# REAL-WORLD EVIDENCE OF PEDIATRIC EXPOSURE TO PSYCHOPHARMACOLOGIC MEDICATIONS

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# REAL-WORLD EVIDENCE OF PEDIATRIC EXPOSURE TO PSYCHOPHARMACOLOGIC MEDICATIONS

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EDITORIAL
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# Editorial: Real-World Evidence of Pediatric Exposure to Psychopharmacologic Medications

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**Keywords: real-world evidence (RWE), pharmacoepidemiology, psychopharmacologic medications, children, youth, psychopharmacologic drugs, adolescents**

## Editorial on the Research Topic

## Real-World Evidence of Pediatric Exposure to Psychopharmacologic Medications

This Research Topic on "Real-world evidence of pediatric exposure to psychopharmacologic medications" comprises nine invited studies reflecting the state of the art in pharmacoepidemiologic research circa 2022. From Europe and North America, these studies offer real-world data (RWD) on pediatric medication practices. In many cases, concerns are raised around how young people are treated (population-based prevalence) and user characteristics. These concerns relate to safety surrounding off-label use due to age or indications, inter-class polypharmacy, risk of long-term pediatric use, and fetal exposure. Two examples, based on follow-up studies, illustrate poor patient monitoring for treatment-emergent events. Five international studies are briefly described below, followed by four US studies.

A Norwegian study conducted by Kiselev et al. on the prevalence of autism spectrum disorders among 2–17-year-olds reaffirms the value of a national registry in assessing the prevalence of the disorder and its psychotropic treatment. The findings indicate a 2014 prevalence of 0.76% of ASD in Norway and the co-occurrence of comorbid diagnoses account for the use of psychotropic drug class use. Comparing their findings to a 2.24% prevalence in young populations from the US, they indicate a far greater ASD prevalence and drug treatment in the U.S. than in Norway. Researchers cooperating across the US—Europe divide have been showing us similar disparities for more than a decade (1).

Following our metaphorical journey through the five international studies, we journey south from Norway to the Netherlands where Minjon et al. examine electronic health records (EHR). The authors aim to bring enhanced information from *new* atypical antipsychotic (AAP) users, i.e., with no prior AAP use for 6 months. A 3-year follow-up was conducted in community-based psychiatric clinics. The outcomes consist of a frequency of reports of physical measures (e.g., weight, pulse, blood pressure) and laboratory parameters (e.g., glucose and triglycerides) at baseline and in subsequent 6-month intervals. The results reveal low frequencies in both physical and laboratory monitoring. While it is exciting to see EHRs are now available for closer, more accessible monitoring of health care, the results suggest the benefit does not necessarily extend to improved prescriber compliance, with recommendations for safer use of second-generation antipsychotics.

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In nearby Germany, Scholle et al. were able to capitalize on the continuity of care from universal healthcare coverage. In this context, the study was able to provide a 4-year baseline from which to identify new users of ADHD medication. The rich dataset enabled a robust analysis of conformance to clinical prescribing standards.

Across the pond in Canada, Gober et al. extracted British Columbia data across 20 years to assess preschoolers (0–5 years) on the relationship of hydroxyzine exposures to subsequent mental health diagnoses in a follow-up to age 10. Young patients with 5 or more hydroxyzine dispensings were significantly more likely to have a diagnosis of tic disorder compared with those receiving one dispensing [odds ratio = 1.40 (1.08–1.81)]. Trends for anxiety and emotional disturbance were also significant. The context of this study suggests it is a "hot topic," and that confirming clinical trial evidence could bring substantial change to current pediatric practice.

Campbell et al. offer a unique example of a Canadian clinical study to assess fetal factors associated with SSRI antidepressant use in 148 pregnant women. Fetal heart rate and heart rate variability (HRV) were assessed at 36-weeks' gestation among 4 groups of pregnant women. While heart rate was not significantly different, HRV was significantly reduced in SSRI-non-depressed exposed male but not female fetuses. The effect increased with higher SSRI dosage. HRV changes were within the normal range of developing fetuses at 36-weeks' gestation, suggesting the effects are not likely of clinical significance. While the authors urge replication, readers of this series on real-world evidence may be reminded of the widespread use of SSRIs among young people as well as pregnant women and the growing concerns about the questionable effectiveness (2) and difficulty withdrawing from SSRIs (3).

Among US research studies, Zhang et al. assessed U.S. data on young people who were commercially insured to extend the stimulant cardiovascular safety question to the increasingly common use of concomitant stimulants and atypical antipsychotic (S+AAP). A time-dependent logistic model calculated the less severe event risk (LSE) for current concomitant S+AAP users compared with past users and non-users. LSE risks appear modest but consistent: 14 LSE per 10,000 person months (p-m) for current users and 8.2 per 10,000 p-m for past users, compared with non-users, respectively. The risk for combination S+AAP was not statistically significant. Nevertheless, the search for safety data on frequently occurring off-label combinations, such as stimulants and atypical antipsychotics, will no doubt continue, especially since commercial datasets reveal relatively short exposures and modest AAP dosage.

Prescribers in recent years have learned of "deprescribing," a term created to address multidrug regimens that may exceed the benefit of combinations, which are mostly off-label and suggest discontinuation. To fill the gap in clinical practice protocols for safe pediatric withdrawal of stimulants, Lohr et al. conducted a systematic review on clinical practices to safely discontinue stimulants for young people treated for ADHD. After a close review of 35 studies, with several clinical trials among them, a subgroup was identified for whom relapse or deterioration did not occur following discontinuation of stimulants. Approximately 30% of stimulant trial participants were found to support community treatment efforts to discontinue stimulants in young people who did not benefit from them.

Deprescribing is again called for by Edelsohn et al. in their U.S. analysis of the concomitant psychotropic prescribing patterns from admission to discharge in residential care. Logistic regression showed that among patient and treatment characteristics only the number of medications prescribed at admission was significant ($p < 0.001$), with more medications at admission contributing to the probability of discharge on four or more concomitant psychotropics.

Further support for safe prescribing protocols can be surmised from the systematic review of U.S. studies of inter-class polypharmacy by Zito et al. (Full disclosure: Zito is the first author of this review). The growth of 3 or more psychotropic class polypharmacy is confirmed and currently, more than 300,000 U.S. polypharmacy medicated young people (4) could benefit from reduced or discontinued medication. Here, as in Lohr et al. and Edelsohn et al., the evidence calls for deprescribing research as well as post-marketing research to establish the effectiveness, safety, and tolerability of complex concomitant regimens in community populations, e.g., in large simple trials.

Collectively, these pharmacoepidemiologic real-world studies reiterate the need for future post-marketing drug studies to assure us that widely used off-label psychopharmacologic agents are beneficial and safe. Perhaps it is time to seek research funds to measure population-based outcomes in sufficient detail (functioning, social development) to assure that the benefits of pediatric psychotropics outweigh the risks.

## AUTHOR CONTRIBUTIONS

JZ drafted the manuscript. SD and BC reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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# Nationwide Study of Neuropsychiatric Comorbidity and Medicines Use in Children With Autism Spectrum Disorder in Norway

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**Purpose:** Autism spectrum disorder (ASD) has a high rate of comorbidity. While many children with ASD are exposed to psychotropic medicines, their efficacy and safety in these patients are unclear. There is a need for more detailed knowledge on which medicines are most commonly used and for which disorders. We aimed to investigate (a) prevalence and incidence rate of ASD among Norwegian children, and further, among newly diagnosed ASD children in 2014, study the (b) co-occurrence of neuropsychiatric disorders, (c) use of psychotropic drugs, and (d) the relationship between co-occurring diagnoses and use of psychotropic drugs.

**Method:** Nationwide registry-based study of children 2–17 years old in Norway.

**Results:** The ASD prevalence was 0.76% and the incidence rate was 0.12% in 2014. Of the children who received an initial ASD diagnosis in 2014 ($n$ = 1,234), 64.8% had one or more co-occurring neuropsychiatric diagnosis. Psychotropic medication use was moderate (~20% used stimulants or hypnotics) in general, and low in children without comorbidity (nearly only hypnotics). There was a good accordance between co-occurring diagnoses and indication for the prescribed medications.

**Conclusions:** Children with newly diagnosed ASD mainly received psychotropic drugs to treat co-occurring neuropsychiatric conditions.

**Keywords: autism, children, psychotropic, CNS, medicines use**

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## INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder, which is usually diagnosed at a young age. Deficits in social interaction and restrictive repetitive behaviors are considered to be the core diagnostic criteria (1). ASD is also associated with a plethora of other symptoms such as aggression, self-harm, irritability, hyperactivity, and many more. Reported prevalence of ASD varies significantly, and depends on region, size, age group, and study methodology (mostly parent questionnaires, insurance claims, and only few nation-wide registry based studies). Prevalence has been reported to be between ~0.3 and 2.8%, seemingly higher in the US than in the Nordic countries (2–10). Co-occurring psychiatric and neurological conditions

are common among children with ASD. In a US study based on insurance claims data, anxiety disorders was present in as many as 17–30% of adolescents with ASD, epilepsy in 3–10%, ADHD in 47–51%, and even among 3–4 year olds up to 15% had two or more co-occurring disorders (11). A systematic review concluded that the median percentage of children (<12 years) and adolescents (12–17 years) with ASD using psychotropic medication is 41.9 and 42.5%, respectively (12). However, the percentage ranged from 3 to 80%. The most commonly used groups of medications include stimulants, antipsychotics, antidepressants and sleeping aids (13, 14). Unfortunately, most of the available studies of medication use have limitations like relying upon data from insurance claims or parent reports. No pharmacological treatments have demonstrated efficacy in reducing core symptoms of ASD, but the high prevalence of comorbidity might explain some of the psychotropic drug use reported in the literature.

In the current study we aim to use a nationwide Norwegian sample of children (2–17 years) diagnosed with ASD:

1) Estimate the prevalence (cumulative incidence) and incidence rate of ASD
2) Estimate the co-occurrence of psychiatric and neurological diagnoses;
3) Investigate the use of psychotropic drugs;
4) Explore the relationship between co-occurring diagnoses and psychotropic drug use.

# MATERIALS AND METHODS

This study is based on data from the Norwegian Patient Registry (NPR), and the Norwegian Prescription Database (NorPD). Individual-level registry data from the NPR and the NorPD were linked using the unique (encrypted) personal identity number assigned to all individuals living in Norway.

## Data Sources

### The Norwegian Patient Registry

The NPR is an administrative database of records reported by the secondary health care, i.e., all hospitals and outpatient clinics owned or reimbursed by the government, thus covering practically all children with psychiatric conditions. Thus, the NPR includes information on patients referred by a GP to secondary health care. The NPR has included unique personal identification numbers since 2008, and consequently the registry contains nationwide individual-level secondary health care data from 2008 and onwards. In this study, we used data from the period 2008–2015. Diagnoses in the NPR are coded according to the International Classification of Diseases, 10th revision (ICD-10). In the present study, the following diagnosis for ASD were identified: autistic disorder (F84.0), Asperger's syndrome (F84.5) and atypical or unspecified autism (AUA) (F84.1, F84.8, F84.9).

Co-occurring psychiatric diagnoses on mental, behavioral or neurodevelopmental disorders (all ICD F diagnosis) overall and specifically on hyperkinetic disorders (F90), behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F91–98), mood [affective] disorders (F30–39), neurotic stress-related and somatoform disorders (F40–48), epilepsy (G40), and sleep disorders (G47) were obtained.

A validation study by Suren et al. indicated a high overall validity of ASD diagnoses assigned by secondary health care and confirmed that the technical aspects of the NPR data collection are functioning well (15).

### The Norwegian Prescription Database (NorPD)

Information on dispensed psychotropic drugs to outpatients from all Norwegian pharmacies were drawn from the NorPD, which covers the entire Norwegian population (∼5.4 million inhabitants) (16). In the present study, we included the patients' unique (encrypted) identity number, sex, age, the date of dispensing, and drug information [Anatomical Therapeutic Chemical (ATC) code]. Data on psychotropic drugs dispensed during a 365-day period after incident diagnoses for ASD in 2014 were included in the analyses. Incident diagnosis was used to ensure that the ASD diagnosis preceded our assessment of drug use. In the following, prescription drugs dispensed, as recorded in the NorPD, are referred to as drugs used, although we do not have information on actual compliance (17).

The following psychotropic drugs were investigated: stimulants (ATC code N06B); antiepileptics (N03A), antidepressants (N06A), antipsychotics (N05A), anxiolytics (N05B), hypnotics (N05C), alimemazine (R06AD01). Alimemazine is used in Norway as a hypnotic, particularly to children (18). Pain relievers as opioids (N02A), NSAIDS (M01A) and prescription paracetamol (N02BE01) were also investigated, but not presented in the tables because of low prevalence of use.

## Study Population

The study population consists of (a) all children aged 2–17 years in Norway in 2008–2014, (b) all children aged 2–17 years in Norway with incident diagnoses of ASD during in 2014. Information on birth year was acquired from NPR and used to calculate age in 2014.

## Analytical Approach

We estimated the *period prevalence (cumulative incidence)* of ASD diagnosis per 1,000 children aged 2–17 years during 2008–2014. Children or adolescents were included if they had been diagnosed with ASD at least once during the period 2008–2014. The denominator in the prevalence analyses was the total number of inhabitants in Norway in the different age groups per July 1st in 2014, as registered by Statistics Norway.

We identified individuals with an *incident diagnosis* of ASD in secondary health care in 2014. A diagnosis was defined as incident if an individual had not been registered in NPR with the diagnosis any of the six previous years back to January 1st 2008. The *incidence rate* was calculated as number of incident cases divided by the number of individuals in the population under risk.

We explored the proportion of ASD subtypes according to age group and gender for the individuals with incident diagnoses of ASD in the NPR in 2014. We calculated the proportion

who got diagnoses for psychiatric and neurological comorbidities from 2008 to 2015. This long time interval was chosen in order to identify lasting comorbidities in children who are using secondary health care rarely. We also calculated the proportion who were dispensed psychotropic drugs during the 365-day period after the date of the first diagnosis for the same groups.

To explore the extent to which users of psychotropic drugs had diagnoses that might have been considered as indications for such use, we calculated the proportion of children with relevant diagnoses in the NPR for all users of stimulants, antiepileptics, antidepressants, and antipsychotics during 365-days after the first ASD diagnosis. The diagnoses were: for stimulants - hyperkinetic disorders (F90); for antiepileptics - epilepsy (G40); for antidepressants - mood [affective] disorders (F30–39) and neurotic, stress-related and somatoform disorders (F40–48), and for antipsychotics - psychotic and bipolar disorders (F20–29, F30, F31, F33.3).

## Ethical Considerations

The register-linkage was approved by The Regional Committee for Medical Research Ethics (2010/131) and by the Norwegian Data Protection Authority (10/00447-5).

# RESULTS

## Periodic Prevalence (Cumulative Incidence) of ASD Diagnosis

The estimated prevalence of ASD in 2014 among 2–17-year-old children was 7.6 per 1,000 (95% confidence interval 7.4–7.8 per 1,000). Among 8-year old, the prevalence was 6.3 per 1,000 (5.7–6.9 per 1,000). The prevalence increased steadily with increasing age but leveled out at around 13 per 1,000 children at the age of 15–17 years. From the age of four, the prevalence was at least three times higher among boys than girls.

## Incidence of ASD Diagnosis in 2014

The incidence rate was 1.2 per 1,000 for 2–17-year-old children. In boys the incidence rate was 1.8 per 1,000 and in girls it was 0.6 per 1,000.

**Table 1** shows the number of boys and girls aged 2–17, divided into three age groups, diagnosed with ASD in 2014 ($n = 1{,}234$), by ASD subtype. Asperger's syndrome was the most common diagnosis ($n = 474$), followed by autistic disorder ($n = 415$) and AUA ($n = 345$). For both Asperger's syndrome and AUA more children got the diagnosis with increasing age, while it was opposite for autistic disorder.

## Co-occurring Diagnoses in Children With Newly Diagnosed ASD

Nearly two thirds (64.8%) of the children with incident ASD diagnosis in 2014 also had another neuropsychiatric diagnosis, and the proportion of comorbidity was especially high (up to 71.9%) among children with Asperger's syndrome or AUA (**Table 2**).

Among girls who received an autistic disorder diagnosis, epilepsy and behavioral/emotional disorders were the two most common co-occurring diagnostic groups: each of the diagnostic groups had prevalence of 12.5%. In boys with an autistic disorder diagnosis, behavioral and emotional disorders and hyperkinetic disorder were most common: 17.9 and 14.3%, respectively.

Co-occurring diagnoses were common for both girls and boys with Asperger's syndrome. Among girls, the dominant diagnoses were hyperkinetic, neurotic/mood, and behavioral/emotional disorders (32.4–22.3%). The two most common conditions among boys were hyperkinetic (32.2%) and behavioral/emotional disorders (26.6%). It was among patients with Asperger's syndrome we saw the most pronounced differences between girls and boys: neurotic disorders were diagnosed in 30.2 vs. 13.4%, and mood disorders in 23.0 vs. 9.0%, respectively.

Neuropsychiatric disorders among children diagnosed with AUA were also common. The same conditions were most common among girls and boys: behavioral/emotional disorders (27.0 vs. 22.7%) and hyperkinetic disorders (25.8 vs. 30.9%).

**TABLE 1 |** Number of all 2–17 years girls and boys with incident diagnoses of autism spectrum disorders (ASD) ($N = 1{,}234$) in 2014 in Norway stratified on age.

| Autism spectrum disorder subtype (ICD-10 diagnosis) | Age group | Girls *N* | Boys *N* | Total *N* |
|---|---|---|---|---|
| **ASD total** | **2–17** | **308** | **926** | **1,234** |
| Autistic disorder (F84.0), $N = 415$ | 2–5 | 37 | 163 | 200 |
| | 6–11 | 21 | 115 | 136 |
| | 12–17 | 22 | 57 | 79 |
| Asperger's syndrome (F84.5), $N = 474$ | 2–11* | 31 | 147 | 178 |
| | 12–17 | 108 | 188 | 296 |
| AUA (F84.1, F84.8, F84.9), $N = 345$ | 2–5 | 20 | 43 | 63 |
| | 6–11 | 23 | 109 | 132 |
| | 12–17 | 46 | 104 | 150 |

*Data from Norwegian Patient Registry.*
*AUA, atypical or unspecified autism.*
**Combined age 2–11 are not shown due to privacy protection regulations.*

## Psychotropic Drug Use in Children With Newly Diagnosed ASD

Children with autistic disorder were mainly prescribed hypnotics (including alimemazine): 16.3 of girls and 17.3% of boys (**Table 3**).

Children with Asperger's syndrome were mainly prescribed stimulants (25.2 of girls and 23.3% of boys) and hypnotics (25.2 of girls and 18.2% of boys). There was a particular disparity in the use of antidepressants: these were prescribed to 16.5% of girls and only 7.2% of boys.

Children with AUA were mainly prescribed stimulants (16.9 of girls and 19.9% of boys) and hypnotics (including alimemazine) (19.1 of boys and 17.6% of girls).

Prescription drugs most commonly combined were stimulants and hypnotics, used by 83 (6.7%) of children with incident ASD.

The children who had ASD in the absence of any of the studied neuropsychiatric comorbidities received very little psychotropic drugs in general. Hypnotic drugs and alimemazine were the only drugs used to some extent by these children; around 13% were

**TABLE 2 |** Number and percentage (%) of 2–17 old Norwegian girls and boys with an incident diagnosis of Autism spectrum disorders (ASD) in 2014 who had psychiatric and neurological comorbidities during period 2008–2015.

| Autism spectrum disorder subtype (ICD-10 diagnosis) | Psychotic disorders F20–29 | Mood [affective] disorders (F30–39) | Neurotic, stress-related and somatoform disorders (F40–48) | Hyperkinetic disorders (F90) | Behavioral and emotional disorders (F91–98) | Epilepsy (G40) | Sleep disorders (G47) | Any ICD-10 F diagnosis except autism spectrum disorder |
|---|---|---|---|---|---|---|---|---|
| **ASD total (*N* = 1,234)** | **15 (1.2)** | ***(around 7)** | ***(around 12)** | **311 (25.2)** | **272 (22.0)** | **92 (7.5)** | ***(around 2)** | **800 (64.8)** |
| **Autistic disorder (F84.0)** | | | | | | | | |
| Girls (*N* = 80) | <4 | <4 | <4 | 8 (10.0) | 10 (12.5) | 10(12.5) | <4 | 42 (52.5) |
| Boys (*N* = 335) | <4 | 6 (1.8) | 11 (3.3) | 48 (14.3) | 60 (17.9) | 29 (8.7) | <4 | 185 (55.2) |
| **Asperger's syndrome (F84.5)** | | | | | | | | |
| Girls (*N* = 139) | 4 (2.9) | 32 (23.0) | 42 (30.2) | 45 (32.4) | 31 (22.3) | 8 (5.8) | 4(2.9) | 100 (71.9) |
| Boys (*N* = 335) | 4 (1.2) | 30 (9.0) | 45 (13.4) | 108 (32.2) | 89 (26.6) | 11 (3.3) | 10 (3.0) | 227 (67.8) |
| **AUA (F84.1,F84.8, F84.9)** | | | | | | | | |
| Girls (*N* = 89) | <4 | 8 (9.0) | 14 (15.7) | 23 (25.8) | 24 (27.0) | 10 (12.2) | 4 (4.5) | 64 (71.9) |
| Boys (*N* = 256) | 4 (1.6) | 11(4.3) | 31 (12.1) | 79 (30.9) | 58 (22.7) | 24 (9.4) | 10 (3.9) | 182 (71.1) |

*Data from the Norwegian Patient Register (NPR).*
*<4 denotes fewer than four individuals in the group. Exact numbers are not shown due to privacy protection regulations.*
**Exact numbers are not shown due to privacy protection regulations.*
*AUA, atypical or unspecified autism.*

**TABLE 3 |** Number and percentage (%) of 2–17 old Norwegian girls and boys with incident diagnoses of Autism spectrum disorders (ASD) in 2014 that were treated with CNS active drugs in the period of 365 days after the first diagnosis.

| Autism spectrum disorder subtype (ICD-10 diagnosis) | Stimulants *N* (%) | Antiepileptics *N* (%) | Antidepressants *N* (%) | Antipsychotics *N* (%) | Anxiolytics *N* (%) | Hypnotics/alimemazine[a] *N* (%) | Any of the drug groups |
|---|---|---|---|---|---|---|---|
| **ASD total (*N* = 1,234)** | **215 (17.4)** | **58 (4.7)** | ***(around 5)** | ***(around 5)** | **36 (2.9)** | **236 (19.1)** | **442 (35.8)** |
| **Autistic disorder (F84.0)** | | | | | | | |
| Girls (*N* = 80) | 6 (7.5) | 7 (8.8) | <4 | <4 | 4 (5.0) | 13 (16.3) | 18 (22.5) |
| Boys (*N* = 335) | 30 (9.0) | 17 (5.1) | <4 | 11 (3.3) | 8 (2.4) | 58 (17.3) | 88 (26.3) |
| **Asperger's syndrome (F84.5)** | | | | | | | |
| Girls (*N* = 139) | 35 (25.2) | 7 (5.0) | 23 (16.5) | 14 (10.1) | 6 (4.3) | 39 (28.1) | 78 (56.1) |
| Boys (*N* = 335) | 78 (23.3) | 5 (1.5) | 24 (7.2) | 15 (4.5) | 4 (1.2) | 64 (19.1) | 133 (39.7) |
| **AUA (F84.1, F84.8, F84.9)** | | | | | | | |
| Girls (*N* = 89) | 15 (16.9) | 8 (9.0) | 6 (6.7) | 2 (2.2) | 4 (4.5) | 17 (19.1) | 32 (36.0) |
| Boys (*N* = 256) | 51 (19.9) | 14 (5.5) | 7 (2.7) | 16 (6.3) | 10 (3.9) | 45 (17.6) | 93 (36.3) |

*Data from the Norwegian Patient Register (NPR) and the Norwegian prescription database (NorPD).*
*[a]Alimemazine is used in Norway as a hypnotic.*
*<4 denotes fewer than four individuals in the group. Exact numbers are not shown due to privacy protection regulations.*
**Exact numbers are not shown due to privacy protection regulations.*
*AUA, atypical or unspecified autism.*

treated with hypnotic drugs (mostly melatonin), independent of ASD subtype and gender.

## Accordance Between Drug Use and Co-occurring Conditions in Children With Newly Diagnosed ASD

There was a relatively good match between prescription of stimulants/ADHD drugs, antiepileptic drugs, and antidepressants, and co-occurring diagnoses for which these drugs are indicated (**Figure 1**). Of boys with an ASD diagnosis who were prescribed antiepileptic drugs, 94.6% had a diagnosis of epilepsy and 98.1% of boys who were prescribed stimulants had a diagnosis of ADHD. The corresponding proportions for girls were 77.3 and 94.4%. Most of the girls who received an antiepileptic drug because of a condition other than epilepsy had a mood or a pervasive and specific developmental disorder. In contrast, only a small proportion of children who received treatment with antipsychotic drugs had a diagnosis where such treatment is indicated (14.3% of the girls and 23.5% of the boys who were treated with antipsychotics had a psychotic condition).

# DISCUSSION

## Main Findings

In this nation-wide study, we have investigated co-occurring diagnoses and use of psychotropic medication among

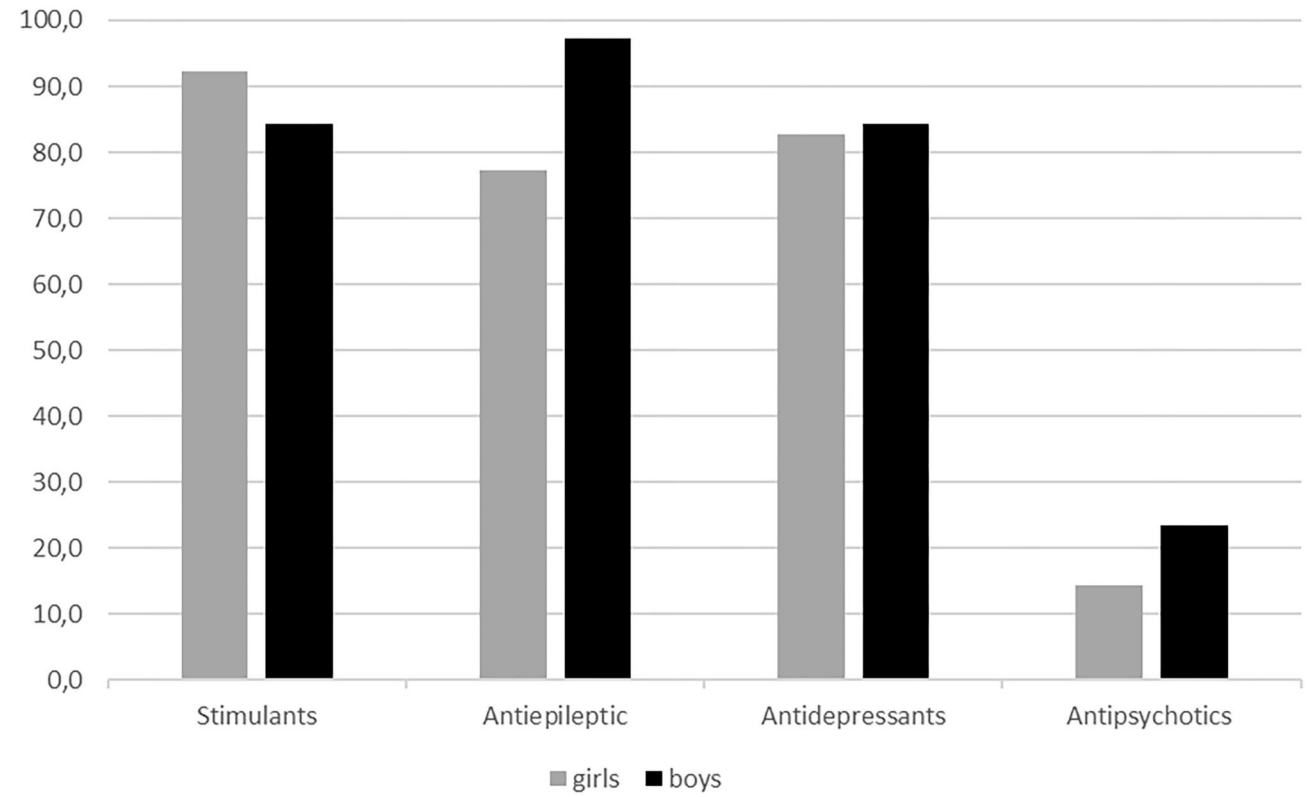


**FIGURE 1 |** Accordance (%) between medication use and diagnosis stratified on gender.

children with ASD in Norway. Most children had one or more neuropsychiatric diagnosis in addition to ASD. Use of psychotropic drugs was common and similar to the UK, yet lower than in the US (19). There was high accordance between psychotropic drug prescriptions and co-occurring conditions where the drugs were indicated, suggesting that the high prevalence of psychotropic drug use mainly was associated with the high co-occurrence of neuropsychiatric conditions. Noteworthy, among ASD patients without a co-occurring condition, use of psychotropic drugs was low and consisted predominantly of hypnotics.

## Prevalence

We have estimated that the periodic prevalence (cumulative incidence) of ASD in 2–17-year-old children in 2008–2014 was 7.6 per 1,000. This is in line with previous studies from Norway (20). Periodic prevalence of ASD among 8-year old was 6.3 per 1,000, which is almost three times lower than in the recent Center for Disease Control (CDC) study from the US (6). The discrepancy between the US and Norwegian estimates might be due to differences in diagnostic approaches, systems – DSM and ICD and differences in methodological approaches, respectively. However, a study from four European countries showed a variation in prevalence among 8 years old children ranging from 4.8 in a South-East France to 31.3 per 1,000 in Iceland (21). Finland and South-West France had very similar prevalence estimates to our study, respectively, 7.7 and 7.3 per 1,000. Predominance of boys over girls in ASD prevalence is consistent with the globally observed pattern (6, 21–23).

## Co-occurring Diagnoses

It is important to be aware of potential neuropsychiatric comorbidity among children with ASD to ensure adequate treatment, and our estimate of 64.8% is consistent with recent findings (24–26). Previous studies have mostly investigated either small cohorts or parent-reported diagnoses, or did not provide numbers specifically for children, or measured symptoms of neuropsychiatric comorbidities rather than registered diagnoses. Although we have used a different approach, our results were overall in agreement with analyses published by others (26–29). Regarding psychotic diagnoses in children with ASD, one study reported these to be below 1% (29). Interestingly, ADHD prevalence seems to be lower in our ASD cohort than in the US-based studies—probably due to differences in diagnostic approach. The use of a national registry has allowed us to study the prevalence of neuropsychiatric comorbidity in the whole ASD population and look specifically into each of three main sub-diagnoses of ASD. Co-occurring conditions were particularly common among adolescents with Asperger's syndrome and AUA, and in the former group we observed a high share of girls with co-occurring neurotic and mood disorders. It remains to be seen whether this difference may be a consequence of underdiagnosing among boys.

## Use of Psychotropic Drugs

No pharmacological treatments have demonstrated efficacy in reducing core symptoms of ASD, and the previously reported high use of psychotropic medication in this group therefore requires further investigations. There is a lack of evidence supporting the benefit of most psychotropic medications in children with ASD, while adverse drug effects are common (10, 12, 30, 31). The safety of medication use in children with ASD is an important consideration, especially since the communication deficits inherent in ASD can impair their ability to verbalize adverse drug effects (32). Importantly, many countries (including Norway) lack national guidelines on treatment of children diagnosed with ASD, and choice of therapy is often based on expert opinions or local experiences. The high prevalence of comorbidity might explain some of the reported psychotropic drug use. Problematic behaviors and associated symptoms may also require use of medications. We observed very low use of psychotropic drugs in ASD-diagnosed children without co-occurring conditions. The only exception was hypnotics (mainly melatonin), which were used by 10.6% - this is not in contradiction to guidelines (31). Others have also reported that ASD patients without co-occurring conditions use less medicines than those with comorbidities (13).

For children with co-occurring disorders there is some evidence base for use of melatonin, risperidone, aripiprazole, methylphenidate, and atomoxetine (31). However, use of risperidone and aripiprazole is associated with significant adverse drug reactions (12). Our study identified hypnotics as the predominant medication group for ASD patients having co-occurring diagnoses, especially for patients with autistic disorder. Stimulants were most commonly used by patients with Asperger's syndrome and AUA, followed by hypnotics. Children with Asperger's syndrome also had prescriptions for antidepressants, especially girls. Use of hypnotics was probably driven by symptoms of anxiety, aggression and irritability in ASD patients, while stimulants and antidepressants might have been prescribed to control co-existing conditions—ADHD and depression. We observed a very low use of antipsychotics (4.8%), apart from girls with Asperger's syndrome (10.1%), in contrast to data on median prevalence of use 8.4–57.4% in a recent meta-analysis (12).

## Accordance Between Drug Use and Diagnoses

Unwarranted use of medications should be avoided particularly among children with ASD as no drugs prove to be effective against core symptoms of the disorder. Children with ASD often present a complicated mosaic of symptoms reflecting both core diagnostic criteria of ASD, associated symptoms and behaviors, and symptoms of the co-existing neuropsychiatric conditions. Use of psychotropic medications is therefore often difficult to attribute to one particular diagnosis, representing a challenge for pharmacoepidemiological studies.

For stimulants, antiepileptics, and antidepressants we observed a good agreement between prescriptions and diagnoses/indications. A moderate disagreement between use of antiepileptics and diagnosis of epilepsy among girls is possibly explained by presence of non-epilepsy indications, such as anxiety or depression. In the case of antidepressants, the observed disagreement is possibly due to use of these drugs to control repetitive behaviors, or non-core symptoms of ASD. The largest discrepancy between medication use and indication was registered for antipsychotics. We believe that the prescriptions of antipsychotics are driven by the desire to control aggression, self-harm and other non-core symptoms of ASD. Evidence of efficiency of antipsychotics in treating irritability in ASD exists only for specific drugs like risperidone and aripiprazole (31).

Although most of the children who were prescribed medications had co-occurring diagnoses for which these medications are indicated, this does not necessarily mean that the medication use was appropriate. There is a lack of consensus on best practice for diagnosing co-occurring disorders in ASD and findings suggest that many co-occurring diagnoses provided by clinicians are not supported by standardized diagnostic tools (33, 34). Furthermore, children with ASD may respond differently to medications than children without ASD. For example, whereas selective serotonin reuptake inhibitors (SSRIs) have demonstrated efficacy in children with obsessive-compulsive disorder, SSRIs do not appear to reduce obsessive-compulsive symptoms in children with ASD (35). Methylphenidate has shown efficacy in treating ADHD in children with ASD, but was less effective and had more side effects than in children with ADHD alone (36).

## Methodological Considerations

A major strength in this study is the use of national registries, which eliminates poor recall and minimizes selection bias. It also allows for linkage of data from the NPR and the NorPD on an individual level.

One limitation is that the NPR has individual level data only from 2008. Our estimation of periodic prevalence (cumulative incidence) may be an underestimation of the lifetime prevalence of ASD in the children who were 6 year and older in 2014 because we lack information about them the first years of their lives. However, as shown in Suren et al. (15), the recapture of ASD cases in consecutive years in NPR are high and therefore we believe that the predicted prevalence is quite similar to lifetime prevalence of ASD. Further the incident cases may not be truly incident cases. Given the restriction to incident ASD diagnoses across the age range of 2 to 17 years, our sample is likely to include a higher proportion of late diagnosed individuals. Another limitation is that we have no information about drugs administered to hospitalized children. However, in Norway, very few children stay in institutions for long periods, and certainly not for ASD.

A limitation in using NorPD data on medications is that the registry only include information on whether a drug has been dispensed, but not whether the medication is actually being used.

# CONCLUSION

Use of psychotropic drugs is common among children with ASD and co-occurring neuropsychiatric diagnoses in Norway, and most children using medications have been diagnosed with a co-occurring condition for which the drug is indicated. Medication

use among children without co-occurring neuropsychiatric conditions is very low. There is a need for studies of efficacy and safety of CNS active medication use among children with ASD.

## DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available due to the restrictions inferred by Norwegian legislation for privacy protection, but anonymised data from this study can be made available upon reasonable request to the corresponding author. Requests to access these datasets should be directed to Yury Kiselev, dr.yurykiselev@gmail.com.

## AUTHOR CONTRIBUTIONS

YK conceptualized the study, interpreted results, drafted the initial manuscript, and reviewed and revised the manuscript. VH obtained the data, interpreted results, and reviewed and revised the manuscript. SS conceptualized and designed the study, analyzed the data, interpreted results, drafted the initial manuscript, and reviewed and revised the manuscript. MH conceptualized and designed the study, drafted the initial manuscript, interpreted results, and reviewed and revised the manuscript. PS and AH conceptualized the study, drafted the initial manuscript, interpreted results, and reviewed and revised the manuscript. TR-K and CS conceptualized and designed the study, interpreted results, and reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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# Monitoring of Adverse Drug Reaction-Related Parameters in Children and Adolescents Treated With Antipsychotic Drugs in Psychiatric Outpatient Clinics

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**Aim:** To assess the frequency of monitoring of adverse drug reaction (ADR) related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics and the considerations when monitoring was not performed.

**Methods:** This retrospective follow-up study included 100 randomly selected outpatients aged ≤18 years who had a first prescription of an antipsychotic drug recorded in the electronic medical records of psychiatric outpatient clinics between 2014 and 2017. They were followed for up to 3 years. This study assessed the frequency of monitoring for physical parameters (weight, height, body mass index, waist circumference, pulse, blood pressure, and an electrocardiogram) and laboratory parameters (glucose, lipids, and prolactin) before the first prescription of an antipsychotic drug as well as during its use. Monitoring frequencies were stratified by the patient characteristics (sex, age, cardiovascular risk factors, and use of other psychotropic drugs), and by location of antipsychotic drug initiation (psychiatric outpatient clinic or elsewhere). Additionally, this study assessed the considerations mentioned in the medical records for not monitoring ADR-related parameters.

**Results:** Overall, physical parameters were monitored more frequently (weight: 85.9% during the first half-year) than laboratory parameters (glucose and cholesterol: both 23.5%). There were no significant differences in monitoring at least one physical as well as in monitoring at least one laboratory parameter during the baseline period and during the total follow-up of antipsychotic drug treatment between the patient characteristics. In total, 3% of the children and adolescents were never monitored for any physical parameter, and 54% were never monitored for any laboratory parameter. For a minority of the children (14.8%) who were never monitored for laboratory parameters, considerations were recorded in their medical records, including refusal by the child or parents and monitoring performed by the general practitioner or elsewhere.

**Conclusion:** Monitoring frequencies of ADR-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics varied and especially monitoring of laboratory parameters was infrequent. Considerations why monitoring was not performed were rarely recorded. The optimal method of monitoring and documentation thereof should become clear to optimize the benefit-risk balance of antipsychotic drug treatment for each child.

**Keywords: drug monitoring, adverse (side) effects, antipsychotic agents, child, adolescent, psychiatry, medical record**

## INTRODUCTION

Antipsychotic drugs are frequently prescribed to children and adolescents (hereafter referred to as *children*) to treat psychiatric disorders, including anxiety disorders, behavioral disorders, irritability associated with autism, tic disorders, and attention-deficit/hyperactivity disorder (ADHD) (1, 2). Prescribing is commonly off-label because the evidence for efficacy of these drugs in this young and vulnerable population is scarce (3, 4). Furthermore, it is well-documented that antipsychotic drugs frequently cause bothersome and even severe adverse drug reactions (ADRs), including cardiometabolic, endocrine, and extrapyramidal adverse effects (4, 5). Examples of these adverse effects include weight gain, hypertension, gynecomastia, and parkinsonism (4–6). These ADRs can differ in frequency and relative impact in children compared to adults (7). Children seem to be more likely to experience somnolence during antipsychotic drug treatment than adults; moreover, the extent of weight gain was found to be greater in children (8). Additionally, antipsychotic-induced hyperprolactinemia is more important in children because it may have an effect on pubertal development. ADRs can have both physical and emotional consequences and thereby negatively impact children's daily lives. Therefore next to monitoring efficacy, monitoring of ADRs is important to carefully evaluate and optimize the benefit-risk balance of antipsychotic drug treatment for each child.

The development of ADRs caused by antipsychotic drugs can be monitored through related parameters, including physical parameters (e.g., weight, height, body mass index (BMI), waist circumference, pulse, blood pressure, and heart examination) and laboratory parameters (e.g., glucose, lipids, and prolactin). Monitoring instructions of these parameters are available in clinical guidelines, and in regulatory drug product information such as the information leaflet (9–12). Despite the existing guidelines and instructions, previous studies have shown a large variability in the monitoring frequencies of ADR-related parameters, and that the overall monitoring frequencies were suboptimal (13–16). The majority of these studies used administrative databases from various settings, such as insurance companies or databases of general practitioners, but questionnaires about monitoring among prescribers have also been assessed (14, 16). In-depth assessments of the medical records of children treated with antipsychotic drugs is of added value in creating a complete overview of the total antipsychotic drug therapy of the individual child and what is actually monitored and recorded in daily clinical practice, including the considerations and choices made concerning (not) monitoring for ADR-related parameters.

The primary aim of this study was to assess the frequency of monitoring of ADR-related parameters in children treated with antipsychotic drugs in psychiatric outpatient clinics and the considerations when monitoring was not performed. The secondary aim was to compare differences in monitoring frequencies between sex, age categories, children with and without cardiovascular risk factors, children who were and were not prescribed other psychotropic drugs, and children who started the antipsychotic drug treatment within the psychiatric outpatient clinics and those who started this therapy elsewhere.

## METHODS

### Setting, Study Population, and Follow-Up

This retrospective follow-up study included 100 randomly selected outpatients aged ≤18 years treated with an antipsychotic drug within Karakter, a large Dutch academic child and adolescent psychiatry organization that operates in 12 locations and offers clinical and outpatient therapy to children aged ≤18 years from across the Netherlands. Children are referred to this organization by, for example, general practitioners, for diagnosis and treatment of various psychiatric disorders, including autism spectrum disorder, ADHD, conduct disorders, depression, anxiety, compulsive disorders, eating disorders, and psychosis.

Patients were eligible for inclusion if they had a first prescription of an antipsychotic drug (ATC code N05A, excluding lithium [N05AN01]) within one of the psychiatric outpatient clinics of Karakter recorded in the electronic medical records between January 2014 and December 2017 and were prescribed an antipsychotic drug more than once. The date of this first prescription (index date) was defined as having no prescription of an antipsychotic drug recorded within the electronic medical records of these psychiatric (outpatient) clinics during the 6 months prior. Children could either have started the antipsychotic drug treatment within one of the psychiatric outpatient clinics of Karakter or elsewhere, for example in another psychiatric clinic. All included children were followed from the index date until the end of antipsychotic drug use recorded within the medical record, transfer out of practice, December 2018, or 3 years of follow-up, whichever came first. During follow-up, children could switch to another type of

antipsychotic drug, and the period that a child was treated with an antipsychotic drug was considered to be continuous if the gap between the end date of one prescription and the start date of the next prescription was <3 months. The children included were never hospitalized within one of the psychiatric clinics of Karakter during follow-up.

Approval for this study was obtained from the organization's institutional review board (Karakter's committee for human research; reference number 148-18). A review by a medical ethics committee was not required because of the observational nature of the study with no involvement in the children's therapy or infringement of the psychological or physical integrity of the children. All data were recoded to secure privacy.

## Data Collection

The electronic medical records were stored within a clinical information system linked to an electronic drug prescription system, which were used by the healthcare professionals to access and update medical records. Within the clinical information system information regarding the child's psychiatric therapy could be consulted, including drug treatment, physical measurements, and the laboratory test results for blood glucose, lipids, and prolactin. The electronic drug prescription system also included information on the physical measurements weight, height, BMI, pulse, and blood pressure. Both systems were used to collect the data needed for this study.

Standard operational procedures (SOPs) and a checklist were used during data collection to ensure validity. Each SOP described the location of specific information in the electronic medical records, including patient characteristics, psychiatric and somatic diagnoses, diagnoses in family history, previous and current drug use, the (main) physician of the child, test requests, physical and laboratory test results, referrals, and the location of antipsychotic drug initiation. While collecting the data, patient numbers were recoded to ensure privacy.

Medical record review and data entry were conducted by two reviewers, and seven medical records were also reviewed by the first author to check for discrepancies. Discrepancies and ambiguities of all medical records were discussed and resolved by consensus with the first author as well as the additional co-authors.

## Outcomes

Baseline information up to 31 days before the index date (start of antipsychotic drug) was collected, as well as data in 6-month timeframes (182 days) during follow-up. We assessed whether children were monitored for each ADR-related physical and laboratory parameter at least once during the baseline period, to assess if monitoring outcomes at the start of the antipsychotic drug treatment were known, and at least once during each fixed 6-month timeframe thereafter. When the follow-up time of antipsychotic drug use did not cover the complete final 6-month timeframe, this timeframe was excluded, and follow-up was censored at the end of the previous timeframe. The physical parameters included weight, height, BMI, waist circumference, pulse, blood pressure, and an electrocardiogram (ECG) and the laboratory parameters included glucose, cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, and prolactin, based on the available clinical guidelines regarding monitoring (9, 10). A child was considered to be monitored in a certain timeframe in case the result of the monitoring parameter was recorded in the medical record of that child.

## Determinants

Differences in monitoring frequencies of the ADR-related physical and laboratory parameters across the following patient characteristics were determined: (1) sex, (2) age categories (0–11 and 12–18 years old at the index date), (3) children with a cardiovascular risk factor at the index date and children without these risk factors, and (4) children who were prescribed other psychotropic drugs within the 6 months before, up to and including the index date, and children who were not prescribed other psychotropic drugs during this period. Additionally, differences in monitoring frequencies of the ADR-related physical and laboratory parameters were determined between children who started the antipsychotic drug treatment within the psychiatric outpatient clinics and those who started this therapy elsewhere. Cardiovascular risk factors were defined as having a recorded diagnosis of diabetes mellitus, hyperlipidemia, cardiovascular disorder, or overweight, hyperlipidemia according to the laboratory results or overweight according to the BMI measurement results. For the laboratory results, the reference values were included in the same document. The BMI measurement results were compared to the cutoff values described in a guideline for pediatricians (17).

## Considerations

Furthermore, this study assessed the considerations when monitoring of ADR-related physical and laboratory parameters was not performed during the antipsychotic drug treatment, which was defined as having no monitoring results included within the medical records.

## Data analysis

Descriptive statistics were used to determine the percentage of children monitored for each physical and laboratory parameter at least once during the baseline period and every fixed 6-month timeframe thereafter. Additionally, the percentage of children was determined who had been monitored for at least one of the physical and at least one of the laboratory parameters during the baseline period and during the total follow-up period thereafter. Monitoring frequencies were stratified by sex, age categories, cardiovascular risk factors at baseline, use of other psychotropic drugs within the 6 months before, up to and including the index date, and location of initiation of the antipsychotic drug treatment. Relative risks (RRs) and 95% confidence intervals (95% CIs) were calculated when comparing strata. Statistical analyses were performed using SPSS Statistics version 25.

