Prescription Medication Use Among Children and Adolescents in the United States

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abstract

BACKGROUND AND OBJECTIVES: Information on the use of prescription medications among children and adolescents in the United States is lacking. We estimate the prevalence of prescription medication use, concurrent use, and potential major drug–drug interactions (DDIs) in this population.

METHODS: We conducted descriptive analyses using nationally representative data for people ≤19 years old from NHANES. Data were derived from a medication log administered by direct observation during in-home interviews. Acute medications were used for ≤30 days. Concurrent use was defined as use of ≥2 prescription medications. Micromedex was used to identify potentially major DDIs.

RESULTS: During 2013–2014, 19.8% of children and adolescents used at least 1 prescription medication, and 7.1% used acute medications. Concurrent use of prescription medications was 7.5% overall and was highest among boys 6 to 12 years old (12%) and among boys and girls ages 13 to 19 years old (10% for both). Using pooled 2009–2014 data, we found that 8.2% of concurrent users of prescription medications were at risk for a potentially major DDI. The vast majority of interacting regimens involved antidepressants and were more common among adolescent girls than boys (18.1% vs 6.6%; $P < .05$), driven largely by greater rates of use of acute medications.

CONCLUSIONS: Many US children and adolescents use prescription medications with nearly 1 in 12 concurrent users of prescription medications potentially at risk for a major DDI. Efforts to prevent adverse drug events in children and adolescents should consider the role of interacting drug combinations, especially among adolescent girls.

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WHAT'S KNOWN ON THIS SUBJECT: Adverse drug events remain a leading cause of death among children and adolescents in the United States. Current information on concurrent use of prescription medications, however, is lacking and can be used to better guide efforts to improve their safe use.

WHAT THIS STUDY ADDS: One-fifth of children and adolescents regularly use prescription medications with nearly 1 in 12 concurrent users of prescription medications at risk for a major drug–drug interaction. Efforts to prevent adverse drug events should consider the role of interacting combinations.

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Prescription medications are often indicated for the treatment of common pediatric and adolescent chronic conditions, such as depression and attention-deficit/hyperactivity disorder,[1–3] and acute ailments, such as respiratory tract and sexually transmitted infections.[4,5] In addition to known clinical benefits, many of these medications are associated with rare but serious adverse effects, such as serotonin syndrome, suicidal ideation, and sudden death.[6–12] Despite the implementation of national programs focusing on medication safety in young children, adverse drug events remain a leading cause of injuries and death among both children and adolescents in the United States.[13–16] Current data on the use and concurrent use of prescription medications can be used to better guide efforts to reduce the burden of adverse drug events in this vulnerable population.

Authors of several national studies have evaluated the use of prescription medications in younger populations.[17,18] Despite important insights from these studies, however, they have several limitations. First, these previous studies have not been used to describe the concurrent use of specific types of acute and chronic prescription medications. This information is important because the use of multiple medications is associated with an increased risk for adverse drug events.[19] Second, the authors of these studies do not provide information on the use of prescription medications among boys and girls separately for children and adolescents. This is important because of known differences in the use of specific drug classes between children and adolescents and between boys and girls. Finally, authors of previous studies do not examine the concurrent use of interacting drug regimens.

We used nationally representative, directly observed data from the most recent 6 cycles of the NHANES to examine the use of prescription medications among children and adolescents in the United States overall and stratified by age group and gender. We also examined the prevalence of potentially contraindicated or major drug–drug interactions (DDIs).

METHODS

Participants

NHANES is a nationally representative survey sampled from the US civilian, noninstitutionalized population conducted by the National Center for Health Statistics. Sampling methods are described elsewhere.[20] We restricted our sample to children and adolescents ages 0 to 19 years who responded to the prescription medication questionnaires. A parent or caregiver provided information for survey participants who were <16 years of age and for those who could not answer themselves. We used the 6 most recent NHANES cycles (2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014). A total of 23 179 children and adolescent participants ages 0 to 19 years were sampled over the 10-year period examined. Twenty-seven participants were excluded because of missing medication information, yielding an analytic subsample of 23 152 participants.

Prescription Medication Data

During the household interview participants were asked whether they had taken a prescription medication in the past 30 days.[21] Those who answered "yes" were asked to show the interviewer the medication containers for all the medications used. If no container was available, the participant was asked to name the prescription medication they used. Prescription medication names and therapeutic classes were coded by using Lexicon Plus (Cerner Multum, Inc, Kansas City, MO), a proprietary database of Cerner Multum, Inc.

We differentiated acute versus chronic prescription medication use on the basis of duration of use. For each medication, participants were asked "How long was medication taken?" We defined acute use as the use of a prescription medicine for ≤30 days and all other use as chronic use. For prescription medications used chronically, approximately three-fourths (73%) were used for >365 days. We defined concurrent use as the simultaneous use of at least 2 prescription medications during the past 30 days. We also identified therapeutic classes most commonly used together, overall and by age group and gender.

We used Micromedex to identify potential DDIs for all prescription medications used in children and adolescents during 2013–2014. Micromedex defines contraindicated combinations as "drugs [that] are contraindicated for concurrent use" and major DDIs as "the interaction may be life threatening, require medical intervention to minimize or prevent serious adverse events, or both."

Analyses

We used descriptive statistics to estimate the prevalence of prescription medication and concurrent use for each of the 6 NHANES cycles examined. For analyses stratified by age group and gender, we focused on the most recent cycle (2013–2014); to increase sample size, however, we pooled the most recent 3 cycles (2009–2010, 2011–2012, and 2013–2014) for the analyses of commonly used combinations of therapeutic drug classes and DDIs. We used Taylor linearization methods to incorporate sample weights to adjust for the complex sampling methods in NHANES for estimate prevalence and conduct statistical tests. For most analyses, we used logistic regression

TABLE 1 Prevalence of Prescription Medication Use in Previous 30 Days Among Children and Adolescents in the United States (2013–2014)

