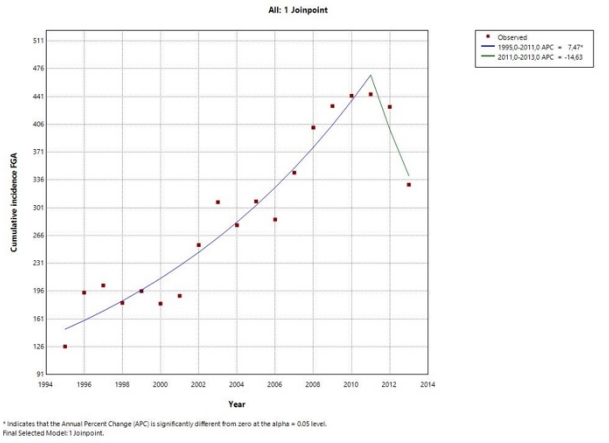
Appendix T1: Steps for identifying most likely indication associated with an antipsychotic prescription
[a] developed in collaboration with a psychiatrist [b]. Individuals with multiple un-approved diagnosis are excluded due to challenges of determining a prioritized order for such diagnoses

a)	***b)***
	
c)	***d)***





e)



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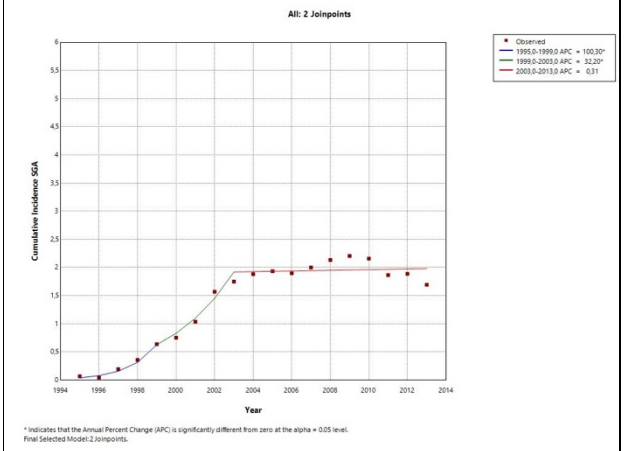


Appendix F1: Outcome tables from joinpoint regression analysis of prevalences and cumulative incidences of the number of patients who redeemed an antipsychotic prescription
a) Joinpoint model fitted to period prevalence b) Joinpoint model fitted to cumultive incidence c) Joinpoint model fitted to period prevalence for FGA d) Joinpoint model fitted to period prevalence for SGA e) Joinpoint model fitted to cumulative incidence for FGA use f) Joinpoint model fitted to cumulative incidence for SGA use. FGA = first generation antipsychotic. SGA = second generation antipsychotic

Indication	Medication*	Number of prescriptions	Number of individuals	**Median dosage (IQR)
Psychotic disorders				
	Chlorprothixene	7687 (10.26%)	1732 (20.77%)	15 mg (15, 15)
	Quetiapine	18122 (24.18%)	1561 (18.72%)	25 mg (25, 200)
	Risperidone	15849 (21.15%)	1261 (15.12%)	1 mg (0.5, 1)
	Aripiprazole	12264 (16.38%)	1141 (13.68'%)	5 mg (5, 10)
Affective disorders				
	Chlorprothixene	3486 (17.53%)	1149 (35.59%)	15 mg (15, 15)
	Quetiapine	4835 (24.32%)	637 (19.73%)	25 mg (25, 50)
	Risperidone	4577 (23.02%)	448 (13.88%)	0.5 mg (0.5, 1)

	Olanzapine	1839 (9.25%)	289 (8.95%)	5 mg (2.5, 5)
Autism spectrum disorders				
	Risperidone	22372 (51.22%)	1027 (35.03%)	0.5 mg (0.5, 1)
	Aripiprazole	6789 (15.54%)	500 (17.05%)	5 mg (1, 5)
	Chlorprothixene	3556 (8.14%)	560 (19.10%)	15 mg (15, 15)
	Quetiapine	3074 (7.04%)	281 (9.58%)	25 mg (25, 25)
Tic disorder				
	Risperidone	7976 (47.14%)	403 (40.14%)	0.5 mg (0.5, 1)
	Pimozide	4335 (25.62%)	226 (22.51%)	1 mg (1, 1)
	Aripiprazole	3176 (18.77%)	194 (19.32%)	5 mg (1, 5)
	Chlorprothixene	357 (2.11%)	75 (4.47%)	15 mg (15, 15)
Substance use disorders				
	Chlorprothixene	1150 (25.67%)	380 (36.93%)	15 mg (15,25)
	Quetiapine	1055 (23.55%)	210 (20.41%)	25 mg (25, 25)
	Risperidone	914 (20.40%)	125 (12.15%)	1 (0.5,1)
	Olanzapine	471 (10.51%)	97 (94.443%)	5 mg (5, 7.5)