# RESULTS

There were 1,877 outpatients who received a prescription of an antipsychotic drug within one of the psychiatric outpatient clinics between 2014 and 2017, who were prescribed an antipsychotic drug more than once, and who were never hospitalized within one of these psychiatric clinics during follow-up. One hundred children were randomly selected (**Table 1**), including only those who were ≤18 years of age at the index date and who did not have an antipsychotic drug prescription within these psychiatric (outpatient) clinics during the 6 months prior to the index date. The majority of the included children were male (79.0%), aged 6–11 years (52.0%), were prescribed risperidone at baseline (59.0%), had the initial antipsychotic drug prescription within one of the psychiatric outpatient clinics (85.0%), and were diagnosed with an autism spectrum disorder (80.0%).

## Monitoring of Physical and Laboratory Parameters

Overall, physical parameters were monitored more frequently than laboratory parameters (**Figures 1A,B**). The physical parameter weight was monitored most frequently in children during the baseline period (74.0%) compared to the other physical and laboratory parameters. After 6 months, 85 children were still treated with an antipsychotic drug, and the physical parameters monitored most frequently in these children during this first half-year of antipsychotic drug treatment were weight ($n = 73$; 85.9%) and height ($n = 66$; 77.6%), and the laboratory parameters monitored most frequently were glucose and cholesterol (both $n = 20$; 23.5%). None of the children were monitored for waist circumference or ECG during the first half-year of treatment.

In total, 75.0% of the children were monitored at least once for one of the physical parameters during the baseline period and 92.0% during the total follow-up of antipsychotic drug treatment thereafter (**Figure 1A**). Additionally, 11.0% of the children were monitored at least once for one of the laboratory parameters during the baseline period and 40.0% during the total follow-up of antipsychotic drug treatment thereafter (**Figure 1B**). Of those children who were not monitored during the baseline period for any physical parameter (n = 25), three (12.0%) were monitored for at least one physical parameter within the first week of antipsychotic drug treatment. Of those children who were not monitored during the baseline period for any laboratory parameter (n = 89), nine (10.1%) were monitored for at least one laboratory parameter within the first week of antipsychotic drug treatment.

## Determinants

There were no significant differences in monitoring of at least one physical parameter as well as in monitoring of at least one laboratory parameter during the baseline period and during the antipsychotic drug treatment thereafter between the patient characteristics, including sex, age categories, cardiovascular risk factors at the start of antipsychotic drug treatment, and use of other psychotropic drugs within the 6 months before the start of antipsychotic drug treatment (**Table 2**). There were

**TABLE 1** | Characteristics of the study population ($n = 100$).

| Characteristic | *n* | (%) |
|---|---|---|
| **Sex** | | |
| Females | 21 | (21.0) |
| Males | 79 | (79.0) |
| **Age at index date (years)** | | |
| 0–5 | 9 | (9.0) |
| 6–11 | 52 | (52.0) |
| 12–18 | 39 | (39.0) |
| **Year of index date** | | |
| 2014 | 27 | (27.0) |
| 2015 | 29 | (29.0) |
| 2016 | 24 | (24.0) |
| 2017 | 20 | (20.0) |
| **Total duration of follow-up (years)**[$] | | |
| < 0.5 | 15 | (15.0) |
| 0.5–1.0 | 19 | (19.0) |
| 1.0–1.5 | 19 | (19.0) |
| 1.5–2.0 | 11 | (11.0) |
| 2.0–2.5 | 7 | (7.0) |
| 2.5–3.0 | 9 | (9.0) |
| 3.0 | 20 | (20.0) |
| **Antipsychotic drug prescribed (at index date)** | | |
| Risperidone | 59 | (59.0) |
| Aripiprazole | 22 | (22.0) |
| Pipamperone | 10 | (10.0) |
| Olanzapine | 4 | (4.0) |
| Quetiapine | 4 | (4.0) |
| Haloperidol | 1 | (1.0) |
| **Initial antipsychotic drug prescription** | | |
| Within the psychiatric clinic | 85 | (85.0) |
| Elsewhere | 15 | (15.0) |
| **Psychiatric disorders (ever before index date)*** | | |
| Autism spectrum disorder | 80 | (80.0) |
| Attention-deficit / hyperactivity disorder | 47 | (47.0) |
| Intellectual disability | 17 | (17.0) |
| Anxiety disorder (incl. OCD, PTSD, phobia) | 16 | (16.0) |
| Mood disorder | 11 | (11.0) |
| Tic disorder | 11 | (11.0) |
| Behavioral disorder | 9 | (9.0) |
| Eating disorder | 4 | (4.0) |
| Sleeping disorder | 4 | (4.0) |
| Other | 23 | (23.0) |
| >1 psychiatric disorder (included above) | 76 | (76.0) |
| **Somatic disorders/problems (ever before index date)*** | | |
| Genetic/congenital/metabolic | 15 | (15.0) |
| Allergies/asthma/eczema | 11 | (11.0) |
| Overweight/obesity | 11 | (11.0) |
| Gastrointestinal/incontinence | 7 | (7.0) |
| Epileptic disorder | 5 | (5.0) |
| Urinary | 5 | (5.0) |
| Fetal alcohol syndrome/neonatal abstinence syndrome | 4 | (4.0) |

*(Continued)*

**TABLE 1** | Continued

| Characteristic | *n* | (%) |
|---|---|---|
| Underweight | 3 | (3.0) |
| Hyperlipidemia | 2 | (2.0) |
| Cardiovascular | 1 | (1.0) |
| Other | 9 | (9.0) |
| **Psychotropic drug use (6 months before index date)*** | | |
| Stimulants and atomoxetine | 33 | (33.0) |
| Hypnotics/sedatives | 26 | (26.0) |
| Antidepressants | 6 | (6.0) |
| Other (clonidine and lithium) | 7 | (7.0) |
| **Somatic drug use (6 months before index date)*** | | |
| Antihistamines | 7 | (7.0) |
| Oral inhalers and montelukast | 6 | (6.0) |
| Antiepileptic drugs | 3 | (3.0) |
| Other | 21 | (21.0) |

*Index date: first prescription of an antipsychotic drug recorded in the electronic medical records of the psychiatric outpatient clinic.*
*OCD, obsessive-convulsive disorder; PTSD, post-traumatic stress disorder.*
[$] *Total duration of follow-up (years): mean 1.6, median 1.4.*
**Recorded in the electronic medical records of the psychiatric clinic, up to and including the index date; several children and adolescents were diagnosed with more than one disorder and used more than one drug.*

also no significant differences between children who started the antipsychotic drug treatment within the psychiatric outpatient clinics and those who started this therapy elsewhere.

Assessing each physical and laboratory parameter separately, there were only few significant differences found regarding the monitoring frequency during the baseline period and during the first 6 months of antipsychotic drug treatment within one of the psychiatric outpatient clinics. There were no significant differences in monitoring between males and females (**Figure 2A**), but there were significant differences between the two age categories, as the physical parameters height and blood pressure were monitored relatively less frequently in children aged 12–18 years than in children aged 0–11 years (RR [95% CI]: 0.7 [0.6–1.0] and 0.7 [0.4–1.0], respectively) during the first 6 months of antipsychotic drug treatment (**Figure 2B**). Overall, children who were treated with other psychotropic drugs within the 6 months before the start of the antipsychotic drug treatment were monitored relatively more frequently during the baseline period and during the first 6 months thereafter for the majority of physical parameters compared to children not treated with other psychotropic drugs, but the only significant difference was found in monitoring for pulse during the baseline period (RR [95% CI]: 1.6 [1.1–2.5]). There were also no significant differences in monitoring the physical as well as the laboratory parameters when assessing only the psychotropic drugs prescribed within one of the psychiatric outpatient clinics and not elsewhere, for example by the general practitioner. Most parameters were monitored relatively more frequently when the antipsychotic drug treatment started within one of the psychiatric outpatient clinics included compared to elsewhere during the baseline period and during the first 6 months of antipsychotic drug treatment. Nevertheless, the only significant differences were monitoring for weight and waist circumference, as weight was monitored relatively more often in children who started the antipsychotic drug treatment within one of the psychiatric outpatient clinics compared to elsewhere (RR [95% CI]: 1.5 [1.0–2.3]) during the first 6 months of antipsychotic drug treatment within one of the psychiatric outpatient clinics, and waist circumference was monitored relatively less often in children who started the antipsychotic drug treatment within one of the psychiatric outpatient clinics compared to elsewhere (RR [95% CI]: 0.2 [0.0–0.8]) during the baseline period.

## Considerations

Of all included children, three were never monitored for any physical parameter during the baseline period or during the follow-up of antipsychotic drug treatment thereafter, and 54 were never monitored for any laboratory parameter. Regarding the three children who were never monitored for physical parameters, considerations why monitoring was not performed were not mentioned in their medical records. For eight of the 54 children (14.8%) who were never monitored for laboratory parameters, considerations for this lack of monitoring results were recorded in their medical records. The considerations or reasons included refusal by the child (e.g., fear of needles; $n = 4$) or parents ($n = 1$) and monitoring performed by the general practitioner or elsewhere ($n = 4$), but these results were not recorded in the medical records of the psychiatric outpatient clinic.

In the medical records of children who were monitored at least once for physical parameters during the baseline period or during the follow-up of antipsychotic drug treatment ($n = 97$), refusal by the child was mentioned in two medical records (2.1%). It was mentioned within several medical records that monitoring of physical parameters was also performed by the parents ($n = 12$; 12.4%), general practitioner ($n = 10$; 10.3%), or pediatrician ($n = 2$; 2.1%), though it was not clear if these monitoring results were always recorded in the medical records of the psychiatric outpatient clinics. In the medical records of children who were monitored at least once for laboratory parameters during the baseline period or during follow-up ($n = 46$), considerations or reasons for a delay in monitoring or a lack of results included also refusal by the child ($n = 5$; 10.9%), delay caused by the parents ($n = 2$; 4.3%), monitoring of glucose by the parents ($n = 1$; 2.2%), or monitoring performed elsewhere ($n = 5$; 10.9%), but the results were not recorded in the medical records of the psychiatric outpatient clinic.

# DISCUSSION

Although most physical parameters were monitored more frequently than laboratory parameters in children treated with antipsychotic drugs in psychiatric outpatient clinics, the monitoring frequencies for the majority of the parameters were low. There were no significant differences in monitoring of ADR-related parameters between sex and between children with and without cardiovascular risk factors at the start of the antipsychotic drug treatment, and only a few between age

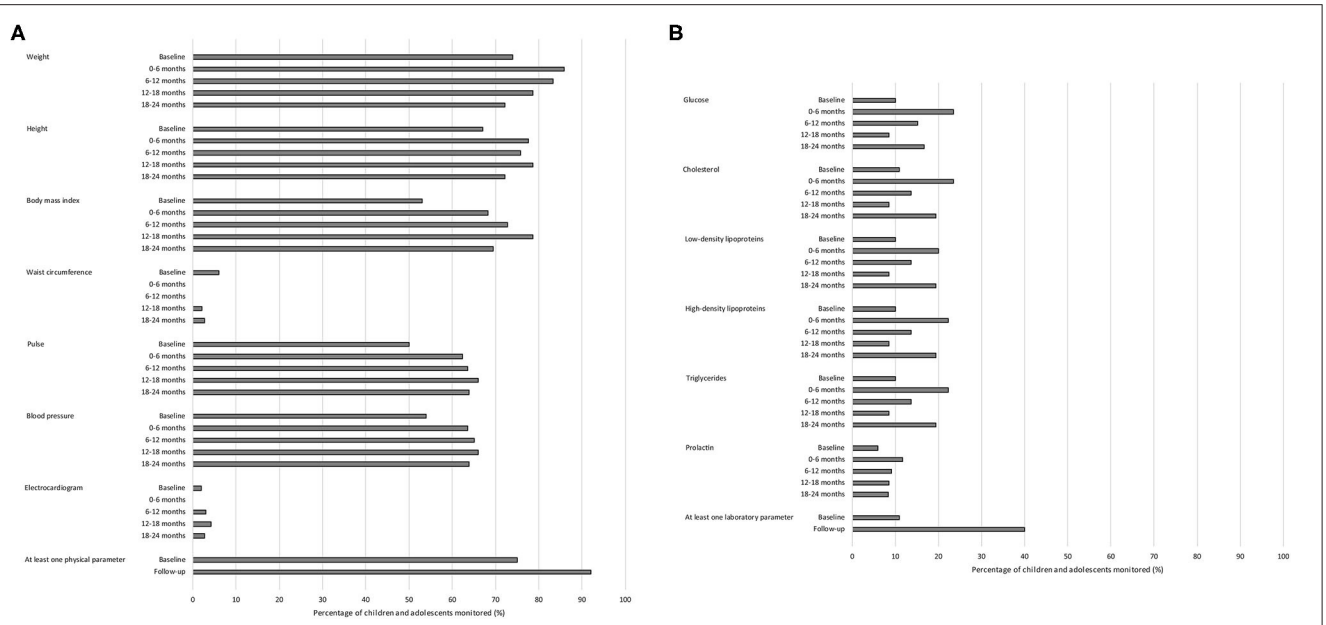


**FIGURE 1 |** Monitoring of adverse drug reaction-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics. **(A)** Monitoring of physical parameters. **(B)** Monitoring of laboratory parameters. Total number of children and adolescents: baseline period $n = 100$; 0–6 months $n = 85$; 6–12 months $n = 66$; 12–18 months $n = 47$; 18–24 months $n = 36$.

categories (height and blood pressure), children who did or did not use other psychotropic drugs within the 6 months before the start of the antipsychotic drug treatment (pulse), and between the initiation of the antipsychotic drug treatment at the psychiatric outpatient clinics or elsewhere (weight and waist circumference). The considerations when there were no monitoring results included in the medical records were only occasionally reported, as, for example, this was only mentioned for 14.8% of the children who were never monitored for laboratory parameters. Considerations mentioned included refusal by the child or parents and monitoring performed by the general practitioner or elsewhere.

Although previous studies have shown differences in monitoring frequencies in children treated with antipsychotic drugs, it is clear that the monitoring frequencies were suboptimal (13, 15, 16, 18). Overall, it has been shown that the physical parameter weight was monitored more frequently in children treated with antipsychotic drugs compared to the laboratory parameters glucose and lipids, and waist circumference was monitored much less, which is in line with the results of this current study (14, 15, 19).

Some differences in monitoring frequencies across sex and age categories were indicated in this study. Although this current study showed no significant differences between sex, it seemed that boys were monitored relatively more frequently than girls. This study demonstrated significant differences between age categories (0–11 and 12–18 years) in monitoring for the physical parameters height and blood pressure, but there were no significant differences in monitoring for laboratory parameters. However, higher monitoring frequencies of laboratory parameters in older children were demonstrated in previous studies (20, 21). This result could also have been expected in the current study, as these differences in monitoring frequencies of laboratory parameters could be due to the fear of needles, which is generally more common in younger children (22).

Especially the monitoring frequencies of the laboratory parameters were low. Monitoring instructions of parameters are available in clinical guidelines, but these guidelines differ in which parameters they recommend to monitor and the frequency of monitoring (9–11, 23). Although there is no national clinical guideline in the Netherlands for monitoring of ADR-related parameters in children treated with antipsychotic drugs, the guideline of Accare, a large academic mental health organization for child and adolescent psychiatry in the northern part of the Nederlands, is widely used by other Dutch healthcare professionals and is published on the national website for child and adolescent psychiatry (https://www.kenniscentrum-kjp.nl/) (9). Strict use of this guideline varies among prescribers, also within Karakter. The low monitoring frequencies of the laboratory parameters could be due to the recommendation of this guideline to monitor the parameters glucose and lipids only at baseline and every 6 months thereafter when there are risk factors present. One of these risk factors is overweight. However, no significant differences were shown by this study between children with and without cardiovascular risk factors, including overweight. Overweight was the most reported cardiovascular risk factor within this study. The risk factors hyperlipidemia and diagnosis for a cardiovascular disorder were only reported in few medical records, and diabetes mellitus in none. This

**TABLE 2 |** Monitoring of adverse drug reaction-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics: stratified by sex, age, cardiovascular risk factors, use of other psychotropic drugs, and location of antipsychotic drug initiation.

| | | Physical parameters | | | | Laboratory parameters | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | | Follow-up | | Baseline | | Follow-up | |
| | *n* | % | RR [95% CI] | % | RR [95% CI] | % | RR [95% CI] | % | RR [95% CI] |
| **Sex** | | | | | | | | | |
| Female | 21 | 66.7 | 1 (ref) | 85.7 | 1 (ref) | 9.5 | 1 (ref) | 23.8 | 1 (ref) |
| Male | 79 | 77.2 | 1.2 [0.8–1.6] | 93.7 | 1.1 [0.9–1.3] | 11.4 | 1.2 [0.3–5.1] | 44.3 | 1.9 [0.8–4.2] |
| **Age** | | | | | | | | | |
| 0–11 years old | 61 | 77.0 | 1 (ref) | 96.7 | 1 (ref) | 16.4 | 1 (ref) | 34.4 | 1 (ref) |
| 12–18 years old | 39 | 71.8 | 0.9 [0.7–1.2] | 84.6 | 0.9 [0.8–1.0] | 2.6 | 0.2 [0.0–1.2] | 48.7 | 1.4 [0.9–2.3] |
| **Cardiovascular risk factor[#]** | | | | | | | | | |
| No | 86 | 74.4 | 1 (ref) | 91.9 | 1 (ref) | 10.5 | 1 (ref) | 40.7 | 1 (ref) |
| Yes | 14 | 78.6 | 1.1 [0.8–1.4] | 92.9 | 1.0 [0.9–1.2] | 14.3 | 1.4 [0.3–5.7] | 35.7 | 0.9 [0.4–1.9] |
| **Other psychotropic drugs[$]** | | | | | | | | | |
| No | 48 | 72.9 | 1 (ref) | 91.7 | 1 (ref) | 14.6 | 1 (ref) | 41.7 | 1 (ref) |
| Yes | 52 | 76.9 | 1.1 [0.8–1.3] | 92.3 | 1.0 [0.9–1.1] | 7.7 | 0.5 [0.2–1.7] | 38.5 | 0.9 [0.6–1.5] |
| **Initiation at the psychiatric clinic** | | | | | | | | | |
| No | 15 | 60.0 | 1 (ref) | 86.7 | 1 (ref) | 6.7 | 1 (ref) | 33.3 | 1 (ref) |
| Yes | 85 | 77.6 | 1.3 [0.8–2.0] | 92.9 | 1.1 [0.9–1.3] | 11.8 | 1.8 [0.2–12.8] | 41.2 | 1.2 [0.6–2.6] |

*Children and adolescents who were monitored for at least one physical and for at least one laboratory parameter during the baseline period and during the total follow-up of antipsychotic drug treatment thereafter.*

*Baseline period: a maximum of 1 month before the first prescription of an antipsychotic drug in the psychiatric outpatient clinic, up to and including the date of this first prescription.*

*[#]Cardiovascular risk factors at baseline: diagnosis for overweight or overweight according to the body mass index measurements (n = 11), diagnosis for hyperlipidemia or hyperlipidemia according to the laboratory results (n = 2), diagnosis for a cardiovascular disorder (n = 1), diagnosis for diabetes mellitus (n = 0).*

*[$]Use of other psychotropic drugs within the 6 months before the first prescription of an antipsychotic drug within the psychiatric outpatient clinic, up to and including the date of the first prescription.*

*n, number of children and adolescents.*

*RR [95%CI], relative risk [95% confidence interval].*

could be because these disorders are rare in children, or this information was not well-reported in the medical records and therefore missing.

Previous studies have shown suboptimal monitoring frequencies in children treated with antipsychotic drugs and low compliance to monitoring guidelines (15, 20, 24). Improvement in monitoring practices is needed, which is seen not only in children treated with antipsychotic drugs, but also the monitoring frequencies for adults treated in psychiatric outpatient clinics have been shown to be suboptimal according to the guidelines (25). Additionally, low monitoring frequencies are not only related to antipsychotic drug use, as low monitoring frequencies and poor adherence to clinical guidelines have also been demonstrated concerning other psychotropic drugs, including lithium, as well as somatic drugs (26–28).

As this study showed only minor differences in monitoring frequencies between patient characteristics, including sex, age categories, and children with and without risk factors present, and suboptimal monitoring frequencies were also shown by other studies including adults and other types of drugs, the reasons for suboptimal monitoring might be with the healthcare professionals (or the system) or children and caregivers themselves. Suboptimal monitoring by the healthcare professionals could be caused by the lack of a clear national clinical guideline, insufficient collaboration with other healthcare professionals, low confidence about monitoring, a lack of a reminder system or insufficient access to the equipment needed, for example a blood pressure machine (29). Despite the lack of a national guideline, the majority of the prescribers of antipsychotic drugs to children are aware that they should monitor for ADRs (14). However, when collaborating with other health care professionals, it is not always clear who is responsible to monitor for ADRs (29–31). As shown in this current study, children could also be monitored by the general practitioner or pediatrician, though it was not always clear which exact parameters were monitored elsewhere and if the results were recorded in the medical records of the psychiatric outpatient clinics, since the electronic systems were not linked. A gap between monitoring for ADRs and the rest of the antipsychotic drug treatment is concerning, as it could lead to poor monitoring, undetected abnormalities in ADR-related physical and laboratory parameters, and insufficient follow-up of the antipsychotic drug treatment. An electronic system for medical records could enhance the monitoring practices by more easily sharing monitoring results and defining whose responsibility it is to monitor the children (29). Electronic medical records do also facilitate as they improve the quality of outpatient clinic notes, including information about ADRs and follow-up information (32). However, documentation quality varies between healthcare professionals and type of care measure

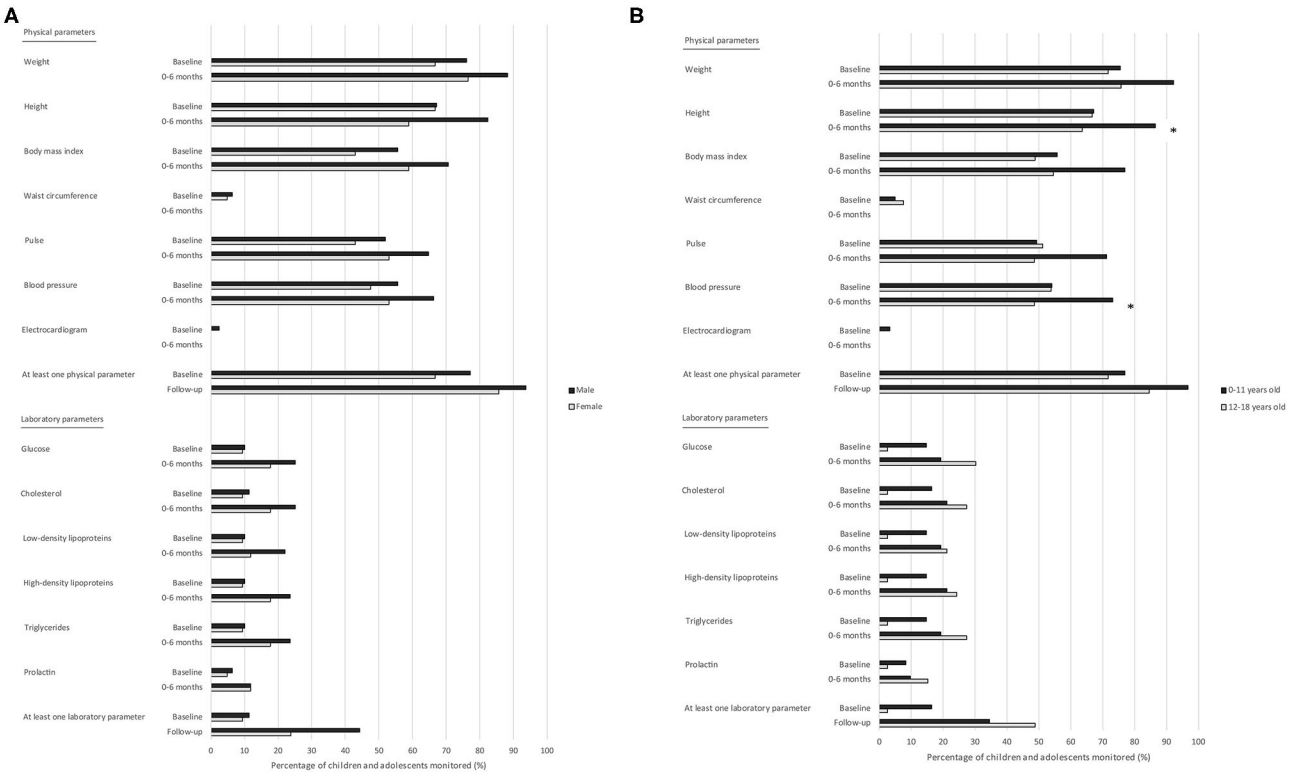


**FIGURE 2 |** Monitoring of adverse drug reaction-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics: stratified by sex and age. **(A)** Stratification by sex. **(B)** Stratification by age. Total number of children and adolescents: Male: baseline period $n = 79$; 0–6 months $n = 68$; Female: baseline period $n = 21$; 0–6 months $n = 17$. Total number of children and adolescents: 0–11 years old: baseline period $n = 61$; 0–6 months $n = 52$; 12–18 years old: baseline period $n = 39$; 0–6 months $n = 33$. Baseline period: a maximum of 1 month before the first prescription of an antipsychotic drug in the psychiatric outpatient clinic, up to and including the date of this first prescription. * Significant difference; $p < 0.05$.

in regard to medication, drug allergies, and compliance with guidelines (33), as also seen in this current study. Electronic systems should be equipped to suit the needs of healthcare professionals in the evaluation and monitoring of ADRs in children treated with antipsychotic drugs (34). For example, this electronic system should also include a reminder system, not only to remind the healthcare professional that monitoring should be performed, but also to assess the parameters outcomes, for example laboratory parameters, on a later moment in time. Furthermore, the children and the caregivers play an important and active role in optimizing monitoring practices. Barriers related to the children of caregivers are refusal by the child, for example because of a fear of needles, as also shown in this study, or the caregivers who resist or simply forget to obtain the laboratory tests (35). Clear instructions and information tailored to the patient would improve monitoring practices (36). Additionally, it is important that the healthcare professional is aware of the barriers present and can anticipate the specific situation.

A strength of this study was that by reviewing the electronic medical records, a complete overview was gained of the total antipsychotic drug therapy of the individual child in the psychiatric outpatient clinics. Medical records review and data entry were conducted by only two reviewers, who used SOPs and the checklist to gather the information needed, which ensured that they gathered information consistently and no important files in the medical records were missed. However, this study also has some limitations. This study included a relatively small number of children in one mental healthcare institution in the Netherlands, although there were multiple locations involved. Especially the numbers when separating in different patient characteristics and the location of initiation of the antipsychotic drug treatment were small. To compare these groups was the secondary aim of the study. More research is needed to detect differences between those groups. The diagnoses (**Table 1**) were those reported in the medical records and we did not validate these diagnoses. However, this does not influence the results of this study as a child treated with an antipsychotic drug should be monitored regardless of the diagnosis. Fifteen children were prescribed an antipsychotic drug elsewhere before they were transferred to one of the psychiatric outpatient clinics, which could lead to a difference in documentation history compared to the children who started the antipsychotic drug treatment within the psychiatric outpatient clinics. Some children did not

have 1 month of valid data available before the index date. Data collected depended on what was reported within the records, and notes could be missing, unclear, or incomplete. However, for this study also the free texts within a medical record were taken into account. Even if missing or unclear data has led to an underestimation of the monitoring frequencies, this would also deteriorate the quality and completeness of the medical records in the psychiatric outpatient clinics in daily clinical practice, and could lead to an incomplete transfer of information to other internal and external healthcare professionals.

### Clinical Implications

By monitoring children treated with antipsychotic drugs, abnormalities in ADR-related physical and laboratory parameters can come to light, and interventions can be performed to optimize the benefit-risk balance of the antipsychotic drug treatment for each child, including lowering the dosage, switching to another drug, a referral to a dietitian or consulting a pediatrician. When monitoring is suboptimal, this could cause severe risks, as abnormalities in blood glucose and a high body weight could result in the development of diabetes mellitus, and abnormalities in blood prolactin levels could lead to gynecomastia and galactorrhea (37, 38). On the other hand, when the monitoring frequency is excessive, this not only increases the healthcare costs, causes unneeded time investments and an administrative burden for the healthcare professionals, this can also impact the child's quality of life, considering the fear of needles and the constant reminder of the psychiatric disorder with which the child has been diagnosed. Further research is needed to gain knowledge about the optimal method of monitoring for ADR-related parameters in children, which should be captured in a clear national clinical guideline to prevent children from developing severe ADRs and to optimize the benefit-risk balance in the individual child.

## CONCLUSION

Overall, monitoring frequencies of ADR-related parameters in children treated with antipsychotic drugs in psychiatric outpatient clinics varied and especially monitoring of the laboratory parameters was low. There were no prominent differences in monitoring between patient characteristics, for example across sex and age categories. Considerations why monitoring was not performed were rarely recorded within the medical records. By gaining more knowledge concerning the optimal frequency of monitoring and the facilitators and barriers for monitoring in psychiatric outpatient clinics as well as for each child, monitoring practices could be improved. Monitoring leads to knowledge about the effects of the antipsychotic drug treatment in the individual child, which is essential to evaluate and improve the benefit-risk balance of the therapy.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the dataset includes information from psychiatric outpatient clinics (for children and adolescents). Requests to access the datasets should be directed to Lenneke Minjon, l.minjon@uu.nl.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Karakter's committee for human research (institutional review board; reference number 148-18). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

Material preparation and data collection were performed by LM, IB, and EB. Analysis was performed by LM, IB, and EH. The first draft of the manuscript was written by LM. All authors commented on previous versions of the manuscript, contributed to the study conception and design, read and approved the final manuscript.

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# First-Time Users of ADHD Medication Among Children and Adolescents in Germany: An Evaluation of Adherence to Prescribing Guidelines Based on Claims Data

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**Background:** Drug utilization studies based on real-world data are vital for the identification of potentially needed improvements to rational prescribing. This is particularly important for the pharmacological treatment of children and adolescents with attention-deficit hyperactivity disorder (ADHD) due to the associated potential side effects and the frequent use. Whereas prevalent use is well-characterized, studies on first-time use of ADHD medication are scarce. This study aimed to evaluate off-label prescribing in first-time users of ADHD medication among children and adolescents in Germany based on three criteria: (i) lack of a documented ADHD diagnosis; (ii) first-time pharmacological treatment with a second-line drug; and (iii) patient age below 6 years.

**Methods:** Based on German claims data, we included children and adolescents aged 0–17 years with a first-time dispensation of any ADHD medication in the period 2015–2017. These first-time users were characterized with regard to sex, age, specialty of the prescribing physician, documentation of an ADHD diagnosis, psychiatric hospitalization, psychiatric comorbidities, and history of other psychopharmacological drugs at first-time use.

**Results:** The study population comprised 18,703 pediatric first-time users of ADHD medication. Of these, 9.8% had no documented ADHD diagnosis. Most of the ADHD drug users received first-line ADHD pharmacotherapy (methylphenidate, atomoxetine), whereas 2.6% were prescribed second-line ADHD medication (lisdexamfetamine, guanfacine, dexamfetamine, multiple ADHD drugs) as first drug. Overall, 1.2% of first-time users were aged below 6 years. A total of 12.7% of the study population met any off-label criterion.

**Conclusions:** About 13% of pediatric first-time users of ADHD medication in Germany received an off-label pharmacotherapy at first-time use. Prescribing ADHD medication without a confirmed ADHD diagnosis was the most common of the three assessed off-label criteria. Off-label prescribing regarding drug choice and age of patients only

occurred in a small percentage of initial pharmacological ADHD treatment. Our results suggest the need for improvement in rational prescribing, especially with regard to diagnostic requirements.

**Keywords: ADHD, adolescents, children, pharmacotherapy, off-label use, pharmacoepidemiology**

## INTRODUCTION

With a worldwide community prevalence between 2 and 7%, attention-deficit hyperactivity disorder (ADHD) is one of the most common mental disorders among children and adolescents (1, 2). The global burden of ADHD is significant (3, 4) and it is estimated that more than 40% of individuals with childhood ADHD continue to experience symptoms and impairment in adulthood (5). National and international guidelines on ADHD recommend a multimodal treatment approach for children and adolescents with a combination of medication and psychosocial interventions (6). Regarding short-term efficacy, current evidence supports pharmacological treatment, particularly stimulants, as the most efficacious ADHD treatment (7). The evidence for long-term effects of drugs to treat ADHD on reducing impairments such as educational outcomes is limited and inconsistent (8). There is a strong evidence base that treatment with ADHD medications reduces negative outcomes such as injuries, cigarette smoking, suicide, and criminal activity (4).

Before initiating medication, the prescriber must ensure that the patient has a confirmed diagnosis of ADHD. Current clinical guidelines recommend a full clinical interview including structured and comprehensive assessments for the ADHD diagnosis (6, 9). In addition to this, stimulants such as methylphenidate (MPH) and lisdexamfetamine (LDX) are basically exempt from reimbursement by statutory health insurance providers in Germany unless strict and comprehensive diagnostic requirements have been fulfilled (10).

Although the evidence base is the same, the approval status and guideline recommendations differ between countries in North America and Europe, particularly regarding LDX. In Germany—as in other European countries—only MPH and atomoxetine (ATX) are approved as the initial—i.e., first-time—pharmacological ADHD treatment without restriction and—in contrast to the approval in, e.g., the US and Canada—LDX (available since June 2013) and dexamfetamine (DEX) require insufficient response to previous MPH treatment. Similarly, guanfacine (GUA; available since January 2016) may be indicated only if stimulants such as MPH are not suitable. In its recommendations, the German guideline on ADHD points out that the approval status of the medication should be taken into account (11).

All mentioned drugs are not approved for children aged below 6 years, i.e., preschool children in Germany. Guidelines do not preclude pharmacological treatment for preschool children but emphasize that psychosocial interventions should be considered first. Medication should only be prescribed to children with residual symptoms and after an individual risk-benefit assessment.

Little is known about adherence to guidelines for ADHD medication prescribed to children and adolescents in routine care. Especially recent drug utilization studies from Europe and including all available ADHD medication are lacking. These are, however, important since LDX and GUA have only been available for a relatively short time in European countries. Early monitoring and identification of characteristics associated with off-label prescribing of these newer drugs is crucial as the safety of newer drugs in routine care is generally not well-understood.

Therefore, this study aimed to evaluate off-label prescribing in first-time users of ADHD medication among children and adolescents in Germany based on three criteria: (i) lack of a documented ADHD diagnosis; (ii) first-time pharmacological treatment with a second-line drug; and (iii) patient age below 6 years.

## MATERIALS AND METHODS

### Data Source

This study used data from the German Pharmacoepidemiological Research Database (GePaRD) (12). GePaRD is a claims database which includes information on persons who have been insured with one of the four participating statutory health insurance providers since 2004 or later. Per data year, GePaRD covers information on ∼20% of the general population of Germany. About 90% of the general population are covered by statutory health insurance in Germany and there is a free choice of providers (13). Children are typically covered with one parent or legal guardian without any surcharges.

In addition to demographic data, GePaRD contains information on reimbursable drug dispensations as well as outpatient (i.e., from general practitioners and specialists) and inpatient services and diagnoses. Drug dispensations are identifiable via the German modification of WHO Anatomical Therapeutic Chemical (ATC) classification codes. Diagnoses are coded according to the German Modification of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD).

### Study Population

We included children and adolescents aged 0–17 years with a dispensation of any ADHD medication between January 1, 2015 and December 31, 2017 and with health insurance coverage on the earliest dispensation date in that period. ADHD medication included all drugs approved to treat ADHD in Germany at the time, which were identified based on ATC codes: MPH (N06BA04), ATX (N06BA09), LDX (N06BA12), DEX (N06BA02), or GUA (N06BA21; only since January 2016).

Individuals were excluded if they did not have a minimum pre-observation time (i.e., health insurance coverage) of 4 years before the earliest dispensation date; those aged 4 years or younger were required to have a pre-observation time since the year of birth. Next, we excluded all individuals with a dispensation date of any ADHD medication in the pre-observation period (i.e., prevalent users).

The final study population can therefore be considered as first-time users of any ADHD medication. Depending on the ADHD medication(s) dispensed on the day of first-time use, each individual was assigned to one of six mutually exclusive groups of users: MPH; ATX; LDX; DEX; GUA; or users of more than one of these drugs.

## Characteristics of the Study Population

Characteristics assessed for each individual of the study population included year of first-time use, sex, and age. We examined whether ADHD (ICD-10 codes F90/F98.8) and/or narcolepsy (for which some MPH preparations are licensed in Germany; ICD-10 code G47.4) had been coded in the 2 years before and including the day (inpatient data) or quarter (outpatient data) of first use. The specialty of the prescribing physician was derived from the prescription. Psychiatric hospitalizations were identified based on hospital admissions with at least one ICD-10 code F00–F99 as main or secondary discharge diagnosis in the year before and including the day of first use. Psychiatric comorbidities were assessed from inpatient data in the year before and including the day of first use; in outpatient data—as outpatient diagnoses are recorded quarterly—psychiatric comorbidities were assessed in the quarter of the day of first use and in the three preceding quarters. History of other psychopharmacological drugs—antipsychotics (ATC codes starting with N05C), anxiolytics (N05B), hypnotics and sedatives (N05C), and antidepressants (N06A)—was assessed in the year before (not including) the day of first use of ADHD medication.

## Data Analysis

Descriptive analyses were conducted in first-time users overall and stratified by (i) whether or not there was a lack of a documented ADHD diagnosis, (ii) whether or not second-line ADHD medication was dispensed on the day of first use, and (iii) whether or not the age was below 6 years.

We additionally evaluated characteristics associated with (off-label) prescribing of a second-line pharmacological treatment as the first ADHD medication. Multivariable logistic regression was used to obtain odds ratios (OR) and corresponding 95% confidence intervals (CI) for the association between the characteristics described above and the prescribed line of treatment, comparing first-time users of second-line drugs (LDX, DEX, or GUA) with those of first-line drugs (MPH or ATX). We did not include all psychiatric comorbidities as independent variables but rather selected those deemed clinically relevant for the decision-making process regarding the prescription of ADHD medication.

# RESULTS

The study population comprised 18,703 pediatric first-time users of ADHD medication (**Figure 1**). Overall, 75% of all first-time users were male (**Table 1**). Any one of the three off-label criteria was fulfilled by 12.7% of the study population. For 9.8%, there was no documented diagnosis of ADHD. This patient group encompassed 0.1% of patients with a diagnosis of narcolepsy without ADHD and 9.7% without either a diagnosis of ADHD or narcolepsy. The most commonly prescribed ADHD medication was MPH, followed by ATX; multiple drugs were dispensed to 19 individuals (0.1%). A total of 2.6% of all individuals were prescribed second-line ADHD drugs as first pharmacological treatment. Overall, 1.2% of ADHD medication users were younger than 6 years.

More than half of all users received the first prescription from a child and adolescent psychiatrist and almost one quarter received the prescription from a pediatrician. The most frequent psychiatric comorbidities were conduct disorders and emotional disorders in childhood or anxiety; about 80% had at least one comorbidity. With regard to history of other psychopharmacological drugs, antipsychotics were most frequently prescribed.

## Lack of a Documented ADHD Diagnosis at First-Time Use of ADHD Medication: Patient and Prescriber Characteristics

Psychiatric hospitalizations occurred less often in first-time users without than in those with a documented ADHD diagnosis (9 vs. 12%; **Table 1**). Most psychiatric comorbidities were less prevalent in individuals with a lack of a documented ADHD diagnosis. For example, conduct disorders were recorded in 19% of first-time users without and in 38% of those with a documented ADHD diagnosis.

## Second-Line Drug as First ADHD Medication: Patient and Prescriber Characteristics

In recipients of second-line ADHD medication, there was more often a lack of ADHD diagnosis compared with individuals receiving first-line ADHD medication (**Table 1**). The percentage of prescribing pediatricians was higher among first-time users of second-line ADHD medication as compared to first-time users of first-line drugs.

The results from the multivariable logistic regression model are shown in **Table 2**. The following characteristics were associated with an off-label prescription of a second-line ADHD medication: Compared with adolescents aged 12–17 years, patients aged below 6 years were more likely to receive a second-line drug. Further, individuals were more likely to receive second-line ADHD medication if they received the prescription from a pediatrician; had a psychiatric hospitalization; were diagnosed with conduct disorders, mental retardation, tic disorders or pervasive developmental disorders; or had a history of antipsychotics.

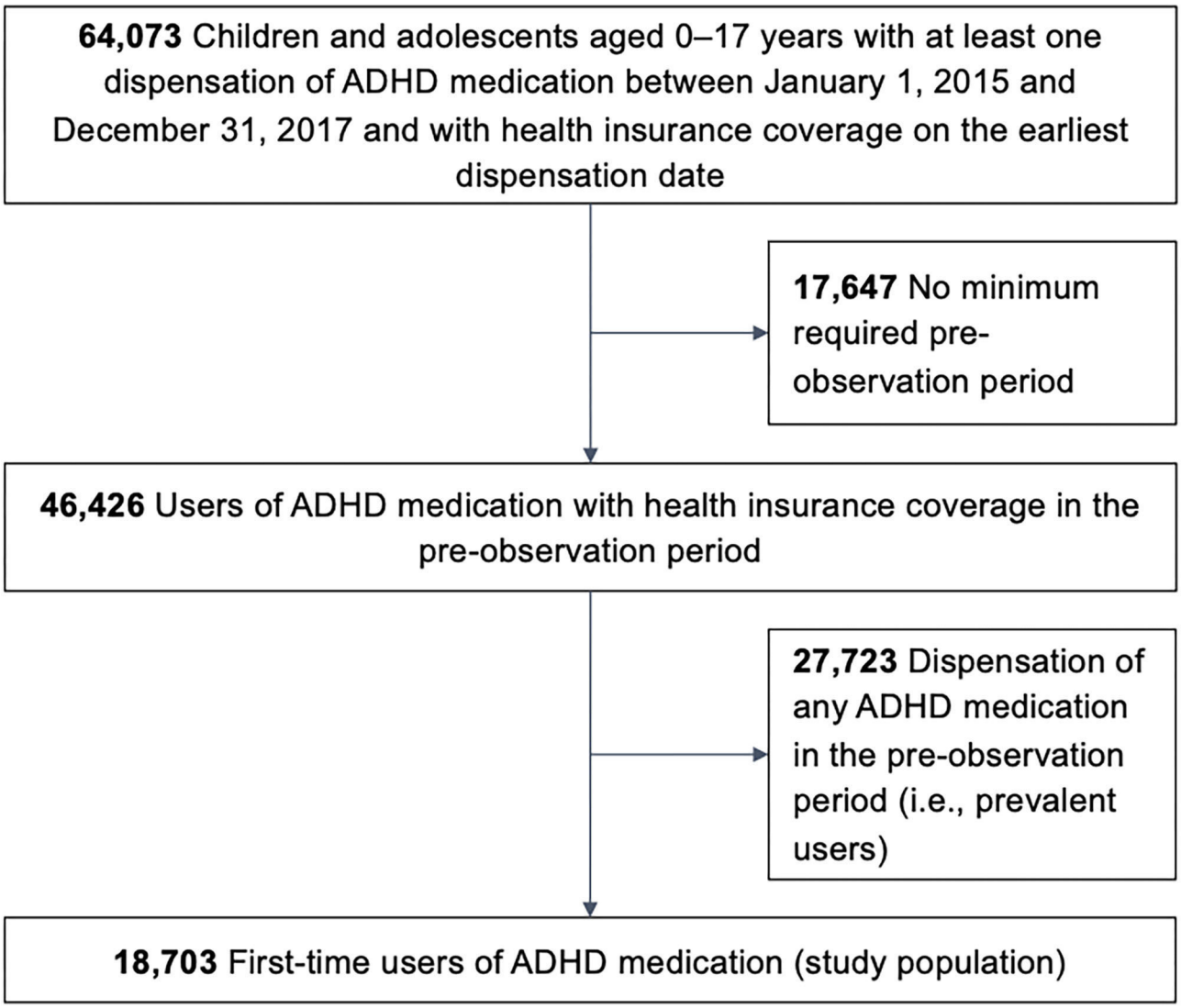


**FIGURE 1 |** Flow diagram. ADHD, attention deficit hyperactivity disorder.

### ADHD Medication Prescriptions in Children <6 Years: Patient and Prescriber Characteristics

In patients aged below 6 years, second-line ADHD medication use was more prevalent (**Table 1**). They also more often had no documented ADHD diagnosis and a pediatrician as the prescribing physician. Among others, conduct disorders and pervasive developmental disorders were more frequent in this patient group. Among all first-time users younger than 6 years ($n = 220$), 10% ($n = 22$) were aged 3 years or younger.

## DISCUSSION

This study evaluated adherence to prescribing guidelines in first-time users of ADHD medication among children and adolescents in routine care in Germany based on three key off-label criteria. Our main finding is that prescribing ADHD medication without a confirmed ADHD diagnosis was relatively common, while rather few first users received prescriptions of a second-line ADHD medication, and only a small percentage of users was aged below 6 years.

### Lack of a Documented ADHD Diagnosis

During the study period, ADHD and narcolepsy were the only licensed indications for each of the ADHD medications assessed in this study (14). As expected, narcolepsy without ADHD was documented in very few cases only. We therefore focused on the off-label criterion indicating a lack of a documented diagnosis of ADHD.

A prior study on LDX used data on prescriptions and diagnoses of ADHD from eight European countries (15). The

main results include that about 62–95% of pediatric and adult LDX first-time users had a recorded diagnosis of ADHD (15). Although the comparability is limited due to the focus on LDX users only, this result is in accordance with our finding.

Given that current clinical guidelines consistently recommend a structured, comprehensive ADHD assessment (6, 9) and that German regulations regarding the reimbursement of stimulants require detailed diagnostics (10), it is striking that in our study about one in 10 patients had no documented diagnosis of ADHD at the time of the first prescription of an ADHD drug. As we reviewed recorded diagnoses from up to 2 years before the first prescription and from any provider—including psychotherapists—we do not believe that recorded diagnoses of ADHD before the first drug treatment or during a prior non-pharmacological treatment have been overlooked.

The characteristics of patients with a lack of a documented ADHD diagnosis do not indicate that they were more severe cases warranting immediate drug treatment. Characteristics such as psychiatric hospitalizations as well as comorbidities that would indicate a more complex psychopathology (e.g., conduct disorders) were even less frequent in first-time users of ADHD drugs with a lack of a documented ADHD diagnosis as compared to those with a diagnosis of ADHD.