	Participants		Prevalence of Use, % (95% CI)		
	n	% (95% CI)	Any Medication	Acute Medication, ≤30 d	Chronic Medication, >30 d
No. participants			786	299	528
Overall	4404		19.8 (17.2–22.8)	7.1 (5.9–8.5)	13.9 (11.7–16.6)
Age group, y					
0–5	1603	25.9 (23.5–28.4)	14.7 (12.4–17.4)**	9.1 (7.6–10.8)*	6.4 (4.8–8.4)**
6–12	1563	37.6 (35.0–40.3)	21.0 (17.7–24.9)	5.5 (4.2–7.2)	16.5 (13.7–19.7)
13–19	1238	36.5 (33.6–39.4)	22.8 (18.0–28.4)	7.1 (5.0–10.0)	17.6 (13.5–22.7)
Gender					
Girl	2161	48.9 (46.3–51.4)	19.3 (16.0–23.2)	8.0 (6.0–10.6)	12.6 (9.7–16.4)
Boy	2243	51.1 (48.6–53.7)	20.3 (17.5–23.4)	6.3 (5.0–7.7)	15.2 (12.9–17.7)
Asthma					
Yes	413	9.7 (8.6–11.0)	58.5 (51.4–65.3)**	11.7 (8.1–16.6)*	51.9 (44.3–59.4)**
No	3577	90.3 (89.0–91.4)	15.9 (13.3–18.8)	6.4 (5.3–7.8)	10.3 (8.2–12.9)
General health condition					
Excellent	1882	43.9 (40.9–46.9)	12.8 (10.5–15.6)**	5.3 (4.1–6.8)*	7.9 (6.0–10.4)**
Very good	1209	29.0 (26.6–31.5)	21.1 (18.0–24.6)	7.5 (6.0–9.2)	14.9 (11.8–18.5)
Good	1054	21.8 (18.7–25.3)	27.1 (21.8–33.2)	8.7 (6.4–11.8)	20.9 (16.3–26.3)
Fair	226	4.6 (3.5–6.0)	39.0 (26.5–53.2)	14.0 (8.9–21.3)	27.4 (16.6–41.8)
Poor	33	0.7 (0.4–1.2)	56.1 (33.2–76.7)	11.5 (3.7–30.4)	50.3 (29.0–71.6)
Race and/or ethnicity					
Non-Hispanic white	1201	53.1 (42.6–63.4)	22.7 (18.2–27.8)*	8.0 (6.1–10.3)	16.3 (12.4–21.1)*
Non-Hispanic African American	1090	13.8 (9.8–19.1)	18.9 (15.1–23.5)	7.3 (5.2–10.1)	13.1 (10.5–16.2)
Hispanic or Latino	1414	23.0 (16.5–31.3)	16.2 (12.2–21.2)	6.3 (4.6–8.6)	10.6 (7.5–14.9)
Other	699	10.0 (8.1–12.4)	14.8 (11.6–18.7)	4.2 (2.7–6.4)	10.9 (8.5–13.9)
Family income-to-poverty ratio, %					
<130	2014	38.3 (31.2–45.9)	21.0 (17.4–25.2)	7.6 (5.8–10.1)	14.3 (11.8–17.3)
130–349	1257	33.8 (29.3–38.7)	21.3 (18.2–24.8)	7.5 (5.5–10.2)	14.9 (11.3–17.3)
>349	803	27.9 (21.2–35.7)	18.2 (15.3–21.6)	6.9 (5.2–9.2)	12.9 (10.6–17.3)
Usual source of care					
Yes	4138	94.0 (92.8–95.0)	20.5 (17.8–23.4)*	7.3 (6.1–8.8)	14.4 (12.0–17.2)**
No	266	6.0 (5.0–7.2)	10.1 (5.3–18.4)	3.4 (1.4–8.3)	6.7 (3.2–13.4)
Insurance status					
No insurance	350	8.1 (6.6–9.8)	6.5 (3.4–11.9)**	2.3 (1.0–5.2)**	4.5 (2.1–9.3)**
Public insurance only	2200	39.6 (33.3–46.2)	21.3 (18.0–25.0)	8.0 (5.9–10.7)	14.8 (12.1–17.9)
Any private insurance	1799	52.3 (45.5–59.1)	20.8 (17.5–24.6)	7.2 (5.9–8.7)	14.7 (11.6–18.6)

Estimates are weighted to account for differential probabilities of selection and differential nonresponse. Acute and chronic medication use are not mutually exclusive (eg, participants can use both types of prescription medications).

** $P < .01$; * $P < .05$ by using χ^2 to test for differences across respondent characteristics.

to test for significance of differences by gender within age groups; to examine gender differences in the concurrent use of therapeutic drug classes and DDIs, the Pearson's χ^2 test was used. We tested for the statistical significance of trends across cycles using logistic regression. We used Stata (Stata Corp, College Station, TX) version 14 to perform all analyses. All *P* values reported are 2-sided. The study was considered exempt by a University of Illinois at Chicago Institutional Review Board.

RESULTS

Table 1 reports prevalence of the use of prescription medications overall and by population characteristics for 2013–2014. Nearly one-fifth (19.8%) of children and adolescents ≤19 years old used at least 1 prescription medication in the previous 30 days; 13.9% used chronic medications, and 7.1% used acute medications. Prescription medication use increased with age, ranging from 14.7% in children ages 0 to 5 years to 22.8% among adolescents (13–19 years). Acute medication use was highest in younger children (9.1%), whereas the use of chronic medications was lowest (6.4%).

Figure 1 depicts the prevalence of the use of prescription medications over time (Fig 1A) and by age group and gender (Fig 1B). The most commonly used prescription medications included respiratory agents, especially bronchodilators (the most common type was albuterol) and psychotherapeutic agents, especially central nervous system (CNS) stimulants (methylphenidate was most common) and antidepressants (fluoxetine was most common) (Table 2). There was a notable decline in the use of acute medications between 2003–2004 and 2013–2014 (10.9% [95% confidence interval (CI), 9.3%–12.9%] to 7.1% [CI, 6.0%–8.4%]; $P < .01$), driven largely by a decrease in the use of antibiotics (7.9% [CI, 6.6%–9.5%] to 4.8% [CI, 3.7%–6.1%]; $P < .01$; Supplemental Table 5).