Appendix T2: **Four most redeemed antipsychotic drugs pr approved indication, and median dosages for each medication**

Data shown as n(%). *Only the four most redeemed antipsychotics are included. ** The median dosage is represented by the median strength of the active ingredient in the redeemed medications.

Indication*	Medication	Number of prescriptions	Number of individuals	**Median dosage (mg (Q1, Q3)
Attention deficit hyperactivity disorders				
	Risperidone	3585 (51.69%)	232 (31.62%)	0.5 mg (0.5, 1)
	Chlorprothixene	745 (10.74%)	203 (27.63%)	15 mg (15, 15)
	Aripiprazole	972 (14.00%)	91 (12.40%)	5 mg (1, 5)
	Quetiapine	725 (10.45%)	90 (12.26%)	25 mg (25, 25)
Adjustment disorders				
	Chlorprothixene	682 (29.03%)	270 (42.66%)	15 mg (15, 15)
	Quetiapine	595 (25.34%)	104 (16.42%)	25 mg (25, 25)
	Risperidone	419 (17.83%)	79 (12.47%)	1 mg (0.5, 1)
	Levomepromazine	117 (4.98%)	35 (5.53%)	5 mg (5, 5)
Conduct disorders				
	Chlorprothixene	421 (18.23%)	90 (32.37%)	15 mg (15, 22.5)
	Risperidone	932 (40.33%)	72 (25.90%)	1 mg (0.5, 1)
	Quetiapine	155 (6.71%)	26 (9.35%)	25 mg (25, 25)
	Levomepromazine	91 (3.94%)	16 (5.76%)	25 mg (5, 25)
Eating disorders				
	Chlorprothixene	171 (16.57%)	63 (34.24%)	15 mg (15,15)
	Olanzapine	381 (36.82%)	56 (30.43%)	5 mg (2.5, 5)

	Risperidone	247 (23.93%	25 (13.59%)	1 mg (0.5, 1)
	Flupentixol	25 (2.42%)	10 (5.43%)	0.5 (0.25, 0.5)
Anxiety disorders				
	Chlorprothixene	204 (25.25%)	80 (45.20%)	15 mg (15, 15)
	Risperidone	135 (16.71%)	31 (17.51%)	1 mg (0.5, 1)
	Quetiapine	146 (18.07%)	26 (14.69%)	25 mg (25,25)
	Olanzapine & Levomepromazine	12/79 (1.49%/9.77%)	9 (5.08%)	2.5 (2.5, 5) 5 mg (5,5)
Obsessive compulsive disorders				
	Risperidone	452 (41.71%)	59 (32.78%)	0.5 mg (0.5, 1)
	Chlorprothixene	205 (18.92%)	55 (30.56%)	15 mg (15,15)
	Quetiapine	122 (11.27%)	22 (12.22%)	25 mg (25,100)
	Aripiprazole	146 (13.48%)	19 (10.56%)	1 mg (1,5)
Emotional disorders				
	Chlorprothixene	81 (18.41%)	29 (43.28%)	15 mg (5, 15)
	Risperidone	105 (23.86%)	13 ((19.40%)	0.5 mg (0.5, 0.75)
	Quetiapine	107 (24.32%)	10 (14.9%)	25 mg (25, 25)
	Flupentixol	23 (5.23%)	>5 (-)	0.5 mg (0.5, 0.5)
Intellectual disability disorders				
	Chlorprothixene	252 (16.25%)	22 (23.91%)	15 mg (5, 25)
	Risperidone	497 (32.02%)	20 (21.74%)	1 mg (0.5, 1)
	Quetiapine	62 (3.99%)	9 (9.78%)	25 mg (25,25)
	Levomepromazine	25 (1.61%)	7 (7.61%)	10 mg (5, 25)

Appendix T3: Four most redeemed antipsychotic drugs pr un-approved indication, and median doses per each medication

Data shown as n(%). *Individuals who received only one diagnosis 6 months before or after their initial antipsychotic prescription were included. Those who received several diagnoses within the period were not included. **The median dosage is represented by the median strength of the active ingredient in the redeemed medications.