We conclude that prescribing ADHD medication to children and adolescents without a clinically confirmed ADHD diagnosis was relatively common. Assuming that in these cases diagnostic requirements were not met, our results indicate irrational prescribing with possible associated consequences such as exposing the patient to unnecessary risks of side effects.

## Second-Line Drug as First ADHD Medication

In our study, characteristics of patients who used second-line as compared to those who used first-line drugs as the first ADHD medication differed markedly. These characteristics—higher prevalence of prior psychiatric hospitalization and of antipsychotic prescription, conduct disorders, mental retardation, tic disorders, and pervasive developmental disorders—indicate a more complex and extensive psychopathology in these patients. In the multivariable regression, these characteristics were positively associated with receiving a second-line drug.

In addition to the above-mentioned characteristics indicating a more complex clinical presentation, both children below 6 years as well as those receiving the prescription from a pediatrician were also more likely to be prescribed a second-line drug as their first ADHD medication.

Regarding potential reasons for starting ADHD treatment with second-line medication, prescribing based on trial data ahead of formal licensing might be a potential cause. Nevertheless, clinical data on efficacy do not support the superiority of LDX, DEX, or GUA (i.e., second-line drugs in this study) over MPH or ATX (i.e., first-line drugs in this study) for patients with the above-mentioned conditions (16). Considering data from randomized controlled trials on tolerability, amphetamines (including LDX and DEX) and GUA—but not MPH—were inferior to placebo in children and adolescents (17). According to network meta-analyses from head-to-head trials in pediatric patients diagnosed with ADHD, LDX was more likely to cause some serious side effects, including sleep disorders and irritability (18). Finally, large post-authorization safety studies evaluating rare outcomes and prescribing in routine care are scarce for LDX, DEX, and GUA—particularly as compared with the abundance of such studies for MPH.

The fact that children aged below 6 years were more likely to receive a second-line drug as the first ADHD medication was especially surprising. A possible reason might be that prescribers estimate the risk of adverse events of second-line ADHD drugs as less than MPH. Yet, such an attitude is not supported by current evidence: To date, there are only few studies assessing safety and efficacy of ADHD medication in children younger than 6 years. This is particularly true for the second-line drugs assessed in this study (i.e., LDX, DEX, and GUA). It is expected that the evidence base on ADHD medication for children younger than 6 years will improve soon as numerous randomized controlled trials are planned or currently running (19). However, second-line drugs should not be preferably prescribed—particularly to preschool children—as long as superiority over first-line drugs is not proven by sound evidence. Currently, MPH is considered the treatment of first choice for preschool children, if pharmacotherapy is indicated, as it is the ADHD drug with the strongest evidence for efficacy and safety in this population (16, 20).

Surprisingly—even when adjusted for age and characteristics indicating the complexity of ADHD cases—patients were more likely to receive a second-line drug as the first ADHD medication when the prescription was made by a pediatrician. This is particularly remarkable as more severe ADHD cases are usually pharmacologically treated by specialized child and adolescent psychiatrists, as was suggested by a previous study (21). Further research is needed to evaluate this potentially irrational off-label prescribing.

## ADHD Medication in Patients Below 6 Years

One study based on UK data found that in a sample of individuals aged below 16 years, 4% of ADHD medication users were aged below 6 years. This percentage is somewhat higher than in our study. Notably, the study was limited to the years 1992–2013, and the more recently approved drugs LDX and GUA were not included (22). Two other European studies, which also presented findings on guideline/label adherence, only evaluated one specific drug—MPH (23) or LDX (15). The study on MPH, based on French prescription data, found that 5% of incident MPH users below 18 years were aged younger than 6 years (23). This is also higher than in our study and might indicate that off-label prescribing to children below 6 years is less common in Germany than in other European countries. The second study on LDX found that fewer than 1% of pediatric and adult LDX users were younger than 6 years (15). This is in accordance with our findings. As discussed earlier, the percentages for receiving second-line ADHD medication were higher in patients aged

**TABLE 1 |** Characteristics of first-time users of ADHD medication, overall and by off-label prescribing criteria.

| Characteristic | Overall (*n* = 18,703) | Lack of a documented ADHD diagnosis | | Second-line drug as first ADHD medication+ | | Patient age below 6 years | |
|---|---|---|---|---|---|---|---|
| | | No (*n* = 16,874) | Yes (*n* = 1,829) | No (*n* = 18,218) | Yes (*n* = 485) | No (*n* = 18,483) | Yes (*n* = 220) |
| **Sex** | | | | | | | |
| Female | 4,634 (24.8) | 4,039 (23.9) | 595 (32.5) | 4,501 (24.7) | 133 (27.4) | 4,590 (24.8) | 44 (20.0) |
| Male | 14,069 (75.2) | 12,835 (76.1) | 1,234 (67.5) | 13,717 (75.3) | 352 (72.6) | 13,893 (75.2) | 176 (80.0) |
| **Documented diagnosis** | | | | | | | |
| Ever ADHD (F90, F98.8) | 16,874 (90.2) | | | 16,486 (90.5) | 388 (80.0) | 16,700 (90.4) | 174 (79.1) |
| Narcolepsy (G47.4) without ADHD | 21 (0.1) | | | 20 (0.1) | 1 (0.2) | 20 (0.1) | 1 (0.5) |
| None of the above | 1,808 (9.7) | | | 1,712 (9.4) | 96 (19.8) | 1,763 (9.5) | 45 (20.5) |
| **Age group in years** | | | | | | | |
| <6 | 220 (1.2) | 174 (1.0) | 46 (2.5) | 200 (1.1) | 20 (4.1) | | |
| 6–11 | 12,661 (67.7) | 11,599 (68.7) | 1,062 (58.1) | 12,402 (68.1) | 259 (53.4) | | |
| 12–17 | 5,822 (31.1) | 5,101 (30.2) | 721 (39.4) | 5,616 (30.8) | 206 (42.5) | | |
| **ADHD medication** | | | | | | | |
| MPH | 17,656 (94.4) | 15,999 (94.8) | 1,657 (90.6) | | | 17,465 (94.5) | 191 (86.8) |
| ATX | 562 (3.0) | 487 (2.9) | 75 (4.1) | | | 553 (3.0) | 9 (4.1) |
| LDX | 261 (1.4) | 222 (1.3) | 39 (2.1) | | | 254 (1.4) | 7 (3.2) |
| DEX | 41 (0.2) | 36 (0.2) | 5 (0.3) | | | 34 (0.2) | 7 (3.2) |
| GUA | 164 (0.9) | 114 (0.7) | 50 (2.7) | | | 158 (0.9) | 6 (2.7) |
| Multiple drugs | 19 (0.1) | 16 (0.1) | 3 (0.2) | | | 19 (0.1) | 0 |
| **Specialty of the prescribing physician** | | | | | | | |
| Child and adolescent psychiatrist | 9,460 (50.6) | 8,751 (51.9) | 709 (38.8) | 9,267 (50.9) | 193 (39.8) | 9,388 (50.8) | 72 (32.7) |
| Neurologist/psychiatrist | 111 (0.6) | 98 (0.6) | 13 (0.7) | 103 (0.6) | 8 (1.6) | 111 (0.6) | 0 |
| Pediatrician | 4,399 (23.5) | 4,080 (24.2) | 319 (17.4) | 4,266 (23.4) | 133 (27.4) | 4,330 (23.4) | 69 (31.4) |
| General practitioner | 407 (2.2) | 353 (2.1) | 54 (3.0) | 394 (2.2) | 13 (2.7) | 400 (2.2) | 7 (3.2) |
| Other specialty | 263 (1.4) | 232 (1.4) | 31 (1.7) | 260 (1.4) | 3 (0.6) | 259 (1.4) | 4 (1.8) |
| Unknown | 4,063 (21.7) | 3,360 (19.9) | 703 (38.4) | 3,928 (21.6) | 135 (27.8) | 3,995 (21.6) | 68 (30.9) |
| **Psychiatric hospitalization** | 2,168 (11.6) | 2,001 (11.9) | 167 (9.1) | 2,035 (11.2) | 133 (27.4) | 2,126 (11.5) | 42 (19.1) |
| **Psychiatric comorbidities** | | | | | | | |
| Conduct disorders (F90.1, F91, and F92) | 6,722 (35.9) | 6,369 (37.7) | 353 (19.3) | 6,488 (35.6) | 234 (48.2) | 6,612 (35.8) | 110 (50.0) |
| Emotional disorders in childhood and anxiety (F40, F41.0, F41.1, F41.3, F41.8, F41.9, and F93) | 4,500 (24.1) | 4,161 (24.7) | 339 (18.5) | 4,374 (24.0) | 126 (26.0) | 4,468 (24.2) | 32 (14.5) |
| Disorders of social functioning (F94) | 849 (4.5) | 777 (4.6) | 72 (3.9) | 819 (4.5) | 30 (6.2) | 837 (4.5) | 12 (5.5) |
| Reactions to severe stress (F43.0, F43.1, F43.8, and F43.9) | 724 (3.9) | 646 (3.8) | 78 (4.3) | 697 (3.8) | 27 (5.6) | 716 (3.9) | 8 (3.6) |
| Mental retardation (F70–F79) | 593 (3.2) | 508 (3.0) | 85 (4.6) | 549 (3.0) | 44 (9.1) | 577 (3.1) | 16 (7.3) |

*(Continued)*

**TABLE 1** | Continued

| Characteristic | Overall ($n$ = 18,703) | Lack of a documented ADHD diagnosis | | Second-line drug as first ADHD medication[+] | | Patient age below 6 years | |
|---|---|---|---|---|---|---|---|
| | | No ($n$ = 16,874) | Yes ($n$ = 1,829) | No ($n$ = 18,218) | Yes ($n$ = 485) | No ($n$ = 18,483) | Yes ($n$ = 220) |
| Depression (F32, F33, F41.2, and F43.2) | 3,151 (16.8) | 2,820 (16.7) | 331 (18.1) | 3,055 (16.8) | 96 (19.8) | 3,136 (17.0) | 15 (6.8) |
| Tic disorders (F95) | 679 (3.6) | 628 (3.7) | 51 (2.8) | 637 (3.5) | 42 (8.7) | 672 (3.6) | 7 (3.2) |
| Substance use disorders (F10–F19) | 163 (0.9) | 132 (0.8) | 31 (1.7) | 155 (0.9) | 8 (1.6) | 161 (0.9) | 2 (0.9) |
| Somatoform disorders (F45) | 1,136 (6.1) | 1,029 (6.1) | 107 (5.9) | 1,092 (6.0) | 44 (9.1) | 1,130 (6.1) | 6 (2.7) |
| Sleep disorders (F51, G47) | 848 (4.5) | 726 (4.3) | 122 (6.7) | 810 (4.4) | 38 (7.8) | 812 (4.4) | 36 (16.4) |
| Specific developmental disorders of speech and language (F80) | 4,365 (23.3) | 3,941 (23.4) | 424 (23.2) | 4,252 (23.3) | 113 (23.3) | 4,239 (22.9) | 126 (57.3) |
| Specific developmental disorders of scholastic skills (F81) | 4,331 (23.2) | 4,074 (24.1) | 257 (14.1) | 4,246 (23.3) | 85 (17.5) | 4,330 (23.4) | 1 (0.5) |
| Specific developmental disorder of motor function (F82) | 3,109 (16.6) | 2,876 (17.0) | 233 (12.7) | 3,044 (16.7) | 65 (13.4) | 3,039 (16.4) | 70 (31.8) |
| Mixed specific developmental disorders (F83) | 2,150 (11.5) | 1,933 (11.5) | 217 (11.9) | 2,075 (11.4) | 75 (15.5) | 2,078 (11.2) | 72 (32.7) |
| Pervasive developmental disorders (F84.0, F84.1, F84.5, F84.8, and F84.9) | 1,107 (5.9) | 918 (5.4) | 189 (10.3) | 1,012 (5.6) | 95 (19.6) | 1,069 (5.8) | 38 (17.3) |
| Non-organic enuresis and/or encopresis (F98.0, F98.1) | 1,329 (7.1) | 1,230 (7.3) | 99 (5.4) | 1,289 (7.1) | 40 (8.2) | 1,319 (7.1) | 10 (4.5) |
| **Number of psychiatric comorbidities[#]** | | | | | | | |
| 0 | 3,347 (17.9) | 2,927 (17.3) | 420 (23.0) | 3,293 (18.1) | 54 (11.1) | 3,325 (18.0) | 22 (10.0) |
| 1 | 5,120 (27.4) | 4,566 (27.1) | 554 (30.3) | 5,007 (27.5) | 113 (23.3) | 5,081 (27.5) | 39 (17.7) |
| 2 | 4,591 (24.5) | 4,178 (24.8) | 413 (22.6) | 4,478 (24.6) | 113 (23.3) | 4,532 (24.5) | 59 (26.8) |
| 3+ | 5,645 (30.2) | 5,203 (30.8) | 442 (24.2) | 5,440 (29.9) | 205 (42.3) | 5,545 (30.0) | 100 (45.5) |
| **History of other psychopharmacological drugs** | | | | | | | |
| Antipsychotics (N05A) | 532 (2.8) | 415 (2.5) | 117 (6.4) | 463 (2.5) | 69 (14.2) | 510 (2.8) | 22 (10.0) |
| Anxiolytics (N05B) | 90 (0.5) | 66 (0.4) | 24 (1.3) | 83 (0.5) | 7 (1.4) | 82 (0.4) | 8 (3.6) |
| Hypnotics and sedatives (N05C) | 198 (1.1) | 158 (0.9) | 40 (2.2) | 176 (1.0) | 22 (4.5) | 178 (1.0) | 20 (9.1) |
| Antidepressants (N06A) | 326 (1.7) | 237 (1.4) | 89 (4.9) | 303 (1.7) | 23 (4.7) | 325 (1.8) | 1 (0.5) |

*Values are numbers (percentages).*

*ADHD, attention deficit hyperactivity disorder; ATX, atomoxetine; DEX, dexamfetamine; GUA, guanfacine; LDX, lisdexamfetamine; MPH, methylphenidate.*

[+]*Second-line drugs: LIS, DEX, GUA, or multiple drugs (including MPH and/or ATX if not used as monotherapy); first-line: MPH or ATX.*

[#]*Exclusively related to the 16 above-mentioned comorbidities.*

**TABLE 2 |** Adjusted odds ratios for characteristics associated with receiving a second-line drug among first-time users of ADHD medication.

| Characteristic | Adjusted odds ratios (95% CI) for receiving second-line as compared to receiving first-line drug* |
|---|---|
| **Male sex (Ref.: female)** | 0.84 (0.68–1.04) |
| **Age group in years** | |
| <6 | **1.70 (1.02–2.85)** |
| 6–11 | **0.78 (0.71–0.86)** |
| 12–17 | Ref. |
| **Specialty of the prescribing physician** | |
| Child and adolescent psychiatrist | Ref. |
| Pediatrician | **1.56 (1.23–1.97)** |
| Other specialty/unknown | 1.16 (0.92–1.47) |
| **Lack of a documented ADHD diagnosis (Ref.: No)** | **2.10 (1.63–2.69)** |
| **Psychiatric hospitalization (Ref.: No)** | **1.90 (1.48–2.43)** |
| **Psychiatric comorbidities (Ref.: No)** | |
| Conduct disorders | **1.54 (1.26–1.88)** |
| Emotional disorders in childhood and anxiety | 0.99 (0.80–1.24) |
| Mental retardation | **1.54 (1.07–2.22)** |
| Depression | 0.91 (0.71–1.17) |
| Tic disorders | **2.08 (1.47–2.94)** |
| Somatoform disorders | 1.23 (0.89–1.72) |
| Pervasive developmental disorders | **2.88 (2.24–3.72)** |
| **History of other psychopharmacological drugs (Ref.: No)** | |
| Antipsychotics | **2.80 (2.05–3.84)** |
| Antidepressants | 1.29 (0.78–2.12) |

*ADHD, attention deficit hyperactivity disorder; CI, confidence interval.*
*Boldface indicates statistical significance.*
**Second-line drug: lisdexamfetamine, dexamfetamine, guanfacine, or multiple drugs (including methylphenidate and/or atomoxetine if not used as monotherapy); first-line: methylphenidate or atomoxetine. The logistic regression model is adjusted for all variables in this table.*

below 6 years as compared to those of higher age although there is a lack of evidence supporting the superiority of these drugs in preschool children (19). It is surprising that more than twice as often no ADHD diagnosis was documented in children below 6 years than in older children. Given the fact that studies on ADHD medication for children aged below 6 years are scarce (19), a comprehensive assessment of the ADHD diagnosis—as consistently recommended by clinical guidelines (6, 9)—should be self-evident as a crucial element of the risk-benefit assessment.

One explanation for not finding recorded diagnoses might be concerns of physicians and/or parents regarding a potential stigmatization of children with ADHD (24). This could have led to a reluctance to diagnose the disorder, particularly in preschool children with regard to school entry. However, as far as public beliefs are concerned, treatment with ADHD medication is even less commonly accepted than the diagnosis (25).

In patients aged below 6 years as compared with older patients, prescribers were less often specialists and more often pediatricians. However, these results do not allow conclusions about the prescribers' specialty or their preferences regarding prescribing off-label to children younger than 6 years as the proportion of individuals with contact to specialists for mental health disorders might be much smaller for younger patients. This was shown for pediatric patients diagnosed with autism spectrum disorders in Germany (26). However, the German guideline on ADHD recommends that drug treatment to preschool children should only be prescribed by a physician with special knowledge of behavioral disorders in this age group (11). Unfortunately, we do not know whether the pediatricians who prescribed drugs to preschool children in our study have this knowledge—in contrast to child and adolescent psychiatrists, who are—by training—best qualified to do so.

The German guideline on ADHD (11)—similar to other guidelines from the UK (27) and US (20)—recommends parent training and/or interventions in kindergarten/school as the first line of treatment in children younger than 6 years. As a caveat in our study, it is unknown whether any of these interventions had been used prior to initiating drug treatment or whether they had proven ineffective, which would justify initiating ADHD medication.

Similar to recipients of second-line drugs, first-time users aged below 6 years more often had psychiatric hospitalizations, conduct disorders, pervasive developmental disorders, and history of antipsychotics, i.e., characteristics indicating more complex clinical presentations. Guidelines do not preclude off-label prescribing to children aged below 6 years in severe cases and after individual risk-benefit assessment. In fact, the guidelines from the UK National Institute for Health and Care Excellence (NICE) differentiate between the age groups below 5 years and older (27). Against this background, it is encouraging that most patients younger than 6 years in our study were aged between 4 and 5 years, i.e., age groups that are not precluded from receiving ADHD medication. However, we found physicians who prescribed ADHD medication to children aged 3 years or younger in our study, which indicates irrational prescribing as there is a lack of evidence in this age group—regarding both, diagnosis and drug treatment.

## Implications

In routine care in Germany, adherence to prescribing guidelines is suboptimal in a substantial proportion of children and adolescents initiating medication to treat ADHD. Physicians should follow current guideline recommendations on ADHD to optimize rational prescribing and avoid adverse events such as insomnia, seizures, tics, loss of appetite, and possible growth deficits. This holds especially true for some pediatricians, who appear to be susceptible to non-adherence to guidelines or label requirements—at least with regard to prescribing second-line drugs as first ADHD medication.

Due to potential side effects and frequent use of drugs to treat ADHD, future research should continue to monitor their off-label use in children and adolescents. Evaluating prescribing behavior following the release of the new German ADHD guidelines in 2018 will provide information for further measures aimed at implementing evidence-based recommendations in routine care.

### Strengths and Limitations

The main strength of this study is that the underlying routinely collected prescription data are not prone to both, non-responder and recall bias. This is particularly important as it cannot be assumed that prescribers would admit if they did not adhere to prescribing guidelines. In addition, we used a large statutory health insurance database covering about one fifth of the German population. Among children and adolescents in Germany, prevalence of drug use does not differ substantially between different types of statutory health insurance providers (28). We therefore believe that the results of this study are representative for patients covered by statutory health insurance in Germany, who account for almost 90% of the general population (13). In our study, we explicitly focused on children and adolescents who were first-time users of any of the ADHD medications available, which allowed us to assess off-label first-time use of second-line drugs. In contrast to other studies, we considered important clinical information, such as psychiatric hospitalizations, comorbidities, and other psychopharmacological drugs.

A general limitation of claims data is that the validity of outpatient diagnoses is suboptimal; also, ADHD in children might be overdiagnosed in Germany (29). This, however, is not a relevant limitation in our study as overdiagnosis would rather lead to underestimating the proportion of first-time users with a lack of an ADHD diagnosis. Although we used information on psychiatric hospitalizations and comorbidities as a proxy for the complexity of ADHD cases, this study is limited by a lack of information on the severity of ADHD. A further limitation, particularly regarding the outcome of ADHD medication in patients below 6 years, is the lack of information on prior non-pharmacological interventions.

## CONCLUSIONS

Our findings show that in more than 10% of pediatric first-time ADHD medication users, prescribers did not adhere to prescribing guidelines. Initiating ADHD drugs without a confirmed ADHD diagnosis was the most common of the three studied off-label criteria. We found off-label use in terms of drug choice and age of patients in a small percentage of pediatric first-time users of drugs to treat ADHD. Since ADHD medication is prescribed frequently in children and adolescents, improving rational prescribing in this area is of high relevance for public health.

## DATA AVAILABILITY STATEMENT

As we are not the owners of the data, we are not legally entitled to grant access to the data of the German Pharmacoepidemiological Research Database. In accordance with German data protection regulations, access to the data is granted only to BIPS employees on the BIPS premises and in the context of approved research projects. Third parties may only access the data in co-operation with BIPS and after signing an agreement for guest researchers at BIPS. Requests to access the datasets should be directed to OS, scholle@leibniz-bips.de.

## ETHICS STATEMENT

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, and Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen, studies based on GePaRD are exempt from institutional review board review.

## AUTHOR CONTRIBUTIONS

OS and CB conceptualized the research question. OS wrote the first draft of the manuscript. BK, OR, and CB revised it critically for important intellectual content and approved the final version to be published. All authors designed the study and participated in the discussion and interpretation of the results.

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**Conflict of Interest:** OS, BK, and OR are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies (PASS) requested by health authorities. The design and conduct of these studies as well as the interpretation and publication are not influenced by the pharmaceutical industry. The study presented was not funded by the pharmaceutical industry.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Intentional Discontinuation of Psychostimulants Used to Treat ADHD in Youth: A Review and Analysis

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**Objectives:** This paper reviews the literature on intentional discontinuation of psychostimulants in ADHD to summarize what is known about clinical course of controlled discontinuation and guide practitioners who are considering stopping these medications for youth with ADHD.

**Methods:** A systematic search was executed in Cochrane CENTRAL, EMBASE, Psychinfo, and MEDLINE databases to identify all articles that addressed the topic of deprescribing of psychotropic medications in children and adolescents. Keywords and search strings were developed using "PICO" framework, involving Population of interest (<18 y.o.), Intervention ("discontinuation," "deprescribing," and synonyms), Comparator (continuation of specific medications), and Outcomes. Ten reviewers conducted the initial screen *via* a single reviewer system. Articles that met a set of three inclusionary criteria were selected for full text review and identification as specific to discontinuation of stimulants in ADHD.

**Results:** The literature review identified 35 articles specifically addressing intentional deprescribing, discontinuation, tapering, or withdrawal of stimulants for children and adolescents with ADHD. In addition to providing broad support for the efficacy of stimulants to treat ADHD and reduce negative outcomes, there is a distinct population of children and adolescents with ADHD who do not relapse or deteriorate when taken off medications for ADHD. The majority of articles addressed either the re-emergence of ADHD symptoms or side effects, both desired and adverse, following discontinuation of stimulants. While confirming the ability of stimulants to treat ADHD in youth, our results support periodic consideration of trials of stopping medications to determine continued need.

**Conclusions:** This systematic review summarizes the literature on deprescribing stimulants for ADHD in children and adolescents. Further research is needed to determine the optimal duration of treatment, identify patients that may benefit from medication discontinuation, and inform evidence-based guidelines for discontinuation when appropriate. More research is needed to understand and define the subgroup of youth who may succeed with stimulant discontinuation.

**Keywords: discontinuation, psychostimulants, ADHD, youth, intentional, evidence**

## INTRODUCTION/OBJECTIVES

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric condition. It is generally considered a long-term condition with up to two-thirds of individuals diagnosed in childhood continuing to experience the condition or symptoms in adulthood (1–3). Research on effective pharmacotherapy of ADHD is largely short-term spanning weeks, with some large randomized controlled trials (RCTs) lasting beyond a year, and prospective data sometimes several years (4). This contrasts with clinical practice, where patients can be treated for longer durations, sometimes decades or beyond.

Psychostimulants are the medications with the highest established efficacy in treating youth with ADHD and are recommended as first-line treatment options (5–7). While the efficacy of stimulants is well-established, optimal duration of treatment and effects of medication discontinuation are less well-characterized (4). Many individuals diagnosed with ADHD, their families, providers, and other stakeholders understandably have questions about how long they should continue on medications as they consider the risks and benefits of medication discontinuation vs. continuation.

These questions have added pertinence as rates of psychiatric medication prescriptions have increased dramatically in the child and adolescent population over the last 20 years (8). In addition, the growth of psychotropic polypharmacy in children and adolescents has raised concerns given the lack of evidence to document efficacy and safety (9). This awareness has given rise to a new medical literature on deprescribing and/or discontinuing of psychotropic medications.

Deprescribing is a structured approach to identifying and discontinuing medications when existing or potential harms outweigh existing or potential benefits. Such deprescribing may be motivated by a variety of reasons, not limited to concerns about polypharmacy, managing adverse effects, changing evidence base or best practices, changing clinical need, or patient preference (10). First introduced in the geriatric population, deprescribing has since been applied to the fields of general and eventually child and adolescent psychiatry (10–12). This process is complicated by generally inadequate evidence to inform the optimal duration of pharmacotherapy, the risks and benefits of medication discontinuation vs. continuation, and standardized processes for tapering and eventual medication discontinuation.

In clinical practice, medication may be discontinued by either patient or provider for many reasons, at times due to adverse effects, lack of symptom control, client or family preference, when diagnostic formulation changes, changing health status, or when it is believed medication may no longer be necessary to maintain functioning (13). This paper reviews the literature on intentional discontinuation by providers of psychostimulants in ADHD to summarize what is known about clinical course of controlled stimulant discontinuation and guide practitioners who are considering, within the process of deprescribing, stopping psychostimulants for youth with ADHD.

## METHODS

This effort was initiated by the American Academy of Child and Adolescent Psychiatry (AACAP) Adoption and Foster Care Committee to develop a resource on deprescribing psychotropic medications in youth. A systematic search was executed in Cochrane CENTRAL, EMBASE, Psychinfo, and MEDLINE databases to identify all articles that addressed the topic of deprescribing of psychotropic medications in children and adolescents. Keywords and search strings were developed using "PICO" framework, involving Population of interest (<18-year-olds), Intervention ("discontinuation," "deprescribing," and synonyms), Comparator (continuation of specific medications), and Outcomes. Ten reviewers conducted the initial records screen of title and abstract via a single reviewer system.

Given the large number of articles to screen, exclusion by a single reviewer was allowed at this step. Reviewers could choose to include, exclude, or tag the article for a second review. In the latter case, two reviewers (WM and MB) reviewed the title, journal, and abstract. Both reviewers were required to agree on either inclusion or exclusion, with discordant responses addressed in conversation. Articles included at this step were identified for full-text review. Full-text review included review of references to detect any potentially relevant articles that had not be identified in the initial database search, and pertinent citations were identified and added to the initial screening step for full review. Additionally, articles were similarly added if identified by reviewers from other mechanisms such as reading of literature or suggestions from experts in the field.

There were three inclusionary criteria, and included studies met all three criteria. First, the topic of the article relates to provider initiated deprescribing, discontinuation, tapering, withdrawal, or reduction of psychiatric medications. Studies focused only on patient non-adherence were not included. Additionally, the article included a psychotropic medication

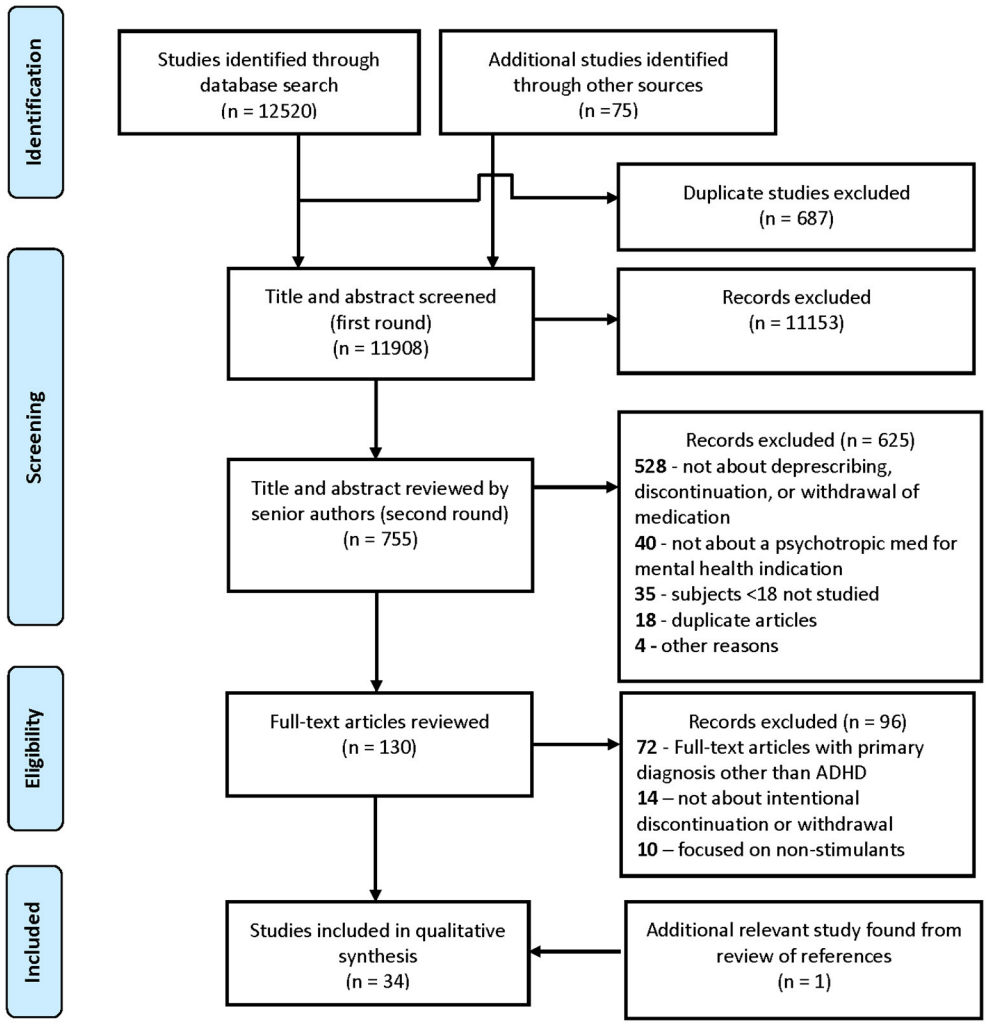


**FIGURE 1 |** Process identification of studies, screening, and eligibility flow diagram for discontinuation of stimulants in children with ADHD.

with behavioral health/mental health indications (not inclusive of supplements and minerals). Medications with psychiatric indications (e.g., clonazepam) being studied for non-psychiatric reasons (e.g., seizures) were included if the outcome measure was pertinent to psychiatry (cognition), as opposed to only neurological (seizure relapse). Finally, the population studied was <18 years of age, or if spanning youth and adult populations, the <18-year-old subset is analyzed independently.

The initial search returned 12,520 citations. An additional 75 (46 new articles and 29 duplicates) references were identified via review of reference or authors knowledge of pertinent studies, including those published after the initial search that met inclusion criteria and came to authors' awareness (see **Figure 1**).

We identified 58 articles specific to ADHD as a primary diagnosis had a second full-text review by two authors (WL and JW) to identify themes and data pertinent to intentional discontinuation, tapering, or withdrawal of medications treating ADHD. Studies relating to medication non-adherence or discontinuation without physician involvement were excluded ($N = 14$), as were those focusing on non-stimulants ($N = 10$). Discontinuation case studies were excluded if the primary diagnosis was not ADHD. Case studies that described side effects that emerged in the process of discontinuation were included. Additionally, a hand search of the bibliographies of full text articles and updates from the published literature yielded one additional study.

## RESULTS

The literature review identified 35 articles specifically addressing intentional deprescribing, discontinuation, tapering, or withdrawal of stimulants for children and adolescents with ADHD. Our review covered 15 case reports, 3 clinical guidelines, 2 literature reviews, 2 observational studies, and 13 RCTs.

We identified 13 RCTs that systematically investigated the effects of discontinuing stimulants in children and adolescents

**TABLE 1 |** Randomized controlled trials that address discontinuation of psychostimulants in children with ADHD.

| Reference | Industry sponsored | Duration of medication discontinuation | Total *N* | Age (years) | Number of boys (% of total) | Medication(s) | Primary outcome measure(s) | Findings |
|---|---|---|---|---|---|---|---|---|
| Abikoff et al. (14) | No | 4 weeks | 50 | 6–12 | 45 (90%) | MPH, dextroamphetamine, pemoline | CTRS<br>BRS<br>Home Hyperactivity Scale<br>Parent Attitude Test<br>Standardized Tests of achievement and cognition | The combination of a stimulant with cognitive training did not facilitate stimulant withdrawal |
| Abikoff et al. (15) | Yes | 1 year | 103 | 7–9.9 | (93%) | MPH | CPRS Home Situations Questionnaire CTRS School Situations Questionnaire | All children relapsed when switched to placebo (single-blind), mean 8.6 vs. 17.1 days for MPH alone vs. MPH with multimodal psychosocial treatments, none of the parent, teacher, or psychiatrist evaluations yielded significant group or interaction effects. |
| Arnold et al. (16) | Yes | 2 weeks | 75 | 6–16 | 61 (81%) | Dexmethylphenidate | CGI-I<br>SNAP-ADHD | Placebo group 3.6× more likely to "fail" treatment (CGI-I 6 or 7); statistically significant deterioration on Teacher and Parent SNAP scales compared to continued medication. |
| Banaschewski et al. (17)* | Yes | 6 weeks | 153 | 6–17 | 119 (78%) | Lisdexamfetamine | CHIP-CE: PRF<br>WFIRS-P | The improvement in health-related quality of life and functional status during the lead-in phase was maintained in the lisdexamfetamine arm while those in the placebo arm had statistically significant deterioration for both. |
| Brown et al. (18) | No | 24 h to 1 week | 35 | 5–14 | 28 (80%) | MPH | ACRS<br>CPRS<br>Various tests of attentional deployment and cognitive style, academic achievement | Neither the combination of a stimulant with cognitive therapy nor a stimulant with attention control therapy for 3 months facilitated stimulant withdrawal |
| Coghill et al. (17)* | Yes | 6 weeks | 153 | 6–17 | 119 (78%) | Lisdexamfetamine | ADHD-RS | Rates of treatment failure were 15.8% in the lisdexamfetamine group and 67.5% in the placebo group. Median time to treatment failure was 17 days for the placebo group. |
| Gillberg et al. (19) | No | 12 months double-blind treatment followed by 3 months of single-blind placebo in both groups. Placebo was tapered over 2 weeks. | 62 | 6–11 | 51 (82%) | Amphetamine | CTRS | The improvement in Conners Teacher and Parent Rating Scale scores during the lead-in phase was maintained in the amphetamine arm while those in the placebo arm had significant deterioration for both; 71% of those in the placebo group withdrew or went into open treatment compared to 29% of those in the amphetamine group. |

*(Continued)*

**TABLE 1** | Continued

| Reference | Industry sponsored | Duration of medication discontinuation | Total *N* | Age (years) | Number of boys (% of total) | Medication(s) | Primary outcome measure(s) | Findings |
|---|---|---|---|---|---|---|---|---|
| Klein et al. (20) | No | Stimulant holiday for 3 months over the summer for two consecutive summers | 58 | 6–12 | 53 (91%) | MPH | Height<br>Weight | At the end of the first summer, the group that had been discontinued from stimulants weighed on average 0.9 kg more than the treatment group; there was no statistically significant difference in height. At the end of the second summer, the group that had been discontinued from stimulants was on average 1.5 cm taller than the treatment group; there was no longer a statistically significant difference in weight. |
| Martins et al. (21) | No (medication supplied by industry) | Stimulant holiday for four weekends | 40 | Mean age 9.0 and 9.6 for MPH and placebo group, respectively | 40 (100%) | MPH | ACRS<br>SERS | There was no difference between groups, suggesting a lack of rebound ADHD symptoms during a short-term MPH weekend discontinuation. The weekend placebo group had significant reduction in insomnia reported, and there was a trend toward reduction in decreased appetite. |
| Matthijssen et al. (22) | No | 3-week taper, 4-week discontinuation | 94 | 8–18 | 73 (78%) | MPH | ADHD-RS<br>CGI-I | Mean scores favored the group that continued MPH treatment on the ADHD-RS. 40% of those who discontinued medication worsened on the CGI-I compared to 16% of those who continued medication. |
| Nolan et al. (23) | No | 2-week crossover | 19 | 6–17 | 18 (95%) | MPH, dextroamphetamine | Various measures of tics and ADHD symptoms | No significant withdrawal effect on tics with placebo. Significant increase in some parent-reported behavioral symptoms, hyperactivity, and aggression while on placebo. |
| Waxmonsky et al. (24) | No | Weekend drug holidays | 71 | 5–12 | | MPH | Weight, height, CGI-S, growth trajectories | Medication use was associated with reductions in height and weight, caloric supplement and drug holidays increase weight velocity more than monitoring |
| Zeiner et al. (25) | No | 3 weeks | 21 | 7–12 | 21 (100%) | MPH | **PACS**<br>CTRS<br>Neuropsychological testing | 76% of boys had a significant worsening in behavioral problems either at home or at school while on placebo |

**One study with two resultant papers.*

*ACRS, Abbreviated Conners Rating Scale; ADHD-RS, ADHD Rating Scale-IV; BRS, Hillside Behavior Rating Scale; CGI, Clinical Global Impression (Severity/Improvement); CHIP-CE: PRF, Child Health and Illness Profile—Child Edition: Parent Report Form; CTRS, Conners Teacher Rating Scale; MPH, methylphenidate; PACS, Parental Account of Childhood Symptoms; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent Report.*

with ADHD (**Table 1**). Of these, seven addressed the re-emergence of ADHD symptoms following discontinuation of stimulant monotherapy, four for methylphenidate derivatives and three for amphetamine derivatives. Three RCTs investigated the discontinuation of stimulants administered with concomitant cognitive or attention control therapies. Just one RCT studied side effects, namely, re-emergence of tics, with discontinuation of a stimulant. One RCT each addressed the effects of weekend or summer stimulant holidays on ADHD symptoms and medication side effects.

## Re-emergence of ADHD Symptoms Following Stimulant Discontinuation

The seven studies below were designed to address the efficacy of short- and long-term use of stimulants for ADHD. However, the studies were included in this review as they all include a randomized placebo-controlled double blind discontinuation arm. While most children experience rapid re-emergence of ADHD symptoms following stimulant discontinuation, there is a subset of the population, ∼30%, who do not relapse or deteriorate when taken off their stimulant. We now look at each study in detail.

Following a 3-month single-blind amphetamine titration period, Gillberg et al. randomized 62 children aged 6–11 to continued treatment or taper to placebo for 12 months in a double-blinded manner, followed by 3 months of single-blind placebo for those continued on amphetamine (19). During the randomized withdrawal phase, all-cause discontinuation was 71% in the placebo group compared to 29% of the amphetamine group, most often within the first 3 months of randomization. The improvement in Conners Teacher and Parent Rating Scale scores during the lead-in phase was maintained in the amphetamine arm while those in the placebo arm had significant deterioration, without difference between older (9–11) than younger (6–8) cohorts. Youth randomized to continued amphetamine were withdrawn in a single-blind fashion at month 15 without significant change in parent or teacher scores at 18 months. Sex, comorbid diagnoses, and WISC scores at baseline did not contribute to outcomes. The study is notable for the long duration of double-blind exposure to stimulant or placebo.

Nolan et al. systemically studied stimulant discontinuation in 19 youth aged 6–17 years with comorbid ADHD and a tic disorder, the majority ($N = 17$) on MPH and two on dextroamphetamine (23). Children were continued on their home medication for 2 weeks, then randomized to placebo or continued treatment for 2 weeks, and then subsequently to the alternate condition, in a placebo-controlled crossover design. Primary outcomes were measures on the quantity and quality of tics (discussed further below). Secondary outcome measures related to ADHD noted significant increase in some parent-reported behavioral symptoms, hyperactivity, and aggression, suggesting continued efficacy of stimulants, though rates of relapse were not reported, and the clinical significance of the findings are not stated. Children had poorer performance on classroom-simulated tests of attention but not dyscontrol or impulsivity.

A study by Zeiner recruited 21 boys aged 9–13 years with a mean MPH prescription duration of 1.75 years (25). The boys were randomized in a double-blind, placebo-controlled, crossover design to MPH or placebo for 3 weeks with a 1-week wash-out period between study arms. As a group, there was a statistically significant increase in both hyperactive and defiant behavior problems at school during the placebo arm and an increase in defiant (but not hyperactive) behavior at home. On the individual level, 76% of boys had a significant worsening in behavioral problems either at home or at school. Based on home ratings, about 40% of boys were the same or better on placebo than methylphenidate, though for school rating, this was only 10%. There was no correlation with age, IQ, or behavioral problems to predict who might fare better or worse during the placebo arm. Attention measures were affected more than measures of impulsivity. This study highlights the importance of feedback from multiple settings when determining impact of medication discontinuation. Authors suggested a protocol for trial discontinuation, starting with a brief 1-week discontinuation, and if results are ambiguous, then placebo substitution for 3–4 weeks.

A large RCT evaluating the withdrawal of dexmethylphenidate utilized a 6-week open-label dose titration lead-in, with 75 "responders" (CGI-I of 1 or 2) proceeding to a 2-week randomized, double-blind, placebo-controlled withdrawal phase (16). The improvement in CGI-I and Teacher and Parent SNAP-ADHD scores during the lead-in phase was maintained in the dexmethylphenidate arm while those in the placebo arm had significant deterioration for both. The proportion of "treatment failures" ($\geq$6 on the CGI-I) was 61.5% in the placebo group and 17.1% in the dexmethylphenidate group. Redefining treatment failure (CGI-I score of $\geq$5) led to rates of 71.8% of the placebo group and 45.8% of ongoing medication. Those in the placebo arm also had significantly worse ratings on teacher-rated SNAP, parent-rated SNAP (3 pm and 6 pm), and math testing. No treatment-related serious adverse events or withdrawal symptoms were noted. Given that inclusion required initial response to stimulants during the open-label phase, it is surprising that nearly immediate discontinuation did not result in worsening in over 1/3 of youth, which may represent placebo responders; authors did not comment on specific patient demographics that contributed to treatment failure.

One study with two resultant papers studied the effects of lisdexamfetamine discontinuation in a large, majority European, multi-center study. Youth aged 6–17 enrolled first into a 26-week open-label lead-in with lisdexamfetamine; completers ($N =$ 157) then enrolled in a 6-week randomized double-blind placebo-controlled withdrawal study. The primary outcome in Coghill et al. was treatment failure, defined as >50% increase in ADHD-RS total score and $\geq$2-point increase in the CGI-S score at any single assessment point during the withdrawal period. Rates of treatment failure were 15.8% in the lisdexamfetamine group and 67.5% in the placebo group (17). Most of those who met criteria for treatment failure did so within the first 2 weeks; the median time to treatment failure was 17 days for the placebo group. One study limitation is that medication was withdrawn abruptly,

and treatment failure could be met at a single time point, so rebound or withdrawal effects could have led to early treatment failure. No serious treatment emergent adverse events were reported during the randomized withdrawal phase. Subsequent analysis showed improvement in health-related quality of life and functional status during the lead-in phase and then maintained in the lisdexamfetamine arm while those in the placebo arm had significant deterioration for both (26).

In the most recent and best-designed study, Matthijssen et al. conducted a randomized, placebo-controlled discontinuation study to characterize the ongoing benefit of methylphenidate and withdrawal effects of discontinuation (22). They enrolled 94 youth aged 8–18 who had received MPH consistently for more than >2 years. For those assigned to placebo, medication was tapered in a stepwise fashion over 3 weeks and then discontinued for 4 weeks. After 7 weeks, mean scores favored the group that continued MPH treatment; effects size ($d = -0.23$) and absolute difference in total scale score (<3 points) were small. Differences were significant for ADHD-RS total score and inattention subscale score, but not hyperactivity–impulsivity subscale score. Differences were significant only for the younger cohort (below median age of 13.8), and when applied to an older subset of youth, no difference was noted. For the secondary outcome measure CGI-I, those who discontinued medication worsened about 40% of the time, compared to nearly 16% in those who continued medication. More participants dropped out due to worsened functioning in the placebo group, though all were included in the analysis above. No serious adverse events were noted; change in appetite and weight change were more commonly reported with medication discontinuation. Authors concluded that a subset of youth was discontinued from methylphenidate without exacerbation of ADHD symptoms and that their data support existing guidelines recommending trial discontinuation on a periodic basis. One limitation is that authors noted that many qualifying participants who declined to participate cited ongoing benefit from MPH, suggesting that the study population may have been biased toward those suspecting limited benefit from ongoing medication and wanting trial discontinuation.

## Re-emergence of ADHD Symptoms Following Stimulant Discontinuation After Non-pharmacologic Interventions

Three RCTs described were designed to determine if concomitant stimulant use with various therapy regimens attenuated ADHD symptom re-emergence when the stimulant was discontinued. Researchers found no difference in youth who received up to 1 year of non-pharmacologic interventions when stimulants were discontinued. Each trial is described in more detail below.

The first study randomized 50 children to continue their home stimulants as usual (MPH, dextroamphetamine, or pemoline), home stimulants with cognitive training, or home stimulants with attention control for 16 weeks before switching to placebo (14). The authors conclude that the combination of a stimulant with cognitive training did not facilitate stimulant withdrawal, as there was no statistically significant difference in the number of subjects who required restarting a stimulant during the placebo phase (77 to 90%), nor was there a difference in number of days subjects were able to tolerate placebo before necessitating stimulant re-prescribing (mean 14.9 to 18.2 days). There were few measures that favored children who had been in the stimulant-only arm. For most measures, there were no differences in the three treatment arms when children were discontinued from their stimulants.

A similar study randomized 34 children to 3 months of cognitive training plus MPH, attention training plus MPH, cognitive training plus placebo, or attention training plus placebo (18). In the two treatment arms in which children received MPH, the stimulant was discontinued 24 to 72 h prior to post-testing. Researchers found no difference in multiple tests of attention, academic achievement, behavior at home, or ADHD and conduct symptoms at school, leading authors to conclude that children must remain on medication to sustain improvements observed with methylphenidate.