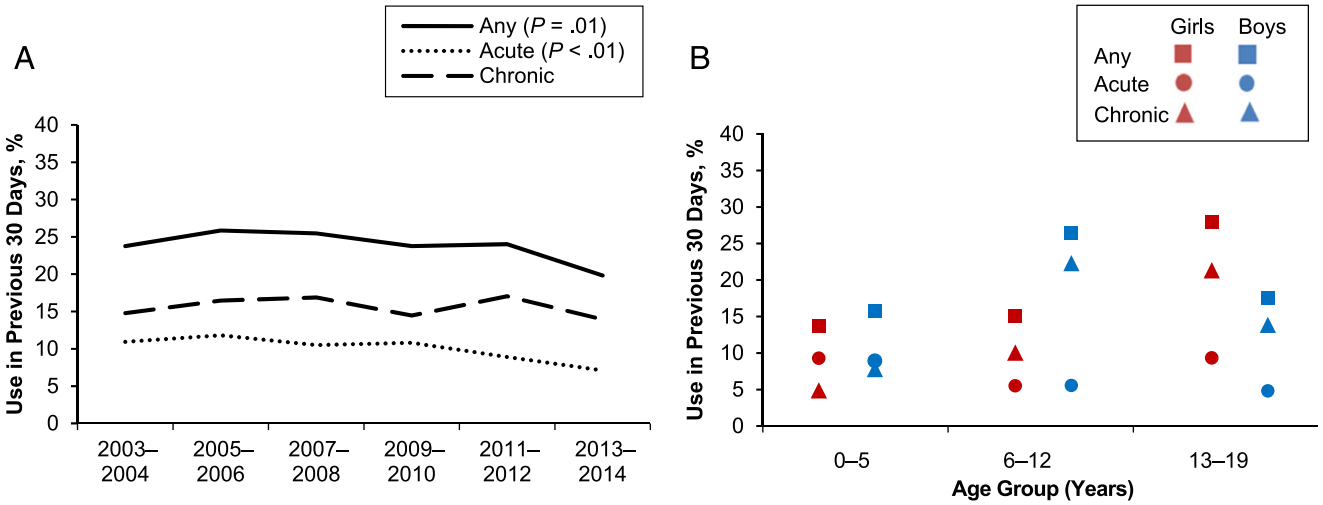

FIGURE 1

Weighted prevalence estimates of prescription medication use over time and by gender and age group among children and adolescents in the United States. Estimates are weighted to account for differential probabilities of selection and differential nonresponse. A, Trends in medication use (2003–2014). B, Medication use by gender and age (2013–2014). Boys ages 6 to 12 years report higher use of any prescription medication and chronic medications than girls ($P < .01$ and $P < .01$, respectively). Adolescent girls (13–19 years) report higher use of any prescription medication, including acute and chronic medications than adolescent boys ($P < .01$, $P < .05$, and $P < .05$, respectively).

The use of prescription medications was highest among adolescent girls (28.0% [CI, 21.3%–35.8%]) and boys ages 6 to 12 (26.5% [CI, 22.5%–30.9%]; Fig 1). Gender differences were also most pronounced in these 2 age groups. Among children ages 6 to 12, boys were nearly twice as likely to use prescription medications compared with girls (26.5% [CI, 22.5%–30.9%] vs 15.1% [CI, 11.8%–19.0%]; $P < .01$); this difference was primarily due to a higher rate of chronic medication use (22.3% [CI, 19.1%–25.9%] vs 10.1% [CI, 7.7%–13.0%]; $P < .01$), especially CNS stimulants (9.4% [CI, 7.2%–12.0%] vs 2.2% [CI, 1.2%–4.1%]; $P < .01$), α-adrenergic agonists (3.3% [CI, 1.9%–5.7%] vs 1.1% [CI, 0.3%–3.5%]; $P < .01$), and leukotriene modifiers (4.0% [CI, 2.5%–6.4%] vs 0.9% [CI, 0.4%–1.9%], respectively; $P < .01$) (Table 2).

During adolescence, however, girls were more likely to use prescription medications than boys; use was 28.0% (CI, 21.3%–35.8%) among girls versus 17.6% (CI, 13.3%–22.9%) among boys ($P < .01$). This difference was due to a higher rate of both acute (9.3% [CI, 5.9%–14.4%] vs 4.8% [CI, 3.2%–7.2%]; $P < .05$) and chronic (21.3% [CI, 15.0%–29.4%] vs 13.8% [CI, 10.2%–18.5%]; $P < .05$) medication use, specifically antidepressants (3.8% [CI, 1.9%–7.6%] vs 1.3% [CI, 0.5%–3.7%]; $P < .01$), antibiotics (6.6% [CI, 3.6%–11.7%] vs 3.5% [CI, 2.0%–6.0%]; $P < .01$), analgesics (3.2% [CI, 1.6%–6.4%] vs 1.2% [CI, 0.6%–2.3%]; $P < .01$), and antiemetics (1.6% [CI, 0.8%–3.3%] vs 0.1% [CI, 0.0%–1.2%]; $P = .06$) (Table 2). Rates of CNS stimulant use, in contrast, were lower in adolescent girls than in boys (1.6% [CI, 0.9%–3.0%] vs 4.3% [CI, 2.3%–7.9%]; $P < .01$).

Concurrent Use of Prescription Medications

Figure 2 depicts the prevalence of the use of concurrent prescription medications over time (Fig 2A) and by age group and gender (Fig 2B). During 2013 and 2014, 7.5% (CI, 6.6%–8.6%) of children and adolescents concurrently used prescription medications, a decrease from 2003–2004 (9.9% [CI, 9.1%–10.8%]; $P < .01$). The concurrent use of prescription medications varied across age groups for both boys and girls and was substantially more common among boys ages 6 to 12 than among girls in this age group (11.9% [CI, 8.8%–15.8%] vs 4.7% [CI, 3.4%–6.7%]; $P < .01$).

Among concurrent users of prescription medications, combinations that involved respiratory agents, such as bronchodilators and leukotriene modifiers, and psychotropic medications, including antidepressants, atypical antipsychotics, and CNS stimulants, were the most prevalent (Table 3). More than 20% (23.7% [CI, 11.1%–43.8%]) of boys ages 6 to 12 and more than half (57.9% [CI, 35.1%–77.7%]) of adolescent boys who used CNS stimulants concurrently used ≥2 other psychotropic medications. Combinations that involved antidepressants were most prevalent among adolescent girls; among these antidepressant users, 51.2% [CI, 19.4%–82.6%] were concurrently using at least 2 psychotropic medications.