	Adjusted		***Unadjusted***	
	OR[a]	**95 % CI**	**OR**	**95 % CI**
Sex				
Male	-	-	1.00	-
Female	-	-	1.09***	1.05-1.13
Age groups				
0-6	-	-	1.00	-
7-12	-	-	1.29***	1.21-1.37
13-17	-	-	2.30***	2.17-2.44
Region [b]				
The Capital Region of Denmark	1.00	-	1.00	-

The North Denmark Region	0.84***	0.77-0.91	0.93**	0.86-1.01
Region Zealand	0.88***	0.83-0.92	0.93***	0.88-0.98
The Region of Southern Denmark	0.73***	0.69-0.76	0.78***	0.74-0.82
The Central Denmark Region	0.65***	0.62-0.69	0.68***	0.64-0.72
Approved indication [c]				
Other [d]	1.00	-	1.00	-
Psychotic disorders	7.61***	7.24-8.01	8.64***	8.23-9.07
Affective disorders	2.00***	1.89-2.11	2.07***	1.97-2.17
Autism spectrum disorders	1.44***	1.36-1.53	1.31***	1.24-1.39
Tic disorders	5.35***	4.84-5.90	4.61***	4.20-5.07
Substance use disorders	4.98***	4.49-5.52	6.05***	5.48-6.68
Un-approved indication [c]				
Other [e]	1.00	-	1.00	-
Anxiety disorders	1.65***	1.47-1.85	1.76***	1.57-1.98
Eating disorders	0.64***	0.56-0.74	0.79***	0.69-0.90
Adjustment disorders	1.19***	1.09-1.30	1.27***	1.17-1.38
Emotional disorders	1.08	0.95-1.24	0.95	0.83-1.08
Conduct disorders	2.01***	1.83-2.22	1.91***	1.74-2.10
Atten deficit hyperactivity disorders	1.45***	1.33-1.59	1.20***	1.11-1.29
Obsessive compulsive disorders	1.07***	1.52-1.92	1.71***	1.52-1.92
Intellectual disorders	1.92***	1.69-2.18	1.76***	1.55-1.99

Appendix T4: Multivariate logistic regression for factors associated with antipsychotic use (treatment versus no treatment)

[a]Adjusted for other covariates such as age, sex, and region. [b] Regional is adjusted for sex and age [c]. Indication for first time prescriptions [d]. Individuals who had other indications than the indication of interest were used as reference for each approved indication. Each approved indication was sequentially removed following the hierarchy. For example, individuals with psychotic disorders were compared with all who did not have psychotic disorders, individuals with affective disorders were compared with all who did not have affective disorders and psychotic disorders etc. [e] Individuals who had other un-approved indications than the one of interest were used as reference. *p < 0.05*, p < 0.001**, p < 0.0001**

	Adjusted		*Unadjusted*	
	OR[a]	**95 % CI**	**OR**	**95 % CI**
Sex				
Male	-	-	1.00	-
Female	-	-	0.76***	0.71-0.82
Age groups				
0-6	-	-	1.00	-
7-12	-	-	1.05	0.83-1.34
13-17	-	-	0.57***	0.45-0.72
Region [b]				
The Capital Region of Denmark	1.00	-	1.00	-
The North Denmark Region	1.30***	1.11-1.51	1.33***	1.14-1.54
Region Zealand	1.02	0.93-1.13	1.02	0.92-1.12
The Region of Southern Denmark	1.11**	1.00-1.22	1.08	0.98-1.19
The Central Denmark Region	1.46***	1.32-1.62	1.47***	1.32-1.53
Approved indication [c]				
Other [d]	1.00	-	1.00	-
Psychotic disorders	1.97***	1.80-2.17	1.62***	1.48-1.77
*Affective disorders**	0.86**	0.78-0.96	0.68***	0.61-1.27
Autism spectrum disorders	1.71***	1.50-1.96	1.99***	1.75-2.26
Tic disorders	2.15***	1.67-2.76	2.80***	2.20-3.59
*Substance use disorders**	0.62***	0.51-0.75	0.52***	0.43-0.63
Un-approved indication [b]				
Other [e]	1.00	-	1.00	-
Anxiety disorders	0.51***	0.44-0.60	0.44***	0.37-0.51
Eating disorders	0.58***	0.46-0.74	0.51***	0.40-0.65
Adjustment disorders	0.72**	0.59-0.88	0.71**	0.58-0.87
Emotional disorders	0.98	0.85-1.12	1.00	0.86-1.15
Conduct disorders	1.33*	1.04-1.71	1.01	0.79-1.29
Attention deficit hyperactivity disorders	0.64**	0.46-0.89	0.66*	0.48-0.91