The largest and most robust RCT addressing the effect of non-pharmacologic intervention on discontinuation of a stimulant randomized a group of 103 children to 1 year of MPH, MPH plus multimodal psychosocial treatment (including parent training and counseling, social skills training, psychotherapy, and academic assistance), or MPH plus attention control psychosocial treatment (15). After a year, subjects were discontinued on their stimulants and started on placebo in a single-blind manner. All children relapsed when switched to placebo and quickly required re-prescribing of MPH. Mean duration of the placebo trials was 8.6 days for MPH alone, 17.1 days for MPH with multimodal psychosocial treatments, and 11.7 days for MPH with attention control psychosocial treatment, which is statistically significant but of uncertain clinical significance. None of the parent, teacher, or psychiatrist evaluations yielded significant group or interaction effects.

## Mitigation of Adverse Effects With Discontinuation of Stimulants

Some auxiliary data can be gleaned from the RCTs on stimulant discontinuation in children with ADHD. A common motivation for medication discontinuation is adverse effects. Stimulants are well-known to contribute to weight loss and blood pressure; it is also hypothesized that stimulant withdrawal can exacerbate tics in at-risk youth. The RCTs with a more adverse effect focus show nominal but often statistically benefit when stimulants are discontinued.

Within these RCTs, there was evidence for and against mitigation of adverse effects when stimulants are discontinued. Weight loss, one of the most common side effects of stimulants, was measured throughout the Coghill et al. trial (17). During the 6-week randomized double-blind placebo-controlled discontinuation of lisdexamfetamine, patients who continued to receive the treatment maintained a stable weight, whereas those who were randomized to placebo increased in weight.

A second study noted that abrupt discontinuation of dexmethylphenidate was not associated with rebound or

**TABLE 2** | Observational studies that address discontinuation of psychostimulants in children with ADHD.

| Reference | Industry sponsored | Duration of medication discontinuation | Total *N* | Age | Number of boys (% of total) | Medication(s) | Primary outcome measure(s) | Findings |
|---|---|---|---|---|---|---|---|---|
| Hoare and Sevar (27) | NR | >24 h | 15 | 4.5–14.6 | 100% | MPH | Primary: CANTAB SNAP-IV | Compared to testing with MPH, youth performed worse on placebo for some test measures (pattern recognition, spatial working memory, intra/extra dimensional set-shifting) primarily relating to executive function, though no effect was noted on other measures. All except one youth had worse SNAP scores on placebo. |
| Sleator (28) | NR | "Within patient" design, 1 month each of three different drug doses and PBO | 42; only 28 received PBO trial | NR | NR | MPH | Conners' teacher's abbreviated symptom questionnaire (ASQ) remission defined as < 15 | 17/42 (40%) showed significant deterioration during PBO; 11/41 (26%) showed no deterioration on PBO |

*CANTAB, Cambridge Neuropsychological Test Automated Battery; Conners' ASQ, Conners Teacher's Abbreviated Symptom Questionnaire; NR, not reported.*

withdrawal symptoms (16). In those that continued medication, blood pressure rise was nominally lower (SBP 2.6 ± 11.6 vs. 3.1 ± 9.5) and increase in heart rate was higher (5.4 ± 12.2 vs. 1.9 ± 10.7) than in the placebo group.

Finally, one study examined if stimulant discontinuation would exacerbate or improve tics in those with premorbid chronic motor tic disorder or Tourette's disorder (23). Based on parent report, clinician report, and direct observation in a simulated classroom, there was "little evidence" that stimulant discontinuation caused tic exacerbation. The only tic-based measure that reached clinical significance was the clinician's 2-min Vocal Tic count, which demonstrated a mean of 1.2 tics in the blinded treatment group and 0.4 tics in the blinded placebo group ($p = 0.0037$).

## How Do Summer or Weekend "Stimulant Holidays" Relate to Long-Term Stimulant Discontinuation?

Three additional RCTs were included in this review that addresses summer and weekend stimulant holidays. While the clinical goals of "stimulant holidays" may not ostensibly coincide with stimulant discontinuation, there is nonetheless clinically relevant data to be gleaned. The below studies support the use of "stimulant holidays" to manage common stimulant side effects without clinical deterioration.

Fifty-eight children on long-term MPH for ADHD were randomly assigned to continue their stimulants throughout the summer or to discontinue for two consecutive summers (20). At baseline, there was no difference in the two groups for age, height, or weight. At the end of the first summer, the group that had been discontinued from stimulants weighed on average 0.9 kg more than the treatment group; there was no statistically significant difference in height. At the end of the second summer, the group that had been discontinued from stimulants was on average 1.5 cm taller than the treatment group; there was no longer a statistically significant difference in weight. This was one of the first studies to link periodic discontinuation of stimulants with benefit to height that have been replicated over the years.

A more restrictive "stimulant holiday" can be found in a double-blind placebo-controlled RCT (21). The 40 boys who entered the study were titrated on MPH from 0.3 mg/kg/day to 0.7 mg/kg/day as tolerated to target ADHD symptoms. Subjects were then randomized to continued MPH or placebo on the weekends to mimic weekend "stimulant holidays." Conners' Abbreviated Rating Scales were administered to teachers and parents on Mondays. Teachers were instructed to assess behaviors for the given Monday, and parents were instructed to assess behaviors for the given weekend. There was no difference between groups, suggesting a lack of rebound ADHD symptoms during a short-term MPH weekend discontinuation. It is also possible that the onset of MPH was rapid enough such that teachers could not appreciate a difference in behaviors with or without the weekend holiday. Importantly, the weekend placebo group had significant reduction in insomnia reported, and there was a trend toward reduction in decreased appetite.

Finally, a recent RCT examined weekend drug holidays as a weight recovery treatment and found this practice along with caloric supplementation and increased monitoring effective in increasing weight velocity in children taking stimulants (24). Adherence to drug holidays was high over the 30-month study duration (95%); in fact, many parents did not give weekend medication even when asked to. Effects on height were not seen.

## Observational Studies

Two observational studies assessed effects of stopping stimulants, the first on neuropsychological testing performance and the second on ADHD symptoms (**Table 2**). Both had significant methodological limitations.

A prospective study assessed effects of acute methylphenidate discontinuation on neuropsychological performance, as evaluated by the Cambridge Neuropsychological Test Automated Battery (CANTAB) test battery, in 15 youth ages 4 to 14 with ADHD (27). Prior to assessment, youth were stabilized on MPH for at least 3 months. For initial testing, youth discontinued MPH for at least 24 h, and retest occurred after resuming for more than 1 week. Three tests (spatial recognition, spatial span, and delayed matching to sample) showed no significant difference between testing conditions, and three tests (pattern recognition, spatial working memory, and intra/extra dimensional set-shifting) showed superior performance while taking MPH. The differences in subtest results were suggestive of MPH treatment effects on executive function in ADHD. All except one youth was clearly rated as more symptomatic for ADHD symptoms while off MPH. Limitations include small sample size and that youth were tested after having been off methylphenidate for only a short time period.

The other observational study completed a prospective, non-controlled trial on 42 youth, followed more than 1 year (13 followed 2 years) after diagnosis of ADHD and treatment with MPH (28). Each youth was given up to three different doses of MPH and placebo × 1 month, with the primary outcome measure being their schoolteacher-rated Conner's Abbreviated Symptoms Questionnaire (ASQ). Of 28 youth who had completed a randomized placebo month, they found that 17 relapsed including 5 whose functioning deteriorated so significantly they could not sustain the protocol's full month of placebo treatment. Eleven remained with Conner's ASQ score < 15 on switch to placebo, with undetectable change in functioning to their schoolteachers. Sustained remission off medication was not predicted by age or IQ. Only 2/3 of sample had completed the trial off medication by time of publication and only teacher-rated outcomes were measured. Authors recommended periodic drug-free trials to assess for ongoing need for medication.

In summary, short-term (>24 h) discontinuation of MPH affected youth performance on neuropsychological testing. Worsening of teacher-rated ADHD symptoms was seen in a majority (60%) but not all youth who were given placebo for 1 month during treatment with methylphenidate.

## Case Reports

A number of case reports describe events related to discontinuation of stimulant medications and provide guidance for the clinician (**Table 3**). Four separate publications describing seven children report acute dystonic reactions after stopping psychostimulants in children on concurrent antipsychotic medications. The stimulants involved include both methylphenidate and amphetamine products, co-prescribed with antipsychotic medications, risperidone, and aripiprazole. In five of the cases, the dystonia onsets within 33 h and within 10 days in two cases. The proposed mechanism is stimulants enhanced synaptic levels of dopamine and their sudden cessation removed a counter to dopamine blockade by antipsychotic and allowed enhanced binding to striatum. Treatment with anticholinergic agents or restarting the stimulants resolved the dystonic movements. A gradual taper of stimulants with careful vigilance for abnormal movements is suggested if stopping stimulants in this context (29–32).

Withdrawal dyskinesias with discontinuation of antipsychotic in children on stimulants are reported in three other case reports. The mechanisms in this case are also felt to reflect competing actions on the dopamine system by antipsychotic medications and stimulants. The abnormal movements were precipitated by sudden or gradual withdrawal of the antipsychotic. In these cases, it appears that the dyskinesias can persist for several weeks after the stimulants are stopped. To minimize this adverse effect, the authors suggested a gradual taper over several weeks of the antipsychotic with prompt discontinuation of the stimulant if abnormal involuntary movements appear (33–35).

Additional case reports highlight withdrawal symptoms that impact both the gastrointestinal and neuromuscular systems. One report involves a 13-year-old female who developed painful muscle cramps in her legs when immediate-release methylphenidate was stopped for a summer holiday. Cramps occurred in the morning after a drug-free day (36). Acute withdrawal symptoms indicating tolerance are reported in a 11-year-old female with ASD who developed vomiting, headaches, light sensitivity, and malaise following abrupt discontinuation of MPH and dose reduction of lisdexamfetamine. Children with ASD may be more sensitive to stimulant medications (37). A case of a child who gained a significant amount of weight and eventually developed an eating disorder after stopping stimulants is reported (38). These case reports provide guidance to the clinician for managing potential adverse effects related to stopping medications in a child treated with both products.

Several case reports describe mental health adverse effects from stopping psychostimulants. Psychiatric complications are reported in two case reports; the first involved severe depression in a child taken off pemoline (39), and the second reports on a psychotic manic-like appearance within 7 days in a child taken off methylphenidate (40). Finally, three case reports describe how behavioral interventions were used to address behaviors and allow discontinuation of stimulants in children with ADHD. In these cases, intensive behavioral management therapies to parents and teachers were able to successfully manage behaviors as stimulants were gradually tapered and stopped (41–43).

These case reports provide guidance to the clinician for managing potential adverse effects related to stopping medications in a child treated with both products.

**TABLE 3 |** Case reports of discontinuation of psychostimulants in children with ADHD.

| Study | Age and sex | Medication | Discontinuation | Adverse reaction | Clinical pearls |
|---|---|---|---|---|---|
| Benjamin 2005 | 9-year-old M<br>9-year-old M<br>13-year-old M | MPH 15 mg TID, risperidone 1.5 mg TID, clonidine 0.1 mg QHS, valproic acid 250 TID<br>Dextroamphetamine racemic 10 mg TID, risperidone 1 mg BID, clonidine 0.1 mg QHS, valproic acid 125 mg qam and 250 mg QHS<br>Fluvoxamine 150 mg BID, MPH 54 mg/day, guanfacine 1 mg BID, risperidone 0.5 mg TID | MPH stopped suddenly<br>AMP stopped suddenly<br>Missed MPH dose over 1 day | Observed dystonic reaction resolved with benztropine<br>Observed dystonic reaction resolved with benztropine<br>Dystonic reaction resolved on own in 24 h after restarting MPH | Sudden discontinuation of stimulant medication used concomitantly with an antipsychotic may lead to acute dystonic reactions. |
| Guler 2015 | 9-year-old M | MPH 54 mg, risperidone 1.5 mg BID | Missed dose of stimulant | Dystonic reaction observed 6–7 h following missed dose | |
| McLaren 2010 | 11-year-old M | Aripiprazole 15 mg BID, OROS MPH 108 mg qam, lithium 600 mg qam and 300 mg QHS, clonidine 0.2 mg BID | Abrupt cessation of OROS MPH | Acute dystonic reaction 33 h after last dose that resolved with IM diphenhydramine | |
| Parraga 2015 | 9-year-old F<br>7-year-old M | MPH CD 50 mg qam and MPH 5 mg every afternoon, aripiprazole 1 mg BID<br>Dextroamphetamine-racemic 30 mg/day and aripiprazole 2 mg daily | Abrupt cessation of MPH CD and MPH<br>Abrupt cessation of dextroamphetamine | Dystonic reaction occurred that responded to diphenhydramine and discontinuation of aripiprazole<br>Dystonic reaction occurred several days after and resolved with decrease in SGA and restarting stimulant | |
| Connor 1995 | 9-year-old M | Perphenazine 16 mg/day, dextroamphetamine 40 mg/day, fluoxetine 20 mg/day, diphenhydramine 50 mg/day | Perphenazine tapered by 4 mg/day, then stopped. Fluoxetine and diphenhydramine suddenly stopped without tapper. Dextroamphetamine continued. | AIMS score became elevated at day 2 from discontinuation of the perphenazine and continued to worsen after 10 days off of the antipsychotic. Stimulant was tapered over 2 days with rapid improvement in AIMS score | Concomitant use of stimulant may increase risk for neuroleptic withdrawal dyskinesias on stopping antipsychotics |
| Connor 1998 | 11-year-old M | MPH 10 mg BID, thioridazine 150 mg/day, | Thioridazine tapered over 3 weeks, MPH continued | One week after stopping thioridazine, increase in abnormal muscle movements and AIMS elevation. | |
| Hollis 2007 | 7-year-old M | Risperidone 1.5 mg, MPH 36 mg | Abrupt discontinuation of risperidone and subsequent initiation of MPH 36 mg 12 h later | Within 8 h, dyskinesias observed that resolved with restarting risperidone | |
| Bernard 2015 | 16-year-old M | Long-term MPH at 30 mg/day | MPH stopped suddenly | After stopping MPH, dramatic increase in weight gain and subsequent development of an eating disorder | Cessation from stimulant medications may cause withdrawal symptoms that impacting GI and neuromuscular systems. |
| Cuskun 2013 | 13-year-old F | IR MPH 20 mg qam | Missed MPH dose | Painful muscle cramps 24 h after missed dose of IR MPH. Switched to OROS MPH and cramps resolved on drug-free days | |
| Krakowski 2018 | 11-year-old F | 1st Trial—OROS MPH 36 mg<br>2nd Trial—Lisdexamfetamine 50 mg/day, guanfacine ER 3 mg/day, fluoxetine 20 mg/day. | 1st—Abrupt cessation of OROS MPH<br>2nd—Taper off lisdexamfetamine by 10 mg | 1st—Acute vomiting and light sensitivity noted following cessation of OROS MPH.<br>2nd—Reduction in stimulant caused migraines and malaise for a 2-day period following each reduction | |

### Clinical Guidelines and Literature Reviews

While confirming the efficacy of psychostimulants for ADHD, three national guidelines for the evaluation and treatment of ADHD suggest consideration of periodic trials of stopping medications to determine continued need. Discontinuing ADHD medications in children requires a plan to monitor for return of symptoms (44). The AACAP Practice Parameter on ADHD suggests in general continuing medication through adolescence due to a high level of maladaptive behavior in patients with ADHD. It further clarifies that if a patient has been symptom free for 1 year, then it is appropriate to consider stopping the medication. Factors that may support discontinuation of medications include no recent need for dose adjustment and lack of deterioration with missed doses or drug holidays (5). Similarly, the National Institute for Health and Care Excellence guidelines for ADHD suggests an annual review of whether medications should be continued. The assessment includes the preference of the youth and family, current benefits of the medications, adverse effects, clinical need, impact on education and employment, effects of missed doses, and need for additional supports (45).

A systematic literature review of 53 articles on how long to treat ADHD provides additional support for the efficacy of treating youth with ADHD with medications for up to a period of 2 years. There is limited evidence for the long-term advantage of medications beyond "mere" symptom control, and information on long-term adverse effects is limited. While acknowledging the substantial clinical experience that many children with ADHD continue to benefit from long-term medication treatment to control symptoms, the authors support annual medication free periods lasting several days to 1 week to determine ongoing benefit (46).

An additional literature review addresses the use of drug holidays as a procedure to minimize or reverse adverse effects of these medications, (e.g., growth retardation, weight loss). This report found 22 studies surveying drug holidays to manage side effects such as child growth and insomnia or reduce tolerance of medications. The review finds the practice to be common in 25 to 70% of families. The practice of drug holidays can be useful as a periodic trial of medication discontinuation to manage risk: benefit ratio and increase voice of youth and families to guide treatment. However, provider's opinions on the value of drug holidays are mixed and more evidence is needed (47).

## DISCUSSION

This review has implications in several areas for consumers and clinicians addressing optimal duration of stimulant treatment for youth with ADHD and potential outcomes if medications are stopped. Few trials set out to answer the question of "how/when/should we discontinue stimulants for ADHD?," so this review attempted to synthesize the available information to help answer this question. Nevertheless, there are important points to guide the consideration of discontinuation.

All reviewed randomized withdrawal studies support the use of medications to reduce symptoms, improve quality of life, or reduce relapse rates. Most studies show early re-emergence of ADHD symptoms for most children discontinuing stimulants. Despite these considerations, there is a significant subpopulation of youth in these RCTs (∼30%) who may tolerate discontinuation without relapse of ADHD (17, 22, 25). A similar observational study that studied 1-month placebo trials in children with ADHD found that 11 out of 42 children (26%) showed no clinical deterioration when medication was stopped (28). One RCT suggested that older youth were less likely to have symptom recurrence than younger youth, with those older than a median age of 13.8 years showing no worsening when switched to placebo (22).

One limitation of these RCTs is that several are industry sponsored, designed to evaluate the efficacy of medications and may be biased toward children who have shown significant early responses and good tolerance to medication (14, 16, 17, 26). Often, the population randomized for possible discontinuation have had lengthy lead-in periods of successful treatment with stimulants. A typical clinical population may experience less robust response or suffer more side effects, altering cost–benefit considerations. With one exception (19), the placebo phase of the discontinuation trials is brief so rates of relapse may not compare equally with those seen in a community population. Trials are either exclusively boys or majority boys and the clinical significance of some RCT differences between active drug and placebo can be questioned.

In addition to controlled intentional discontinuation studies, analyses of administrative databases can offer insights into continued ADHD medication effects. These studies compare outcomes during periods after prescriptions are filled to periods when prescriptions are not filled. After filling ADHD medication prescriptions, youth are less likely to suffer from unintentional injuries and substance-related events and visit EDs for unintentional injuries including traumatic brain injuries and trauma-related events (48–52). In Sweden, after filling ADHD prescriptions, young people scored higher on college entrance exams and adolescents and adults underwent fewer criminal convictions, while filling SSRI prescriptions showed no effects (53, 54). Limits of database studies to consider are the fact that they are associational, cannot imply causation, and carry a risk of selection bias. However, these studies support the continued effect of treatment for ADHD to reduce injuries, motor vehicle crashes, criminality, and substance abuse. ADHD medication prescriptions are not filled for many reasons, so these studies were not included in our search, but may help inform stakeholder cost–benefit considerations when contemplating medication discontinuation.

The long-term observational MTA study may offer clues to identifying children with ADHD who may tolerate discontinuation of stimulants. Latent classes were identified by the trajectories of long-term response to treatment, and by 6 to 8 years, the type of treatment at 14 months did not predict functioning (55). Adherence was an issue during follow-up; 62% of cohort had stopped medication or not on medication at 8-year follow-up. By then, three trajectories of ADHD were proposed,

illustrating a natural course of disease. "Class 1" showed a gradual improvement with increasing benefit of medication at 3 years, "class 2" showed a larger initial improvement with medication maintained over time, and "class 3" showed an initial positive response to medications and then a return to pretreatment levels (56). It is possible that a careful consideration of risks and benefits of continued stimulant treatment in youth matching a "class 3" subtype could lead to a decision to discontinue stimulants.

Brain maturation and/or the development of compensatory strategies may facilitate discontinuation of medications for ADHD. As children age into adults, working memory, planning, and problem solving become more efficient (57). Similarly, as children with ADHD age, measures of executive function improve (58). The age and overall maturity of the individual are additional variables in a decision to discontinue stimulants. One may expect psychosocial functioning of children with ADHD to improve with therapy. Three RCTs examining the effect of behavioral therapies did not show benefit of behavioral therapies to augment discontinuation of stimulants but case reports suggest such an approach may succeed.

Deprescribing as a systematic approach to providing the minimum effective dose or number of medications identifying can be applied to youth with ADHD. The strength of the diagnosis and natural course of the condition along with previous responses to psychostimulants are considered along with an assessment of their risks and benefits. Periodic discontinuation trials of psychostimulants in ADHD are supported by the practice guidelines (5, 45, 59). While an annual medication free trial is suggested, stopping stimulants is a clinical decision made on an individual basis considering many factors (46).

It is important to have a shared decision discussion on whether stimulants should be continued with the family and youth in which one reviews comorbid conditions, adverse effects, timing with school or other important events, and if they still feel the medications are needed (19, 22). Differences in medication discontinuation in minority youth have been reported, so it is important to evaluate the discussion within the context of racial and ethnic disparities (60). The setting and expectations of the child during a discontinuation period are also important considerations as measures of increased ADHD symptoms may differ between home and school (25).

The drug holiday trials support intentional short periods of discontinuation to not only identify youth who may no longer require medications to succeed but manage side effects as well. Stimulants tend to have quick onset of action and short half-life allowing for short-term "drug holidays," such as weekends or school holidays, to mitigate adverse effects including growth retardation, weight loss, and insomnia (20, 24, 47). Weekend drug holidays were not shown to effect school performance (21) and planned drug holidays also help clinicians identify candidates for discontinuation (61). Drug holidays are well accepted by parents (24). Periodic trials of stimulant discontinuation are also supported by long-term observational studies that show that consistent stimulant treatment of 16 years is associated with significant decreases in height and increases in weight (62). This suggests that some youth will enjoy relief from growth deficits with intermittent use.

The literature supports careful monitoring as necessary for any discontinuation trial. Many of the case reports describe the emergence of side effects associated with stopping stimulants used to treat ADHD and provide clinical guidance on safety of discontinuation or withdrawal of medications. Temporary movement disorders may emerge when stimulants are discontinued and may occur more frequently with concomitant antipsychotics. Psychostimulants have been associated with motor tics, but in RCT, abrupt withdrawal of medications did not exacerbate tics (23) and led to no rebound or withdrawal symptoms (16). Clinicians also need to consider whether the stimulants are short-acting or long-acting as adverse effects associated with discontinuation may differ between drug types with different half-lives (63).

In most cases, relapse is noticed within 2 weeks, so a discontinuation trial could be brief (17, 18). One RCT lays out a potential plan for discontinuation suggesting a 1-week drug-free trial with assessment of the child in multiple different settings. If this is inconclusive, the authors suggest a placebo-controlled trial of stimulants lasting 3–4 weeks and consideration of higher dose (25). However, a conservative approach would suggest a gradual taper of a medication used to treat ADHD over the course of several weeks to months to reduce the likelihood of immediate adverse effects and rapid symptom reemergence.

## LIMITATIONS

While the recent inclusion of deprescribing as a PubMed search term provided some reference, a comprehensive search of the desired search was difficult to design, and studies with relevant data often used different descriptors. By necessity, the review evolved from the systematic review to a targeted review as initial results revealed little guidance on informing the question of deprescribing or planned discontinuation of stimulants. It is possible that some relevant articles have not been located. Also, our focus was on intentional discontinuation of stimulants by providers so literature on patient adherence with ADHD medications was not included in the review (13). Due to this restriction, our identified studies may include more cooperative families and less impaired subjects and alter the focus of this paper from typical treatment experiences.

Industry sponsorship and study design may influence the findings. Six RCTs were sponsored grants. Three of the RCTs were sponsored by pharmaceutical companies, and these coincided with the three of the four largest RCTs ($n \geq 75$) and showed discontinuation of stimulants (with or without therapies), resulting in rapid re-emergence of ADHD symptoms. Also, the study populations included many more males in their cohorts.

## CONCLUSIONS

This systematic review summarizes the literature on deprescribing stimulants for ADHD in children and adolescents, in particular characterizing rates of symptom re-emergence and

medication withdrawal-emergent side effects. In summary, our review indicates that a significant group of youth may tolerate discontinuation of stimulants, but more research is needed to clearly understand and identify them. Further research is also needed to determine the optimal duration of treatment and inform evidence-based guidelines for discontinuation when appropriate.

## AUTHOR CONTRIBUTIONS

WL, JW, MB, EG, WM, DC, and TL were involved in the conception and design of the work, which includes drafting and revising the intellectual content. All authors approve the version now submitted and agree to be accountable for all aspects of the work.

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# Cardiovascular Risk of Concomitant Use of Atypical Antipsychotics and Stimulants Among Commercially Insured Youth in the United States

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**Objectives:** To investigate the risk of cardiovascular events associated with concomitant use of stimulants and atypical antipsychotics (AAPs) among youth and evaluate whether AAP dose and duration of concomitant use modifies the risk.

**Methods:** We used IQVIA PharMetrics® Plus data from 2006 to 2015 to construct a retrospective cohort of commercially-insured youth aged 5–17 years old who initiated a stimulant medication. Time-varying concomitant stimulant/AAP use was defined as current, past and no concomitant use based on person months. The primary time-varying Cox proportional hazard regression analysis evaluated the risk of cardiovascular events comparing current concomitant use with past and no concomitant use, adjusted for baseline cardiovascular risk. A secondary analysis assessed the risk of cardiovascular events comparing AAP daily doses (<1, 1–2, >2 mg) and duration (<3, 3–6, >6 months) of current concomitant use to no concomitant use. Cardiovascular outcomes included severe (i.e., stroke, acute myocardial infarction, ischemic heart disease) and less severe (i.e., angina pectoris, cardiac dysrhythmias, transient cerebral ischemia, hypertensive disease, tachycardia, palpitations, syncope).

**Results:** For this cohort of 61,438 youths, the incidence rate of severe cardiovascular events was 0.18 per 10,000 person-months, and all events occurred in no concomitant use months. The risk of less severe cardiovascular events was significantly higher in current concomitant users compared with no [HR: 2.59 (95%CI: 1.72, 3.90)] and past [HR: 1.89 (95%CI: 1.10, 3.24)] concomitant users. Compared to no concomitant use, the risk of less severe cardiovascular events was significantly higher at all AAP daily doses [HR: <1 mg: 2.82 (95%CI: 1.72, 4.61); 1–2 mg: 2.22 (95%CI: 1.16, 4.25); >2 mg: 2.65 (95%CI: 1.50, 4.71)]. The risk of less severe cardiovascular events significantly elevated for all duration of use and was higher for <3 months of concomitant use [HR: <3 months: 3.45 (95%CI: 2.17, 5.47) relative to 3–6 months: 2.60 (95%CI: 1.29, 5.25) or >6 months: 2.61 (95%CI: 1.59, 4.30)].

**Conclusions:** Severe cardiovascular events are rare. Concomitant stimulant/AAP use elevates the risk of less severe cardiovascular events. Periodic heart rate or blood pressure monitoring for youth on stimulant/AAP treatment may be warranted.

**Keywords: youth, atypical antipsychotics, stimulants, cardiovascular risk, drug safety**

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# INTRODUCTION

Stimulants are considered the first-line pharmacological treatment for Attention-Deficit/Hyperactivity Disorder (ADHD), and are widely used among youth in the U.S. (1). While the efficacy of stimulants for ADHD is well-supported (2, 3), the cardiovascular safety of stimulants has been equivocal. Several large population-based studies have not found a significant elevated risk of serious cardiovascular events, including stroke, myocardial infarction, and cardiac sudden death, related to stimulant use among youth (4, 5). But other studies have reported an increased risk of cardiac-related hospitalization and emergency department visits associated with stimulant use among youth and young adults (6, 7). The current US Food and Drug Administration (FDA) labeling warns against prescribing stimulants to patients with serious heart problems and recommends periodic heart rate or blood pressure monitoring among youth prescribed stimulants (8).

The majority of the evidence for the cardiovascular safety of pediatric stimulant use does not account for the concomitant use of stimulants with other psychotropic classes, such as atypical antipsychotics (AAPs), which happens after initiating the simulant treatment among some children and adolescents (9). AAPs are FDA approved for the treatment of pediatric schizophrenia, bipolar disorder, irritability associated with autism, and Tourettes' disorder, but are also commonly used for non-approved purposes (i.e., off-label use), such as managing behavioral symptoms (10–12). The concomitant use of AAPs with stimulants presents potential cardiac safety concerns because AAP use in youth is associated with increased cardiovascular events (13). Concomitant use of medications from multiple psychotropic classes is known to produce adverse drug reactions that can be additive (14, 15), but there is limited evidence for or against the cardiovascular effects of concomitant stimulant and AAP use beyond possible drug-drug interactions (16). Given recent increases in the use of AAPs concomitantly with stimulants among US youth (17–19), the scarcity of research that has examined the cardiovascular safety with such concomitant use represents a significant evidence gap. The primary objective of this study was to investigate the cardiovascular risk of concomitant stimulant and AAP use in a large retrospective cohort of commercially-insured youth in the US. Since prior studies suggest that risk of cardiovascular events can be associated with dose of AAP (13), a secondary objective investigated whether AAP dose and duration of concomitant use moderate cardiovascular risk among youth. The study was approved by the University *[blinded for review]* Institutional Review Board.

# METHODS

## Study Design

A new user retrospective cohort was constructed among commercially-insured US youth. A cohort of youth who newly initiated a stimulant medication and had no baseline AAP use was selected.

## Study Cohort

The study cohort comprised youth aged 5–17 years old at the time of their first stimulant prescription identified in the data between July 1 2006 and September 30 2015. The date of the first stimulant prescription defined the index date. To be included in the cohort, youth were further required to be continuously enrolled in their healthcare insurance for at least 180 days prior to the index date and have no AAP prescriptions or cardiovascular events of interest during the 180-day look-back period. We further excluded youth with serious medical conditions related to a high risk of developing cardiovascular outcomes. These conditions included aplastic anemia, cancer, cerebral palsy, congenital immune deficiencies, cystic fibrosis, dialysis/end stage renal disease, Down syndrome, other lethal chromosomal anomalies, fatal metabolic diseases, human immunodeficiency virus (HIV) infection, organ transplant, respiratory failure or receipt of hospice care (1, 4, 20). Cohort selection is shown in **Figure 1**.

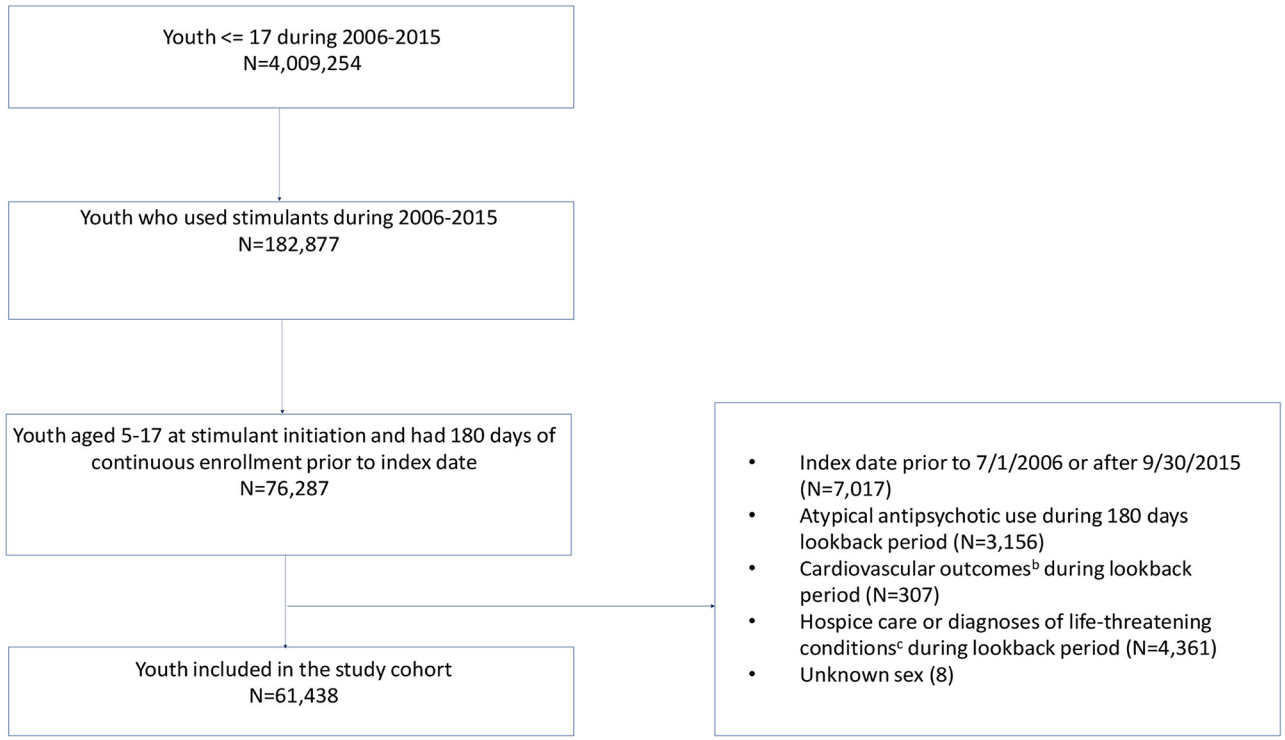
## Data Source

We used a 10% sample of IQVIA PharMetrics® Plus data from 2006 through 2015. IQVIA PharMetrics® Plus data contains fully adjudicated medical and pharmacy claims and is generally representative of the commercially insured population in the US. The data provides de-identified person-level information including year of birth, sex, and monthly enrollment in medical and pharmacy benefits and claim-level information for medical service use and pharmacy dispensings. The medical service use represents inpatient, outpatient and emergency department visits, which contain information on clinical diagnoses recorded as the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and on procedures performed during the visit recorded with the Current Procedural Terminology (CPT-4) codes or the Healthcare Common Procedure Coding System (HCPCS) codes. Pharmacy data, which represent prescriptions filled at outpatient pharmacies, include a unique National Drug Code (NDC) that specifies the drug name and strength, a generic product identifier (GPI) that identifies the therapeutic classification, the dispensing date, the quantity dispensed, and the days supplied.

## Stimulant and Antipsychotic Exposure Measures

### Stimulant and AAP Use

Stimulants and AAPs were identified from outpatient pharmacy claims data. Stimulants included methylphenidate and mixed amphetamine salts. AAPs included aripiprazole, olanzapine, clozapine, quetiapine, paliperidone, risperidone, ziprasidone, asenapine, and iloperidone. Using the date of dispensing and the days supplied of the medication, we determined whether each day of follow-up was a stimulant use day, an AAP use day, or no stimulant or AAP use day. A day that was both stimulant and AAP use was defined as a concomitant stimulant/AAP use day. We allowed a 30-day lag to account for the carry-over effect of AAPs. Carry-over effect refers to the effect that continues after the treatment ceases and is applied in previous studies of AAPs (13, 21, 22). AAP use days were classified as a no AAP use day when the prescription was discontinued for 30 days or more. No




a. Data source: IQVIA PharMetrics® Plus, January 2006 – December 2015
b. Acute myocardial infarction, stroke, ischemic heart disease, heart failure, respiratory arrest, angina pectoris, cardiac dysrhythmias, transient cerebral ischemia, hypertensive disease, cardiovascular tachycardia, palpitations and syncope.
c. Aplastic anemia, cancer, cerebral palsy, congenital immune deficiencies, cystic fibrosis, dialysis/end stage renal disease, Down syndrome, other lethal chromosomal anomalies, fatal metabolic diseases, human immunodeficiency virus (HIV) infection, organ transplant, respiratory failure.

**FIGURE 1 |** Cohort identification of commercially-insured youth (5–17 years old) who were new users of stimulants, 2006–2015.[a] [a]Data source: IQVIA PharMetrics® Plus, January 2006–December 2015. [b]Acute myocardial infarction, stroke, ischemic heart disease, heart failure, respiratory arrest, angina pectoris, cardiac dysrhythmias, transient cerebral ischemia, hypertensive disease, cardiovascular tachycardia, palpitations and syncope. [c]Aplastic anemia, cancer, cerebral palsy, congenital immune deficiencies, cystic fibrosis, dialysis/end stage renal disease, Down syndrome, other lethal chromosomal anomalies, fatal metabolic diseases, human immunodeficiency virus (HIV) infection, organ transplant, respiratory failure.

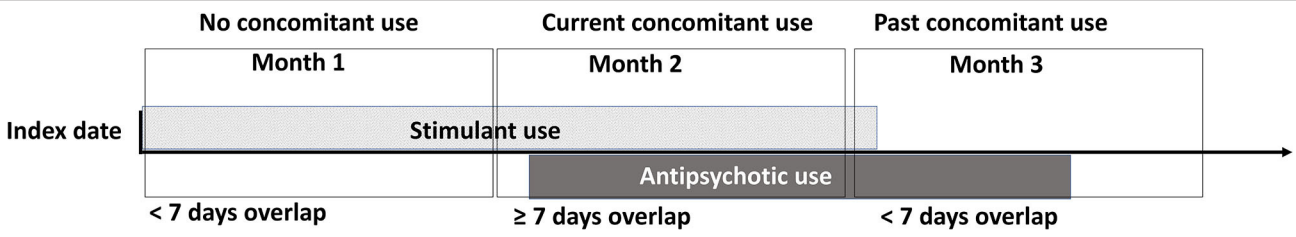



**FIGURE 2 |** Illustration of time-varying definition of concomitant stimulant/AAP use.

lag was applied to classify stimulant use days since no carryover effects of stimulants are reported in the literature (23, 24).

## Concomitant Use of Stimulants and AAPs

**Figure 2** provides a sample to illustrate the definition of time-varying concomitant stimulant/AAP use. Exposure to concomitant stimulant/AAP use was defined in a time-varying manner based on follow-up months. As the cohort was nested in youth who initiated a stimulant medication and had no previous AAP use, all follow-up time started as "no concomitant use." A month of "current concomitant use" was defined as a month with 7 days or more of overlapping use of stimulant and AAP. A month with <7 days of overlapping stimulant/AAP use that followed a period of current concomitant

use was categorized as "past concomitant use." A youth was allowed to switch back and forth between current and past concomitant use.

### AAP Dose and Duration of Concomitant Use

To calculate the average daily AAP dose for each follow-up month, we multiplied the strength of AAP by the quantity dispensed in the 30-day month divided by 30. We used an established formula (13) to convert the average AAP daily dose to risperidone equivalents to permit dose comparisons across individual agents. The average daily AAP dose was classified into three categories: <1, 1–2, and >2 mg.

Concomitant stimulant/AAP use duration was a time-varying measure of the cumulative number of current concomitant use months since the index date. The duration of concomitant use was classified into three categories: <3, 3–6, and >6 months of use.

## Cardiovascular Outcomes

Our study outcome was guided by prior research that documented the association between stimulants and serious cardiovascular events (i.e., stroke, myocardial infarction, ischemic heart disease), and cardiovascular symptoms (i.e., cardiac dysrhythmias, tachycardia, palpitations) (1, 4, 6, 8, 13). Therefore, we assessed two composite cardiovascular outcomes in this study: (1) severe cardiovascular events and (2) less severe cardiovascular events. Severe cardiovascular events were defined as an incident inpatient or emergency department (ED) visit claim with a primary or secondary diagnosis of acute myocardial infarction (ICD-9-CM:410), stroke (ICD-9-CM: 430, 431, 433, 434, and 436), ischemic heart disease (ICD-9-CM: 411.89), heart failure (ICD-9-CM: 428) or respiratory arrest (ICD-9-CM: 799.1). The codes for stroke, acute myocardial infarction, and ischemic heart disease are validated in adults (25–29) and acute myocardial infarction and stroke are also validated in youth (4). All codes listed for severe cardiovascular events have been applied in previous studies to define severe cardiovascular events among youth (1, 13). Less severe cardiovascular events were defined as an incident inpatient or ED visit claim with a primary or secondary diagnosis of angina pectoris (ICD-9-CM: 413), cardiac dysrhythmias (ICD-9-CM:427), transient cerebral ischemia (ICD-9-CM: 435), hypertensive disease (ICD-9-CM:401-405), cardiovascular tachycardia (ICD-9-CM: 785.0), palpitations (ICD-9-CM:785.1) or syncope (ICD-9-CM: 780.2), or two incident consecutive outpatient visits of cardiac dysrhythmia or palpitations within 14 days. The listed codes for less severe cardiovascular events have been utilized in prior studies to identify cardiovascular symptoms among youth taking psychotropic medications (1, 6, 13, 30, 31).

## Baseline Covariates

The 180-day lookback period defined the baseline period. Covariates examined during the baseline period included age, sex, and psychiatric comorbidities (i.e., ADHD, schizophrenia, development disorders, Tic disorder, bipolar disorder, disruptive behavior disorder, depressive disorder, anxiety disorder, adjustment disorder, communication and learning disorder, alcohol and other substance and other psychiatric disorders). To generate real-world evidence of actual clinical practice and to follow methods used other studies in order to maintain consistency with and comparison to prior research, we assessed baseline cardiovascular disorders which were not defined as study outcomes (e.g., abnormal heart sound, cardiac shock, etc.), respiratory conditions (e.g., asthma, bronchitis, etc.), use of medications to treat cardiovascular disease or other predisposing conditions (e.g. ACE inhibitors, cardiac-selective β blockers, antiarrhythmics, etc.) or metabolic conditions (e.g., diabetes, hyperlipidemia, thyroid related disorders, etc.), and use of contraceptive medications and devices (1, 13, 20). Likewise, we assessed congenital anomalies of the heart and circulatory system at baseline because youth with these anomalies are vulnerable to adverse cardiac effects of medications in concert with prior research (4). The covariates were identified based on ICD-9-CM diagnosis codes, CPT-4 procedure codes, and generic drug names. The generic product identifier was also used to identify cardiovascular medications and anxiolytics. The full list of baseline covariates is in Appendix A in **Supplementary Material**.

## Statistical Analysis

The descriptive analysis of baseline characteristics included frequencies and proportions for categorical variables, and medians and inter-quartile range (IQR) for continuous variables. The cohort was characterized by age group (5–9, 10–14, 15–17), sex, US region of residence, psychotropic use, psychiatric comorbidities, and length of follow-up in the study.

Time-dependent Cox proportional hazard regression models were used to estimate the risk of cardiovascular events accounting for time-varying exposure to concomitant stimulant/AAP use. The unit of analysis was person-month. Youth were followed from the index date until they experienced either a severe or less severe cardiovascular event or were censored (whichever came the first). For those with repeated cardiovascular events, only the first occurrence was counted. Censoring events included the development of an aforementioned serious medical condition identified as exclusion criteria, stimulant discontinuation, age 21, loss to follow-up, or the end of the study (September 30, 2015). Stimulant discontinuation was defined as no stimulant prescriptions for six or more consecutive months during the follow-up. Youth were considered loss to follow-up if they lost the health insurance coverage for six or more consecutive months. To evaluate the potential impact of missingness due to uninsured months on the risk estimate and the interpretation of our finding, we conducted a sensitivity analysis allowing no more than 1 month of loss of health insurance coverage during follow-up.

We constructed a disease risk score (DRS) using Miettinen full-cohort approach to adjust for confounding (32, 33). DRS is a summary score to describe the probability of developing the outcome as a function of baseline covariates. Unlike the propensity score that models the likelihood of receiving treatment, the DRS balances confounders of the underlying risk to develop the outcome. Full-cohort DRS performs similarly to a propensity score but reduces the computational complexity of fitting models with multiple time-varying exposures (34–36). Using a logistic regression model, the DRS was developed

for a composite outcome, consisting of all cardiovascular events included in the study, in which baseline covariates were independent variables. The constructed DRS was categorized into tertile ranks and included as a covariate in the final time-varying Cox proportional hazard regression models.

We estimated the risk of severe and less severe cardiovascular events in separate regression models. The primary Cox regression model estimated the hazard ratios (HRs) of cardiovascular events comparing current with no concomitant use, past with no concomitant use, and current with past concomitant use, adjusted for average AAP daily dose, duration of concomitant use and DRS. The secondary Cox regression model estimated the HRs of cardiovascular events for average AAP daily doses (<1, 1–2, >2 mg) and duration (<3, 3–6, >6 months) of current concomitant use comparing with no concomitant use, adjusted for DRS.

# RESULTS

## Baseline Characteristics of the Cohort

There were 61,438 youth who were new stimulant users, among whom 67.8% initiated with methylphenidate and 32.2% initiated with mixed amphetamine salts. The median length of follow-up was 11 months (IQR: 20 months). The majority of youth were male (68.2%), and aged 10 to 17 years old (59.2%). During baseline, the leading psychotropic medication use, in addition to stimulants, included selective serotonin reuptake inhibitors (SSRIs) (6.4%), centrally acting agonists (4.3%), atomoxetine (3.0%), mood stabilizers (1.6%) and anxiolytics (1.1%). The most common psychiatric comorbidities were anxiety disorder (7.9%), adjustment disorder (7.8%), disruptive behavior disorders (7.6%), and depressive disorder (6.5%) (**Table 1**).

**TABLE 1 |** Baseline characteristics of commercially insured youth who initiated stimulants, 2006–2015[a] (*N* = 61,438).

| Demographic and clinical factors | *N* | % |
|---|---|---|
| **Demographic characteristics** | | |
| Age group (years) | | |
| 5–9 | 25,078 | 40.8 |
| 10–14 | 23,054 | 37.5 |
| 15–17 | 13,306 | 21.7 |
| **Sex** | | |
| Female | 19,536 | 31.8 |
| Male | 41,902 | 68.2 |
| **Region** | | |
| East | 13,805 | 22.5 |
| Middle West | 18,374 | 29.9 |
| South | 23,212 | 37.8 |
| West | 6,047 | 9.8 |
| **Psychotropic use** | | |
| Stimulants | | |
| Amphetamine | 19,769 | 32.2 |
| Methylphenidate | 41,669 | 67.8 |
| Atomoxetine | 1,815 | 3.0 |
| Centrally acting agonists | 2,613 | 4.3 |
| **Antidepressants**[b] | | |
| SSRI | 3,901 | 6.4 |
| SNRI | 179 | 0.3 |
| TCA | 268 | 0.4 |
| Anxiolytics | 645 | 1.1 |
| Mood Stabilizers | 981 | 1.6 |
| **Psychiatric Diagnoses** | | |
| Attention deficit hyperactivity disorder | 42,057 | 68.5 |
| Development disorders | 1,588 | 2.6 |
| Schizophrenia | 92 | 0.2 |
| Tic disorder | 362 | 0.6 |
| Bipolar disorder | 417 | 0.7 |
| Disruptive behavior disorders | 4,670 | 7.6 |
| Depressive disorder | 4,004 | 6.5 |
| Anxiety disorder | 4,832 | 7.9 |
| Adjustment disorder | 4,782 | 7.8 |
| Communication and learning disorder | 2,129 | 3.5 |
| Alcohol and other substance abuse | 436 | 0.7 |
| Other psychiatric disorders | 3,770 | 6.1 |

[a] *Data source: IQVIA PharMetrics® Plus, January 2006–December 2015.*
[b] *SSRIs are selective serotonin reuptake inhibitors. SNRIs are serotonin and norepinephrine reuptake inhibitors. TCAs are tricyclic antidepressants.*

## Incidence Rates of Severe and Less Severe Cardiovascular Events

In total, there were 1,096 cardiovascular events (1,064 less severe and 32 severe) over 1,809,861 person-months of follow-up (24,257 current concomitant use, 27,917 past concomitant use, and 1,757,687 no concomitant use). All severe cardiovascular events occurred in person-months with no concomitant and the incidence rate was 0.18 per 10,000 person-months. The incidence rate for less severe cardiovascular events was 14.02 per 10,000 person-months for current concomitant use, 8.24 per 10,000 person-months for past concomitant use, and 5.73 per 10,000 person-months for no concomitant use.