Potential Major DDIs

Among concurrent users of ≥2 prescription medications during 2013–2014 ($N = 301$), a total of 156

TABLE 2 Weighted Prevalence in the Use of Prescription Medications in the Previous 30 Days by Therapeutic Drug Class Among Children and Adolescents in the United States, Overall and by Gender and Age Group (2013–2014)

	Prevalence of Use, % (95% CI)						
	Overall, *n* = 4404	0–5 y		6–12 y		13–19 y	
		Girls (*n* = 775)	Boys (*n* = 828)	Girls (*n* = 746)	Boys (*n* = 817)	Girls (*n* = 640)	Boys (*n* = 598)
Respiratory agents	6.8 (5.8–8.0)	3.9 (2.3–6.6)	5.1 (3.3–7.8)**	5.7 (4.1–8.0)	11.5 (8.9–14.7)*	6.4 (4.2–9.7)	7.0 (4.9–9.9)
Bronchodilators	3.5 (3.0–4.1)	2.7 (1.5–4.7)	2.7 (1.5–4.8)	3.0 (1.7–5.5)	5.5 (4.3–6.9)*	3.4 (1.7–7.0)[a]	3.2 (2.1–5.0)
Albuterol	3.0 (2.5–3.6)	2.6 (1.5–4.5)	2.5 (1.4–4.5)	2.6 (1.4–4.8)	4.5 (3.1–6.6)	3.1 (1.4–6.9)[a]	2.6 (1.8–3.6)
Levalbuterol	0.3 (0.1–0.6)[a]	0.2 (0.0–1.5)[a]	0.2 (0.0–0.8)[a]	0.4 (0.1–2.5)[a]	0.4 (0.2–1.0)[a]	0.1 (0.0–1.0)[a]	0.2 (0.1–1.1)[a]
Fluticasone and salmeterol	0.1 (0.1–0.3)[a]	0.0	0.1 (0.0–0.8)[a]	0.0	0.4 (0.2–0.8)[a]	0.3 (0.1–1.5)[a]	0.0
Antihistamines	1.8 (1.3–2.6)	0.9 (0.3–2.6)[a]	1.4 (0.7–2.7)[a]	2.1 (1.1–4.0)[a]	3.2 (2.1–5.0)	1.0 (0.7–1.7)	2.0 (0.8–5.0)[a]
Cetirizine	1.0 (0.6–1.6)	0.9 (0.3–2.6)[a]	0.8 (0.5–1.4)	0.9 (0.4–2.3)[a]	1.3 (0.7–2.4)	0.7 (0.4–1.4)[a]	1.2 (0.3–4.2)[a]
Loratadine	0.4 (0.3–0.7)	0.0	0.1 (0.0–0.7)[a]	0.3 (0.1–1.4)[a]	1.2 (0.7–2.0)	0.1 (0.0–0.6)[a]	0.7 (0.2–2.8)[a]
Cyproheptadine	0.2 (0.1–0.6)[a]	0.0	0.1 (0.0–0.9)[a]	0.0	0.8 (0.2–2.7)[a]	0.1 (0.0–1.0)[a]	0.0
Leukotriene modifiers	1.7 (1.3–2.2)	0.3 (0.1–1.0)[a]	0.8 (0.4–1.7)[a]**	0.9 (0.4–1.9)[a]	4.0 (2.5–6.4)**	1.9 (1.1–3.1)	1.8 (0.8–3.7)[a]
Montelukast	1.7 (1.3–2.2)	0.3 (0.1–1.0)[a]	0.8 (0.4–1.7)[a]**	0.9 (0.4–1.9)[a]	4.0 (2.5–6.4)**	1.9 (1.1–3.1)	1.8 (0.8–3.7)[a]
Respiratory inhalant products	1.3 (0.8–1.9)	0.4 (0.1–1.5)[a]	1.3 (0.6–3.0)[a]	1.0 (0.4–2.4)[a]	3.1 (2.1–4.5)	0.2 (0.0–1.0)[a]	1.4 (0.5–3.7)[a]
Beclomethasone	0.5 (0.3–0.9)	0.1 (0.0–0.6)[a]	0.7 (0.2–2.4)[a]	0.4 (0.1–1.1)[a]	1.2 (0.5–2.4)[a]*	0.1 (0.0–1.0)[a]	0.6 (0.1–3.1)[a]
Fluticasone	0.7 (0.4–1.2)	0.3 (0.1–1.1)[a]	0.6 (0.2–1.9)[a]	0.6 (0.2–1.6)[a]	1.6 (0.9–2.7)	0.1 (0.0–0.7)[a]	0.7 (0.2–2.8)[a]
Psychotherapeutic agents[b]	5.0 (4.0–6.3)	0.1 (0.0–0.6)[a]	1.5 (0.5–5.0)[a]	3.5 (1.8–6.7)[a]	10.9 (8.7–13.6)**	6.4 (4.1–9.9)	5.7 (3.4–9.5)
CNS stimulants	3.3 (2.5–4.4)	0.1 (0.0–0.6)[a]	1.1 (0.3–4.3)[a]	2.2 (1.2–4.1)	9.4 (7.2–12.0)**	1.6 (0.9–3.0)	4.3 (2.3–7.9)**
Methylphenidate	1.6 (1.0–2.4)	0.1 (0.0–0.6)[a]	0.2 (0.0–1.5)[a]	0.5 (0.1–2.5)[a]	5.2 (3.2–8.3)**	0.8 (0.2–2.9)[a]	1.8 (0.8–3.9)[a]
Lisdexamfetamine	0.7 (0.5–1.0)	0.0	0.0	0.8 (0.2–2.8)[a]	1.7 (1.0–3.2)	0.1 (0.0–1.0)[a]	1.1 (0.4–2.8)[a]
Amphetamine and dextroamphetamine	0.4 (0.2–0.9)[a]	0.0	0.6 (0.1–5.1)[a]	0.3 (0.1–1.5)[a]	0.9 (0.4–2.0)[a]	0.3 (0.1–1.0)[a]	0.4 (0.1–2.1)[a]
Antidepressants	1.2 (0.7–2.0)	0.0	0.0	0.1 (0.0–0.7)[a]	1.3 (0.5–3.5)[a]*	3.8 (1.9–7.6)[a]	1.3 (0.5–3.7)[a]**
Fluoxetine	0.3 (0.2–0.6)	0.0	0.0	0.0	0.5 (0.2–1.6)[a]	0.7 (0.2–2.1)[a]	0.5 (0.2–1.6)[a]
Escitalopram	0.2 (0.1–0.9)[a]	0.0	0.0	0.0	0.0	0.8 (0.1–4.9)[a]	0.5 (0.1–3.9)[a]
Trazodone	0.2 (0.0–0.8)[a]	0.0	0.0	0.1 (0.0–0.7)[a]	0.0	0.9 (0.2–4.6)[a]	0.0