Obsessive compulsive disorders	1.13	0.83-1.55	1.12	0.82-1.52
Intellectual disorders	1.09	0.84-1.41	1.04	0.80-1.17

Appendix T5: Multivariate logistic regression for factors associated with antipsychotic use (FGAs versus SGAs)
[a] Adjusted for other covariates such as age, sex, and region. [b] Regional is adjusted for sex and age. [c] Indication for first time prescriptions. [d] Individuals who had other indications than the indication of interest were used as reference for each approved indication. Each approved indication was sequentially removed following the hierarchy. For example, individuals with psychotic disorders were compared with all who did not have psychotic disorders, individuals with affective disorders were compared with all who did not have affective disorders and psychotic disorders etc. [e] Individuals who had other un-approved indications than the one of interest were used as reference. *p < 0.05*, p < 0.001**, p < 0.0001**

	Adjusted		***Unadjusted***	
	OR[a]	**95 % CI**	**OR**	**95 % CI**
Sex				
Male	-	-	1.00	-
Female	-	-	0.80***	0.75-0.83
Age groups				
0-6	-	-	1.00	-
7-12	-	-	0.91	0.71-1.13
13-17	-	-	0.45***	0.35-0.57
Regional [b]				
The Capital Region of Denmark	1.00	-	1.00	-
The North Denmark Region	1.04	0.89-0.99	1.11	1.00-1.25
Region Zealand	0.90**	0.81-0.99	1.01	0.94-1.08
The Region of Southern Denmark	0.96	0.87-1.05	1.21***	1.13-1.29
The Central Denmark Region	0.92	0.83-1.02	1.38***	1.23-1.49
Approved indication [c]				
Other [d]	1.00	-	1.00	-
Psychotic disorders	2.04***	1.87-2.23	1.67***	1.53-1.82
*Affective disorders**	0.82***	0.74-0.92	0.63***	0.57-0.70
Autism spectrum disorders	1.50***	1.32-1.70	1.80***	1.60-2.04
Tic disorders	2.23***	1.74-2.84	3.10***	2.44-3.92
*Substance use disorders**	0.71***	0.59-0.86	0.56***	0.46-0.68

Un-approved indication [c]				
Other [e]	1.00	-	1.00	-
Anxiety disorders	0.74*	0.58-0.95	0.63***	0.49-0.80
Eating disorder	0.73*	0.56-0.94	0.56***	0.44-0.72
Adjustment disorders	0.71***	0.60-0.82	0.55***	0.47-0.64
Emotional disorders	0.74*	0.53-1.04	0.76	0.55-1.06
Conduct disorders	1.01	0.83-1.24	0.98	0.80-1.19
Attention deficit hyperactivity disorders	1.00	0.86-1.16	0.99	0.86-1.15
Obsessive compulsive disorders	0.87	0.67-1.12	0.82	0.64-1.05
Intellectual disorders	1.66**	1.22-2.27	1.56**	1.15-2.12
Antipsychotics [f]				
Other [g]	1.00	-	1.00	-
Chlorprothixene	0.58***	0.54-0.63	0.03***	0.03-0.04
Risperidone	1.59***	1.46-1.73	0.11***	0.10-0.12
Quetiapine	1.05	0.95-1.17	0.06***	0.06-0.07
Aripiprazole	1.55***	1.38-1.76	0.12***	0.11-0.13
Olanzapine	1.25***	1.10-1.43	0.08***	0.07-0.10
Pimozide	1.56***	1.28-1.90	0.17***	0.14-0.21
Levomepromazine	0.70***	0.58-0.85	0.06***	0.05-0.07