## Cardiovascular Risk and Concomitant Stimulant/AAP Use

Due to the lack of positivity for severe cardiovascular events across concomitant use groups, the analysis was limited to less severe cardiovascular events. In the primary analysis, current concomitant stimulant/AAP use was associated with a significantly increased risk of less severe cardiovascular events compared with no concomitant use [HR:2.59 (95%CI: 1.72, 3.90)] and with past concomitant use [HR: 1.89 (95%CI: 1.10, 3.24)]. Past concomitant use was not significantly associated with increased risk of less severe cardiovascular events compared with no concomitant use [HR: 1.37 (95%CI: 0.89, 2.12)] (**Table 2**).

The secondary analysis evaluated the association between the risk of less severe cardiovascular events and (1) average daily AAPs dose of current concomitant use, and (2) duration of current concomitant use. Compared with no concomitant use, the average AAP daily dose (<1, 1–2, and >2 mg/day) of current concomitant use were associated with increased risk of less severe cardiovascular events with no apparent dose response

**TABLE 2 |** Incidence rates and hazard ratios of less severe cardiovascular risk comparing concomitant use of antipsychotics and stimulants with only stimulant use[a].

| Status of concomitant use | Person-months | Cases | Incidence rate (per 10,000 person months) | Adjusted hazard ratio | 95% CI |
|---|---|---|---|---|---|
| No concomitant use[b] | 1,757,687 | 1,007 | 5.73 | 1.00 | ref |
| Past concomitant use[b] | 27,917 | 23 | 8.24 | 1.37[c] | (0.89, 2.12) |
| Current concomitant use[b] | 24,257 | 34 | 14.02 | 2.59[c] | (1.72, 3.90) |
| | | | | 1.89[d] | (1.10, 3.24) |
| **Current concomitant use by AAP dose[e]** | | | | | |
| Average daily dose of AAP | | | | | |
| <1 mg/day | 12,353 | 14 | 11.33 | 2.82[c] | (1.72, 4.61) |
| 1–2 mg/day | 6,087 | 9 | 14.79 | 2.22[c] | (1.16, 4.25) |
| >2 mg/day | 5,817 | 11 | 18.91 | 2.65[c] | (1.50, 4.71) |
| **Current concomitant use by duration of use[f]** | | | | | |
| Cumulative days of concomitant use | | | | | |
| <3 months | 8,418 | 13 | 15.44 | 3.45[c] | (2.17, 5.47) |
| 3–6 months | 4,355 | 5 | 11.48 | 2.60[c] | (1.29, 5.25) |
| >6 months | 11,484 | 16 | 13.93 | 2.61[c] | (1.59, 4.30) |

[a] *Data source: IQVIA PharMetrics® Plus, January 2006–December 2015.*
[b] *The model was adjusted for AAP daily dose, duration of AAP use, and DRS.*
[c] *Compared with no concomitant use.*
[d] *Compared with past concomitant use.*
[e] *The model was adjusted for exposure status (no, past, or current concomitant use), duration of AAP use, and DRS.*
[f] *The model was adjusted for exposure status (concomitant use or not), average daily dose of AAP, and DRS.*

relationship [HR (95% CI): <1 mg/day: 2.82 (1.72, 4.61); 1–2 mg/day: 2.22 (1.16, 4.25); >2 mg/day: 2.65 (1.50, 4.71)]. Relative to no concomitant use, the risk of a less severe cardiovascular event increased across all durations of current concomitant use [HR (95% CI): <3 months: 3.45 (2.17, 5.47); 3–6 months: 2.60 (1.29, 5.25); >6 months: 2.61 (1.59, 4.30)]. The risk of less severe cardiovascular events was highest among youth with current stimulant/AAP concomitant use < 3 months. The risk decreased slightly with longer duration of use but remained significant (**Table 2**).

The sensitivity analysis which allowed only 1 month of loss in health insurance coverage generated similar results as the primary analyses with two exceptions. First, the risk of less severe cardiovascular events comparing current with past concomitant use was not significant [HR (95% CI): 1.52 (0.88, 2.63)]. Second, the risk of less severe cardiovascular events among youth prescribed 1–2 mg AAP daily dose of current concomitant use relative to no concomitant use was not significant [HR (95% CI): 1.90 (0.97, 3.74)].

## DISCUSSION

In a cohort of commercially-insured US youth aged 5–17 years old who were stimulant new users, the incidence rate of severe cardiovascular events was rare. We found a significantly higher risk of less severe cardiovascular events among youth with current concomitant stimulant/AAP use compared with no concomitant use and past concomitant use. We did not observe a significant dose or duration response relationship between AAP dose or duration and the risk of less severe cardiovascular events.

The finding of rare severe cardiovascular events among youth stimulant users is consistent with previous studies (1, 6, 31), however, the significantly increased risk of less severe cardiovascular events related to current concomitant stimulant/AAP use differs from a previous study (30). To the best of our knowledge, this is the only published population-based study that examined the association between concomitant stimulant/AAP use in a cohort of youth who were new stimulant users and the investigators did not find a statistically significant increased cardiovascular risk (30). The differences in findings between our study and the previously published study might be explained by differences in the study design. First, investigators in the prior study defined stimulant/AAP concomitant use as more than 14 days of same day stimulant and AAP use. Our definition examined concomitant use as a time-varying exposure which enabled us to distinguish changes in the regimen over time. Our findings suggest differing risk of less severe cardiac events for current and past concomitant use, which implies a transient risk that may diminish upon discontinuation of concomitant stimulant/AAP use. It is also possible that concomitant use was stopped among youth who showed signs of cardiovascular complications which might explain the lower risk of less severe cardiac event related to past concomitant use relative to current concomitant use. Second, the length of follow-up differed in our study from the previously published study. Instead of focusing on the risk of cardiovascular events within 1 year following stimulant initiation, our study utilized information over a 10-year period. Half of the youth in our cohort had 11 months or more of follow up. This enabled our study to account for the long-term risk of incident less severe cardiovascular events.

We did not observe a dose-response relationship between AAP dose and the risk of less severe cardiovascular events.

Other investigators have reported a higher risk of cardiovascular events with increasing AAP dose (13, 20, 37), however the doses reported in these studies were much higher than those observed in our cohort. For example, a study based on Medicaid-insured children observed a 2-fold higher risk of incident cardiovascular events with an AAP daily dose of 3.75 mg or more (risperidone equivalent) compared with 1.25 mg or less (13). In our study, the majority of youth who received concomitant stimulants and AAPs were prescribed AAPs <2 mg per day (risperidone equivalent). The narrow range of average daily dose of AAPs in our study may have limited our ability to detect an AAP dose-response for cardiovascular risk. On the other hand, our findings suggest that concomitant use of stimulants with even low dose of AAP (e.g., <1 mg per day) can increase the risk of developing cardiovascular events among youth. Our study also found that the risk of less severe cardiovascular events was highest in stimulant/AAP concomitant use <3 months, which indicates that adverse cardiovascular events are observed early in the course of the treatment. The risk remained significant with longer duration of use, but lower than that in the first 3 months. It is possible that youth who were least tolerant developed cardiovascular events early in the course of treatment than those who had a longer duration of use. It is also possible that youth may adapt physiologically to the medication over the course of treatment, and thus the cardiovascular risk decreased over time (38).

Our study has several strengths. First, this work adds to the limited evidence of cardiovascular safety related to concomitant use of stimulants and AAPs among youth in the U.S. Second, this is the first study to investigate the cardiovascular safety of AAP dose and duration when prescribed concomitantly with stimulants among youth. Third, we applied a new user design to mitigate prevalent user bias. Fourth, the time-varying approach to define concomitant use accounted for changes in treatment during the follow-up. Nonetheless, this study is not without limitations. Cardiovascular events are rare among youth and thus we had small numbers (i.e., <10) of events for certain subgroups of concomitant stimulant/AAP use, which led to wide confidence intervals of estimated hazard ratios. This may indicate limited precision in risk estimate for these groups. Although a DRS was constructed to adjust for baseline confounders, potential time-varying covariates, including incident physical and psychiatric diagnoses during follow-up, were not considered. Unmeasured confounders may remain as claims data only captures billable health service use and prescribed medications. Therefore, we could not measure use of over-the-counter medications or other potential confounders such as family history, lifestyle, and socioeconomic status. We defined medication use based on prescriptions dispensed in outpatient pharmacies which may not reflect the actual consumption. Our definition of loss to follow-up may lead to missingness due to uninsured months. The sensitivity analysis using a definition that minimized the number of uninsured months showed that the impact of missingness on risk estimates are minimum. Finally, the study may not generalize to US youth who are uninsured or insured through Medicaid, even so the cohort is representative of commercially insured youth.

## CONCLUSION

Although the incidence of severe cardiovascular events is rare, concomitant stimulant/AAP use is associated with an increased risk of less severe cardiovascular events, including angina pectoris, cardiac dysrhythmias, transient cerebral ischemia, hypertensive disease, tachycardia, palpitations and syncope, among youth stimulant users. The recommendation of periodic monitoring of heart rate and blood pressure may be warranted for youth whose stimulant treatment is augmented to AAPs.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from IQVIA. Requests to access these datasets should be directed to https://www.iqvia.com/.

## AUTHOR CONTRIBUTIONS

CZ: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, drafting of the manuscript, and statistical analysis. CZ and SD: concept and design. SD and GR: supervision. All authors: acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.640244/full#supplementary-material

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BRIEF RESEARCH REPORT
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# Inter-class Concomitant Pharmacotherapy in Medicaid-Insured Youth Receiving Psychiatric Residential Treatment

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**Background:** Concomitant pharmacotherapy has become increasingly common in the treatment of youth, including in psychiatric residential treatment facilities (PRTF) despite limited efficacy and safety data. Research is reported on the prevalence of any class and interclass concomitant pharmacotherapy, specific class combinations of psychotropics, and changes in number of medications from admission to discharge for Medicaid insured youth treated in PRTFs in one mid—Atlantic state.

**Methods:** Medicaid administrative claims data were examined for youth under age 18 years who were discharged from one of 21 PRTFs during calendar year 2019. Descriptive statistics were calculated to examine patterns of service utilization 90 days prior to admission. The rates of concomitant psychotropic use at admission were compared to the rates at discharge. Logistic regression models were used to examine covariates associated with discharging on 4 or more medications.

**Results:** Fifty-four % of youth were admitted on either two or three psychotropics, while 25% were admitted on four or more psychotropics. The proportion of youth admitting and discharging on 2 or 3 medications was stable. There was a 27% increase in number of youth discharging on 4 medications with a 24% decrease in those on a 5- drug regimen. Only the number of medications prescribed at admission was found to be significant ($p < 0.001$), with more medications at admission contributing to probability of discharging on 4 or more medications.

**Conclusions:** Concomitant pharmacotherapy is common in PRTFs. These findings support the practice of deprescribing and underscore the need for further research.

**Keywords: concomitant pharmacotherapy, polypharmacy, children and adolescents, Medicaid, residential treatment**

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## BACKGROUND

Concomitant psychotropic use, also referred to as polypharmacy, has become widespread and data suggest that it is increasing (1–4). A 29 state Medicaid fee-for-service study found the prevalence of any class and inter-class polypharmacy increased from 21.2 and 18.8% in 1999–2000 to 27.3 and 24.4% in 2009–2010, respectively in medicated youth <18 years of age (4). A single state

retrospective cohort study using 2012–2015 claims data found 38% of youth on psychotropic medication for at least 90 days were prescribed two or more psychotropic medications during the study period (1). A cross sectional study used national household survey data, and found the number of youths younger than 18 years treated with three or more psychotropic classes increased from 101,836 (1999–2004) to 293,492 (2011–2015) (5).

Concomitant psychotropic pharmacotherapy has been utilized as a strategy to address residual symptoms and incomplete response to monotherapy, to augment response to other psychotropics, to mitigate side effects of concurrent medication, to treat medical comorbidity and to increase medication tolerability (6). The combination of multiple medications may offer benefits for specific clinical conditions such as the use of a stimulant and alpha agonist for the treatment of attention deficit hyperactivity disorder (ADHD); however, overall the evidence base for concomitant pharmacotherapy in pediatric psychiatric practice is limited while risk for harm is significant (7). Using concomitant psychotropics increases the risk of for drug-drug interactions, additive drug adverse reactions, and may create a cycle of using one drug to treat the adverse effects of another. Another concern is the unknown impact of long-term exposure (7–10). Burcu et al. (10) found twice the of risk of type 2 diabetes among Medicaid youth receiving concurrent atypical antipsychotics with SSRI/SNRI antidepressants. A series of case reports of presumed serotonin syndrome in children receiving multiple concurrent psychotropics including SSRIs, stimulants, and atypical antipsychotics underscores the risk of serotonin toxicity when prescribing multiple medications (11–13). There is emerging evidence that many classes of psychotropic medications can have a negative impact on pediatric bone health and increase the risk for osteoporosis (14). The most evidence exists for anticonvulsant mood stabilizers prompting recommendations for routine baseline and monitoring of vitamin D levels for all children on anticonvulsants and vitamin D supplementations for those on chronic mood stabilizers (15). As atypical antipsychotics and SSRIs can increase prolactin levels through different mechanisms, it is important to monitor bone health for children prescribed combinations of antipsychotics, mood stabilizers and SSRIs (14).

Psychiatric residential treatment facilities (PRTFs) are non-hospital facilities that provide intensive, 24/7 level treatment under the direction of physician with a range of therapeutic interventions including psychopharmacotherapy provided by a multidisciplinary team. PRTF services are an optional Medicaid benefit serving individuals up to age 21years. Youth entering a PRTFs share a history of multiple episodes of treatment, including community-based services and acute inpatient mental health hospitalization, and concomitant psychotropic use.

Studies of concomitant psychotropic use in residential settings are heterogeneous with regards to types of facilities such as child welfare and/or juvenile justice placements, group homes, residential treatment centers and PRTFs. Residential settings vary with regards to census, population characteristics, intensity, types of treatment offered, and dedicated psychiatric time. Connor et al. (16) found that 76% of youth admitted to a residential treatment center were on psychotropics, with 40% on more than one psychotropic medication. A retrospective naturalistic study of a single residential treatment setting over a 9-year period found that the number of children on multiple concurrent medications decreased from 78% at admission to 48% at discharge (17). Factors correlated with a reduction in medication included a decrease in psychopathology scores, youth admitted from more intact families (biological or adoptive), and those treated with non-stimulant medications. A retrospective study of 1,010 youth at a large group-home facility during 2001–2004 found a decrease from 40% on any medications at admission to 26% on no medications at discharge. Several studies published from 2013 to 2016 reported a reduction of psychotropics and concomitant pharmacotherapy with the use of structured psychosocial treatment programs and implementation of evidence-informed prescribing practices (18–21). Bellonci et al. (18) study of two different residential treatment centers found a decrease in the average numbers of psychotropics from admission (3.5) to discharge (1.4) with improved outcomes. Of note the psychiatrists at both sites embraced the principle of sufficiency with regards to medication use. Lee et al. (20) 10-year study (2003–2012) found a 26% cost reduction in psychotropic medications at a juvenile justice residential treatment program implementing psychiatric practice guidelines without an increase in aggression compared to cost increases found (104%, 152%) at two comparison programs.

Community Care Behavioral Health Organization (CCBHO), part of the UPMC Insurance Services Division, is a non-profit behavioral health managed care organization (BHMCO) that manages behavioral health services for 41 of Pennsylvania's 67 counties, which represents 38% of all Medicaid members in Pennsylvania. Given the expanded use of concomitant pharmacotherapy in youth, and the limited evidence for efficacy and safety, the BHMCO examined utilization of concomitant psychotropic medications in the Medicaid- enrolled pediatric population receiving services in PRTFs. First, we describe the utilization of concurrent psychotropic medication in PRTFs by gender, race, ethnicity, age group, and diagnosis. Second we compare changes in both number of medications and the number of concurrent classes of medications from admission to discharge. We report the prevalence of inter-class concomitant pharmacotherapy for 2, 3, and 4 or more medication classes and the common combinations of classes of medications. Third, we test a model to examine if covariates are associated with being discharged on four or more medications.

# METHOD

## Data Source

Medicaid administrative claims data were examined for 548 Medicaid enrolled youth <18 years within the BHMCO network who discharged from a PRTF in calendar year 2019. Claims from all 21 PRTFs across the BHMCO's network with eligible discharges were included. The study was approved through UPMC Quality Review Committee.

## Study Measures

### Sociodemographic Characteristics

Demographic information including age, gender, race, and ethnicity were derived from administrative eligibility data from the state. Youth were categorized by age group into 6–12 and 13–17 years. Race and ethnicity were recorded from self-reported eligibility information. Race was categorized as Black, White or other; ethnicity was recorded as Hispanic/non-Hispanic.

### Diagnosis Groupings and Behavioral Health Services

Diagnoses (ICD 10 codes) were obtained from claims data. Up to three admitting diagnoses were recorded from each claim. Diagnoses were categorized into the following groups: Disruptive Mood Dysregulation Disorder (DMDD), Attention Deficit Hyperactivity Disorder (ADHD), Mood Disorders (major depressive disorders and persistent mood disorders), Anxiety, Trauma and Stress Disorders, Disruptive, Impulse and Conduct Disorders, Autism Spectrum Disorder (ASD), and Psychotic Disorders. A list of ICD-10 codes is provided in **Supplemental Table 1**. As DMDD is a relatively recent diagnosis without an FDA- indicated treatment medication, it was decided to not incorporate it into another diagnostic grouping. The diagnostic groups are not mutually exclusive, and each youth can potentially be counted in more than one diagnostic group. All behavioral health service claims data in the 90 days prior to admission to PRTF were grouped into broad categories: outpatient services, school and community- based programs, case management, medication management, substance use treatment, partial hospital programs and inpatient mental health.

Receipt of a behavioral health service was considered as any claim for that service in the 90 days prior to PRTF admission. We dichotomized youth into those who had IPMH treatment over that interval and those who did not. A youth could be counted in more than one service level as he/she could have had multiple claims and multiple services in the 90 days prior to PRTF admission, but the youth is only assigned to one group (with or without IPMH).

### Medications

Psychotropic medication data were obtained from paid pharmacy claims. All psychotropics were categorized into the following classes: antipsychotics, antidepressants, alpha- 2-agonists, mood stabilizers, stimulants, melatonin, anticholinergic agents, antianxiety medication, atomoxetine, benzodiazepines, substance use disorders medications, antihistamines and hypnotics. Lithium was included in the class of mood stabilizers. Diphenhydramine was the only antihistamine identified. A list of medications within subgroups is provided in **Supplemental Table 2**.

### Definition of Concomitant Psychotropic Use

Concomitant psychotropic use was defined as the presence of at least 2 concurrent psychotropic medication prescription dispensing events. Inter-class pharmacotherapy was defined as at least 2 different classes of medication that would be used at the same time for at least 60 consecutive days. The allowable gap for medication fills was 7 days. Paid pharmacy claims at 30 days post admission and at 30 days prior to discharge served as proxies for admission and discharge medications. The requirement of at least 60 consecutive days to qualify as concurrent psychotropic use was applied for the entire duration with the exception of the first and last 30 days.

### Covariates

We obtained the following covariates on all participants: age at admission, race, ethnicity, gender, length of stay in days, inpatient mental health services (IPMH) in the 90 days prior to residential treatment admission, number of medications at admission, number of medications at discharge, diagnoses, and Medicaid eligibility groups.

### Statistical Analysis

Descriptive statistics were calculated to examine demographic data (age groups, race, gender), length of stay, and history of behavioral health services in the 90 days prior to admission to the PRTF. The most common combinations of medication classes were determined for inter-class concurrent medications. Prevalence rates for the number of youth dispensed any psychotropics as well as the number of youth dispensed inter-class combinations were obtained for admission and discharge medications.

L1 regularized regression (LASSO regression) is a linear regression model with an additional penalty term to encourage sparsity of the coefficients (22). It can therefore be used as a type of features selection because it drops unnecessary covariates, such as those that are highly correlated, those with a small effect size, or those that are not predictive of the outcome. Logistic LASSO regression models were used to predict discharging on 4 or more medications. Data were restricted to the youth that fit the criteria. The regularization parameter was set to alpha =5. The following covariates were included in the model: number of medications at the time of admission, length of stay, inpatient mental health treatment 90 days prior to admission, race, age >13 years, Medicaid eligibility groups, and the presence of any of the following diagnoses: DMDD, bipolar disorder, ASD, and psychotic disorders.

# RESULTS

## Demographic and Clinical Characteristics of Youth at Admission to PRTF

**Table 1** presents the demographic and clinical characteristics of youth as well as the behavioral health services received in the 90 days prior to admission to PRTF. Adolescents accounted for 70% of youth admitted. All youth received a range of behavioral health services prior to admission, and 50% were treated in an inpatient mental health service in the previous 3 months.

## Number of Medications and Classes of Medications at Admission and Discharge

**Table 2** presents the rates of specific medication classes prescribed at time of admission with antipsychotics (62%) antidepressants (53%), and alpha−2-agonists (37%) being the most prevalent.

**TABLE 1 |** Demographic and clinical characteristics of youth at time of admission to PRTF.

| Categories | Total *N* = 548 | Percent |
|---|---|---|
| **Age groups** | | |
| 6–12 | 166 | 30.3% |
| 13–17 | 382 | 69.7% |
| **Race** | | |
| Black | 97 | 17.7% |
| White | 410 | 74.8% |
| Other | 41 | 7.5% |
| **Ethnicity** | | |
| Non-Hispanic | 512 | 93.4% |
| Hispanic | 36 | 6.6% |
| **Gender** | | |
| Female | 248 | 45.3% |
| Male | 300 | 54.7% |
| **Diagnostic groups** | | |
| Disruptive mood dysregulation disorder | 121 | 22.1% |
| Attention-deficit hyperactivity disorder | 120 | 21.9% |
| Mood disorders (major depressive disorder, persistent depressive disorder) | 116 | 21.2% |
| Anxiety, trauma, stress disorders | 113 | 20.6% |
| Disruptive, impulse & conduct disorders | 98 | 17.9% |
| Other | 81 | 14.8% |
| Bipolar disorder | 74 | 13.5% |
| Autism spectrum disorder | 54 | 9.9% |
| Psychotic disorders | 10 | 1.8% |
| **Medicaid eligibility groups** | | |
| SSI | 255 | 46.5% |
| TANF | 191 | 34.9% |
| THM | 102 | 18.6% |
| **BH services 90 prior to admission** | | |
| Inpatient mental health (IPMH)+ other services | 274 | 50% |
| BH services without IPMH | 274 | 50% |

*SSI, supplemental security income; TANF, temporary assistance for needy families; THM, TANIF, healthy horizons, and MAGI (modified adjusted gross income); BH, behavioral health.*

Changes in the number of medications prescribed at admission compared to the number of medications prescribed at discharge are shown in **Table 3**. Of the 548 youth who were discharged from PRTFs in CY 2019, 54.3% were admitted on either 2 or 3 psychotropic medications, while 25% of youth were admitted on 4 or more medications. The number of youth admitting and discharging on one medication decreased slightly. There was little change in the number of youth on 2 or 3 medications from admission to discharge. There was a 27% increase in number of youth discharging on 4 medications, with a 24% decrease in the number of youth discharging on a 5 or more-drug regimen. The pattern of changes from admission to discharge for number of inter-class combinations was stable for 2 and 3 inter-class combinations, with a 6% increase in number of youth discharging on 4 or more inter-class combinations.

**TABLE 2 |** Psychotropic medications at admission.

| Medication class | Number of children | % (Den = 548) |
|---|---|---|
| Atypical antipsychotics | 341 | 62.20% |
| Antidepressants | 290 | 52.90% |
| Alpha-2 agonist | 202 | 36.90% |
| Mood stabilizers | 190 | 34.70% |
| Stimulants | 136 | 24.80% |
| Melatonin | 50 | 9.10% |
| Antihistamines | 27 | 4.90% |
| Anticholinergics | 24 | 4.40% |
| Anti-anxiety meds | 23 | 4.20% |
| Atomoxetine | 23 | 4.20% |
| Benzodiazepines | 19 | 3.50% |
| SUD/alcohol meds | 5 | 0.90% |
| Hypnotics | 4 | 0.70% |

**TABLE 3 |** Changes in number of medications from admission to discharge.

| | Number of medications | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 or more |
| Number of youth at admission | 41 | 72 | 143 | 155 | 83 | 54 |
| Number of youth at discharge | 36 | 69 | 145 | 152 | 105 | 41 |

## Duration of Medications, Inter-class Combinations and Same Class Concurrent Psychotropics

Of the 548 youth, 86.9% received 2 or more different psychotropics for at least 60 days, with a median duration of 110 days (range of 60–1,114 days). 64.6% of youth received 3 or more different psychotropics for at least 60 days with a median of 109 days (range 60–917 days). For children receiving 3 or more different classes of medication, 55.7% received these medications for 90 days or more with a median of 146 days (range 90–917 days).

**Table 4** shows the most common combinations of classes of medications found for each level of inter-class concomitant psychotropic use. Antidepressants, alpha-agonists, and antipsychotics were the most frequently combined classes present in three concurrent inter-class psychotropics, followed by mood stabilizers and stimulants. Data for combinations prescribed to fewer than 5 children were grouped as "Other" revealed many different combinations too numerous to list. Twenty-two percent of youth received same class concurrent medication with antidepressants being most frequent (13%), antipsychotics and mood stabilizers (3%) each, respectively, while alpha-2-agonists, stimulants, and anticholinergic medications were negligible.

## Covariates Associated With Discharge on 4 or More Medications

The logistic regression model to predict discharging on 4 or more medications included the following variables: age in years, race,

**TABLE 4 |** Most common drug classes in concurrent medications prescribed at discharge.

| Concurrent medication | Most common drug classes | Total children (*N* = 548) | % of group |
|---|---|---|---|
| 2 medication | (AD, AP) | 37 | 22.42 |
| classes (*N* = 165) | (AA, AP) | 20 | 12.12 |
| | (AP, MS) | 17 | 10.30 |
| | (AA, AD) | 16 | 9.70 |
| | (AD, MEL) | 9 | 5.45 |
| | (AP, STM) | 9 | 5.45 |
| | (AD, MS) | 8 | 4.85 |
| | (AD, STM) | 8 | 4.85 |
| | (AA, MS) | 5 | 3.03 |
| | Other | 36 | 21.82 |
| 3 medication | (AA, AD, AP) | 18 | 10.98 |
| classes (*N* = 164) | (AD, AP, MS) | 17 | 10.37 |
| | (AA, AP, MS) | 15 | 9.15 |
| | (AA, AP, STM) | 12 | 7.32 |
| | (AA, AD, STM) | 11 | 6.71 |
| | (AD, AP, STIM) | 10 | 6.10 |
| | (AD, MS, STM) | 6 | 3.66 |
| | (AA, AD, MEL) | 6 | 3.66 |
| | (AA, AD, MS) | 5 | 3.05 |
| | Other | 64 | 39.02 |
| ≥4 medication | (AA, AD, AP, STM) | 10 | 9.52 |
| classes (*N* = 105) | (AA, AD, AP, MS) | 8 | 7.62 |
| | (AA, AD, MS, STM) | 6 | 5.71 |
| | Other | 81 | 77.14 |

*AD, antidepressant; AP, antipsychotic; AA, alpha agonist; MS, mood stabilizer; MEL, melatonin; STM, stimulant; Other, combinations of medication classes prescribed to fewer than 5 children.*

ethnicity, indicator for any inpatient mental health service 90 days prior, number of medications on admission, length of stay (days), Medicaid eligibility groups, and admitting or discharging with a diagnosis of DMDD, or bipolar disorder or ASD, or psychotic disorder.

Only the number of medications prescribed at admission was found to be significant ($p < 0.001$), with more medications at admission contributing to probability of discharging on 4 or more medications.

## DISCUSSION

Our finding that 54% of youth were admitted on either 2 or 3 psychotropic medications, while 25% of youth were admitted on 4 or more medications aligns with previous reports of the prevalence of concomitant pharmacotherapy prior to or at the time of admission to residential settings (16, 18–21, 23). Children served in the public sector, in foster care, those who have experienced trauma, and those with intellectual disability are vulnerable to high rates of concomitant psychotropic medication (7, 24–26).

PRTFs offer a longer duration of multimodal treatment in a structured therapeutic setting conducive to re-evaluating prior interventions and obtaining multiple observation points in time to assess the benefits and risks of medications. However, we did not find a reduction in concomitant prescribing over the course of treatment in PRTFs. Most youth were discharged on the same number of medications on which they entered. Medications tended to be added if a youth was admitted on three or less medications and reduced if a youth was admitted on five or more medications. It is quite possible the dosage of medications would have been titrated over the course of treatment or that specific medications would have changed during the treatment episode; however, we did not obtain that information for this report. Clinical practice guidelines typically target the treatment of single disorders, leaving prescribing clinicians without adequate tools to address the increased use of concomitant pharmacotherapy. Youth in our sample received multiple psychiatric diagnoses, a finding congruent with previous reports of the complex behavioral health needs of youth in residential treatment settings. Bellonci et al. (18) highlight several challenges facing psychiatrists working in residential treatment settings including unknown diagnostic and treatment histories, limited efficacy and safety data about psychotropics, and finding existing algorithms and guidelines are not sufficient for this population. As youth enter PRTF on multiple medications and having not been successfully maintained in the community, we speculate that that there may be an underlying assumption that inter-class concurrent pharmacotherapy is to be expected. Physician training around medications has historically focused on initiation, titration and monitoring (levels, side effects) of medications, with less attention given to re-assessment of the risk/benefit or indications for discontinuation. In view of the unknown risk of long-term exposure to multi-class psychotropic medication, potential for drug-drug interactions and additive drug adverse reactions, coupled with the limited safety and efficacy data, implementing a deprescribing practice is warranted. Deprescribing guidelines would fill the gap identified in current guidelines.

The growth in antipsychotic medications is attributed to their use to address disruptive and aggressive behaviors, including such behaviors often present among those with ADHD. The diagnosis of ADHD does increase the likelihood of concomitant psychotropic use; however, it appears the ADHD diagnosis serves as proxy for maladaptive behaviors (e.g., aggression, behavioral dysregulation) frequently experienced by some youth with ADHD (27, 28). It is likely these associated behaviors that drive the use of concomitant psychotropic use. The T-MAY guidelines for maladaptive aggression in youth recommend that only after trials of psychosocial treatment and stimulants have been deemed ineffective should there be consideration for antipsychotics (29). In our study ADHD and DMDD were the two most prevalent diagnoses.

Stimulants are effective not only for ADHD but are also effective in controlling aggression. Our finding of greater concomitant use of alpha agonists and antipsychotics rather than alpha agonists and stimulants raises questions as to why optimizing treatment with stimulants was not preferred over antipsychotics, given their relative risks and benefits.

The only covariate found to be significantly associated with discharging on 4 or more medications was the number of medications present at admission. Connor et al.'s (16) study of the use of psychotropics in a residential treatment school found 70% of youth who had received trials of multiple concurrent pharmacotherapy prior to admission continued to receive such combinations at admission.

Some challenges exist in comparing our PRTF findings of concomitant psychotropic use to findings from other studies carried out in other residential settings given their heterogeneity noted earlier. Prior studies conducted in residential settings may have excluded youth with diagnoses of intellectual disability or psychotic disorders and utilized diagnostic criteria that predated DSM-5. The rates of concurrent psychotropics (3 or more) prescribed at time of admission from our study were comparable to earlier studies in residential settings. A number of studies that found a reduction in medication over time were explicit in their use of guidelines or included physicians with a shared approach to judicious prescribing (22, 24–28).

## STRENGTHS

Our retrospective study utilized more recent Medicaid claims data, examined one level of care, PRTF, rather than a variety of residential settings that differ in the population served and mental health treatment services offered and provided data on inter-class polypharmacy and specific combinations of classes. Unlike previous residential studies of psychotropic utilization drawing on data from one or two facilities, our study encompassed 21 different PRTFs.

## LIMITATIONS

This study utilized Medicaid claims data of youth receiving PRTF services covered by CCBHO from the majority of counties in Pennsylvania and may not represent prescribing practices in residential treatment facilities in other regions. PRTFs in Pennsylvania are not evenly distributed across the state and can contract with multiple BHMCOs. We acknowledge the limitation however believe our data are representative of prescribing practices in PRTFs. We have no reason to believe that the prescribing psychiatrists in the PRTFs would alter their overall prescribing practices based on the BHMCO covering the youth. Administrative claims data do not provide detailed clinical information; symptom and behavioral data that may be associated with concurrent pharmacotherapy are not available. Claims data are valuable in providing estimates of prescribing patterns found in PRTFs, but it does not reveal why child and adolescent psychiatrists utilize concomitant psychotropic agents nor does it provide clinical outcomes data on the risks and benefits of combined medications for this population. We did not have information at the provider PRTF level regarding specific initiatives on reducing concomitant pharmacotherapy. Data about foster care and juvenile justice status for youth at the time of entry or exit from PRTF would have been useful; however, the state did not provide us with that information.

## CLINICAL, RESEARCH, AND POLICY IMPLICATIONS

Concomitant pharmacotherapy has become an accepted practice across levels of care and across age groups, though it is lacking strong evidence of its benefits with few exceptions and has associated risks. Our finding that significant proportions of youth in the most intensive level of care receiving 2, 3, and 4 or more classes of psychotropics provides data for future studies to evaluate the benefits and risks of common combinations. We endorse the call for additional research on complex inter-class regimens that has been made repeatedly (1, 4, 5, 7, 30). Research studies on the benefits and risk of combined treatment would address the evidence gap challenging psychiatrists providing clinical care, provide data regarding the effectiveness for populations, and tackle questions regarding the safety of chronic exposure to concurrent psychotropics.

Each day physicians must make clinical decisions with regards to concomitant pharmacotherapy; as such we advocate for the adoption of deprescribing practices by psychiatrists and other prescribing clinicians. Deprescribing is part of good prescribing practice, providing a systematic approach to identify and discontinue medications when the harms outweigh the benefits. The American Academy of Child and Adolescent Psychiatry (AACAP) practice parameter on the use of psychotropic medication includes two key principles relevant to deprescribing: (1) the need for a clear rationale for using medication combinations and (2) discontinuing medications requires a specific plan (31). Deprescribing has its origins in geriatric medicine (32) and since has gained attention by psychiatry (33) and child and adolescent psychiatry (34–38). The American Academy of Pediatrics (AAP) and AACAP appreciate that maltreated children are more likely to receive psychotropic medication than their peers and has issued guidance on trauma-informed assessment and pharmacologic treatment considerations (39). Gupta et al. (33) and Bellonci et al. (34) offer practical stepwise guidance on deprescribing.

State level quality improvement interventions initially focused on antipsychotic prescribing for children enrolled in Medicaid and/or in foster care and later expanded efforts to address polypharmacy. Strategies include antipsychotic prior authorization policies, mandatory peer review, and voluntary psychiatric consultation programs. As of 2018, 23 states and Washington DC offered telephonic psychiatric consultation, often aimed at primary care physicians (40). Evaluating the impact of these interventions is beyond the scope of this paper. One Medicaid statewide quality improvement program included both pediatricians and psychiatrists (in community mental health centers and residential treatment settings) and found a significant decrease in polypharmacy for the psychiatrist group (41). Managed care organizations may have opportunities to incentivize safe and judicious prescribing through the use of value-based performance contracting.

## CONCLUSION

Concomitant psychotropic pharmacotherapy is common practice in many PRTFs in Pennsylvania with antipsychotic, antidepressant, alpha-2-agonist, mood stabilizers, and stimulants frequently used in combination despite limited efficacy and safety data. These findings support adoption of deprescribing practices and support the call for publicly funded research on the effectiveness and safety of inter-class pharmacotherapy.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Study was approved by the UPMC (University of Pittsburgh Medical Center) Quality Review Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

GE contributed to the study design, writing, and literature review. KE contributed to the data analysis and revisions. MP contributed to the data analysis. NR contributed to study design and critiqued the manuscript, AH critiqued and edited the manuscript. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.658283/full#supplementary-material

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REVIEW
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# Psychotropic Polypharmacy in the US Pediatric Population: A Methodologic Critique and Commentary

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**Background:** Psychotropic concomitant medication use for the treatment of youth with emotional and behavioral disorders has grown significantly in the U.S. over the past 25 years. The use of pharmacy claims to analyze these trends requires the following: age of the selected population, overlapping days of use, and precision of the outcome itself. This review will also address the gaps in reporting of pediatric psychotropic polypharmacy.

**Methods:** An electronic literature search was undertaken for the period 2000 through 2020 using keywords such as "pediatric," "concomitant," "polypharmacy," "multiple medications," and "concurrent psychotropic"; Relevant references in textbooks were also used. Only English language and U.S. studies were included, resulting in 35 inter-class studies.

**Results:** Studies were organized into seven groups according to data sources and clinical topics: (1) population surveys; (2a) multi-state publicly insured populations; (2b) single/two state studies; (3) privately insured populations; (4) diagnosed populations; (5) foster care populations; (6) special settings. Across 20 years it is apparent that pediatric psychotropic polypharmacy affects substantially more children and adolescents today than had been the case. As many as 300,000 youth now receive 3 or more classes concomitantly. The duration of concomitant use is relatively long, e.g., 69–89% of annual medicated days. Finally, more adverse event reports were associated with 3-class compared with 2-class drug regimens.

**Discussion:** Factors that contribute to the growth of pediatric psychotropic polypharmacy include: (1) predominance of the biological model in psychiatric practice; (2) invalid assumptions on efficacy of combinations, (3) limited professional awareness of metabolic and neurological adverse drug events, and (4) infrequent use of appropriate deprescribing.

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**Conclusion:** A review of publications documenting U.S. pediatric psychotropic polypharmacy written over the last 20 years supports the need to standardize the methodologies used. The design of population-based studies should maximize information on the number of youth receiving regimens of 3-, 4-, and 5 or more concomitant classes and the duration of such use. Next, far more post-marketing research is needed to address the effectiveness, safety and tolerability of complex drug regimens prescribed for youngsters.

**Keywords: polypharmacy, pediatric, concomitant psychotropic, children, adolescents, multiple medications or concurrent psychotropics**

## INTRODUCTION

Of U.S. youth less than age 20 years, 21.9% used a prescription drug in the past month according to a recent federal population survey by Hales et al. (1). Furthermore, 39% of these youth used 2 or more prescription drugs of *any* therapeutic class in the previous month. While the prevalence of many therapeutic classes of drugs was stable across the 15 years surveyed, there were prominent increases for several classes. Particularly more widely prescribed were psychotropics used to treat the emotional and behavioral disorders of youth. These included ADHD medications, particularly amphetamine type stimulants, as well as antipsychotics and alpha-adrenergic agents. Unfortunately, the survey authors (1) did not address concomitant use of 2 or more psychotropics, i.e., polypharmacy.

Compared to youth, research on adult polypharmacy in psychiatry has received prominent attention for many years, particularly for adults with serious chronic conditions such as schizophrenia and bipolar disorder (2, 3). The prevalence of 2 or more concomitant classes involved as many as 60% of adult outpatient visits to psychiatrists in 2006 (4).

The definition of polypharmacy varies depending on the parameters measured: the length of overlapping days of exposure and the width of the period assessed (5). Data sources for polypharmacy include population surveys as well as claims-based analyses. Population-based surveys typically measure health care services per 100 eligible persons, often derived from physician office visits. Survey methods typically measure concomitant use as a point prevalence at a single point per year in a population-based model (4). By contrast, period polypharmacy prevalence is more common in administrative claims studies where annual datasets are available to provide a wider window for measurement.

Outcome measures include two types of polypharmacy: within class, e.g., 2 concomitant antipsychotics, and inter-class (multi-class), e.g., concomitant antipsychotic and antidepressant. Within class antipsychotic polypharmacy has been featured in many pediatric studies (6, 7) presumably because it raises concerns with respect to treatment emergent risk, especially for metabolic adverse effects (8, 9). For simplicity of presentation, the most commonly used definition of psychotropic polypharmacy is the use of 2 or more psychiatric medications in the same patient (10).

Medicaid administration programs have sought to reduce the overprescribing of antipsychotics and other psychotropics in children and adolescents, especially foster care youth in response to government reports on overuse (11, 12). As a consequence, state Medicaid oversight programs have produced research showing reduced antipsychotic usage in children (13, 14). The administrative claims data of large populations covered by health insurance have been frequently used to assess inter-class polypharmacy and such studies may feature a single year or multi-year trend analysis. Similarly, all enrolled youth may be represented or youth in a particular subgroup, e.g., foster care youth (15).

This review features inter-class psychotropic polypharmacy for the treatment of youth (16–18). More specifically, the review aims to support administrative claims study methods to:

1) Increase precision in the outcome of polypharmacy beyond "2 or more concomitant drugs" so that 3, 4, and 5 or more class (drug) regimens are reported in terms of the *number and percent of youth as a proportion of psychotropic medicated youth* in a year (19).
2) Standardize methods to:
   - Measure overlapping medication days for 60 or 90 or more days to avoid counting unintentional polypharmacy caused by switching from one drug to another (18, 20).
   - Restrict the denominator of the outcome to all psychotropic medicated youth so as to avoid readers' potential to dismiss low risks, e.g., 20/100,000 (0.02%) enrollees vs. 20/100 (20%) medicated youth.
   - Target meaningful subgroups, e.g., selecting children with autism spectrum disorder (21, 22) or focusing on foster care youth, a high-risk vulnerable population (23, 24).

## METHODS

A PubMed literature review for the period January 1, 2000-December 31, 2020 was undertaken. Keywords included: Psychotropic OR Psychotropic polypharmacy OR Psychiatric polypharmacy OR Antipsychotics OR Stimulants OR Pharmacotherapy OR Psychotropic medication OR Psychopharmacology; Concomitant OR Concurrent OR Multiple OR Polypharmacy OR Multiclass; Child OR Adolescent OR Youth OR Pediatric; papers were restricted to the English language and U.S. population. In addition, many review

papers were scanned for references on quantitative analyses of polypharmacy that may not have been identified in our computerized search. The search results were validated using Embase search. **Figure 1** illustrates the search process. We selected 35 papers with quantitative analysis on pediatric psychotropic inter-class polypharmacy for this review. These studies are population-based, mainly relying on either federal physician office visit surveys, parent surveys or administrative drug payment claims.

# RESULTS

Summaries of pediatric psychotropic polypharmacy studies were organized by data source into tables for 7 groups from the latest to the earliest across 20+ years from: (1) Federal and other health care treatment surveys; (2a) MedicaidAnalytic eXtracts (MAX) data for national or multistate analyses; (2b) Single or two state comparisons of publicly funded programs; (3) Privately insured populations; (4) Studies featuring a specific clinician-diagnosed subgroup; (5) The foster care population; and (6) Special treatment settings. **Tables 1–6** briefly capture data sources, design, selected populations, critical measurements, and polypharmacy outcome. Many studies fit more than one category but appear only on the most appropriate table.

## Federal and Other Population-Based Surveys on Pediatric Psychotropic Polypharmacy

**Table 1** identifies key characteristics for comparison of polypharmacy outcomes in 6 studies with increased growth starting in the early '90s (28). Major conclusions include: First, Zhang, dosReis et al. (19) showed that across 22 years, the continued growth of regimens of 3 or more concomitant psychotropic classes through 2015 was unmistakable, affecting nearly 300,000 youth treated with complex psychotropic medication regimens (19). Treatment for ADHD, even without comorbidities, is common among complex regimens of U.S. youth (25), often with an antipsychotic and stimulant, a combination with questionable pharmacologic rationale (51). Second, in a 2–24-year-old population of ADHD medication users, recent data showed use of ≥2 ADHD medications (stimulant, atomoxetine, or alpha-agonist) grew from 16.8 to 20.5%, while the much larger pool of ADHD medicated youth received prescriptions for ≥2 other psychotropic classes concomitantly [e.g., antipsychotics and selective serotonin reuptake inhibitors (SSRIs)] and grew during that period from 26.0 to 40.7%. Moreover, the majority of youth in that study were 6–18 years old and psychotropic polypharmacy comprised 73.1% compared with 26.9% for other age groups [2–5 and 19–24-year olds together (26)]. Third, in Hilt et al. (27), parent reports revealed a significantly greater association of adverse drug event reports with 3-drug regimens compared with 2-drug regimens (27). This survey reconfirms the relationship between complex regimens and increased risk of adverse drug events (52). Taken together, all six studies support the need for robust evidence to show the benefit/risk balance in large study cohorts with rigorous methods to assess diagnosis by research standards, monitor drug consumption and measure functional outcomes. Examples include large simple (pragmatic) trials in community treated youth populations to reduce unnecessary treatment and the adverse drug events accompanying that use (53).

## Polypharmacy Studies of Publicly Funded Programs

### Pediatric Psychotropic Polypharmacy Studies of Publicly Funded Programs Using Medicaid Analytic EXtract (MAX) Data

**Table 2a** lists 3 studies that analyzed multistate data to provide generalizable Medicaid findings across broad regions of the country. Major assessments from these studies involve the number of classes for outcome and the length of overlap to define polypharmacy. First, the most recent MAX study by Saucedo et al. (29) has outcomes measured in a convenient metric: those with any polypharmacy, whether within or inter-class and those with inter-class only. The outcome showed any 2 or more concomitants (within or inter-class) grew from 21.2% (1999) to 27.3% (2010) across 12 years, a growth of 146,807–189,048 youth among those <18 years old who had any psychotropic dispensing. The vast majority (89.4%) of concomitant use was inter-class rather than within class. Had the data included precise information on 3-class and 4-class concomitant growth, perhaps a stronger case could be made to bring new research on the effectiveness and safety of these common, largely off-label regimens. Second, Chen et al. (30) illustrated the impact of varying the length of overlapping days on 2 or more concomitant classes: longer overlaps decreased the pool identified as having polypharmacy regimens. Widening the prescription overlap from 14 to 30 to 60 or more days reduced polypharmacy from 28.8 to 27.2 to 20.9%. For 60-day overlaps, the overall result is that more than 25% fewer youths are identified, and the captured population is unlikely to include unintentional polypharmacy, i.e., switching drugs. Third, Kreider et al. (31) assessed 6–18-year olds who had continuous annual enrollment and 14 or more overlapping days, but the outcome was limited to pairs of concomitants which does not provide a clear profile of the percentages of youth with 3-, 4-, or 5 or more concomitant classes.