Antipsychotics	0.9 (0.7–1.1)	0.0	0.0	0.8 (0.3–2.7)[a]	1.9 (1.1–3.3)*	1.2 (0.6–2.5)[a]	1.1 (0.3–3.3)[a]
Aripiprazole	0.2 (0.1–0.5)[a]	0.0	0.0	0.0	0.5 (0.3–0.7)	0.4 (0.1–1.7)[a]	0.4 (0.1–3.3)[a]
Risperidone	0.4 (0.3–0.7)	0.0	0.0	0.8 (0.3–2.7)[a]	0.9 (0.3–3.1)[a]	0.1 (0.0–0.9)[a]	0.6 (0.2–2.5)[a]
Quetiapine	0.2 (0.1–0.4)	0.0	0.0	0.0	0.7 (0.4–1.1)	0.5 (0.2–1.9)[a]	0.0
Anticonvulsants	0.8 (0.3–1.9)[a]	0.0	0.2 (0.0–1.5)[a]	1.0 (0.3–3.6)[a]	0.4 (0.1–1.4)[a]	1.7 (0.5–5.6)[a]	1.2 (0.4–3.8)[a]
Topiramate	0.3 (0.1–1.1)[a]	0.0	0.2 (0.0–1.5)[a]	0.3 (0.2–0.5)	0.0	1.1 (0.2–6.7)[a]	0.3 (0.1–1.5)[a]
Lamotrigine	0.3 (0.1–0.9)[a]	0.0	0.0	0.0	0.0	0.9 (0.2–4.6)[a]	0.6 (0.1–3.4)[a]
Divalproex sodium	0.1 (0.0–0.5)[a]	0.0	0.0	0.0	0.2 (0.0–1.7)[a]	0.2 (0.0–1.3)[a]	0.2 (0.0–1.1)[a]
Anxiolytics, sedatives, and hypnotics	0.3 (0.2–0.4)	0.0	0.3 (0.0–2.4)[a]	0.2 (0.1–0.4)[a]	0.1 (0.0–0.4)[a]	0.8 (0.2–2.9)[a]	0.2 (0.0–1.2)[a]**
Hydroxyzine	0.2 (0.1–0.4)	0.0	0.3 (0.0–2.4)[a]	0.2 (0.1–0.4)[a]	0.1 (0.0–0.4)[a]	0.7 (0.2–3.1)[a]	0.1 (0.0–0.9)[a]
Antibiotics	4.8 (3.7–6.2)	7.0 (5.2–9.4)	5.8 (4.5–7.4)	3.0 (1.6–5.6)	3.5 (2.0–6.1)*	6.6 (3.6–11.7)	3.5 (2.0–6.0)**
Penicillins	2.2 (1.6–3.0)	4.5 (3.3–6.1)	3.1 (2.2–4.4)	1.1 (0.5–2.6)[a]	1.4 (0.7–2.8)[a]	2.6 (1.1–6.0)[a]	1.1 (0.3–3.8)[a]**
Amoxicillin	1.8 (1.4–2.4)	4.4 (3.2–6.1)	2.9 (2.0–4.3)	0.6 (0.2–1.6)[a]	1.4 (0.7–2.8)[a]	1.1 (0.6–2.0)	1.1 (0.3–3.8)[a]
Macrolide derivatives	0.8 (0.5–1.4)	0.2 (0.0–1.0)[a]	1.0 (0.4–2.3)[a]	1.2 (0.4–3.8)[a]	1.4 (0.5–3.6)[a]	0.9 (0.3–2.8)[a]	0.2 (0.0–1.0)[a]*
Azithromycin	0.8 (0.5–1.2)	0.2 (0.0–1.0)[a]	0.9 (0.4–2.1)[a]	1.2 (0.4–3.8)[a]	1.4 (0.5–3.6)[a]	0.5 (0.1–2.9)[a]	0.2 (0.0–1.0)[a]
Cephalosporins	0.5 (0.2–1.3)[a]	0.7 (0.2–3.1)[a]	0.9 (0.3–2.7)[a]	0.2 (0.0–1.1)[a]	0.3 (0.0–2.3)[a]	0.6 (0.1–4.9)[a]	0.5 (0.1–2.8)[a]
Cefdinir	0.2 (0.1–0.6)[a]	0.2 (0.0–1.3)[a]	0.2 (0.1–0.8)[a]	0.1 (0.0–1.2)[a]	0.3 (0.0–2.3)[a]	0.0	0.4 (0.1–3.3)[a]
Topical agents	3.0 (2.5–3.5)	1.2 (0.6–2.3)	1.7 (1.0–2.9)	1.9 (1.0–3.5)	4.9 (3.2–7.5)	3.7 (1.8–7.4)[a]	3.7 (1.7–8.0)[a]
Nasal preparations	1.5 (1.0–2.3)	0.1 (0.0–1.3)[a]	0.7 (0.3–1.5)[a]	0.5 (0.2–1.3)[a]	4.2 (2.5–7.1)**	0.8 (0.2–3.1)[a]	2.0 (0.7–5.5)[a]
Fluticasone nasal	1.0 (0.6–1.7)	0.0	0.3 (0.1–1.6)[a]	0.3 (0.1–1.2)[a]	2.4 (1.1–4.9)[a]*	0.6 (0.1–3.0)[a]	2.0 (0.7–5.5)[a]
Mometasone nasal	0.5 (0.2–0.9)[a]	0.1 (0.0–1.3)[a]	0.2 (0.0–1.4)[a]	0.1 (0.0–0.7)[a]	1.7 (0.7–4.3)[a]*	0.2 (0.0–2.0)[a]	0.2 (0.0–0.7)[a]
Dermatological agents	1.2 (0.7–1.9)	0.5 (0.2–1.2)[a]	0.6 (0.2–1.5)[a]	1.4 (0.7–3.0)[a]	0.7 (0.3–1.7)[a]**	2.8 (1.1–6.9)[a]	0.9 (0.2–3.1)[a]
Tretinoin topical	0.2 (0.1–0.7)[a]	0.0	0.0	0.1 (0.0–1.0)[a]	0.0	0.7 (0.1–4.4)[a]	0.3 (0.0–2.6)[a]
Hormones or hormone modifiers	2.1 (1.5–2.8)	1.0 (0.5–2.1)[a]	1.1 (0.5–2.6)[a]**	1.2 (0.5–2.5)[a]	0.9 (0.2–3.3)[a]	7.2 (5.3–9.5)	0.7 (0.2–2.1)[a]**
Contraceptives[c]	2.5 (1.8–3.5)	0.0	0.0	0.0	0.0	7.0 (5.2–9.3)	0.0
Ethinyl estradiol–norethindrone[c]	0.9 (0.4–2.1)[a]	0.0	0.0	0.0	0.0	2.5 (1.1–5.6)[a]	0.0
Adrenal cortical steroids	0.6 (0.4–1.0)	1.0 (0.5–2.1)[a]	0.9 (0.4–2.2)[a]**	0.7 (0.2–2.4)[a]	0.4 (0.1–1.8)[a]	0.2 (0.0–1.0)[a]	0.6 (0.2–2.0)[a]**
Budesonide	0.3 (0.2–0.7)[a]	0.5 (0.2–1.6)[a]	0.4 (0.2–1.2)[a]	0.5 (0.1–2.6)[a]	0.4 (0.1–1.9)[a]	0.1 (0.0–1.0)[a]	0.1 (0.0–1.0)[a]