Appendix T6: Multivariate logistic regression for factors associated with duration of antipsychotic use (Long duration versus short duration at a cut off value of 571 days)

[a]Adjusted for other covariates such as age, sex, and region. [b]Regional is adjusted for sex and age. [c] indication for first time prescriptions. [d] Individuals who had other indications than the indication of interest, were used as reference for each approved indication. Each licenced indication was sequentially removed following the hierarchy. For example, individuals with psychotic disorders were compared with all who did not have psychotic disorders, individuals with affective disorders were compared with all who did not have affective disorders and psychotic disorders etc.[e] Individuals who had other un-approved indications than the one of interest were used as reference. [f] The seven most redeemed antipsychotics are shown. [g] All other antipsychotics were used as reference for each antipsychotic of interest. $p < 0.05$*, $p < 0.001$**, $p < 0.0001$*

	Adjusted		*Unadjusted*	
	OR[a]	**95 % CI**	**OR**	**95 % CI**
Sex				
Male	-	-	1.00	-
Female	-	-	0.79***	0.75-0.83
Age groups				
0-6	-	-	1.00	-
7-12	-	-	0.92	0.73-1.16
13-17	-	-	0.38***	0.30-0.48
Regional [b]				
The Capital Region of Denmark	1.00	-	1.00	-
The North Denmark Region	1.11	0.89-0.99	1.11	1.00-1.23
Region Zealand	0.87**	0.79-0.96	1.00	0.94-1.07
The Region of Southern Denmark	0.97	0.88-1.07	1.22***	1.14-1.30
The Central Denmark Region	0.93	0.84-1.36	1.40***	1.30-1.50
Approved indication [c]				
Other [d]	1.00	-	1.00	-
Psychotic disorders	1.86***	1.70-2.03	1.45***	1.33-1.58
*Affective disorders**	0.80***	0.71-0.90	0.58***	0.52-0.65
Autism spectrum disorders	1.64***	1.45-1.86	2.02***	1.80-2.28
Tic disorders	2.32***	1.83-2.94	3.41***	2.71-4.28
*Substance use disorders**	0.59***	0.48-0.74	0.44***	0.36-0.55
Un-approved indication [c]				
Other [e]	1.00	-	1.00	-
Anxiety disorders	0.58*	0.44-0.77	0.49***	0.37-0.64
Eating disorder	0.73*	0.55-0.97	0.52***	0.40-0.69
Adjustment disorders	0.62***	0.52-0.73	0.46***	0.39-0.54
Emotional disorders	0.62*	0.43-0.89	0.66	0.46-0.93
Conduct disorders	1.05	0.85-1.29	1.01	0.82-1.22
Attention deficit hyperactivity disorders	0.93	0.79-1.09	0.92	0.79-1.07

Obsessive compulsive disorders	0.87	0.67-1.12	0.82	0.64-1.05
Intellectual disorders	1.65**	1.21-2.25	1.54**	1.13-2.09
Antipsychotics [f]				
Other [g]	1.00	-	1.00	-
Chlorprothixene	0.62***	0.59-0.68	0.03***	0.03-0.03
Risperidone	1.59***	1.46-1.73	0.11***	0.10-0.12
Quetiapine	0.95	0.86-1.06	0.05***	0.04-0.05
Aripiprazole	1.47***	1.30-1.66	0.10***	0.09-0.11
Olanzapine	1.25***	1.10-1.43	0.08***	0.07-0.10
Pimozide	1.54***	1.28-1.88	0.15***	0.13-0.19
Levomepromazine	0.70***	0.58-0.85	0.06***	0.05-0.07

Appendix T7: Results from sensitivity analysis for multivariate logistic regression for factors associated with duration of antipsychotic use, altering the cut off value from 571 to 717 days