### Single/Two State Medicaid Pediatric Psychotropic Polypharmacy Studies Using State-Based Data

**Table 2b** lists 7 studies derived from state-specific datasets which are often less costly to acquire and offer potential advantages in terms of providing information to local quality assurance programs. Data from the 7 states fell into 3 periods: recent (2012), mid-period (2002–2008), and early years (1999). Working backward from the most recent data, several key points follow. First, among behavioral diagnosed young people <age 18, continuously enrolled for 90 or more days, 39.5% of psychotropic medicated youth ($N$ = 29,909/75,639) had 2 or more classes overlapping for 90 or more days, and the percent rose to 62.6% for foster care enrollees (18). Examples of 3 drug classes were given but summary data on 3, 4, and 5 or more drug combinations would have identified the size of populations on complex

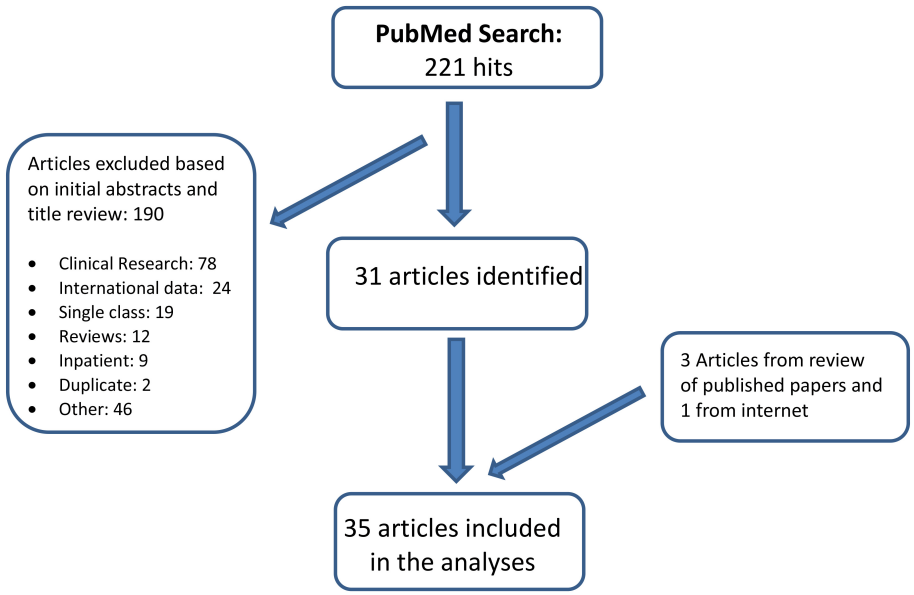


**FIGURE 1 |** Flow chart of the review process.

**TABLE 1 |** Federal and other population-based surveys on pediatric psychotropic polypharmacy.

| Data source, Study period, References | Age, years | Other | No. psychotropic concomitants | Point prevalence, denominator | Outcome |
|---|---|---|---|---|---|
| MEPS, 1999–2015<br>Zhang et al. (19) | 0–17 | 3 periods, 1999–2015, parent reported, trends | ≥3 classes | 0–17 y/o with any psychotropic dispensing | In 2015, nearly 300,000 youth received ≥3 classes concomitantly, a doubling in 12 years |
| NAMCS/NAHMCS, 2003–2010<br>Burcu et al. (25) | 6–19 | Any behavioral diagnostic code (312–314) excluding serious conditions approved for antipsychotic use | Antipsychotic + 1 or ≥2 concomitant classes | 6–19 y/o with any prescribed antipsychotic | 85% with ADHD diagnosis;<br>1 concomitant + ATP = 50.7%;<br>2 concomitants + ATP = 39.1% |
| NAMCS, 2006–2015; NHAMCS, 2006–2011<br>Girand et al. (26) | 2–24 | ADHD diagnosed | ≥2 ADHD medications alone;<br>≥2 ADHD medication + other psychotropics | 2–24 y/o with any prescribed ADHD medication | ≥2 ADHD meds: 16.8–20.5%<br>≥2 ADHD + other psychotropic classes: 26.0–40.7% |
| Community pharmacy-based parent survey<br>Hilt et al. (27) | 3–17 | Is polypharmacy associated with more adverse drug events? *N* = 1,347 Parent reports of any psychotropic dispensing. | 2 classes;<br>≥3 classes concomitantly | *N* = 1,348 youth w/ any psychotropic dispensing | Compared with montherapy: 2 classes had 17% increase in likelihood of *ADEs;<br>≥3 classes had 38% increase in *ADEs |
| NAMCS, 1996–2007<br>Comer et al. (16) | 6–17 | Any prescribed psychotropics, trends | ≥2 classes | 6–17 y/o with any prescribed psychotropic | From 14.3 to 20.2% across 11 years |
| NAMCS, 1993–1998<br>Bhatari et al. (28) | 0–17 | Stimulant users, trends | Stimulant + ≥1 psychotropics | 0–17 y/o with any prescribed psychotropic | 2.9 to 6.9 to 14.7% of stimulant users had ≥1 other psychotropics |

**ADEs, Adverse Drug Events.*

regimens which lack robust evidence that benefits outweigh risks. Such data would compel action for research on widely used off-label combinations of marketed medications, e.g., in large simple trials in community treated populations. Comparison with the 1999 pioneering data of Martin et al. (32) is limited by design and overlap rule differences but it seems clear across 20+ years that polypharmacy in Medicaid populations grew significantly among large proportions of psychotropic treated youth. In addition, documenting long exposures to medication in youngsters highlights the issue of unknown risks to developing youth. Second, 2002–2008 trends in continuously enrolled <18-year olds with any psychotropic dispensing showed substantial

**TABLE 2a |** Pediatric psychotropic polypharmacy studies of publicly funded programs using medicaid analytic eXtract (MAX) data.

| Data source, Study period, References | Age, years | Other | Psychotropic concomitants | Overlapping days | Outcome |
|---|---|---|---|---|---|
| 1999–2010, 29 states (MAX), Soria Saucedo et al. (29) | 0–17 | $N = 692,485$ with a psychotropic dispensing, 12 year trend, | ≥2 within or Interclass | ≥45 | 21.2% (1999) to 27.3% (2010) for any concomitants, within or interclass. 89% of concomitant use is interclass. ∼200,000 youth with ≥2 concomitants in 2010. |
| 2005, 4 large states (MAX), assesses impact of length of overlap re number and % of medicated youth Chen et al. (30) | 6–18 | $N = 282,910$ with a psychotropic dispensing | ≥2 interclass | ≥14<br>≥30<br>≥60 | ≥14 = 28.8% (81,478)<br>≥30 = 27.2% (76,951)<br>≥60 = 20.9% (59,128)<br>Illustrates the impact of avoiding unintentional polypharmacy, i.e., switching. |
| 2004–2008, 42 states (MAX), Kreider et al. (31) | 6–18 | $N = 490,000$ children; $N = 540,000$ adolescents continuous annual enrollees, with a psychotropic class & atypical antipsychotic, 5 year trend, | Inter-class Pairs w/antipsychotic | ≥14 | Pairs of concomitants: stimulant + ATP = 22.4%; ATD + ATP = 31.7%; mood stabilizer + ATP = 52.1%. Duration of concomitant pairs affected 69–89% of annual medicated days. |

growth (19.8–27.3%) by 2008 in 3 or more within or inter-class regimens—primarily (>80%) in interclass rather than within class for 22.3% of foster care medicated youth (33). These data yield a clear pattern of growth of complex regimens in the 2000s compared with earlier years. Third, quality assurance efforts can be useful. Essock et al. analyzed a cohort of psychotropic medicated youth on 4/1/2008, 12.7% had 3 or more psychotropic classes for 90 or more days which was triggered by a flag for a "questionable" clinical prescribing practice based on expert advisory committee consensus (34). For full impact, a follow up comparison study would establish the value of monitoring questionable practices at the state level. In a somewhat similar fashion, Medhekar et al. (35) assessed the impact of physician specialty (psychiatry or primary care) on polypharmacy in a southern state managed care population ($N = 24,147$). The findings on polypharmacy (2 or more classes for 60 or more days) were 5.3 and 3.6 times more likely for single or multiple providers that included psychiatrists.

## Polypharmacy in Privately Insured Populations

Do public and private polypharmacy patterns differ? This compelling question arises from earlier analyses of antipsychotic use comparing prevalence from Medicaid and privately insured youth (54). Crystal et al. compared findings from separate studies of public and private insurance data and reported a roughly 5-fold greater proportion of youth with antipsychotic use in poor and vulnerable youth than in privately insured youth (54). In the present study, no direct comparative analysis of polypharmacy between public and privately insured youth was identified. Opportunities from federal survey data are limited to point prevalence data (16). For polypharmacy, comparisons are difficult partly because of limited access except broadly from separate studies of data sources (7, 54). In general, greater polypharmacy patterns are expected in publicly insured than privately insured youth. Federal oversight policies (11, 12) support the inference. Fuller discussion of the discrepant patterns are beyond the limits of this paper.

Three striking factors from **Table 3** studies include the following. First, the two most recent studies by the same team used Market Scan data, featured off-label concomitant use for ADHD and were industry funded (37, 38). In the earlier study, the authors analyzed data separately for children and adolescents with a diagnosis of ADHD alone or with comorbidities and with a stimulant dispensing. The outcome for 6–12-year olds showed stimulant plus 2 or more medications affected 35.3% of those with ADHD with comorbidities and 13.3% of non-comorbid ADHD diagnosed children. The later study (37) followed similar criteria and found slight increases in concomitant use, emphasizing the use of common off-label combinations of stimulants and selective serotonin reuptake inhibitors (SSRIs) or second-generation antipsychotics. While a number of studies have profiled ADHD diagnosed polypharmacy [(26), **Table 1**; (17), **Table 4**], the comparisons are limited by varying study populations, age groups, design, overlap rules and the precision of the outcome itself. Second, Bali et al. analyzed IMS LifeLink data to address a very specific question on the combination of a long-acting stimulant with a subsequent antipsychotic in the follow-up year (39). Only 3.9% of 37,981 had an antipsychotic added in the follow-up year. Attributing the 71-day longer persistence of the concomitant users as a benefit to adherence is questionable. Third, the earliest privately insured polypharmacy study (40) was unique in presenting survey data from volunteer psychiatrist members of the American Psychiatric Association. Because the data on 332 youth managed by 189 treating psychiatrists originated at physician offices, a precise profile of psychotropic medication treatment was possible: monotherapy (40%); 2 concomitant medications (30.5%); 3 concomitant medications (10.2%); 4 or more medications (2.9%), and no medication (16.2%). The data were collected in 1997 and 1999 and findings from a later Medicaid source support patterns of polypharmacy in psychiatric specialty care exceeding that of primary care (35).

**TABLE 2b |** Single/two state medicaid pediatric psychotropic polypharmacy studies using state-based data.

| Data source, Study period, References | Age, yrs. | Other | Psychotropic concomitants | Overlapping days | Outcome |
|---|---|---|---|---|---|
| Kentucky Medicaid, 2012–2015, Lohr et al. (18) | <18 | *N* = 273,393, continuously enrolled w/ behavioral diagnosis across 4 years | ≥2 inter-class | ≥90 | 39.5% of the cohort had ≥2 inter-class concomitants for 90 or more days. 57.2% had 2 classes; 10.2–13.4% had 3 classes for ≥90 days. |
| Connecticut, 1999, Medicaid, Martin et al. (32) | <19 | *N* = 9,447 with any psychotropic dispensing | ≥2 inter-class | ≥7 | Among those with a psychotropic dispensing, 13.6% had 2 or more classes concomitantly. |
| Ohio Medicaid, 2002–2008, 7 year trends, Fontanella et al. (33) | <18 | *N* = 26,252–50,311, continuously enrolled w/ any psychotropic dispensing | Any ≥3 classes, within or inter-class by eligibility group | Codispensed: 1) any meds 2) inter-class | 1) *FC: 19.8–27.3%; **SSI 18.0–24.9%. 2) *FC: 17.0–22.3%; **SSI 14.3–19.5%, illustrates that interclass is more prevalent than within class polypharmacy. |
| New York, point prevalence, Essock et al. (34) | <18 | *N* = 46,828 Prescribed psychotropic classes on 4/1/2008, w/ >90 days duration | ≥3 inter-classes defined as clinically questionable | ≥90 | 12.7% of 25,727 had long use (>90 days) of ≥3 psychotropics that triggered a flag for questionable practice by expert advisory board. |
| Texas Managed Care, 2013–2015, to assess single/multiple providers associated w/ pediatric psychotropic polypharmacy, Medhekar et al. (35) | <19 | *N* = 24,147 w/ single or multiple prescribers and a mental health diagnosis | ≥2 inter-class | ≥60 | 20.1% of youth had 2 or more psychotropic classes. Patients with a psychiatrist involved in the treatment had 5.3 and 3.6 times higher odds of receiving polypharmacy as single or multiple prescribers, respectively. |
| 2 abutting mid-Atlantic states, 1999, Medicaid & SCHIP, dosReis et al. (36) | <20 | *N* = 8,953 (State A); 48,080 (State B), any continuously enrolled | ≥2 inter-class within same month | Duration of overlapping months | Any months of 2 or more classes for State A (27.9%) and State B (29.7%); 5–12 months of concomitant use for A (43.2%) & B (37.5%). |
| Mid-Atlantic Medicaid, 2014, Zito et al. 2020 (20) | <20 | *N* = 237,393, continuously enrolled w/ any antidepressant dispensing | ATD + 1 class; ATD + 2 classes; ATD+ ≥3 classes | ≥60 | ***ATD + 1 class=22.1%; ATD + 2 classes=14.2%; ATD+ ≥3 classes=5.65%. 25% of ATD-medicated youth had a behavioral diagnosis. Examples: ATD + ATP, ATD+stimulant, and ATD+α-agonist. |

**FC, Foster Care; **SSI, disability insured; ***ATD, Antidepressant.*

## Polypharmacy in Diagnosed Populations

The goal of polypharmacy research is enhanced when clinically meaningful designs are chosen. Among the six studies assessing a clinically diagnosed population, several findings stand out. First, depression comorbidities increased exposure to polypharmacy (41). The growth of comorbidities is, in itself, on the rise (47, 55) and are beyond the present review. McIntyre and Jerrell examined 1996–2005 trends, which occurred during the decade that covered the dramatic time when a meta-analysis of antidepressant (ATD) pediatric clinical trials showed a significant association with suicidal thoughts (56). That provocative study led to the FDA boxed warning on the official antidepressant label and subsequently reduced ATD prevalence in practice. The reduction was most prominent for younger aged children and least for those diagnosed with major depressive disorder (57). Analyzing data from 1,544 younger than 18-year olds in a southern state, McIntyre and Jerrell examined antidepressant polypharmacy in a 24 month follow up of new antidepressant users. By removing switching of antidepressants, the authors identified polypharmacy of 2 or more psychotropic medications which rose dramatically from 6.7% (1996) to 41.6% (2005). The authors identified this decade as "epochal" in the growth of inter-class polypharmacy as common practice. Second, four studies investigated polypharmacy among youth diagnosed with autism spectrum disorders (ASD) (21, 22, 42, 43). These studies cover a considerable time period (2001–2009) yet provide little consistency because of differences in the age of youth selected, number of overlapping days selected, and the imprecise polypharmacy outcome. Also, the value of restricting outcomes to pairs of classes is unclear as the extent that pairs are part of 3 and 4 or more class concomitants is unknown but hides the increased risk of drug interactions and the wider range of

**TABLE 3 |** Pediatric psychotropic polypharmacy in privately insured populations.

| Data source, Study period, References | Age, yrs. | Other | Psychotropic concomitants | Overlapping days | Outcome |
|---|---|---|---|---|---|
| 2011–2014 Truven Market Scan, Zhou et al. (37) | 6–17 | 133,354–157,303 children; 95,632–111,280 adolescents. ADHD alone or w/comorbidity, Continuously enrolled w/ ≥1 stimulants | Any 2,3,4, ≥5 concomitant medications | ≥30 | Stimulant + 1 or more medications increased for: Children: 22.9–25.0%; Adolescents: 25.2–28.2%. Off label: stimulant + *SSRI; stimulant + **AAP were common |
| 2009, Truven Market Scan, Betts et al. (38) | 6–17 | *N* = 71,201 children 6–12; *N* = 49,959 adolescents 13–17. ADHD alone or w/ comorbidity and stimulant use | Stimulant + 14 other class pairs within & interclass | ≥30 | 12.6% of non-comorbid ADHD had ≥2 classes while 41.7% of ADHD with comorbidities experienced combinations. *SSRIs and **AAPs were common. |
| 2004–2006, IMS LifeLink, Bali et al. (39) | 6–16 | *N* = 37,981 long-acting stimulant users w/ 1 year followup for antipsychotic users | ***LAS w/ or without concomitant antipsychotic | ≥14 | Only 3.9% of LAS users had a concomitant antipsychotic added. 71 day greater persistence in the off-label combination was deemed improved adherence compared with LAS alone. |
| 1997–1999 surveys of ****APA member volunteers, Duffy et al. (40) | 2–17 | 189 prescribing psychiatrists for 332 youth | 2; 3; ≥4 within or interclass | Point prevalence | 40% monotherapy; 30.5% 2 medications; 10.2% 3 medications; 2.9% ≥4 medications, 16.2% no medication prescribed. |

**SSRI, Selective Serotonin Reuptake Inhibitor; **AAP, Atypical Antipsychotic; ***LAS, Long-acting stimulant; ****APA, American Psychiatric Association.*

adverse drug events for more complex regimens (42). Third, a rough comparison made between public and privately insured populations suggests that the use of 3 inter-class concomitant regimens are similar in some studies, 15% privately insured and 20% publicly insured (21, 22). Lastly, Winterstein et al. provide a clinically rich study designed to assess 3 or more class polypharmacy in the 5 years following an initial stimulant dispensing with 25.3% receiving a 3-class regimen at least once in a subsequent year (17).

## Polypharmacy in the Foster Care Population

**Table 5** confirms a well-established fact, namely that foster care youth are likely to be exposed to polypharmacy in many times greater proportions than their non-foster peers as documented by Government Accounting Office studies (11, 12). Several points can be made from studies shown on **Table 5**. First, two single state Medicaid studies found there was a 5-fold greater proportion of foster care users of inter-class concomitant regimens than their non-foster care Medicaid peers (44, 45). In the study with the latest data (2016), Keast et al. reported outcomes less precisely, i.e., 2–3 or more and 4–5 or more (44) which limits opportunities for comparisons. Second, Raghavan et al. (46) present useful clinical information on a cohort of 403 17-year olds aging out of foster care in a Midwest state. One-third of patients in the cohort who would be aging out of foster care were receiving 3, 4, or 5 concomitant psychotropics. The likelihood that they would make a smooth transition to other health coverage is not known, but the risk associated with abrupt discontinuation of potent combinations is known (58). Third, in terms of precise outcomes, several studies provide exact percentages on inter-class concomitant use.

Rubin et al. (24) analyzed state-specific concomitant regimens of 3 or more classes making clear the wide range of findings across 44 states from 0.5 to 13.6%, many including an antipsychotic medication. Several assessments had precise outcomes but did not eliminate switching by using a point prevalence overlap (23) or up to 30 days overlap (15).

## Polypharmacy in Special Settings

The last group of papers pertains to program evaluation (48) to reduce polypharmacy in Medicaid outpatients and 2 studies in restricted settings (49, 50). Three findings these studies emphasize are: First, publication of peer reviewed assessments of public programs is critical for accountability on treatment of vulnerable or restricted populations and lends strength to quality improvement efforts. This is particularly true when youth status is involuntary and there is a potential for punitive action. Second, the extensive use of antipsychotics in this and other studies of complex regimens highlights the need to evaluate the role of psychotropic drugs for disruptive and aggressive behaviors. The limited interest by federal agencies in assessing medication treatment of childhood aggression essentially amounts to turning a blind eye for more than 20 years, which indirectly contributes to the growth of second-generation antipsychotics for behavior disorders. The TOSCA study is an exception (59) but the findings indicated that although adding risperidone to a long-acting stimulant produced some initial improvement at 9 weeks, the combination was deemed only moderately more effective than placebo. At 1 year, active drug and placebo group treatment

**TABLE 4 |** Pediatric psychotropic polypharmacy in diagnosed populations.

| Data source, Study period, References | Other | Age, years | Diagnosed population | Psychotropic concomitants | Outcome |
|---|---|---|---|---|---|
| Southern state, 1996–2005, McIntyre and Jerrell (41) | Cross-sectional | 0–17 | *N* = 1,544 w/ Depression diagnosis, continuously enrolled 9/12 months | ≥2 psychotropic medications | Polypharmacy increased from 6.7% (1996) to 41.6% (2005)—a 6-fold increase & is largely off-label. Polpharmacy increased with increased comorbidity. |
| US privately insured, 2001–2009, Spencer et al. (21) | Polypharmacy prevalence | <20 | Autism Spectrum Disorder (ASD), w/ ≥6 months continuous enrollment, *N* = 33,565 | ≥2 or ≥3 classes with ≥30 days overlap | Among the diagnosed cohort, 35% had ≥2 classes, 15% had ≥3 concomitant classes. The median duration of polypharmacy was 346 days. |
| MAX, 2001, 50 states + D.C., Mandell et al. (22) | Polypharmacy prevalence | <21 | Autism Spectrum Disorder, *N* = 60,641 with ASD diagnosis & psychotropic rx | ≥3 medications with ≥30 days overlap | 20% of foster care psychotropic medicated youth had ≥3 concomitants among 6 psychotropic classes compared with 7% for poverty subgroup and 11% with disability status. |
| MAX, 41 states, 2000–2003, Schubart et al. (42) | 4 year trend analysis, x-sectional | 3–17 | *N* = 12,843–18,562 with Autism Spectrum Disorder diagnosis | ≥60 day overlap for pairs of psychotropics | 26–30% had pairs in 6 groupings. |
| Southern State ASD treatment program, 2000–2008, Logan et al. (43) | Polypharmacy prevalence | 8 | The state is part of a CDC Autism Spectrum Disorder surveillance program. *N* = 629 | Six 2-class combinations with ≥30 days overlap | Among the 60% (∼377) with a dispensed psychotropic, 41% (∼150) had 2-class combinations. Unfortunately, the extent of 3 or 4 or more class concomitant use is not known. |
| MAX, 28 states, 1999–2006, Winterstein et al. (17) | 1–5 year follow up (f/u) study | 0–17 | Attention Deficit Hyperactivity Disorder (ADHD), 3–18 years old, *N* = 16,626 w/ f/u for new users of stimulantc. | ≥3 classes, any days overlap | Psychiatric polypharmacy of ≥3 classes increased from 8.5% (year 1) to 13.4% (year 5) for children 3–9 years old at initiation of stimulant. Any ≥3 classes in a subsequent year affected 25.35%. |

differences were not apparent. The authors called for more research on this question and why the combination is widely prescribed. Third, restricted populations may age out of their insurance coverage and, upon discharge, experience abrupt discontinuation with potentially severe withdrawal syndrome. As the Raghavan et al. (46) cohort of youth aging out of foster care illustrated (**Table 5**), 37% of foster youth will leave publicly funded care with 2–5 concomitant psychotropic medications and uncertainty about follow up health insurance coverage. It is not known if comprehensive treatment planning will assure transition to new coverage in a timely way to avoid drug withdrawal.

## DISCUSSION

Despite the wide range of criteria in the design of the studies reported above, several points are clear. First, pediatric psychotropic polypharmacy affects substantially more children and adolescents today than was the case 20+ years ago. As many as 300,000 youth received 3 or more classes concomitantly in 2011–2016 (19). Second, the duration of concomitant use is relatively long, e.g., 69–89% of annual medicated days (31). Third, adverse event reports were associated with more complex regimens (3-class compared with 2-class concomitant regimens (27). In another study, increased depression comorbidities were associated with more complex polypharmacy (41). These findings raise questions about the long-term effectiveness and safety of off-label combinations as well as the relationship of multiple comorbidities to overprescribing. At the core of pediatric psychotropic prescribing lies a deeper question about the U.S. standard of medical care for the off-label treatment of behavioral problems of children and adolescents, a topic beyond the scope of this review.

We acknowledge the limitations of this review. First, some studies may have been missed as titles and abstracts do not always provide critical data on inter-class polypharmacy. Second, some studies combined same class and inter-class polypharmacy and we chose to include them to illustrate that inter-class regimens are the greater proportion of affected youth. Overall, the trends are clear, although study designs are varied and metrics are imprecise so that their implications can be missed. Nonetheless, we appreciate that some studies demonstrate clear, complete and precise profiles of prescribing patterns (19, 24, 40, 46).

**TABLE 5 |** Pediatric psychotropic polypharmacy in the foster care population.

| Data source, Study period, References | Other | Age, years | Population | Psychotropic concomitants | Outcome |
|---|---|---|---|---|---|
| 2016, soutwestern state Medicaid, Keast et al. (44) | Foster care vs. non-foster care, x-sectional | <21 | $N = 9,325$ foster care; $N = 639,868$ non-foster care | ≥2 interclass for ≥90 overlapping days | 9.2% concomitant use in foster care vs. 1.9% in non-foster care youth. As a percent of foster care psychotropic medicated youth, 41.3% had ≥2 classes: 35% w/ 2–3 classes and 6.3% w/ 4–5 classes. |
| Medicaid drug utilization oversight program, Colorado DUR (45) | Compare 2012 and 2015 foster care polypharmacy | <18 | $N = 16,789$ foster care; 406,124 non-foster care. | ≥2, ≥3, ≥4 interclass for ≥60 overlapping days | In 2015, 26% of foster care youth received one or more psychotropic classes, roughly 5 times greater than non-foster care; 7% received ≥2; 2% received ≥3; <1% received 4 or more. Similar pattern 12 &15. |
| Midwest state Medicaid, Dec 2001–May 2003, face to face surveys, Raghavan et al. (46) | To assess medication patterns in a cohort aging out of foster care | 17 | $N = 403$, Participants self-reported medication use in past month | 2,3,4,5,7 concomitant classes | $N = 146$ with any psychotropic medication; 2 concomitant (47); 3 concomitant (22), 4 concomitant (18); 5 concomitant (7). ∼One-third of medicated youth had 3, 4, or 5 or more concomitant psychotropics. |
| 2002–2007, 47 states + D.C., 6 year trend, Rubin et al. (24) | State-specific polypharmacy prevalence | 3–18 | Foster care, continuously enrolled & with antipsychotic dispensing, $N =$ 686,080 | ≥3 class for ≥30 overlapping days | Wide variation in 3 class polypharmacy across states: 0.5%−13.6% had ≥3 classes, one of which was antipsychotic. |
| Southeastern state 2003–2008, Brenner et al. (23) | Community intervention trial of "treatment foster care" | 2–21 | $N = 240$, parent-reports at baseline of intervention program | 2, 3, or ≥4 psychotropics; point prevalence | Of the psychotropic medicated youth, 35% had 2 medications; 15.% had 3 medications and 9.2% had ≥4 concomitant medications. |
| Southeastern state, 2004, foster care population, Zito et al. (15) | Polypharmacy Prevalence | <20 | $N = 472$ medicated youth in a random month | Manual review of overlapping dispensings of 2, 3, ≥4 classes | Of foster care youth w/ any psychotropic dispensing, 31.1% had 2 concomitant classes; 25.4% had 3 concomitant classes; and 15.9% had ≥4 concomitant classes. |

**TABLE 6 |** Pediatric psychotropic polypharmacy in special settings.

| Data source, Study period, References | Other | Age, years | Population | Psychotropic concomitants | Outcome |
|---|---|---|---|---|---|
| Mid-Atlantic state continuity of care outpatient program Wu et al. (48) | Quasi-experimental program evaluation | 3–21 | $N = 496$, continuously enrolled for 1 year pre, during and post-intervention | ≥3 classes w/ ≥15 day overlap | Compared psychotropic polypharmacy of youth enrolled in continuity of care program (≥90 days) with propensity score matched youth in usual care. Polypharmacy did not significantly differ between groups, affecting 29 to 31 to 21% across 3 years. |
| A state residential treatment center vanWattum et al. (49) | prevalence of polypharmacy change, admission to discharge | 11–18 | $N = 131$, Admission to discharge change in polypharmacy | ≥2 psychotropic medications | Discharged youth had fewer polypharmacy treated youth and 60% increase in the non-medicated subgroup. |
| Juvenile secure facility, 1 year, 2007–2008 Lyons et al. (50) | Change in polypharmacy, admission to discharge | 12–22 | $N = 668$; 68 with psychotropic medication | ≥2 psychotropic medications in the same month | There were 10.2% medicated within 1st month of admission; 48.5% received ≥2, with atypical antipsychotics and antidepressants most common. |

The decision to limit analysis to U.S. studies was based on the authors' knowledge of the literature broadly in the past 30 years. U.S. medication prescribing and usage is generally regarded as more intensive than in other western countries. A 2015 review of international pediatric pharmacotherapy by a leading European scholar makes the point that pediatric psychotropic use is "many

times more in U.S. than in all other countries" (60). In one example of a polypharmacy review from Europe, there were few European papers with a claims analysis (61).

In the following sections, we attempt to broaden the discussion to several implications of the growth of pediatric psychotropic polypharmacy.

## Why Are 3 or More Inter-class Pediatric Psychotropic Regimens Increasing?

### Biopsychosocial Model Is Ignored

In the 43 years since psychiatrist George Engel called for a new medical model in a biopsychosocial framework (62), his model has been overtaken by the biological psychiatry model (63). Many reasons have been identified for failing to fully integrate non-pharmacologic therapies (workforce, insurers, insufficient family time) or to not fund community-based alternatives. No doubt, these are formidable challenges and will take a massive commitment from multiple stakeholders (academic research, government authorities and funders, and prescribing physician societies) to reform the system. Stakeholder silence has led to further reliance on pills—even for social determinants of poor child behavior such as poor family stability, unsafe schools, and shelter living. Like the cobbler who responds to every problem as a shoe problem, when society asks medicine to relieve social ills, we get prescriptions. After analyzing more than 20 years of data and at least 35 studies on psychotropic polypharmacy, the prescriber's response that "This is all I have" seems woefully inadequate.

### Pharmacologic Assumptions Are Not Valid

Accepting the appropriateness of complex, off-label regimens in the pediatric population may reflect various beliefs. First, the efficacy from individual drug trials may be assumed to be cumulative across classes of concomitants and will not be exceeded by the collective adverse events. Hilt et al. (27) illustrated the fallacy of this assumption, as did Turner et al. (52). While this assumption is sometimes justified for serious emotional and mental disorders, e.g., schizophrenia, it is difficult to justify for behavioral conditions, e.g., ADHD without comorbidities (17, 25, 26, 37).

In addition, complex combinations increase the risk of drug-drug interactions. Drug-drug interactions among 3-, 4-, or 5 or more classes is mathematically far more complicated and there is relatively little work in this area for pediatric psychotropic combinations (64). For a common example likely to be found in some youth, the combination of an SSRI and a second-generation antipsychotic in long-term concomitant regimens has been shown to produce blockade of P-450 enzymes caused by competitive inhibition of the enzymes (64) and could lead to a serotonin syndrome or to toxic levels of an antipsychotic. An adult study analyzed pharmacoepidemiologic data from Scottish adults across all medications for medical and mental conditions (65). Comparing 1995 with 2010, the authors found a nearly 3-fold increase in risk of a potentially serious drug-drug interaction among adults receiving a CNS drug (1.2–3.4%) (65).

Adverse events from polypharmacy combinations may be difficult to distinguish from new behavioral symptoms and lead to more medications (66). Furthermore, the evidence of the effectiveness and safety of concomitant regimens is often assumed to be adequate. However, the published literature does not support that assumption. Pediatric clinical trials of concomitant use are criticized for weak designs (67) and haven't improved much.

### Post-marketing Evidence Is Ignored

Effectiveness studies of second-generation antipsychotics (SGA) have failed to show superiority over first generation products as demonstrated for children diagnosed with early-onset schizophrenia and schizoaffective disorder in the TEOSS study (68). In addition, SGAs can lead to new, serious adverse drug events e.g., treatment emergent diabetes (9, 69). A sobering post-marketing picture has emerged in the 25 years since SGAs were introduced (70). The ethical decisions that support SGA use for severe emotional and mental disorders, e.g., schizophrenia are largely based on severity and relief of suffering but are in stark contrast to the less justifiable use of atypical antipsychotics in combination with a stimulant and antidepressant in ADHD diagnosed youth. These off-label combinations lack robust evidence that the benefits outweigh the risks. Similarly, there is strong concern voiced about the use of SSRIs for the treatment of children (71) both in terms of weak efficacy, biased maintenance research studies, and on the alarming uncertainty that benefits exceed risks (72, 73).

The FDA is a stakeholder of great importance in creating new knowledge on approved medications. Phase 4 of the FDA drug development model constitutes the post-marketing phase when new information about a drug's effectiveness and safety in large populations of community treated persons could be analyzed. Wider usage potentially will reveal new knowledge that the proprietary trials conducted for FDA approval were not powered to reveal. Post-marketing effective studies can provide support for off-label pediatric drug use (74). It is not clear why the drug development graphic on the FDA website has changed over the years to one that only emphasizes safety for (phase 4) post-marketing research rather than for both effectiveness and safety.

At the broadest level, the low value of healthcare procedures with unknown effectiveness but with known risk of harm deserves attention (75). In this thoughtful commentary, Brownlee and Korenstein provide an analysis applicable to the unnecessary use of off-label medications for the mental and behavioral treatment of youth. They suggest "…the failure to focus greater attention on the physical and psychological harms of overuse has hampered efforts to reduce it," resulting in resistance to calls to rein in overprescribing.

## New Developments in the Prescribing Practice Literature Could Reduce Unnecessary Polypharmacy

In the past decade, pediatric clinical researchers have begun to create protocols to support the needs of clinicians who "inherit" new patients with complex regimens that the clinician may view as excessive or pose challenges to careful management (76). Adapting the methods of geriatric pharmacology,

"deprescribing" is slowly growing in importance to address mental health prescriber needs (77), probably an indirect consequence of the ever-growing use of complex concomitant regimens. A recent survey of primary care and psychiatry clinicians in community public health centers focused on overprescribing and respondents acknowledged concerns about complex drug regimens in children but suggested resources are needed to support deprescribing (78). An additional concern relates to the patient experience of problems to successfully discontinue psychotropics. The problems of adults with difficulties discontinuing benzodiazepines are joined by more recent concerns on the withdrawal syndrome associated with SSRIs (79). When youth who are seen by multiple clinicians and not known well by any clinician, it is easy to understand the skepticism of some clinicians that SSRIs are hard to discontinue. Indeed, a separate literature on patient-focused medication problems has emerged (80).

Concerns about overdiagnosis and overtreatment have been articulated by non-US academic psychiatrists (81) and by dissenting U.S. leaders (82). Within the U.S. psychiatric community, Steingard's recent book, *Critical Psychiatry,* elucidates controversies related to the Diagnostic and Statistical Manual (DSM-5); deprescribing; and the role of the pharmaceutical industry in creating biased analyses for their heavily promoted, initially costly new products (83). Such critical discourse parallels the growing disappointment with clinical experience over decades, for example, described by Rosenheck as "irrational exuberance" for antipsychotic use (70). The problem is particularly acute with respect to children where widespread adoption of second-generation antipsychotics for non-psychotic youth in complex regimens is evidenced in the tables above. While adoption of SGA antipsychotics has been trending downward) in publicly insured youth (7, 13, 14), oversight of inter-class polypharmacy and research on it is far less prominent.

## Research Funding

The clamor for effectiveness research in the studies reviewed above is remarkable; many authors ended their discussions with firm calls for research to establish the effectiveness, safety and tolerability of complex concomitant regimens in community-treated populations. In light of the weak or absent evidence for widely used combinations of second-generation antipsychotics and antidepressants in youth, large randomized simple trials or other post-marketing effectiveness research in community populations should be prioritized for public funding (53). Several regional academic sites with electronic health records could follow randomized trial protocols with consenting patients to evaluate response to less complex regimens against usual treatment.

We join the call seeking federal and foundation funding for deprescribing research (78, 84). Also, we urge robust responses to the request for proposals from the Patient Centered Outcomes Research Institute (PCORI) for large simple trials. Large simple trials with a patient-centered focus especially fit the need to establish the benefits and risks of complex concomitant regimens that will be acceptable and tolerably consumed by youngsters in community treated populations.

# CONCLUSION

A review of 20 years of pediatric psychotropic polypharmacy supports standardizing criteria in the design of population-based studies so as to maximize information on the number of youth receiving regimens of 3-, 4-, and 5 or more concomitant classes and the duration of such use. Calling together leadership in mental health services, child psychiatry and pediatrics would kickstart this effort in the hope of generating a clinical call for post-marketing research to address the effectiveness, safety and tolerability of complex drug regimens in youngsters.

# AUTHOR CONTRIBUTIONS

JZ: supervised the literature search and analyzed 35 studies for inclusion, and wrote and revised the draft. YZ: conducted the computerized search and read revised drafts. DS: reviewed drafts, edited text, and collaborated on content of discussion. All authors contributed to the article and approved the submitted version.

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# Maternal Serotonin Reuptake Inhibitor Antidepressants Have Acute Effects on Fetal Heart Rate Variability in Late Gestation

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**Background:** Prenatal exposure to serotonin reuptake inhibitor (SRI) antidepressants increases risk for adverse neurodevelopmental outcomes, yet little is known about whether effects are present before birth. In relation to maternal SRI pharmacokinetics, this study investigated chronic and acute effects of prenatal SRI exposure on third-trimester fetal heart rate variability (HRV), while evaluating confounding effects of maternal depressed mood.

**Methods:** At 36-weeks' gestation, cardiotocograph measures of fetal HR and HRV were obtained from 148 pregnant women [four groups: SRI-Depressed ($n = 31$), SRI-Non-Depressed ($n = 18$), Depressed (unmedicated; $n = 42$), and Control ($n = 57$)] before, and ∼5-h after, typical SRI dose. Maternal plasma drug concentrations were quantified at baseline (pre-dose) and four time-points post-dose. Mixed effects modeling investigated group differences between baseline/pre-dose and post-dose fetal HR outcomes. *Post hoc* analyses investigated sex differences and dose-dependent SRI effects.

**Results:** Maternal SRI plasma concentrations were lowest during the baseline/pre-dose fetal assessment (trough) and increased to a peak at the post-dose assessment; concentration-time curves varied widely between individuals. No group differences in fetal HR or HRV were observed at baseline/pre-dose; however, following maternal SRI dose, short-term HRV decreased in both SRI-exposed fetal groups. In the SRI-Depressed group, these post-dose decreases were displayed by male fetuses, but not females. Further, episodes of high HRV decreased post-dose relative to baseline, but only among SRI-Non-Depressed group fetuses. Higher maternal SRI doses also predicted a greater number of fetal HR decelerations. Fetuses exposed to unmedicated maternal depressed mood did not differ from Controls.

**Conclusions:** Prenatal SRI exposure had acute post-dose effects on fetal HRV in late gestation, which differed depending on maternal mood response to SRI pharmacotherapy. Importantly, fetal SRI effects were sex-specific among mothers with persistent depressive symptoms, as only male fetuses displayed acute HRV decreases.

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At trough (pre-dose), chronic fetal SRI effects were not identified; however, concurrent changes in maternal SRI plasma levels suggest that fetal drug exposure is inconsistent. Acute SRI-related changes in fetal HRV may reflect a pharmacologic mechanism, a transient impairment in autonomic functioning, or an early adaption to altered serotonergic signaling, which may differ between males and females. Replication is needed to determine significance with postnatal development.

**Keywords: serotonin reuptake inhibitor antidepressants, prenatal exposure, fetal heart rate variability, sex differences, antidepressant pharmacokinetics, maternal depressed mood, pregnancy, third-trimester**

## INTRODUCTION

Up to 20% of women experience depressed mood during pregnancy (1, 2), and nearly one half of these women are treated with a serotonin reuptake inhibitor (SRI) antidepressant (3). Since their introduction nearly 30 years ago, the decision to start, continue or discontinue SRI antidepressant treatment during pregnancy remains complex, as clinicians and women continue to weight risks of adverse outcomes against relapse (4, 5). Prenatal SRI exposure has been associated with increased risks for preterm birth, lower birth weight and neonatal behavioral disturbances (6), as well as altered stress-regulation, social-emotional behaviors and other neurodevelopmental outcomes from infancy-to-childhood (7–13). However, many of these long-term associations may be confounded by the underlying maternal psychiatric disorder (14). Antenatal maternal mood disturbances are, similarly, associated with altered neurobehavioral outcomes in infancy (15–17), stress-regulation in childhood (18) and a risk for later psychopathology, emotional, or behavioral disturbances (19). Whether the early origins of these outcomes are already evident before birth remains unclear. This study was undertaken to investigate the effect of prenatal exposure to SRIs on fetal heart rate (HR) and relationships to maternal antidepressant pharmacokinetics in late gestation, controlling for the effects of depressed mood.

Both maternal psychiatric distress and its treatment with SRI antidepressants are early exposures that may influence the *in utero* environment (20–22), possibly through the modulation of fetal, maternal, or placental serotonin (5-hydroxytryptamine; 5-HT) signaling (23, 24). In particular, SRIs act by inhibiting the reuptake of the extracellular 5-HT leading to an increased duration and magnitude of serotonergic activity on pre- and postsynaptic receptors. During development, 5-HT is present from early gestation (25) and has been identified as a key neurotrophic factor regulating the construction and plasticity of neuronal circuits within its own and non-serotonergic systems (26). Across the lifespan, 5-HT also has extensive roles in neuropsychological and other central, autonomic, and peripheral nervous system processes (27). As SRIs are lipophilic compounds with high placental permeability, it is conceivable that altered 5-HT signaling before birth may have broad neurodevelopmental and physiologic implications.

To date, only few studies have investigated whether outcomes of prenatal SRI exposure emerge before birth: during the period of drug exposure. Fetal SRI exposure has been associated with disrupted cardiovascular function (28–30) and increased fetal motor activity (28, 31–33); though, findings are not consistent, primarily due to variations in methodology, gestational age and the ability to account for maternal mood. In SRI exposed fetuses, Mulder et al. report increased motor activity in the second trimester and increased motor activity during quiet sleep state (i.e., stable fetal HR, low variability) in the third-trimester; however, SRI-treated mothers had comparable psychiatric symptoms to the unmedicated depressed group (28). Gustafsson et al. also observed increased motor activity in SRI-exposed fetuses, but only prior to 30-weeks' gestation and found no SRI-related effect on fetal HR, HR variability, or HR-movement coupling (31). Conversely, lower fetal HR variability at 36-weeks' gestation and reduced cerebral blood flow resistance was observed in SRI-exposed fetuses (30), as well as elevated pulmonary blood flow in SRI-exposed fetuses who experienced transient respiratory difficulties at birth (29). Critically, outcomes from previous fetal SRI studies remain confounded by maternal psychiatric symptoms. A case in point, altered fetal motor activity, HR and HR variability have also been associated with antenatal maternal depression (34–37) and anxiety [e.g., reviewed in (38)]. Thus, investigating fetal outcome related to prenatal SRI exposure requires appropriate control groups for maternal mood.

Fetal outcome may also be differentially sensitive to acute and chronic drug effects, whereby outcomes vary depending on the time of assessment relative to SRI exposure. In fetal sheep studies, acute and chronic SRI effects have been observed, with transient reductions in uterine blood flow and reduced fetal oxygenation status following acute SRI infusion (39), but a sustained decrease in low-voltage electrocortical fetal brain activity with prolonged SRI exposure (40). While it is presently unknown whether SRI exposure has distinct acute and chronic effects on human fetuses, a pharmacologic mechanism has been suggested (41, 42). SRI dose-relationships with fetal, obstetric, and neonatal outcomes have been reported (28, 43, 44), and there is high correspondence between maternal and fetal plasma drug concentration ratios in amniotic fluid (45) and cord blood (46, 47) that vary with SRI type. Importantly, fetal exposure to other psychoactive agents have produced differential acute outcomes, such as an acute suppressive effect of buprenorphine on fetal HR and movement (48) and decreased fetal HR variability following acute nicotine exposure (49). Together, these studies suggest that fetal HR may be sensitive in detecting differences between acute and chronic psychotropic drug exposures.

Fetal HR and its variability are prenatal markers of cardiovascular regulation and can be studied non-invasively using Doppler ultrasound-based technologies, such as cardiotocography. Fetal HR and HR variability are widely described as indies of early autonomic functioning (50, 51), and the coalescence of fetal HR patterns and accelerations with motor activity around 32-weeks' gestation is viewed as organized neurobehavior (52–54). As the fetus matures, the well-characterized decrease in fetal HR and increase in HR variability (52, 55–58) are thought to reflect increasing sympathetic responsiveness and an emerging influence of parasympathetic (i.e., vagal) modulation (51). Fetal HR variability has been described as a psychophysiological construct with behavioral trait-like correspondence (50), reflecting an individual's emerging capacities for adaptive flexibility and interaction with environment, serving to prime the fetus for extrauterine life (59). Fetal cardiac patterning demonstrates developmental stability into the postnatal period, as it's highly correlated with neonatal and infant HR (60) and predicts temperament and neurodevelopmental outcomes in infancy (61–63), as well as behavioral regulation in childhood (64).

The present study was undertaken to investigate acute and chronic effects of prenatal SRI antidepressant exposure on fetal HR and HR variability in late gestation, while evaluating the concurrent effects of prenatal maternal depressed mood. Chronic effects of SRI exposure were determined by comparing fetal outcomes at a baseline period prior to typical morning oral SRI dose (i.e., pre-dose; at pharmacologic trough). Acute SRI-exposure effects were determined at peak drug levels (∼4–5 h post-dose). Maternal SRI plasma drug concentrations across five time-points were used to characterize pharmacokinetics and assess drug level changes relative to periods of chronic and acute SRI exposure. To distinguish SRI-related effects from prenatal maternal depressed mood, we compared fetal HR outcomes from a control group (non-SRI treated/non-depressed) with three prenatal exposure groups: fetuses of mothers who were SRI-treated/depressed, SRI-treated/non-depressed, and non-SRI treated/depressed. These groups captured how maternal response to SRI pharmacotherapy, namely whether depressive symptoms persisted or remitted, may differentially influence the fetus. We hypothesized that acute SRI exposure would be associated with reduced fetal HR variability and that SRI-exposed fetuses with concurrent exposure to maternal depressed mood would have the greatest changes compared with outcomes in non-exposed fetuses.