TABLE 2 Continued

	Overall, *n* = 4404	Prevalence of Use, % (95% CI)					
		0–5 y		6–12 y		13–19 y	
		Girls (*n* = 775)	Boys (*n* = 828)	Girls (*n* = 746)	Boys (*n* = 817)	Girls (*n* = 640)	Boys (*n* = 598)
Gastrointestinal agents	1.5 (0.8–2.6)	1.7 (1.0–3.0)	1.6 (0.9–2.6)	1.0 (0.4–2.7)[a]	1.4 (0.5–3.9)[a]	2.0 (0.8–4.9)[a]	1.3 (0.4–3.7)[a**]
PPIs	0.6 (0.3–1.3)[a]	0.2 (0.0–0.9)[a]	0.5 (0.2–1.3)[a]	0.1 (0.0–0.7)[a]	0.6 (0.1–2.8)[a]	1.1 (0.4–3.1)[a]	1.0 (0.2–4.6)[a]
Omeprazole	0.3 (0.1–1.2)[a]	0.1 (0.0–1.0)[a]	0.1 (0.0–0.6)[a]	0.1 (0.0–0.7)[a]	0.6 (0.1–2.8)[a]	0.1 (0.0–0.8)[a]	0.9 (0.2–4.8)[a]
H_2 antagonist	0.5 (0.3–1.0)[a]	1.4 (0.7–3.1)[a]	1.0 (0.6–1.9)	0.5 (0.1–2.1)[a]	0.3 (0.1–1.2)[a]	0.2 (0.0–1.3)[a]	0.1 (0.0–0.8)[a**]
Ranitidine	0.5 (0.3–1.0)[a]	1.4 (0.6–3.1)[a]	1.0 (0.6–1.9)	0.5 (0.1–2.1)[a]	0.3 (0.1–1.2)[a]	0.2 (0.0–1.3)[a]	0.1 (0.0–0.8)[a]
Antiadrenergic agents, centrally acting	1.1 (0.8–1.6)	0.0	0.2 (0.0–1.3)[a]	1.1 (0.3–3.5)[a]	3.3 (1.9–5.7)[**]	0.2 (0.0–1.9)[a]	1.4 (0.5–4.1)[a**]
Clonidine	0.8 (0.5–1.3)	0.0	0.2 (0.0–1.3)[a]	1.0 (0.3–3.5)[a]	2.1 (0.8–5.0)[a]	0.2 (0.0–1.9)[a]	0.9 (0.2–4.5)[a]
Guanfacine	0.4 (0.2–0.9)[a]	0.0	0.0	0.2 (0.0–0.8)[a]	1.5 (0.6–3.6)[a**]	0.0	0.5 (0.1–2.3)[a]
Analgesics	1.1 (0.7–1.6)	0.2 (0.0–0.8)[a]	1.0 (0.4–2.3)[a]	0.6 (0.2–1.9)[a]	0.2 (0.0–0.7)[a]	3.2 (1.6–6.4)[a]	1.2 (0.6–2.3)[a*]
Nonsteroidal anti-inflammatory agents	0.7 (0.4–1.2)	0.2 (0.0–0.8)[a]	0.9 (0.4–2.2)[a*]	0.3 (0.1–1.1)[a]	0.0	1.8 (0.8–4.2)[a]	1.0 (0.5–2.2)[a]
Diclofenac	0.1 (0.0–0.8)[a]	0.0	0.0	0.0	0.0	0.6 (0.1–4.9)[a]	0.1 (0.0–0.7)[a]
Narcotics	0.4 (0.2–0.8)	0.0	0.1 (0.0–0.6)[a*]	0.5 (0.1–1.8)[a]	0.2 (0.0–0.7)[a]	1.5 (0.7–3.5)[a]	0.2 (0.0–0.9)[a**]
Hydrocodone	0.3 (0.2–0.7)[a]	0.0	0.1 (0.0–0.6)[a]	0.2 (0.0–1.0)[a]	0.1 (0.0–0.8)[a]	1.3 (0.5–3.4)[a]	0.2 (0.0–0.9)[a]
Oxycodone	0.2 (0.1–0.5)[a]	0.0	0.0	0.3 (0.0–2.2)[a]	0.0	0.8 (0.3–2.6)[a]	0.0
Antiemetic agents	0.7 (0.5–1.1)	0.5 (0.1–1.6)[a]	1.1 (0.3–3.3)[a]	0.8 (0.3–2.4)[a]	0.2 (0.1–0.6)[a]	1.6 (0.8–3.3)[a]	0.1 (0.0–1.2)[a]
Ondansetron	0.5 (0.3–0.8)	0.1 (0.0–1.1)[a]	0.7 (0.2–2.8)[a]	0.5 (0.1–2.3)[a]	0.1 (0.0–0.5)[a]	1.1 (0.4–3.2)[a]	0.1 (0.0–1.2)[a]
Diphenhydramine	0.2 (0.1–0.3)[a]	0.2 (0.0–0.8)[a]	0.0	0.1 (0.0–1.2)[a]	0.2 (0.0–0.8)[a]	0.5 (0.2–1.6)[a]	0.0
Promethazine	0.1 (0.0–0.4)[a]	0.1 (0.0–0.9)[a]	0.4 (0.1–1.8)[a*]	0.1 (0.0–1.0)[a]	0.0	0.0	0.0
Antidiabetic agents	0.5 (0.2–1.2)[a]	0.0	0.0	0.1 (0.0–0.7)[a]	1.3 (0.3–5.2)[a]	1.4 (0.5–3.7)[a]	0.1 (0.0–1.0)[a]
Metformin	0.2 (0.1–0.6)[a]	0.0	0.0	0.0	0.1 (0.0–0.4)[a]	1.1 (0.3–3.7)[a]	0.0
Insulin	0.3 (0.1–0.8)[a]	0.0	0.0	0.1 (0.0–0.7)[a]	1.2 (0.3–5.3)[a*]	0.3 (0.1–0.6)[a]	0.1 (0.0–1.0)[a]