[a]Adjusted for other covariates such as age, sex, and region. [b]Regional is adjusted for sex and age. [c] indication for first time prescriptions. [d] Individuals who had other indications than the indication of interest, were used as reference for each approved indication. Each licenced indication was sequentially removed following the hierarchy. For example, individuals with psychotic disorders were compared with all who did not have psychotic disorders, individuals with affective disorders were compared with all who did not have affective disorders and psychotic disorders etc.[e] Individuals who had other un-approved indications than the one of interest were used as reference. [f] The seven most redeemed antipsychotics are shown. [g] All other antipsychotics were used as reference for each antipsychotic of interest. $p < 0.05$*, $p < 0.001$**, $p < 0.0001$*

6.2 Literature search

The search term used for literature search are presented in table x. Articles were included if they were register-based studies investigating prescription trends of antipsychotic medication among children and adolescents diagnosed with any of the psychiatric diagnosis in the ICD-10 F chapter. Studies were excluded first by title, then by abstract, and finally by reading the full article (Appendix F2).

Keywords1: Child [Mesh] OR Adolescent [Mesh] OR child OR children OR adolescent* OR teen* OR teenager* OR youth*

Mesh: "Child" [Mesh] "Adolescent" [Mesh]

Keywords2: "Psychotropic Drugs" [Mesh] OR antipsychotic* OR "major tranquilisers" OR neuroleptic* OR psychotropic

Mesh: "Psychotropic Drugs" [Mesh]

Keywords3: Prescription [Mesh] OR prescribing OR ordination

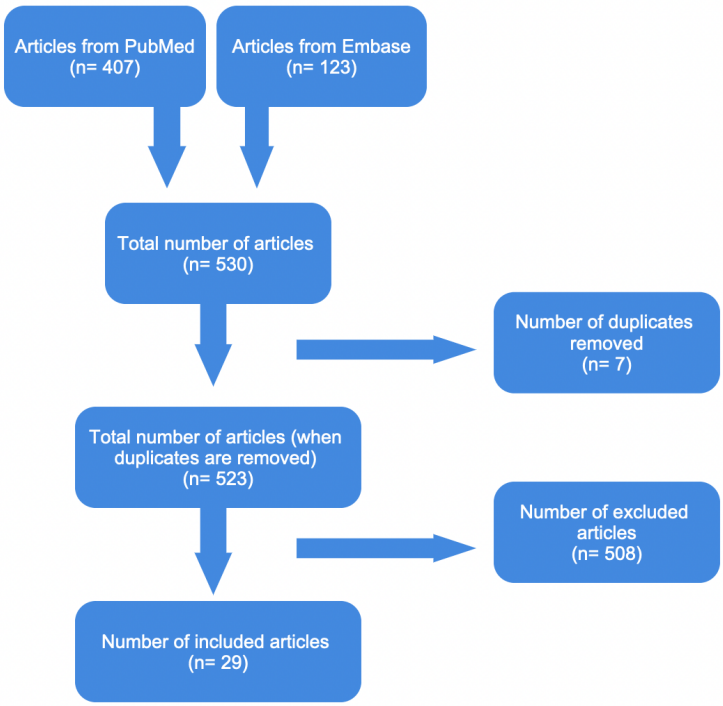
Mesh: “Prescription” [Mesh]

Keywords4: “Anxiety Disorders”[Mesh] OR “Feeding and Eating Disorders”[Mesh] OR “Mood Disorders”[Mesh] OR “Schizophrenia Spectrum and Other Psychotic Disorders”[Mesh] OR “Substance-Related Disorders“[Mesh] ‘’substance use disorders’’ OR ‘’psychotic disorders’’ OR ‘’affective disorders’’ OR ‘’anxiety disorders’’ OR ‘’obsessive compulsive disorders’’ OR ‘’adjustment disorders’’ OR ‘’eating disorders’’ OR ‘’intellectual disability’’ OR ‘’autism spectrum disorder’’ OR ‘’attention-deficit disorder’’ OR ‘’conduct disorders’’ OR ‘’tic disorders’’

Mesh: “Anxiety Disorders” [Mesh] OR “Feeding and Eating Disorders” [Mesh] OR “Mood Disorders” [Mesh] OR “Schizophrenia Spectrum and Other Psychotic Disorders” [Mesh] OR “Substance-Related Disorders“[Mesh]

Keywords5: “Cohort Studies” [Mesh] OR “cohort study” OR trend OR “population-based”

Mesh: “Cohort Studies” [Mesh]



Appendix F2: Flowchart describing the steps in literature search

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