# MATERIALS AND METHODS

## Study Cohort

The study protocols were approved by the UBC Clinical Research Ethics Board and the BC Women's Hospital Research Review Committee (H05-70629 and H12-00733). During the late second trimester, 188 women with singleton low-risk pregnancies were recruited in two cohorts from the Reproductive Mental Health Clinic at BC Women's Hospital and Health Center, community midwives, or family physicians in metropolitan Vancouver, Canada (from November 2006–January 2010 and March 2013–August 2017). Informed consent was obtained from all participants. Both SRI-treated and non-SRI-treated women were recruited who were experiencing a range of antenatal depressive symptoms, some meeting a diagnostic threshold for a DSM-V mood disorder (65), while others were symptomatic at a subthreshold level or were relatively euthymic. Inclusion criteria for SRI-treated women required the initiation of pharmacotherapy before or during pregnancy for a minimum of 90 days prior to delivery (i.e., entire duration of the third-trimester). Demographic characteristics were collected by clinician interviews and health records chart review. Fetal gestational age was calculated using the first trimester dating scan, as per the Society of Obstetricians and Gynaecologists of Canada Clinical Practice Guidelines (66). Exclusion criteria comprised of maternal psychiatric disorders other than unipolar depression or anxiety, illicit substance use, gestational hypertension or diabetes, placental insufficiency, or any other significant maternal or fetal medical condition. Fetuses born prior to 36-weeks' gestation were excluded.

Of the 188 recruited women, 153 were eligible for inclusion in the present study. Reasons for exclusion were as follows: cancelation for technical reasons ($n = 12$), preterm delivery ($n = 8$), obstetrical complications ($n = 8$), emergent issues during the study protocol necessitating clinical assessment ($n = 4$), voluntary withdrawal ($n = 2$), and development of an exclusion criterion after recruitment ($n = 1$).

Of note, the present study reports on two maternal-fetal cohorts that underwent nearly identical data collection sequences at 36-weeks' gestation, with the exception of maternal blood collection (detailed below) on the first cohort only. These cohorts did not differ in clinical or demographic characteristics. Subsets of data from participants in the present study had been included in two prior reports investigating fetal outcomes in healthy, uncomplicated pregnancies ($n = 68$) (67), and SRI-exposure effects on brain blood flow ($n = 74$) (30). While primary study protocols were similar, the present study investigated acute and chronic effects of SRI exposure in relation to fetal HR variability, maternal pharmacologic data and the potentially confounding effects of depressed mood. These augmented data and outcomes have not been previously reported.

## Maternal Depressed Mood and SRI Antidepressants

Maternal depressive symptoms were assessed with the Hamilton Rating Scale for Depression (HAM-D) (68), a 17-item clinician-rated questionnaire administered by trained research staff, blinded to SRI exposure-status. Mothers were considered to be symptomatically depressed with a total HAM-D score > 8 (69). In this study, SRI antidepressants included any selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).

To detect SRI-related fetal effects and distinguish them from exposure to maternal depressed mood, mothers were then grouped based on SRI treatment and the presence of depressive symptoms at 36-weeks' gestation, yielding four study groups:

SRI-Depressed (SRI-treated + HAM-D > 8, i.e., depressive symptoms persisted), SRI-Non-Depressed (SRI-treated + HAM-D ≤ 8, i.e., depressive symptoms remitted), Depressed (non-SRI-treated + HAM-D > 8), and Control (non-SRI-treated + HAM-D ≤ 8). Thus, fetal outcome was assessed as an exposure to one of these groups.

## Study Protocol

**Figure 1** outlines the fetal and maternal data collection sequence that occurred at 36-weeks' gestation. On the day of the study, all participants were instructed to eat and drink as per usual prior to arrival. Participants underwent two sequential fetal assessments in a dedicated quiet room at the BC Women's Hospital Center for Prenatal Diagnosis, first in the morning (AM/baseline; ∼09h30) and again in the afternoon (PM; ∼13h30); methodological details are described below. Mothers were positioned in the left recumbent position to prevent aortocaval compression. Fetal assessments were separated by a 2-h controlled break, involving the administration of the HAM-D and time for participants to mobilize and have lunch (provided).

To investigate chronic and acute SRI effects on the fetus, SRI-treated women were asked to withhold their typical morning oral dose until ∼10h00, resulting in the AM/baseline and PM fetal assessments corresponding to pre-dose and post-dose periods, respectively. To characterize concurrent SRI pharmacokinetics across the study protocol, plasma drug concentrations were quantified at baseline (pre-dose) and four time-points post-dose; details on the drug level assay and pharmacologic variables are described below. Timing for each component of this study considered the need for a sufficient antidepressant baseline (pharmacologic trough), half-life, and time-to-peak plasma levels, weighted against length of study in effort to minimize maternal discomfort/inconvenience and potential effects of diurnal variations in the fetal variables obtained.

## Fetal Cardiotocography

Fetal cardiotocography (CTG) was used to investigate patterns of fetal HR and HR variability. Fetal HR was recorded continuously for 50-min using a *Sonicaid Fetal Care* computerized CTG system (*Huntleigh Healthcare Ltd.*; Cardiff, UK; software version 2.2.3.0), a clinical tool widely used for antenatal fetal surveillance (70). Briefly, the software baseline-fits the continuous fetal HR tracing then computes several variables based on its averaging algorithm (71, 72): *basal fetal HR* (i.e., average resting HR, in beats per minute; bpm), number of fetal HR *accelerations* and *decelerations*, as well as three measures of fetal HR variability: *short-term variation* (STV), *high variability* and *low variability*. STV, a measure of micro-fluctuations in fetal HR, was computed as the average epoch-to-epoch variation across the entire HR tracing in pulse intervals (i.e., time between consecutive heart beats, in milliseconds; ms). Whereas high and low variability reflect specific HR patterns that occur during periods of fetal activity and quiescence, respectively. Episodes of high and low variability were computed as the sum of all individual episodes (in minutes) each HR pattern was displayed in the tracing, corrected to 50-min. Additionally, the number of maternally-perceived fetal movements (FMs) during each CTG was recorded using a handheld event marker, which we assessed as an indirect measure of fetal motor activity. Refer to Pardey et al. for further details on reported measures (72).

## Maternal SRI Plasma Levels

Changes in maternal plasma drug concentration between fetal assessments were determined by analyzing blood samples from SRI-treated mothers pre-dose ($T_0$, baseline levels; ∼08h00) and at four time-points post-dose: $T_1$ (∼10h30), $T_2$ (∼12h30), $T_3$ (∼13h30), and $T_4$ (∼14h30). Serum was separated by centrifugation at 3,000×g for 10 min, transferred to polypropylene tubes and stored at −70°C until analysis. High performance liquid chromatography tandem mass spectrometry, performed offsite (CANTEST Ltd.; Burnaby, Canada), was used to determine levels of fluoxetine, norfluoxetine, paroxetine, sertraline, citalopram, escitalopram and venlafaxine. The calibration range was 0.1–100 ng/ml for analytes (except sertraline, where the lower limit of quantification was 0.25 ng/ml). The intra- and inter-assay coefficients of variation and relative errors were < 20% for all drugs and metabolites.

Plasma drug concentrations were adjusted for maternal oral dose (ng/ml·mg). To quantify the relative change in maternal SRI level between the pre- and post-dose fetal assessments, the difference in dose-adjusted plasma drug concentration between $T_0$ and $T_3$ was determined. Plasma concentrations for metabolites were not reported as they reflect parent drugs.

### SRI Pharmacokinetics and Standardized Dose

Maternal SRI plasma levels were further characterized by performing a non-compartmental pharmacokinetic analysis, yielding estimates of maximum plasma drug concentration ($C_{max}$), time-to-peak ($T_{peak}$) and area under the curve ($AUC_{last}$). Pharmacokinetic variables were calculated using the *PKNCA* R package (73).

Further, we computed a standardized SRI dose variable to investigate whether dose-dependent relationships were present among SRI-related fetal outcomes. As per methods described by Mulder et al. (28), standardized SRI dose was defined according to the World Health Organization Anatomical Therapeutic Chemical-Defined Daily Dose (ATC-DDD) Index (74). DDDs were as follows: 10 mg for escitalopram; 20 mg for citalopram, fluoxetine, and paroxetine; 50 mg for sertraline; 100 mg for venlafaxine; and 300 mg for moclobemide. Mothers prescribed their antidepressant's DDD were set to 1; higher or lower doses were expressed as a multiple of the DDD.

## Statistical Analyses

Statistical analyses were performed using *R Statistical Computing Environment* version 3.6.1 (75); the significance level was set at $\alpha = 0.05$. Group differences in maternal and fetal characteristics were assessed using one-way analysis of variance (ANOVA) or Kruskal-Wallis rank sum test for continuous normal and ordinal data, respectively; significant between-group effects were further explored using *post hoc* Tukey's HSD or the Dunn test. Chi Square tests were used for group comparisons of categorical variables.

Generalized linear mixed-effects models (GLMMs) were used to investigate group differences in fetal HR and HR variability

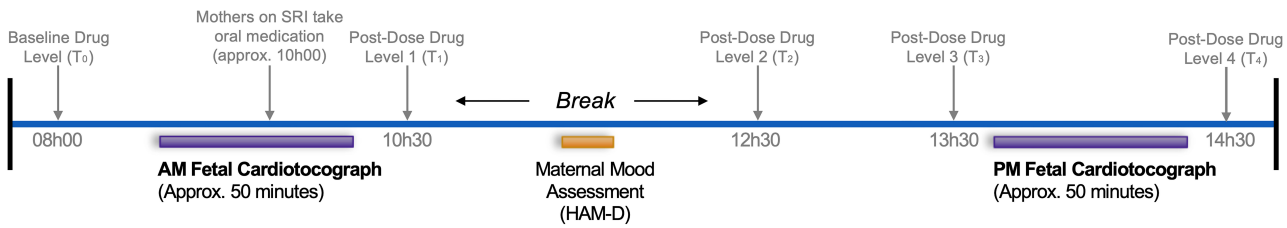


**FIGURE 1 |** Data collection sequence at 36-weeks' gestation assessing pre- and post-SRI dose effects on the fetus. Text in gray pertains to SRI-treated mothers only. Times are approximate and represent the median, rounded to the nearest 30-min.

outcomes across time. GLMMs describe each outcome as a linear combination of fixed and random effects; here, fixed effects were an interaction between one between-factor (*Group*: Control, Depressed, SRI-Depressed, SRI-Non-Depressed) and one within-factor (*Time*: AM/pre-dose, PM/post-dose). Gestational age at the time of assessment and fetal sex were also included as fixed effects terms. Because pre- and post-dose outcomes were not independent, random effects were specified to account for individual differences at baseline (AM/pre-dose; i.e., random intercept for subjects) and the within-subject variability explained by the repeated measures (i.e., random slope for subjects across *Time*) (76). Linear or Poisson (log) link functions were specified according to the underlying distribution. Mixed modeling was conducted using the *lme4* library in R (77) and fit by restricted maximum likelihood. Type III Wald *F*-statistics (or $X^2$-statistic, if Poisson model) and associated p-values are reported for significant interaction or main effects; effective degrees of freedom were estimated with the Kenward-Roger approximation.

*Post hoc* tests explored significant *Group* × *Time* interactions to detect group differences at AM/pre-dose and PM/post-dose assessments, as well as within-group changes across time. Results are reported as the estimated difference between relevant factor contrasts, along with 95% confidence intervals (CI) and associated *p*-values, adjusted for multiple comparisons with Tukey's method. Further, given the previous reports of sex differences in fetal HR [e.g. (78)], we also investigated whether any significant effect differed between male and female fetuses. Additional *post hoc* GLMMs examined *Group* × *Sex* × *Time* (three-way) interactions, adjusted for gestational age. *Post hoc* testing was performed using the *emmeans* R package (79).

# RESULTS

Of the 153 mother-fetal participants, 148 were included in the study sample: one SRI-treated mother was not compliant with study protocols, one fetus did not meet the Dawes/Redman criteria for normality during CTG sessions (71, 72), one fetus was found to have a cardiac abnormality, one fetus had overall poor data, and one fetus was consistently an outlier in analysis. The final study cohort comprised 57 Control, 42 Depressed, 31 SRI-Depressed, and 18 SRI-Non-Depressed mother-fetus pairs. Maternal and fetal characteristics did not differ between those included in the analysis sample ($n = 148$) compared to those who did not participate/were excluded ($n = 40$) (**Supplementary Table 1**), other than in characteristics related to exclusion criteria (i.e., preterm delivery).

## Maternal and Fetal Characteristics

Maternal characteristics generally did not differ between groups (**Table 1**), apart from maternal weight at 36-weeks' gestation, which was higher in both Depressed ($p_{adj} = 0.05$) and SRI-Depressed ($p_{adj} = 0.05$) women compared to Controls. Maternal depressed mood symptoms differed between groups, with significantly higher HAM-D scores in the Depressed and SRI-Depressed groups compared to women in both the Control and SRI-Non-Depressed groups (all: $p_{adj} < 0.001$). Mood symptoms among SRI-Non-Depressed women did not differ from Controls ($p_{adj} = 0.4$).

SRI-treated women were taking a daily oral dose within the typical therapeutic range and were prescribed their antidepressant for the entire duration of pregnancy, except four mothers with third-trimester exposure only (i.e., $n = 4$ taking SRI for 137 ± 44 days prior to delivery). Neither standardized SRI dose nor length of gestational SRI exposure differed between SRI-Depressed and SRI-Non-Depressed mothers. Included in the SRI-Non-Depressed group was one mother treated with moclobemide, a reversible inhibitor of monoamine oxidase-A, which also acts to increase serotonergic activity by inhibiting 5-HT deamination within neurons and synaptic vesicles (80).

Fetuses were assessed at 35.9 ± 0.81 weeks' gestation; their characteristics are summarized in **Table 2.** All fetuses included in analysis were delivered at term and were clinically healthy newborns discharged from hospital according to routine schedules. Gestational age at birth was significantly lower for fetuses in the SRI-Depressed group compared to the Control ($p_{adj} < 0.001$) and Depressed ($p_{adj} = 0.002$) groups. In the newborn period, the SRI-Depressed group also had lower birth weight, length and head circumference compared the Control and Depressed groups; however, these effects all diminished when adjusting for gestational age at birth.

## Maternal SRI Pharmacokinetics

Plasma drug concentrations were quantified for a minimum of three of the five time-points in 24 of the 49 SRI-treated women.

**TABLE 1 |** Maternal characteristics ($n = 148$).

| | Control ($n = 57$) | Depressed ($n = 42$) | SRI-Depressed ($n = 31$) | SRI-Non-Depressed ($n = 18$) | Test statistic ($p$-value) |
|---|---|---|---|---|---|
| Maternal age (years) | 32.9 ± 3.5 | 34.5 ± 4.5 | 33.9 ± 5.9 | 35.1 ± 5.1 | $F_{(3, 144)} = 1.6$ (0.2) |
| Maternal weight at 36-weeks' (kg) | 75.1 ± 9.7 | 81.9 ± 16.0 | 82.5 ± 15.0 | 79.6 ± 9.8 | $F_{(3,144)} = 3.2$ (0.02)* |
| Parity | 0 (0, 1) | 0 (0, 1) | 0 (0, 1) | 0 (0, 0) | $H_{(3)} = 1.9$ (0.6) |
| Education (total years) | 18.7 ± 3.1 | 18.0 ± 3.9 | 17.3 ± 3.6 | 18.3 ± 3.7 | $F_{(3, 144)} = 1.1$ (0.3) |
| Alcohol during pregnancy (*n* total drinks)† | 0 (0, 2) | 0 (0, 2) | 0 (0, 2.5) | 1 (0, 4.75) | $H_{(3)} = 2.6$ (0.5) |
| Smoking during pregnancy (*n* smoker/*n* non-smoker) | 0/57 | 1/41 | 1/30 | 1/17 | (0.2) |
| HAM-D at 36-weeks' | 4.7 ± 2.3 | 12.7 ± 4.0 | 13.4 ± 3.1 | 6.0 ± 2.1 | $F_{(3, 144)} = 88$ (< 0.001)*** |
| **SRI antidepressants (*n*, [dose range])** | | | | | |
| Citalopram ($n = 14$) | — | — | 10 [10–60 mg] | 4 [10–50 mg] | — |
| Escitalopram ($n = 7$) | — | — | 3 [5–20 mg] | 4 [10 mg] | — |
| Fluoxetine ($n = 5$) | — | — | 2 [20–80 mg] | 3 [20–60 mg] | — |
| Paroxetine ($n = 4$) | — | — | 3 [20–40 mg] | 1 [30 mg] | — |
| Sertraline ($n = 6$) | — | — | 4 [50–200 mg] | 2 [75–200 mg] | — |
| Venlafaxine ($n = 12$) | — | — | 9 [75–262.5 mg] | 3 [75–150 mg] | — |
| Moclobemide‡ ($n = 1$) | — | — | — | 1 [150 mg] | — |
| Standardized daily SRI dose | — | — | 1.5 (1.0, 2.0) | 1.0 (1.0, 1.5) | $t_{(47)} = 0.9$ (0.4) |
| Length of gestational SRI exposure (days) | — | — | 264 ± 36 | 260 ± 48 | $t_{(47)} = 0.31$ (0.8) |

*Continuous variables reported as mean ± SD if normally distributed, or median (first, third quartile) if skewed. Categorical variable reported as total number (n). Test statistics, degrees of freedom, and associated p-values are reported for between-group differences using: one-way ANOVA (F), Kruskal-Wallis test (H), Fisher's Exact test, or two-sample t-test (t), where appropriate. P-value significance levels: *p < 0.05, **p < 0.01, ***p < 0.001.*

*SRI, serotonin reuptake inhibitor; HAM-D, total score from Hamilton Rating Scale for Depression; kg, kilograms; mg, milligrams.*

†*Alcohol during pregnancy represents n total standard drinks consumed during the course of pregnancy (study sample range: 0–52 total drinks).*

‡*Reversible monoamine oxidase inhibitors included in cohort as "SRI-exposed."*

**TABLE 2 |** Fetal characteristics ($n = 148$).

| | Control ($n = 57$) | Depressed ($n = 42$) | SRI-Depressed ($n = 31$) | SRI-Non-Depressed ($n = 18$) | Test statistic ($p$-value) |
|---|---|---|---|---|---|
| Gestational age at fetal study (weeks) | 36.0 ± 0.9 | 35.9 ± 0.8 | 35.9 ± 0.7 | 35.9 ± 0.8 | $F_{(3, 144)} = 0.1$ (> 0.9) |
| Gestational age at birth (weeks) | 39.9 ± 1.1 | 39.8 ± 1.3 | 38.9 ± 1.2 | 39.6 ± 1.5 | $F_{(3, 144)} = 5.5$ (0.001)** |
| Sex (*n* male/*n* female) | 26/31 | 26/16 | 14/17 | 6/12 | $\chi^2_{(3)} = 5.0$ (0.2) |
| Birth weight (g) | 3532 ± 408 | 3588 ± 416 | 3312 ± 490 | 3514 ± 431 | $F_{(3, 144)} = 2.7$ (0.05) |
| Length at birth (cm) | 52.0 ± 2.1 | 51.7 ± 2.3 | 50.3 ± 1.8 | 51.4 ± 2.7 | $F_{(3, 144)} = 4.2$ (0.007)** |
| Head circumference at birth (cm) | 35.2 ± 1.3 | 35.1 ± 1.4 | 34.3 ± 1.4 | 34.9 ± 1.1 | $F_{(3, 144)} = 3.6$ (0.02)* |
| Apgar at 5 min | 9 (9, 9) | 9 (9, 9) | 9 (9, 9) | 9 (9, 9) | $H_{(3)} = 2.2$ (0.5) |

*Continuous variables reported as mean ± SD if normally distributed, or median (first, third quartile) if skewed. Categorical variable reported as total number (n). Test statistics, degrees of freedom, and associated p-values are reported for between-group differences using: one-way ANOVA (F), Kruskal-Wallis test (H), or Chi Square test ($\chi^2$), where appropriate. P-value significance levels: *p < 0.05, **p < 0.01, ***p < 0.001.*

*SRI, (fetal exposure to) serotonin reuptake inhibitor antidepressant; g, grams; cm, centimeters.*

One mother's plasma drug concentrations were below lower levels of quantification (<0.1 ng/ml) at $T_0$ and $T_1$, and marginally above quantification for remaining pose-dose levels; this subject's drug data were excluded, resulting in a maternal SRI plasma level sample of $n = 23$. Aside from having higher weight at 36-weeks' gestation, these mothers were considered representative of the larger SRI-treated study sample as there were no other differences between those with ($n = 23$) and without ($n = 26$) drug level data (**Supplementary Table 2**). Refer to **Supplementary Table 3** for times of maternal blood collection and corresponding plasma drug level (ng/ml) data.

**Figure 2** shows the inter-individual variability in concentration-time curves across the study protocol, grouped by antidepressant type. Baseline levels between $T_0$ and $T_1$ were the lowest plasma concentrations, reflecting a pharmacologic trough at apparent steady-state prior to oral SRI dose, which occurred 1.8 ± 0.3 h after $T_0$ and a median of 26 h (interquartile range (IQR): 24–27) since the reported previous dose. Concentration-time curves illustrate an expected increase in plasma drug concertation as part of the absorption phase following oral dose, with individuals on citalopram, paroxetine and sertraline, as well as some individuals on venlafaxine, reaching maximum

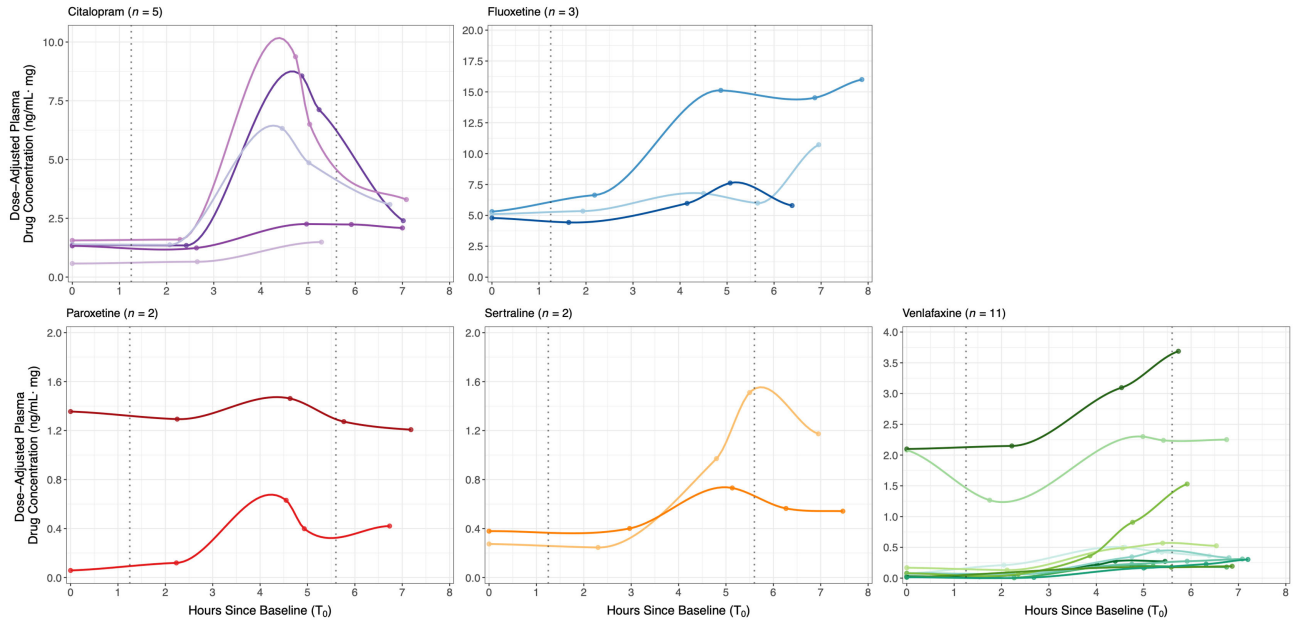


**FIGURE 2 |** Dose-adjusted plasma drug concentrations (ng/ml·mg) at baseline ($T_0$) and four time-points post-dose across the study protocol for 23 SRI-treated mothers, grouped by antidepressant type. Concentration-time curves demonstrate inter-individual variability in SRI pharmacokinetics and maternal drug levels relative to the start of each fetal assessment; curves were fit to each individual's data with local polynomial regression. SRI oral dosing occurred a median of 1.83 h after $T_0$. Median blood collection times were: baseline ($T_0$) at 08h06, post-dose 1 ($T_1$) at 10h21, post-dose 2 ($T_2$) at 12h50, post-dose 3 ($T_3$) at 13h38, and post-dose 4 ($T_4$) at 14h57. Median start times of the baseline/pre-dose and post-dose fetal assessments were at a 1.3 and 5.6 h after $T_0$, respectively (dotted vertical lines).

**TABLE 3 |** Maternal pharmacokinetic variables (mean ± SE) for each antidepressant type on a subset of SRI-treated women ($n = 23$).

| Antidepressant | *N* | $AUC_{last}$ | $C_{max}$ (ng/ml) | $T_{peak}$ (h) | Δ T3-T0 (ng/ml·mg) |
|---|---|---|---|---|---|
| Citalopram | 5 | 906 ± 271 | 274 ± 92 | 4.9 ± 0.14 | 3.2 ± 1.0 |
| Fluoxetine† | 3 | 3221 ± 1919 | 613 ± 342 | 5.8 ± 1.0 | 4.3 ± 2.5 |
| Paroxetine | 2 | 125 ± 66 | 24 ± 5.2 | 4.6 ± 0.04 | 0.13 ± 0.21 |
| Sertraline | 2 | 728 ± 256 | 197 ± 105 | 5.3 ± 0.18 | 0.71 ± 0.53 |
| Venlafaxine | 11 | 621 ± 314 | 163 ± 74 | 5.7 ± 0.30 | 0.43 ± 0.13 |

*$AUC_{last}$, area under the curve from $T_0$ (baseline) to the last measured plasma drug concentration ($T_4$); $C_{max}$, maximum (peak) plasma drug concentration (ng/ml); $T_{peak}$, time (hours) from baseline to reach $C_{max}$; Δ T3-T0, change in dose-adjusted plasma concentration (ng/ml·mg) from baseline ($T_0$) to post-dose 3 ($T_3$), representing the change in maternal drug concentration between baseline/pre-dose and post-dose fetal assessments.*

†*Fluoxetine not yet reached maximum plasma concentration at time of last blood collection (i.e., $T_4$ estimated as $T_{peak}$). $AUC_{last}$ and $C_{max}$ for fluoxetine may be underestimations.*

concentration ($C_{max}$) between 4.5–6 h ($T_{peak}$), followed by the initial elimination phase. Fluoxetine-treated mothers appear to still be in the absorption phase when final drug levels were collected ($T_4$), consistent with a $T_{peak}$ of 6–8 h. $AUC_{last}$, representing total observed maternal drug exposure during our study protocol, was highest for fluoxetine and lowest for paroxetine. Maternal pharmacokinetic responses are summarized in **Table 3**.

### Validation of Study Design: Fetal Assessments at Pharmacologic Trough and Peak

**Figure 2** also illustrates the start times of each fetal assessment relative maternal plasma SRI levels. For the antidepressants studied, the baseline/pre-dose fetal assessment started a median 1.3 h (IQR: 0.99−1.5) after $T_0$ and 0.92 h (IQR: 0.87−1.00) before $T_1$, which therefore occurred during the period of steady-state pharmacologic trough ($T_0$-$T_1$). At a median of 5.6 h (IQR: 5.2−6.0) after $T_0$, the start of the post-dose fetal assessment corresponded to the late absorption phase or early elimination phase, depending on SRI type. Dose-adjusted plasma drug concentration significantly increased between baseline/pre-dose and post-dose fetal assessments [$n = 23$; paired $t$-test: $t_{(21)} = 3.13$, $p = 0.005$], with a mean (± SE) change from $T_0$-to-$T_3$ of 1.54 ± 0.48 ng/ml·mg.

## Fetal HR and HR Variability

Fetal CTG measures ($n = 148$) are presented in **Table 4**, and were within clinically normative ranges for gestational age (56, 77). AM/pre-dose and PM/post-dose fetal CTG sessions were 50.1 ± 3.0 min with minimal HR tracing signal loss (3.5 ± 5.4 %); neither

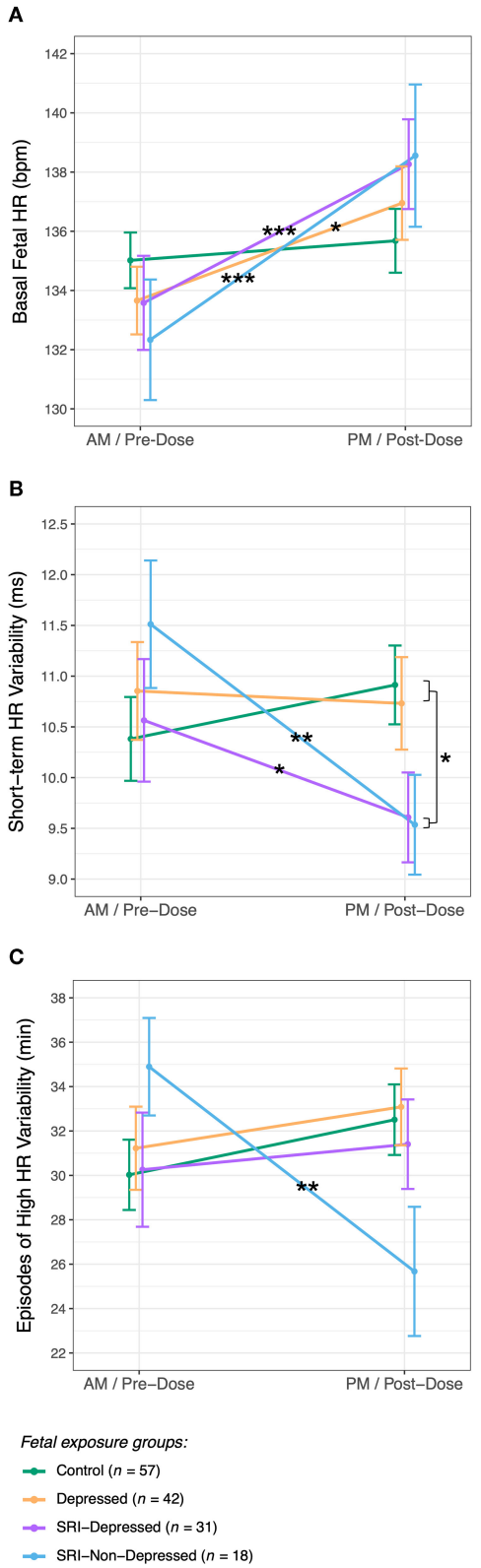


**FIGURE 3 |** Fetal HR and HR variability (mean ± SE) for each exposure group across AM/pre-dose and PM/post-dose fetal assessments for **(A)** basal fetal HR, **(B)** short-term variability, and **(C)** episodes of high fetal HR variability (*post hoc* test significance levels: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

the duration nor amount of signal loss differed between groups at either fetal assessment.

## Basal Fetal HR

There were no group differences in basal fetal HR at either fetal assessment. However from AM/pre-dose, fetal HR increased to be significantly higher at the PM/post-dose assessment in all fetal groups, except the Controls (*Group* × *Time* interaction: $F_{(3,\ 142.0)} = 3.4$, $p = 0.02$) (**Figure 3A**). Between assessments, basal fetal HR increased by 5 bpm (95% CI: 2.3, 7.7; $p_{adj} < 0.001$) in the SRI-Depressed group, by 6 bpm (95% CI: 2.7, 9.8; $p_{adj} < 0.001$) in the SRI-Non-Depressed group, and by 3 bpm (95% CI: 0.8, 5.4; $p_{adj} = 0.01$) in the Depressed group. In contrast, fetal HR in the Control group did not change between assessments ($p_{adj} = 0.4$). There were no covariate effects on basal fetal HR.

## Fetal HR Accelerations and Decelerations

Fetuses had a median of 14 HR accelerations (IQR: 11–18) and 1 HR deceleration (IQR: 0–2) during each 50-min CTG session (**Table 4**). Fetal HR accelerations did not differ between groups at either assessment; however, averaged across groups, the number of HR accelerations significantly increased relative to AM/pre-dose assessment (main effect of *Time*: $X^2_1 = 8.9$, $p = 0.003$). Whereas, fetal HR decelerations did not significantly differ between groups nor across time, but were found to be positively associated with gestational age ($X^2_{(1)} = 4.2$, $p = 0.04$).

## Short-Term HR Variability

STV, reflecting the average HR variation across each CTG tracing, in pulse intervals (ms) (72), did not differ between groups at the AM/pre-dose fetal assessment. Following SRI dose, a significant decrease in STV was observed relative to baseline among fetuses in both SRI-exposed groups (*Group* × *Time* interaction: $F_{(3,\ 142.6)} = 5.1$, $p = 0.002$) (**Figure 3B**): STV decreased by 1.0 ms (95% CI: 0.05, 1.9; $p_{adj} = 0.04$) in SRI-Depressed group fetuses and by 2.0 ms (95% CI: 0.80, 3.2; $p_{adj} = 0.001$) in SRI-Non-Depressed group fetuses. These post-dose decreases resulted in SRI-exposed fetuses to have 1.1 ms (95% CI: 0.80, 3.2; $p_{adj} = 0.04$) lower STV compared to non-exposed fetuses at the PM/post-dose assessment, controlling for covariates.

## High and Low Fetal HR Variability

Episodes of high fetal HR variability did not differ between groups at the AM/pre-dose fetal assessment; however post-SRI dose, a *Group* × *Time* interaction was identified ($F_{(3,\ 142.9)} = 3.7$, $p = 0.01$), whereby the time fetuses in the SRI-Non-Depressed group spent displaying high HR variability decreased by 9.2 min (95% CI: 3.0, 15.4; $p_{adj} = 0.004$), controlling for covariates (**Figure 3C**). No between-group differences were found for episodes of low HR variability.

## Fetal Motor Activity

Fetal movements (FMs), which did not differ between groups, occurred at a median frequency of 48 (IQR: 32–70) and 53 (IQR: 32–83) movements/hour during the AM/pre-dose and PM/post-dose assessments, respectively (**Table 4**). As expected, the number of FMs per minute during episodes of high HR variability was significantly higher than during low HR variability

**TABLE 4 |** Fetal HR, HR variability and movement ($n = 148$).

| | Control ($n = 57$) | | Depressed ($n = 42$) | | SRI-Depressed ($n = 31$) | | SRI-Non-Depressed ($n = 18$) | |
|---|---|---|---|---|---|---|---|---|
| **Fetal variables** | **AM** | **PM** | **AM** | **PM** | **AM/pre-dose** | **PM/post-dose** | **AM/pre-dose** | **PM/post-dose** |
| Basal HR (bpm)[a] | 135 ± 7 | 136 ± 8 | 134 ± 7 | 137 ± 8 | 134 ± 9 | 138 ± 8 | 132 ± 9 | 139 ± 10 |
| HR accelerations (*n*)[b] | 14 (11, 18) | 16 (13, 20) | 16 (11, 20) | 15.5 (12, 19) | 12 (9, 15) | 14 (12, 17) | 14 (10, 18) | 13.5 (10, 15) |
| HR decelerations (*n*) | 1 (0, 1) | 1 (0, 2) | 0 (0, 2) | 1 (0, 2) | 1 (0, 2) | 1 (0, 2) | 1 (0, 2) | 2 (0.25, 3) |
| STV (ms)[a] | 10.4 ± 3.1 | 10.9 ± 2.9 | 10.9 ± 3.1 | 10.7 ± 3.0 | 10.6 ± 3.4 | 9.6 ± 2.4 | 11.5 ± 2.7 | 9.5 ± 2.1 |
| High HR variability (min)[a] | 30.0 ± 13.0 | 32.5 ± 11.9 | 31.2 ± 12.1 | 33.1 ± 11.2 | 30.3 ± 14.3 | 31.4 ± 11.0 | 34.9 ± 9.3 | 25.7 ± 12.4 |
| Low HR variability (min) | 0.97 ± 2.5 | 1.8 ± 4.1 | 1.7 ± 4.2 | 1.4 ± 4.0 | 1.5 ± 2.9 | 0.70 ± 2.2 | 0.50 ± 1.9 | 1.8 ± 4.4 |
| Fetal movements/hour (*n*)[†] | 50 (31, 66) | 53 (35, 82) | 53.5 (37, 77) | 57 (38, 86) | 46 (28, 62) | 47 (30, 69) | 43.5 (30, 83) | 60 (32, 83) |

*Fetal variables for each group are summarized as mean ± SD if continuous and normally-distributed, or median (first, third quartile) if skewed or count data.*
*GLMM Statistics: significant fixed effects are identified as: [a]significant Group × Time interaction; [b]significant effect of Time; and [c]significant effect of Group. Refer to text for model statistics and estimated marginal means between relevant factor contrasts.*
*AM, morning/baseline fetal assessment; PM, afternoon fetal assessment; HR, heart rate; STV, short-term variation; bpm, beats per minute; n, total number; ms, milliseconds; min, minutes.*
*[†]Maternally-perceived fetal movements per hour (adjusted from ~50 min).*

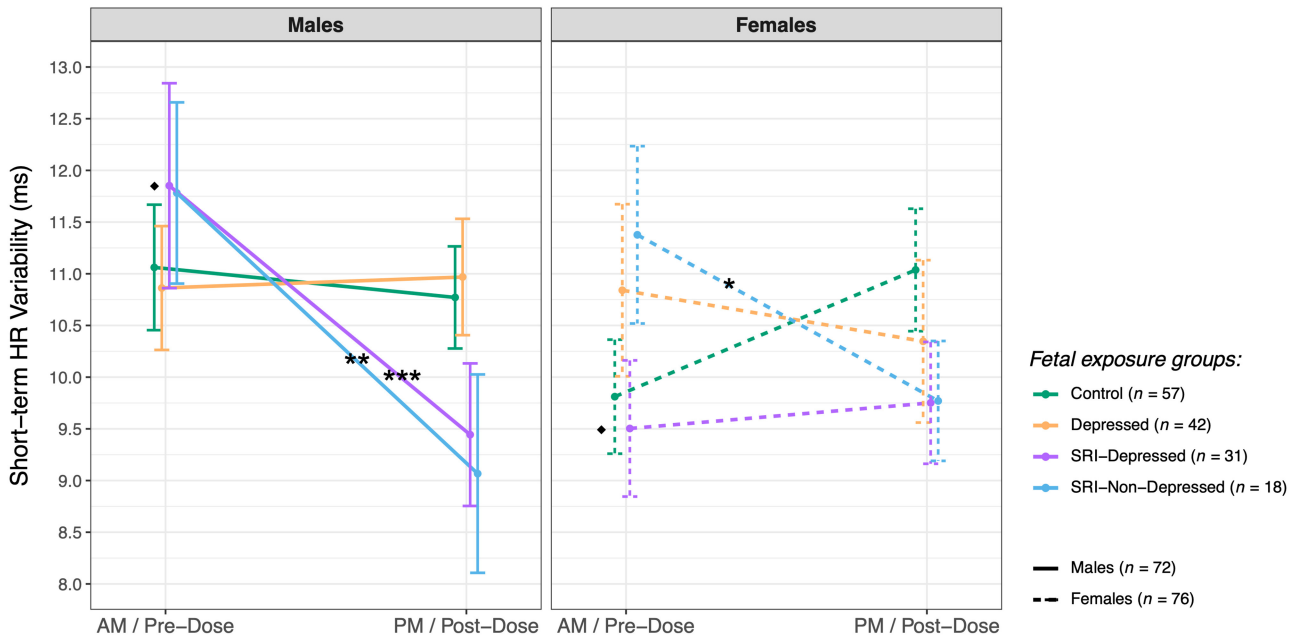


**FIGURE 4 |** Sex differences in fetal short-term HR variability (mean ± SE) between exposure groups (*post hoc* test significance levels: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; *indicates within-sex group difference, ♦ indicates within-group sex difference).

($t = 6.8$, $p < 0.001$); this also did not differ between groups, nor across assessments. There were no covariate effects on FMs.

## Sex-Specific Fetal SRI Effects

*Post hoc* analysis revealed sex-specific effects on group differences in fetal STV (three-way interaction: $F_{(3, 138.4)} = 2.7$, $p = 0.04$) (**Figure 4**). In the SRI-Depressed group, only male fetuses underwent a significant post-dose decrease in STV: from pre- to post-dose assessments, STV decreased in SRI-Depressed group males by 2.4 ms (95% CI: 1.1, 3.7; $p_{adj} < 0.001$), in SRI-Non-Depressed group males by 2.7 ms (95% CI: 0.75, 4.7; $p_{adj} = 0.008$), and in SRI-Non-Depressed group females by 1.6 ms (95% CI: 0.22, 3.0; $p_{adj} = 0.02$). Conversely, female fetuses in the SRI-Depressed group did not undergo this post-dose decrease in STV, but instead, were found to have 2.2 ms (95% CI: 0.13, 4.4; $p_{adj} = 0.04$) lower STV than SRI-Depressed males at the baseline/pre-dose assessment and remained unchanged post-dose. There were no other significant effects of fetal sex on group differences reported.

## SRI Dose-Dependent Fetal Effects

Maternal SRI oral dose (standardized) was found to be significantly associated with the number of fetal HR decelerations during 50-min CTG sessions (**Figure 5**). Higher SRI doses were

associated with a greater number of fetal HR decelerations ($n$ = 49; $F_{(1, 47)}$ = 7.6, $p$ = 0.008). This did not differ between SRI-exposure groups, and effects were evident at both pre- and post-dose assessments. No other dose-dependent effects were observed in SRI-related fetal HR outcomes we report, nor were there differences related to antidepressant class (i.e., SSRIs vs. SNRIs).

## DISCUSSION

This study reports three key findings. In late gestation, fetal SRI exposure was associated with: (1) post-dose decreases in fetal HR variability, (2) sex-specific fetal HR outcomes, and (3) concurrent changes in maternal drug levels that reflected pharmacologic trough/peak (acute) periods. Fetal HR increased while fetal HR variability decreased in SRI-exposed fetuses relative to the AM/pre-dose assessment, reflecting an acute effect of SRI exposure. Importantly, fetal outcomes varied depending on maternal response to SRI pharmacotherapy; namely whether the mothers' depressed mood remitted or remained symptomatic (i.e., SRI-Non-Depressed, SRI-Depressed). In particular, STV acutely decreased among fetuses in both SRI-Depressed and SRI-Non-Depressed groups, thus occurring independent of concurrent maternal mood; whereas, high HR variability was found to acutely decrease only among fetuses in the SRI-Non-Depressed group. SRI-related sex differences in fetal HR variability also varied with maternal mood context, with differences between male and female fetuses observed only in the SRI-Depressed group. Further, higher maternal SRI doses were associated with a greater number of fetal HR decelerations across both study periods. Since neither standardized dose nor length of gestational SRI exposure differed between SRI-Depressed and SRI-Non-Depressed women, fetal outcomes in these groups may be acute drug exposure-related effects. In particular, we did not observe group differences pre-dose during a period of pharmacologic trough, which would have reflected a chronic/sustained effect of SRI exposure.

Importantly, changes in fetal HR variability we report were within normative ranges for healthy typically developing fetuses at 36-weeks' gestation (56, 78), and thus, are likely not clinically significant. However, even within a normative range of fetal physiology, we observe group differences that may reflect adverse developmental effects of SRI exposure before birth that vary with respect to the timing of maternal oral dose.

### Fetal SRI Exposure at Pharmacologic Trough and Peak

Maternal SRI plasma concentrations increased following a typical daily oral SRI dose in the third-trimester, demonstrating an expected concentration-time relationship. Women in this study were on long-term SRI pharmacotherapy (most prior to conception) and appear to have trough plasma SRI levels consistent with a pharmacologic steady-state, which were similar to third-trimester maternal dose-adjusted plasma trough levels previously reported (81). Although sample size was limited, women taking citalopram, sertraline, and paroxetine reached $C_{max}$ and were in the early elimination phase at the post-dose

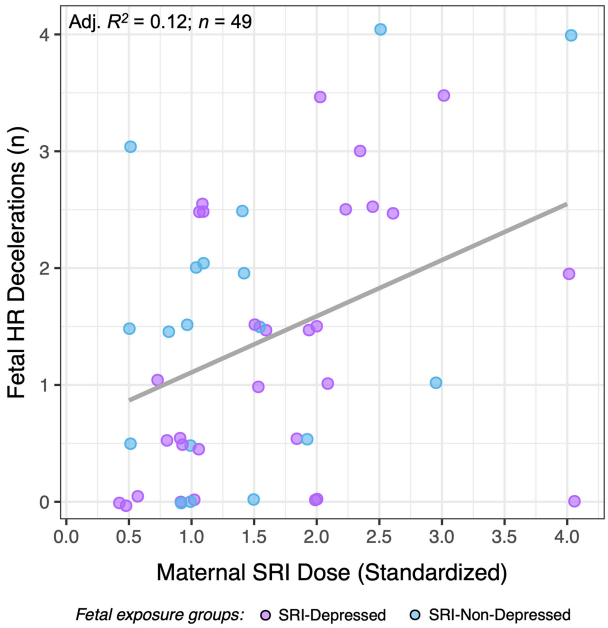


**FIGURE 5 |** The relationship between standardized maternal SRI oral dose and the number of fetal HR decelerations for SRI-exposed fetuses (SRI-Depressed and SRI-Non-Depressed groups). Data presented represent average HR decelerations across 50-min CTG sessions, which did not differ across time.

fetal assessment. In contrast, women taking venlafaxine and fluoxetine were still in the absorption phase by the last blood collection. Trough and peak levels are an accepted phenomenon for multiple oral dosing regimens, but the critical finding from this study was that the extremes of trough/peak observed translated to a variable fetal response.

Our findings demonstrate that the fetus may experience a chronic exposure to steady-state plasma SRI levels, but subject to continual fluctuations in such exposure with respect to maternal oral dose across a typical day in late gestation. Although this does not directly indicate that equivalent drug changes in fetal circulation occur, changes in maternal SRI plasma levels would have implications toward factors that may impact the extent of fetal SRI exposure. SRIs have high placental permeability (46, 82), and in rodents, fetal citalopram exposure was found to exceed that of the mother 2-h after maternal drug administration (83). Beyond transplacental drug transfer, several other factors could also influence SRI pharmacology in this setting, such as genetic variations in maternal metabolic enzymes (further discussed below), fetoplacental metabolism and clearance, or exposure to other pharmacologic agents (41, 42, 84, 85). Hence, it is almost certain that fetal SRI exposure is not consistent and the distinct acute SRI-related outcomes we report suggest a differential fetal sensitivity may exist to varying maternal SRI plasma levels and/or acute physiologic changes secondary to SRI exposure.