Estimates are weighted to account for differential probabilities of selection and differential nonresponse. H_2, histamine$_2$; PPI, proton pump inhibitors.

[a] Estimates are unreliable; relative SE >30%.

[b] Derived from Multum classification of psychotherapeutic agents, CNS stimulants, anticonvulsants, and anxiolytics, sedatives, and hypnotics.

[c] Among girls only.

** $P < .01$; * $P < .05$ by using logistic regressions to test differences between girls and boys.

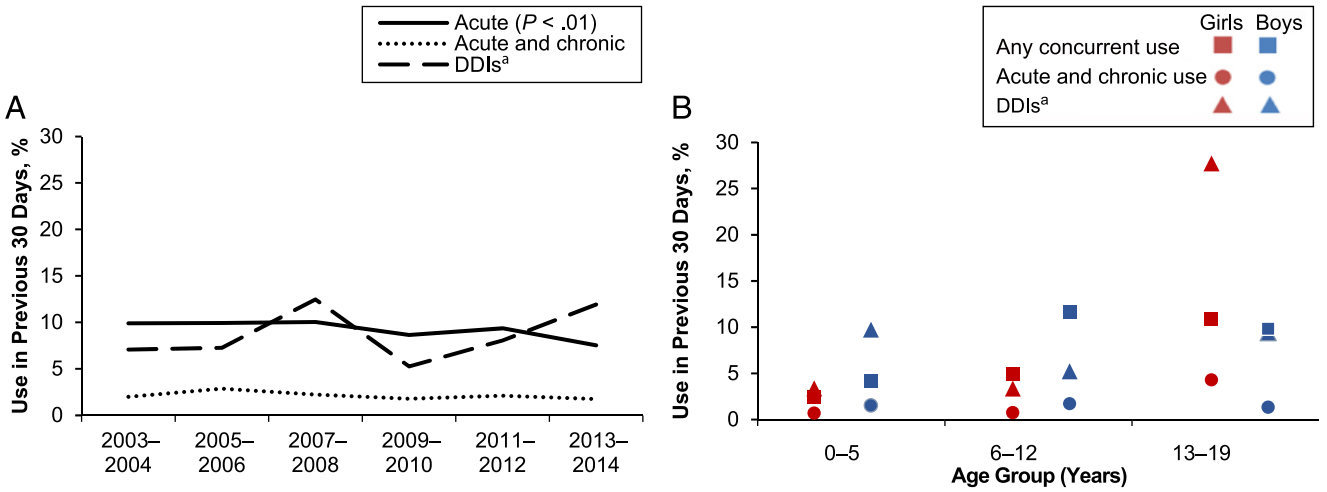

FIGURE 2

Weighted prevalence estimates of concurrent (≥2) prescription medication use over time and by gender and age group among children and adolescents in the United States. Estimates are weighted to account for differential probabilities of selection and differential nonresponse. A, Trends in concurrent medication use (2013–2014). B, Concurrent use by gender and age group (2013–2014). Boys ages 0 to 5 and 6 to 12 years report higher prevalence of concurrent medication use than girls ($P = .05$ and $P < .05$, respectively). [a] Prevalence of potential DDIs restricted to children who concurrently use ≥2 prescription medications; because of the small number of DDI cases, trend estimates are unstable.

unique prescription medications were used (Supplemental Table 6). Using Micromedex, a total of 826 potential DDIs (contraindicated [$n = 29$] or potentially major [$n = 797$]) for these 156 medications were identified. In the pooled 2003–2014 sample, 101 unique combinations of these potential DDIs were used by 158 people (Supplemental Table 7). In the pooled 2009–2014 sample, 63 unique DDI combinations were used

TABLE 3 Most Common Prescription Medication Combinations Used Among Children and Adolescents Concurrently Using Prescription Medications Overall and by Gender and Age Group in the United States (2009–2014)