### Fetal HR Variability Decreases Following Acute SRI Exposure

Transient reductions in fetal HR variability with acute SRI exposure may indicate impairments in autonomic functioning.

The Dawes-Redman parameter of STV, a standardized clinical marker of perinatal compromise (56, 72, 86), not only summarizes overall HR variation, but may also be a surrogate for fetal sympathovagal regulation. In a comparative study by Seliger et al., CTG-derived STV was highly correlated with the standard deviation of normal-to-normal beat intervals, as well as HR in the low frequency power spectra (87). These indices are commonly obtained from fetal electrocardiography, which has higher temporal resolution than ultrasound-based CTG (i.e., ability to detect QRS complexes in continuous cardiac signal) and are among parameters widely used to examine sympathetic and integrative sympathovagal-mediated HR fluctuations (88). Thus, acute decreases in STV, accompanied by acute increases in basal fetal HR we report in SRI-exposed fetuses, may be consistent with sympathetic activation and/or autonomic withdrawal leading to diminished HR variability.

In adults, reduced HR variability is associated with major depressive disorder (89, 90); however, these effects appear to be strongly mediated by antidepressants (91, 92). Additionally, higher SRI doses may have cardiac side effects in adults, such as QT interval prolongation (93). However, to our knowledge, only two other groups have assessed fetal HR variability in relation to prenatal SRI exposure (28, 31), who each described fetal cardiac patterning using differing methodology, consequently limiting direct comparison with our findings. Critically, neither study reported fetal outcome with respect to the timing of maternal SRI oral dose, so it is unknown whether previous findings reflect fetal outcomes of chronic or acute SRI exposure and may be why no SRI effect on fetal HR/variability was observed in Gustafsson et al. (31). Despite these methodological differences, our findings may have consistencies with disrupted neurobehavioral state previously reported in the near-term fetus by Mulder et al. (28). These effects may reflect altered fetal autonomic functioning, particularly given the roles of serotonin as a neuromodulator of autonomic pathways (94, 95). In the postnatal period, altered cardiac autonomic function following an acute noxious event (phenylketonuria heel lance) was observed in both 2–3 day-old neonates (7) and infants at 2-months of age (8) with prenatal SRI exposure. Additional studies are needed to further characterize acute SRI-related changes in fetal HR variability and determine to what extent such changes exert a fetal programming effect on long-term neurodevelopmental outcome in stress-reactivity, emotion/affective processes, and self-regulation.

Importantly, our findings suggests that maternal mood response to SRI pharmacotherapy may be a key modifier of fetal outcome. However, it remains unknown as to why fetuses of SRI-treated mothers whose depressive symptoms remitted would uniquely display acute reductions in high HR variability: a cardiac pattern that, when coupled with HR accelerations and movement, occurs during periods of active neurobehavioral states (72). Although our study did not assess patterns of fetal motor activity, previous studies have identified fetal state based on HR variability alone [e.g. (96, 97)]. Given the high incidence of concordance between fetal HR and motor activity by 32-weeks' gestation (52), it is conceivable that reduced episodes of high HR variability may indicate fewer and/or shorter periods of active states among fetuses in the SRI-Non-Depressed group, possibly reflecting acute impairments or delayed development. Our findings highlight the need for future studies focused on how SRIs interact with maternal mood to influence fetal autonomic functioning and neurobehavior.

## Acute SRI Effects on Fetal HR Variability Are Sex-Specific

Acute SRI-related outcomes in fetal HR variability were found to be moderated by fetal sex. Specifically, the post-dose decrease in STV was observed among SRI-Depressed group male fetuses, compared with the relative stability in STV between assessments in SRI-Depressed females. Indeed, sex difference in fetal HR variability have been reported in low-risk singleton pregnancies (98, 99), for example in a large CTG study, males had lower baseline HR but higher STV than females throughout gestation (78). Although basal HR and STV in males and females in the Control group did not differ significantly, SRI-Depressed males did have higher STV than SRI-Depressed females at the baseline/pre-dose assessment, pointing to a chronic/sustained SRI-related sex difference that is evident when maternal depressive symptoms persist. Sex differences were not observed in the SRI-Non-Depressed group, further suggesting that sex-specific SRI effects vary with maternal mood. Several rodent studies report sex-specific neurodevelopmental outcomes following perinatal SRI exposure, with outcomes that vary with maternal stress/psychiatric context (100). For example, hippocampal neurogenesis and plasticity appear to have a particular sex-specific sensitivity to SRIs and maternal stress (101); interestingly, hippocampal-brainstem connectivity has critical integrative roles in vagal modulation of cardiovascular function (102). In humans, studies reporting sex-specific infant or child outcomes following prenatal SRI exposure are extremely scarce; however, Erickson et al. report that male and female infant temperament trajectories from 3–10 months are differentially associated with prenatal SRI exposure and maternal internalizing symptoms (103), and recently, we identified sex-specific alterations in brain microstructure in neonates with prenatal SRI exposure (104). Moreover, sex differences may influence pharmacologic factors contributing to the extent and effect of SRI exposure on the fetus, such placental functioning (23), metabolic enzyme activity and synaptic transmission (105). While our findings provide the first preliminary evidence that sex-specific SRI effects may emerge in the fetal period with outcomes varying with maternal mood, this topic warrants further investigation in a larger sample.

## Maternal SRI Pharmacology

High inter-individual variability in maternal SRI plasma concentrations was observed in this study, particularly in the concentration-time curves. These differences are indicative of the known population-level heterogeneity in pharmacokinetic factors, likely compounded by pregnancy-induced physiologic changes that influence drug disposition, such as increased gastrointestinal motility, plasma volume, cardiac output and renal function (106). In particular, hepatic cytochrome P450 (CYP) enzymes, which metabolize SRIs, have altered expression

and activity across gestation (107, 108). CYP450s are highly polymorphic with high-to-low activity allelic variants (109) and have been associated with individual differences in drug disposition and treatment outcome (110); thus without genetic screening, antidepressant levels will vary widely and unpredictably (111). Indeed, variations in *CYP2D6* genotype are reported to have divergent effects on maternal plasma levels and SRI efficacy during pregnancy (112), which may partially explain why over 60% of our SRI-treated sample remained symptomatic.

Additional factors may also contribute to variable antidepressant efficacy, such as history and initial severity of mental illness, treatment compliance, and other neurobiological factors associated with the pathophysiology of depression and/or antidepressant mechanisms, such as individual differences in synaptic transmission in multiple brain regions (105), genetic expression and endogenous signaling molecules [e.g., reviewed in (113)]. For example, polymorphisms in the serotonin transporter gene promoter (5-HTTLPR) are associated with antidepressant efficacy (114). Emerging evidence also suggests that microRNAs may have regulatory roles in psychological stress pathways, with potential to serve as biomarkers for monitoring antidepressant treatment response (115, 116). In this study, the extent to which each SRI-treated woman experienced symptom remission—or relapse, possibly due to increased maintenance dose requirements with advancing gestation (81)—remains unknown. Future studies combining extended mental health histories with genetic screening, use of novel biomarkers, etc. are needed to elucidate why some women and not others benefit from prenatal SRI treatment, and by extension, how this impacts fetal development.

## Limitations

We note several key limitations pertaining to sample size, study design and methodology in this study. First, sample sizes of fetal exposure groups were relatively small, especially when assessing sex differences. Thus, our findings should be replicated to determine their generalizability. We were also unable to determine whether acute fetal SRI effects were related to specific antidepressants, although we found that fetal outcomes did not differ between antidepressant classes (i.e., SSRIs vs. SNRIs). Further, maternal blood was collected on a subsample of participating women, resulting in particularly small numbers for the SRI pharmacokinetic analysis. Inherent differences in bioavailability and half-life between formulations, along with other factors influencing SRI pharmacokinetics (as discussed above), limited our ability to pool dose-adjusted concentrations for analysis. Between a lack of pooling, small sample size and limited time-frame for sampling (7–8 h), relationships between maternal pharmacokinetic variables (i.e., $AUC_{last}$, $C_{max}$, $T_{peak}$) and SRI-related fetal outcomes were not identified. Future work should investigate whether pharmacokinetic variables, or other biomarkers, may be predictive of acute or chronic fetal outcome as routine blood sampling is rapid and economical.

Our use of four prenatal exposure groups allowed for the distinction between SRI-related fetal HR outcomes from those related to maternal depressed mood, thereby addressing the key methodological constraint of "confounding by indication". While this approach identified appropriate exposure groups, the impact of maternal depressive illness severity, or variations in symptoms across pregnancy, could not be addressed. Moreover, women scoring close to the depressed/non-depressed cut-off may not differ in a clinically meaningful manner, even though a HAM-D score > 8 (as used here) has been clinically validated as a cut-off between symptomatic and asymptomatic depression (69). However, our findings suggest a differential fetal sensitivity may exist in the context of maternal response to SRI treatment, highlighting the importance of making such distinctions in future studies.

Regarding study design limitations, it is possible diurnal rhythms in fetal cardiovascular variables [e.g., (117, 118)] were an unmeasured source of variability. Even with effort to minimize diurnal effects with the careful consideration of timing for each component of this study, such influences may be driving the increase in basal fetal HR and HR accelerations observed between assessments. It is also possible maternal mood and/or antidepressant treatment may impact maternal circadian cycles, to which the developing fetus may be sensitive (119, 120). Further, with a cross-sectional approach at 36-weeks' gestation, these findings are only relevant to the late gestation fetus and may not reflect changes across earlier periods of prenatal development. Future studies should determine if other aspects of fetal physiology or neurodevelopment demonstrate varying chronic/acute outcomes with respect to maternal SRI dosing.

Lastly, key methodological limitations should also be considered. Doppler-based detection of continuous fetal HR with CTG suffers from low temporal resolution compared to more sophisticated tools, such as fetal electrocardiography or magnetocardiography that can be used for complex HR variability analyses and resolving fast vagal activity (121). However, fetal CTG is widely accessible, cost-effective, and does not require a specialist to administer, thereby aiding in reproducibly. Our findings may also have clinical implications, as fetal CTG measures are implemented in national guidelines for antenatal fetal monitoring (70). Another methodological limitation was the measure of fetal motor activity by maternal perception. Although this provides a crude index of relative fetal activity during the assessment period, many factors can influence maternal perception of her fetus, such as BMI, levels of maternal activity, and the size/growth rate of the fetus (50, 122). As such, the lack of independently recorded fetal movement data limited our ability to separately assess fetal neurobehavioral state from HR tracings. Although it is possible acute decreases in HR variability may reflect variations in fetal state, future studies are needed to investigate fetal HR-movement coupling in this context.

# CONCLUSIONS

Prenatal SRI antidepressant exposure had acute, but not chronic, effects on fetal HR and HR variability in late gestation, which differed depending on maternal mood response to SRI pharmacotherapy. Maternal SRI pharmacokinetics had

high inter-individual variability, but suggested that fetal SRI exposure is inconsistent and may be sensitive to periods of chronic (trough) and acute (peak) maternal SRI levels. This study also identified sex-specific fetal SRI effects, as SRI-exposed male fetuses displayed post-dose decreases in fetal HR variability, whereas outcomes in SRI-exposed females varied with maternal depressed mood. It remains to be determined whether acute SRI-related decreases in fetal HR variability reflect a transient impairment in fetal autonomic functioning, a pharmacologic mechanism on fetal cardiac patterning, or an *in utero* adaption to long-term altered serotonergic signaling. While replication is needed, these findings may have potential clinical implications for antenatal fetal monitoring and may ultimately improve understanding of developmental risk associated with maternal psychotropic medication use during pregnancy. Future work will investigate longitudinal relationships with postnatal outcomes in infant temperament, stress-regulation and broader neurobehavior, and the manner in which maternal SRI pharmacology, psychiatric distress, and other factors, such as sex, interact to exert a fetal programming effect.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UBC Clinical Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

KC aided in data acquisition, performed all data processing and statistical analyses, interpreted the findings, and prepared the manuscript. AC interpreted pharmacologic findings and contributed to manuscript writing. MI contributed to statistical analyses. UB facilitated participant recruitment/retention and aided in data acquisition. DR, TO, and KL conceptualized the study design, obtained funding, interpreted findings, and contributed to manuscript writing. All authors read, critically revised and approved the submitted manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.680177/full#supplementary-material

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# Hydroxyzine Use in Preschool Children and Its Effect on Neurodevelopment: A Population-Based Longitudinal Study

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We identified the first-generation antihistamine hydroxyzine as the earliest and most frequently prescribed drug affecting the central nervous system in children under the age of 5 years in the province of British Columbia, Canada (1. 1% prevalence). Whereas, the antagonism of H1-receptors exerts anti-pruritic effects in atopic dermatitis and diaper rash, animal studies suggest an adverse association between reduced neurotransmission of histamine and psychomotor behavior. In order to investigate hydroxyzine safety, we characterized the longitudinal patterns of hydroxyzine use in children under the age of 5 years and determined mental- and psychomotor disorders up to the age of 10 years. We found significantly higher rates of ICD-9 and ICD-10 codes for disorders such as tics (307), anxiety (300) and disturbance of conduct (312) in frequent users of hydroxyzine. Specifically, repeat prescriptions of hydroxyzine compared to a single prescription show an increase in tic disorder, anxiety and disturbance of conduct by odds ratios of: 1.55 (95%CI: 1.23–1.96); 1.34 (95%CI: 1.05–1.70); and 1.34 (95%CI: 1.08–1.66) respectively in children up to the age of 10 years. Furthermore, a non-significant increased trend was found for ADHD (314) and disturbance of emotions (313). This is the first study reporting an association between long-term neurodevelopmental adverse effects and early use of hydroxyzine. Controlled studies are required in order to prove a causal relationship and to confirm the safety of hydroxyzine in the pediatric population. For the time being, we suggest the shortest possible duration for hydroxyzine use in preschool-age children.

**Keywords: antihistamine, hydroxyzine, preschool-age children, atopic dermatitis, neurodevelopmental disorders, longitudinal study, tics, mental disorders**

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## INTRODUCTION

Between birth and 5 years of age, the human brain exhibits its fastest rate of development (1). The use of drugs which affect the central nervous system (CNS) is challenging in children due to the lack of pediatric studies and the difficulty in diagnosis of mental disorders in preschool-aged children (2). The original purpose of our study was the assessment of psychotropic drug use and

associated diagnosis patterns in children under the age of 5 years. We identified the first-generation antihistamine drug hydroxyzine, as the earliest prescribed drug affecting the CNS in infants and toddlers and even more so, as the most frequently prescribed sedating medication in children under the age of 5 years in British Columbia, Canada. In contrast to the second-generation antihistamines, exhibiting a high specificity for peripheral histamine H1-receptors, there is little knowledge on the complex neuro-pharmacodynamics and safety of the first-generation drugs especially in young children (3). Due to the increasing prevalence of allergic rhinitis in children of school age and in adolescents, studies were conducted to address the impact of disease and medication on learning and academic achievement. The result of clinical cohort studies in children at school age and adolescents with allergic rhinitis suggests that use of sedative antihistamine drugs has a more negative impact on learning and academic performance compared to allergic rhinitis alone or if non-sedative second-generation antihistamine drugs are used (4, 5).

However, the specific relevance of histamine neurotransmission in the brain has been addressed only so far in basic science and animal studies. Rat models have demonstrated the involvement of neuronal histamine in the formation of long-term memory, as early as in the 1980's (6). More recently, a mutation in histidine decarboxylase was identified to be associated with inherited Tourette's syndrome in men (7). Subsequent animal studies on mice deficient for histidine decarboxylase confirmed the phenotype of a tic spectrum disorder and the involvement of neuronal histamine on the regulation of psychomotor activity (8).

So far there is only one published controlled trial on the neuropsychiatric outcome of an antihistamine drug in children under the age of 5 years. This controlled prospective long-term safety study was conducted on cetirizine, an active metabolite of hydroxyzine. The trial enrolled 817 children between 1 and 2 years of age with atopic dermatitis treated with systemic cetirizine or placebo. No difference was found between cetirizine and placebo in cognitive abilities, behavior and development up to 18 months after discontinuation of therapy (9, 10). However, cetirizine is a second-generation antihistamine and minimally penetrates the blood brain barrier compared to its precursor molecule hydroxyzine (11). In contrast, a recent observational study provided evidence that early life exposure to antihistamine drugs, especially the first-generation drug diphenhydramine, may be an independent risk factor for development of attention-deficit hyperactivity disorder (ADHD) in childhood (12).

In Canada, hydroxyzine is licensed for the alleviation of pruritic skin disease, allergic rhinitis and for the mitigation of anxiety and nausea. The only pediatric safety study with hydroxyzine conducted in 1984 involved 12 children between 2 and 10 years of age with severe atopic dermatitis and a total drug exposure time of 2 weeks (13). This study focused on pharmacokinetics and dose finding and did not report any adverse effects besides sedation. There is no minimum age restriction for its use in pediatrics.

The lack of pediatric safety studies on hydroxyzine together with its frequent use in infants and toddlers, and animal studies suggesting a crucial function of histamine as neurotransmitter, prompted us to investigate hydroxyzine's safety.

The aims of the current study were to characterize the longitudinal patterns of systemic hydroxyzine prescription in children under the age of 5 years and to evaluate whether frequent use of hydroxyzine in this young population might be associated with mental- and psychomotor diseases.

# METHODS

## Study Design and Data Sources

A population-based retrospective observational study was conducted using administration databases from the province of British Columbia, Canada. Data extracted includes all children under the age of 19 years who had prescription of drugs acting on the CNS between fiscal years 1997 and 2018. Research Ethics approval was provided by the University of British Columbia, Children's and Women's Hospital's Research Ethics Board (H18-01247).

The following health resource utilization data were obtained: Medical Services Plan (MSP) Payment Information File (14), Discharge Abstract Database (Hospital Separations) (15), PharmaNet Data and Consolidation File (MSP Registration & Premium Billing) (16). These data files provide patients demographics, diagnosis codes and prescription dispensing records. This study was focused on psychotropic drug use in children: 0–5 years of age.

## Hydroxyzine Administration in Children

Initial screening shows that among all CNS medications, hydroxyzine was the predominant one prescribed to children under the age of 5 years. For ease of administration to children, a liquid formulation of hydroxyzine is available in Canada (Atarax® syrup). This sweet tasting syrup contains 473 ml with 0.95 gram of hydroxyzine and available only on prescription. In our data, the medication is mainly prescribed by one formula (HYDROXYZINE HCL 10MG/5ML oral solution).

## Diagnosis of Neurodevelopment Disorders

In the pediatric population, assessment of neurodevelopment disorders is a complex and challenging practice; there are fewer strict diagnosis tools like DSM-V used in adults. Our data only have the ICD-9 and ICD-10 codes available for the diagnoses of mental health conditions. **Table 1** listed all ICD codes associated with mental- and psychomotor disorders according to their potential relevance in neurotransmission of histamine.

We defined three disease categories for investigation: (1) psychomotor disorders; (2) learning deficiencies; and (3) mental disorders. Specifically, tic disorder and hyperkinetic syndrome in childhood were assigned to the psychomotor disorder; intellectual disabilities and specific delays in development were assigned to learning deficiencies; anxiety disorder, disturbance of conduct and disturbance of emotions were assigned to the mental disorders.

**TABLE 1 |** ICD-9 and ICD-10 diagnosis codes for psychomotor and mental health disorders used in this analysis.

| | Disease | ICD-9 codes | ICD-10 codes |
|---|---|---|---|
| Psychomotor disorders | Tic disorders | 307 | F95.0–F95.2<br>F95.8–F95.9 |
| | Hyperkinetic syndrome of childhood | 314 | F90.0<br>F90.8–F90.9 |
| Learning deficiencies | Intellectual disabilities | 317–319 | F70–F73<br>F78–F79 |
| | Specific delays in development | 315 | F80.0–F80.2<br>F81.8–F81.9<br>F82<br>F84.1<br>F84.3–F84.5<br>F84.8–F84.9 |
| Mental disorders associated with Tics | Anxiety disorders | 300 | F40.0–F40.2<br>F40.8–F40.9<br>F41.0–F41.3<br>F41.8–F41.9<br>F42.0–F42.2<br>F42.8–F42.9<br>F48.9<br>F93.0–F93.3<br>F99 |
| | Disturbance of conduct | 312 | F91.0–F91.3<br>F91.8–F91.9<br>F92.0<br>F92.8–F92.9 |
| | Disturbance of emotions | 313 | F93.8–F93.9<br>F94.0–F94.2<br>F94.8–F94.9<br>F98.8 |

## Statistical Analysis

Our first analysis was generated for the distributions of patients under the age of 5 years across all the CNS drug classes. Hydroxyzine prescription patterns were followed for each patient from birth to age 5. Longitudinal patterns of use were compared in patients receiving only 1 prescription (short-term user), 2–4 prescriptions (intermediate user) and more than 4 prescriptions (long-term user). The frequency of specific mental and neuropsychiatric disorders was evaluated in those 3 groups by tracking the ICD-9 and ICD-10 diagnostic codes in two periods: birth to first dispensation, first dispensation to age 10. We conducted Cochran Armitage trend tests and logistic regression with generalized estimating equation (GEE) models to describe the prescription trends and their association with mental and neuropsychiatric disorders. The GEE logistic regression models were adjusted by patient's age, gender and geographic region of prescription. In a secondary analysis, we used Cox regression to model the incidence of tic development (time from initiation of hydroxyzine treatment to first tic diagnosis) and calculated the hazard ratios associated with cumulated hydroxyzine prescriptions. Statistical analyses were performed using SAS (version 9.4, SAS Inc, Cary NC).

# RESULTS

## Hydroxyzine Prescription Patterns

**Figure 1** shows the distribution of first CNS medications used by children before age 5. Among a total of 24,371(63.6%) children prescribed hydroxyzine, 49.6% have received it before age 2 (**Figure 2**). The median age of starting hydroxyzine treatment was 2.2 years (IQR: 1.2–3.3). Hydroxyzine had been prescribed with a single formula (HYDROXYZINE HCL 10MG/5ML oral solution). This suggests that number of prescriptions up to age 5 can be used to represent cumulative exposure to the medicine. Within all the hydroxyzine users, 1,478 (6.1%) had received more than 4 repetitive prescriptions; 5,659 (23.2%) with 2–4 prescriptions; and 17,324 (70.7%) with one prescription only (**Table 2**). The group of frequent users (prescriptions $\geq$ 5) had an average of 9 prescriptions, corresponding to a maximum exposure of 8.5 grams before attaining school age.

## Indication for Prescribing

Among 24,371 hydroxyzine users, 20,226 (82.9%) had dermatological diagnoses ever before receiving hydroxyzine. By evaluation of the diagnosis codes related to dermatologic disease up to a period of 1 month prior to prescription, we found 68.2% of disorders be known to be associated with pruritus as predominant symptom, such as atopic- and contact dermatitis. 21.5% were ill-defined diagnoses of dermatologic conditions (ICD-9 code 782) and the remaining 10.3% relates to skin disease with an uncertain prevalence of pruritus, such as alopecia and rash diagnoses (**Figure 3**). In summary, the initial prescription of hydroxyzine in children under the age of 5 years was in accord with the licensed indication for pruritic skin conditions, with the obvious intention to alleviate the itch–scrape cycle for improving skin healing and nocturnal sleep.

## Neuropsychiatric Outcome Associated With Hydroxyzine Use

We used age of 5 as endpoint for the last refill of hydroxyzine in order to assess its effect on the most vulnerable phase of neurodevelopment, while age of 10 was chosen as endpoint for tracking disease development, due to the increased likelihood of symptom recognition and diagnosis at school age (**Figure 4**).

Before conducting the comparison in the rates of mental health disorders after receiving hydroxyzine in the three user's groups, we first examined if there were difference in preexisting conditions before treatment initiation. This baseline data showed no significant difference between the user's groups. As an example, tic was diagnosed overall by 1.92% in the whole cohort, with 1.98% in short-term users and 1.96% in frequent users ($p$-value = 0.448).

## Main Analysis

**Table 3** shows the prevalence of mental health diagnoses for all children between initiation of hydroxyzine and age 10. Across the three levels of exposure to hydroxyzine, we found significant increasing trends of disorders in tic, anxiety and disturbance of conduct from short-term to long-term users. Specifically, the proportion of tic disorders goes from 3.77% in short-term user to

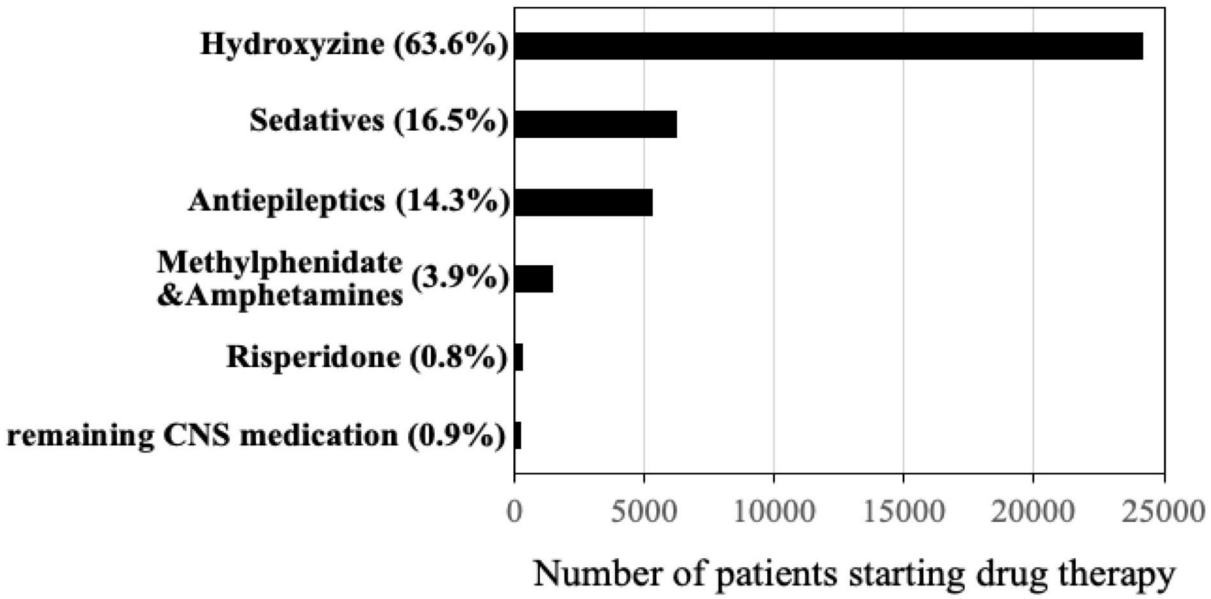


**FIGURE 1 |** Distribution of first psychotropic drugs received under age of 5 years (total $n = 38{,}016$ children) in British Columbia, Canada (years 1997–2017).

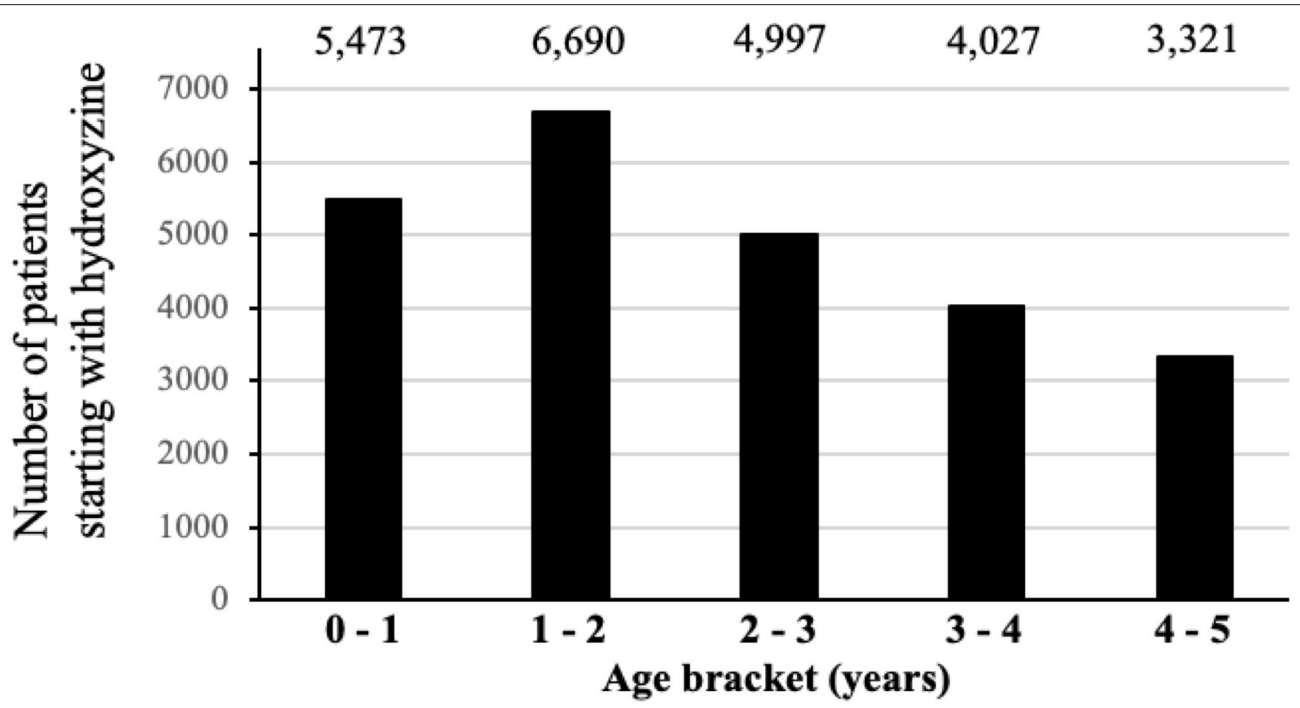


**FIGURE 2 |** Distribution of children receiving hydroxyzine treatment by age level.

5.68% in frequent user; anxiety from 4.21 to 5.41%; and conduct disorder from 5.13 to 6.77%, respectively. After adjusting for age, gender, and health authority regions in multivariate logistic regression models, comparing frequent user of hydroxyzine to short-term user, the odds ratio for tic disorder is 1.44 (95% CI: 1.14–1.83), anxiety 1.28 (95% CI: 1.03–1.63) and disturbance of conduct 1.33 (95% CI: 1.07–1.66) respectively. ADHD and disturbance of emotions showed a tendency for increase with frequent use of hydroxyzine, while learning deficiencies were not altered by the quantity in use of hydroxyzine. Specifically, the

**TABLE 2 |** Frequencies of prescription and accumulative exposure to hydroxyzine in children under age of 5 years.

| | Short-term user 1 prescription | Intermediate user 2–4 prescriptions | Long-term user ≥ 5 prescriptions |
|---|---|---|---|
| Number of patients | 17,234 (70.7%) | 5,659 (23.2%) | 1,478 (6.1%) |
| Number of prescriptions (total) | 17,234 | 14,148 | 13,302 |
| Average number of prescriptions per patient | 1 | 2.5 | 9 |
| Liters of hydroxyzine syrup (average) | 0.47 | 1.17 | 4.23 |
| Max. exposure to hydroxyzine in grams (cumulative) | 0.95 | 2.4 | 8.5 |

proportion of ADHD goes from 6.21% in short-term user to 7.44% in frequent users ($p$-value = 0.164); and disturbance of emotions from 2.28 to 2.98% ($p$-value = 0.112) respectively.

## Sensitivity Analyses

We provide three additional analyses to assess the robustness of our results about the association between frequent hydroxyzine use and mental health disorders. Tic disorder is the primary outcome in these analyses.

## Children With Complete 10 Years Follow-Up Time

In this sub-analysis, we examined the children who had 10 full years of follow-up time (**Table 4**). This strategy allows equal time length for each child to assess their mental health conditions. Despite the reduction of number of patients to 18,758; tic disorders remained significantly higher in frequent users of hydroxyzine compared to short-term user (6.1 vs. 4.1%; odds ratio = 1.40; 95% CI: 1.08–1.81).

## Children With Dermatological Conditions

As our data only include children who received psychotropic medications; children who had dermatological diseases, but not using psychotropic drugs were not available. This makes it difficult to get a complete cohort of children with dermatological diseases. Nevertheless, we conducted the comparison among children with dermatologic conditions (20,226 out of the total 24,371). Tic disorders goes from 3.8% in short-term users to 5.3% in frequent users (odds ratio = 1.38; 95% CI: 1.08-1.80).

## Time From Hydroxyzine Initiation to Tic Development

In this analysis, we used Cox regression to model the time from initiation of hydroxyzine to first tic development. After receiving hydroxyzine, the median time of developing tic is 3.5 years (IQR: 1.5–5.6). By taking short-term users as the reference group, the hazard ratio for users with 2-4 prescriptions was 1.15 (95% CI: 0.99–1.34), and the hazard ratio for users with 5 or more prescriptions was 1.36 (95% CI: 1.07–1.73).

# DISCUSSION

We found that the repetitive use of the first-generation antihistamine drug hydroxyzine in children of preschool age, was associated with elevated rates for tic disorder, anxiety and disorder of conduct up to the age of 10 years, by odds ratios of 1.55 (95%CI: 1.23–1.96); 1.34 (95%CI: 1.05–1.70) and 1.34 (95%CI: 1.08–1.66) respectively. Hereby, repetitive use was defined as a minimum of 5 prescriptions, which correspond to an accumulative exposure to hydroxyzine of more than 3.8 g before the age of 5 years. Review of the literature, such as PubMed, Micromedex, regulatory drug information for hydroxyzine syrup and the pharmacovigilance data analysis tool OpenVigil, did not reveal any information or surveillance data for tic disorders from the use of antihistamine medication. To our knowledge, there is no previous study reporting an association between extensive antihistamine drug use and the subsequent occurrence of tics, conduct- and anxiety disorders. Our investigation was originally driven on findings from using animal data (6, 8) and a human genetic linkage study (7), which demonstrate the involvement of histaminergic neurons in psychomotor behavior.

Study limitations are the absence of an untreated cohort and the lack of information regarding concomitant medication outside of CNS medication and OTC drugs. Therefore, we can't exclude a direct association between tic disorder and the severity of atopic dermatitis. There is evidence that atopic dermatitis is associated with the occurrence of cancer, cardiovascular- and neuropsychiatric disease (17). Although, a recent meta-analysis encompassing 35 studies found that children and adolescents with atopic dermatitis have an overall higher risk of total mental disorders, they did not detect a significant difference in any specific disease (18). Longitudinal studies adjusted for medication usage are missing to confirm a direct causal relationship between atopic dermatitis and neuropsychiatric disorders.

Another limitation in our study is the absence of information on OTC drug usage in Canada, such as diphenhydramine, since a recent publication has shown evidence for early life exposure to diphenhydramine as independent risk factor for the development of ADHD (12). Another limitation is the reliance on the rather general code 307 in the ICD-9 classification to capture tic disorders. The ICD-9 diagnostic codes specific for tic disorder are not billable by health insurances and therefore rarely used in British Columbia. This fact makes it also impossible to further distinguish between Tourette's syndrome (307.23), transient (307.21)- and chronic tic disorders (307.22).

The strengths of this study are firstly the longitudinal character, which allows a follow up of each individual patient from birth to the age of 10 years in drug usage and diagnosis. Second, the combination of drug usage with medical diagnoses, encompassing the entire spectrum of diagnostic codes in hospital- and ambulatory care settings of every patient from

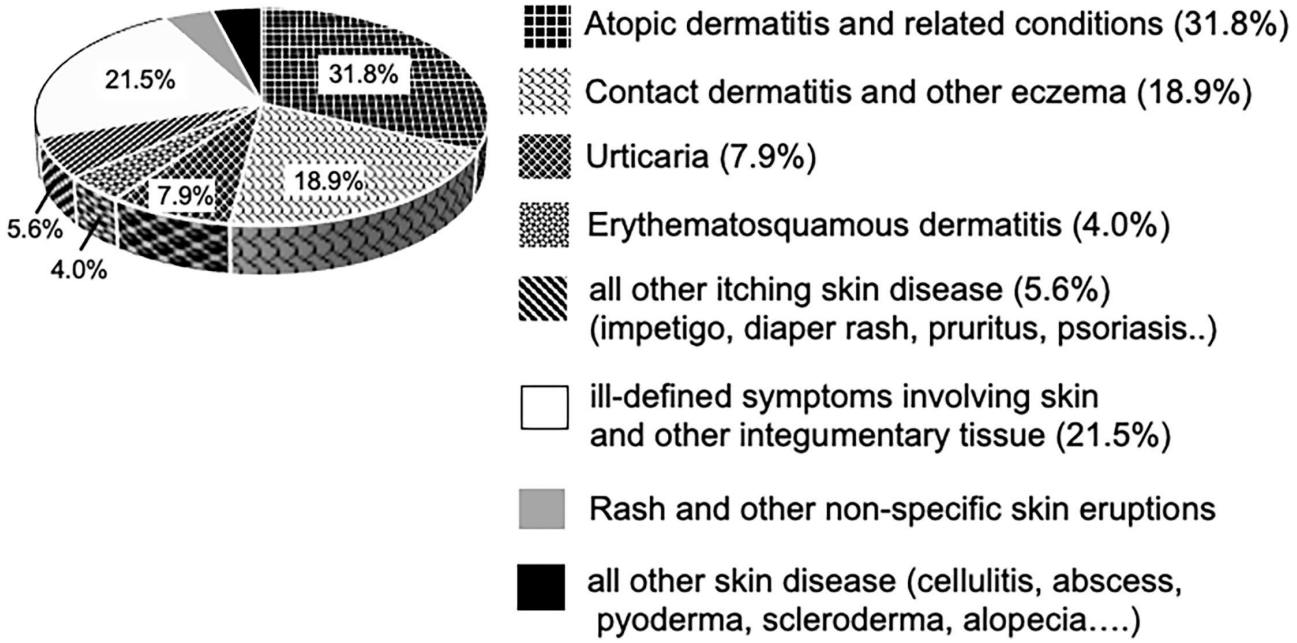


**FIGURE 3 |** Dermatological disease diagnoses in hydroxyzine cohort ($n$ = 20,226 children). Segments in diagram representing diagnoses associated with pruritus, are textured.

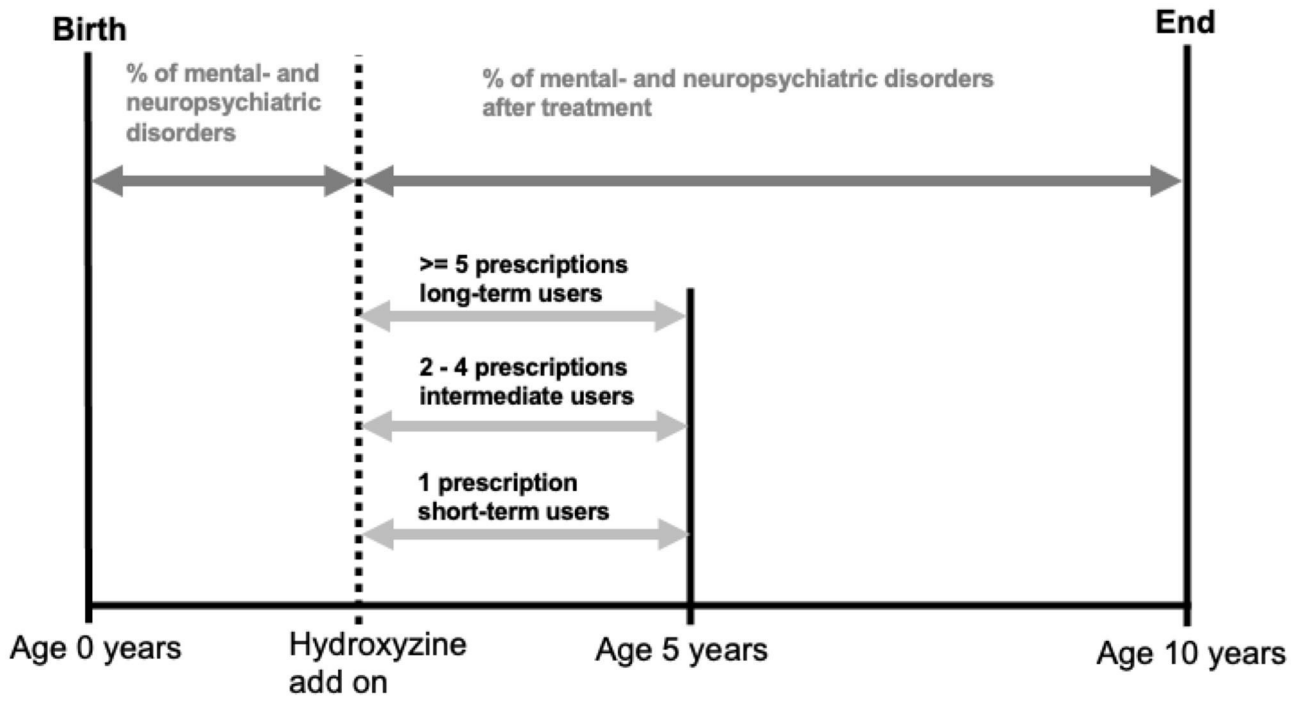


**FIGURE 4 |** Illustration of quantifying hydroxyzine exposure and calculating prevalence of mental and neuropsychiatric disorders.

**TABLE 3 |** Prevalence of psychomotor and mental health disorders between initiation of hydroxyzine and age 10 years.

| | Short-term user $n = 17,234$ | Intermediate user $n = 5,659$ | Long-term user $n = 1,478$ | Trend Test ($p$-value) |
|---|---|---|---|---|
| Tic disorders | 3.77 % | 4.56 % | 5.68 % | 0.0002 |
| Hyperkinetic syndrome of childhood | 6.21 % | 6.18 % | 7.44 % | 0.1649 |
| Intellectual disabilities | 0.35 % | 0.46 % | 0.34 % | 0.4794 |
| Specific delays in development | 7.07 % | 6.8 % | 7.85 % | 0.3734 |
| Anxiety disorders | 4.21 % | 3.85 % | 5.41 % | 0.0286 |
| Disturbance of conduct | 5.13 % | 5.48 % | 6.77 % | 0.0216 |
| Disturbance of emotions | 2.28 % | 2.07 % | 2.98 % | 0.1121 |

**TABLE 4 |** Prevalence of psychomotor and mental health disorders between initiation of hydroxyzine and age 10 years (for children with full 10 years follow-up).

| | Short-term user $n = 13,194$ | Intermediate user $n = 4,390$ | Long-term user $n = 1,174$ | Trend Test ($p$-value) |
|---|---|---|---|---|
| Tic disorders | 4.11 % | 4.62 % | 6.05 % | 0.0046 |
| Hyperkinetic syndrome of childhood | 6.94 % | 6.97 % | 7.75 % | 0.5796 |
| Intellectual disabilities | 0.34 % | 0.48 % | 0.43 % | 0.4229 |
| Specific delays in development | 6.95 % | 6.51 % | 8.01 % | 0.1928 |
| Anxiety disorders | 4.45 % | 3.85 % | 5.37 % | 0.0541 |
| Disturbance of conduct | 6.06 % | 6.08 % | 7.58 % | 0.111 |
| Disturbance of emotions | 2.53 % | 2.26 % | 3.41 % | 0.0813 |

birth to the age of 10 years. Third, the length of the study period provides a sufficient number of patients to improve statistical power, even if subgroups are analyzed. Lastly, the previous published data on animal studies allowed a hypothesis driven investigation of adverse effects, further strengthening the outcome we found in our patient cohorts.

Tic is a neuropsychiatric disease frequently observed in children at school age with an average prevalence of 2.99% (95% CI: 1.60–5.61), largely dependent on age cohort and study conditions applied (19). Although tics may resolve without treatment in most patients, later recurrences in adolescence or adulthood and psychiatric comorbidities are characteristics of this disease. Approximately 85% of children with chronic tic disorder have an associated mental disease, such as anxiety, attention deficit hyperactivity disorder (ADHD), disorders of conduct, obsessive-compulsive disorder or disturbance of emotions (20, 21). Indeed, we could confirm elevations in diagnostic codes for ADHD and anxiety in our cohort of long-time hydroxyzine user. The typical onset of tics occurs between ages 3 and 8 years and greatest severity is reported by the age of 10 years (19). Although in many cases its manifestations largely remit by adulthood, the disorder can persist for life. In our study we have limited the follow up to the age of 10 years, since highest severity and subsequent diagnosis concurs with early school age. It remains to be investigated whether the remission of tics by adulthood, completely resolves the predisposition for the associated psychiatric diseases, such as anxiety and obsessive compulsive disorder.

Hydroxyzine is considered as a selective antagonist for the H1-receptor. While antagonism of H1-receptors by antihistamine drugs at the cerebral cortex and medulla oblongata are considered to be responsible for the sedating effects, the antagonism of histamine at the hippocampal-cortical circuit may interfere with memory formation (22). It remains to be elucidated whether the observed adverse effects on memory of those first-generation antihistamine drugs in elderly patients is mediated via their antagonism of cerebral acetylcholine receptors or rather histamine-receptor antagonism. However, blockade of the neuronal histaminergic innervation in the striatum, as part of the basal ganglia, is most likely responsible for the adverse effect on psychomotor behavior observed in Tourette patients with defect in histidine decarboxylase (7).

The increasing prevalence of atopic dermatitis in infants and toddlers is the driving force behind the frequent use of hydroxyzine and other antihistamines. Atopic dermatitis is associated with sleep disturbance in children due to pruritus (23, 24). Despite the recommendation to prefer second-generation antihistamine drugs, such as loratadine, for treatment of pruritic skin disease (25), the adverse effect of sedation in first-generation antihistamines may be considered as advantage in children with additional sleep problems. Although we were unable to find any evidence in our analysis, we cannot exclude that the prolonged prescription of hydroxyzine in our long-time user cohort is motivated due to the convenience of sedation. Besides hydroxyzine, diphenhydramine is available as sedative first-generation antihistamine in a liquid syrup formulation for infants and toddlers and sold as OTC drug Benadryl®. This drug was introduced in 1946 before current licensing standards, and thus it did not pass the rigorous safety and

efficacy standards required today (26). Such as for hydroxyzine, dosing regimes and age limits are not precisely specified for diphenhydramine.

In summary, our study found an association between the prevalence of mental disorders and the frequency of hydroxyzine prescription in preschool-age children. Controlled studies are required to proof a causal relationship between frequency of hydroxyzine use and the incidence of tics and mental disorders. The safety of hydroxyzine needs to be reassessed and it should be provided for a limited duration only. In addition, alternative therapies for atopic dermatitis and nocturnal itching, such as local antihistamines or corticosteroids, should be considered in preschool-age children. If emphasis is placed on the treatment of sleep disorders, alternative sedatives with minimum disturbance of sleep architecture, such as liquid trazodone formulations may be considered for children with neurological disorders.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

Research Ethics Approval was provided by the University of British Columbia, Children's and Women's Hospital's Research Ethics Board (H18-01247). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.721875/full#supplementary-material

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