	Prevalence of Combinations, No. (%) [95% CI]						
	Overall, *n* = 993	0–5 y		6–12 y		13–19 y	
		Girls (*n* = 112)	Boys (*n* = 159)	Girls (*n* = 156)	Boys (*n* = 244)	Girls (*n* = 170)	Boys (*n* = 152)
Bronchodilators–respiratory inhalants	123 (10.5) [7.9–13.7]	12 (10.1) [5.1–19.3][a]	21 (21.4) [13.0–33.1]*	24 (13.8) [6.6–26.6][a]	38 (12.0) [8.1–17.4]	11 (3.5) [1.7–7.0][a]	17 (9.2) [5.1–15.9]**
Bronchodilators–leukotriene modifiers	99 (8.2) [6.3–10.4]	6 (4.6) [2.1–10.0][a]	12 (6.6) [3.0–13.8][a]	20 (8.9) [5.6–13.8]	36 (12.7) [8.4–18.6]	11 (6.6) [2.6–15.8][a]	14 (6.7) [3.5–12.6][a]
Bronchodilators–adrenal cortical steroids	96 (6.9) [5.1–9.2]	24 (15.8) [10.1–23.9]	29 (13.8) [8.0–22.7]	14 (10.4) [4.6–21.8][a]	18 (4.4) [2.7–7.2]**	6 (3.1) [1.1–8.3][a]	5 (5.1) [2.0–12.1][a]
CNS stimulants–α adrenergic blockers	54 (5.4) [3.7–7.7]	0 (0.0)	1 (0.4) [0.1–3.4][a]	8 (4.1) [1.8–9.2][a]	33 (13.8) [8.5–21.5]***	0 (0.0)	12 (8.7) [4.5–16.1][a]***
Bronchodilators–nasal preparations	56 (5.3) [3.6–7.7]	1 (0.9) [0.1–6.5][a]	7 (4.6) [1.8–11.5][a]*	9 (3.5) [1.6–7.6][a]	25 (9.1) [5.4–14.9]*	5 (3.2) [0.7–13.0][a]	9 (6.7) [3.2–13.7][a]
Leukotriene modifiers–nasal preparations	47 (4.9) [3.2–7.3]	0 (0.0)	4 (2.4) [0.9–6.3][a]	11 (6.8) [3.1–14.3][a]	21 (8.9) [5.5–14.1]	2 (2.5) [0.4–14.0][a]	9 (5.2) [2.3–11.6][a]
Bronchodilators–antihistamines	50 (3.7) [2.6–5.1]	5 (4.2) [1.6–10.6][a]	4 (2.0) [0.7–6.0][a]	12 (6.1) [3.6–10.1]	18 (5.7) [3.2–9.9]	5 (2.3) [0.8–6.3][a]	6 (2.5) [1.2–5.0][a]
CNS stimulants–atypical antipsychotics	38 (3.5) [2.3–5.2]	0 (0.0)	0 (0.0)	5 (4.8) [2.1–10.4][a]	24 (8.2) [4.8–13.9]	2 (0.6) [0.1–2.5][a]	7 (4.5) [1.8–10.6][a]***
Nasal preparations–antihistamines	35 (3.4) [2.3–5.1]	0 (0.0)	0 (0.0)	6 (3.0) [1.5–5.7][a]	20 (8.2) [4.8–13.6]	2 (0.6) [0.1–2.8][a]	7 (5.3) [2.5–11.0][a]***
CNS stimulants–antidepressants	33 (3.4) [2.1–5.6]	0 (0.0)	0 (0.0)	7 (3.6) [1.4–8.5][a]	13 (5.4) [2.8–10.1][a]	6 (2.5) [0.7–8.3][a]	7 (5.6) [2.0–14.8][a]
Leukotriene modifiers–respiratory inhalants	42 (3.0) [2.1–4.4]	3 (2.1) [0.6–6.8][a]	5 (2.7) [1.1–6.5][a]	6 (2.4) [0.9–6.2][a]	19 (6.9) [3.8–12.5]**	4 (1.0) [0.3–2.8][a]	5 (2.3) [0.9–5.5][a]
Atypical antipsychotic–α adrenergic blockers	23 (2.6) [1.7–4.1]	0 (0.0)	0 (0.0)	2 (2.3) [0.5–10.8][a]	15 (7.2) [4.0–12.5]	1 (0.7) [0.1–4.7][a]	5 (2.9) [1.0–8.0][a]
CNS stimulants–antihistamines	24 (2.5) [1.3–4.6][a]	0 (0.0)	0 (0.0)	7 (4.2) [1.7–10.2][a]	13 (7.5) [3.5–15.4][a]	2 (0.4) [0.1–3.1][a]	2 (0.6) [0.1–2.9][a]
Bronchodilators–penicillins	38 (2.4) [1.6–3.5]	16 (12.0) [7.2–19.4]	12 (6.0) [3.2–10.9][a]*	5 (1.9) [0.7–5.6][a]	3 (0.7) [0.2–2.2][a]	1 (1.3) [0.2–9.1][a]	1 (0.4) [0.1–3.2][a]
Bronchodilators–CNS stimulants	26 (2.3) [1.4–3.9]	0 (0.0)	0 (0.0)	8 (4.2) [1.7–9.8][a]	12 (3.2) [1.9–5.4]	1 (1.9) [0.3–12.9][a]	5 (2.8) [0.8–8.9][a]
Antidepressants–anticonvulsants	11 (1.8) [0.8–4.4][a]	0 (0.0)	0 (0.0)	2 (3.0) [0.7–12.3][a]	2 (0.5) [0.1–2.1][a]*	5 (3.5) [0.8–14.0][a]	2 (2.1) [0.4–9.6][a]
Respiratory inhalants–adrenal cortical steroids	14 (1.7) [0.8–3.6][a]	2 (1.7) [0.4–7.1][a]	2 (1.7) [0.4–7.1][a]	4 (4.6) [1.0–18.7][a]	3 (0.9) [0.3–2.9][a]*	2 (0.9) [0.2–4.1][a]	1 (1.6) [0.2–11.0][a]
CNS stimulants–penicillins	22 (1.6) [0.9–3.0]	6 (4.9) [1.8–12.4][a]	5 (2.3) [0.9–5.8][a]	4 (1.9) [0.7–5.1][a]	3 (1.3) [0.4–4.0][a]	3 (1.7) [0.4–7.4][a]	1 (0.4) [0.0–2.9][a]
Narcotic analgesics–NSAIDs	13 (1.6) [0.7–3.6][a]	0 (0.0)	1 (0.2) [0.0–1.7][a]	2 (1.0) [0.2–4.4][a]	0 (0.0)	5 (2.4) [0.7–7.7][a]	5 (4.2) [1.3–13.1][a]
Contraceptives–antidepressants[b]	6 (2.9) [1.2–7.0][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.3) [2.2–12.0][a]	0 (0.0)
Adrenal cortical steroids–leukotriene modifiers	22 (1.3) [0.8–2.2]	3 (1.9) [0.6–5.8][a]	7 (3.9) [1.5–9.6][a]	3 (1.1) [0.3–3.4][a]	5 (1.3) [0.4–3.5][a]	3 (0.9) [0.3–3.1][a]	1 (0.3) [0.0–2.5][a]
Bronchodilators–antidepressants	8 (1.3) [0.5–3.1][a]	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6) [0.2–2.1][a]	4 (4.0) [1.3–11.2][a]	1 (0.6) [0.1–4.7][a]*
Narcotic analgesics–penicillins	11 (1.2) [0.6–2.5][a]	0 (0.0)	0 (0.0)	1 (0.4) [0.0–2.6][a]	2 (0.7) [0.2–3.0][a]	6 (3.3) [1.2–8.8][a]	2 (0.8) [0.2–3.2][a]*
Adrenal cortical steroids–penicillins	12 (1.1) [0.5–2.3][a]	2 (1.0) [0.2–4.0][a]	5 (3.6) [1.4–9.4][a]	1 (0.3) [0.0–2.1][a]	2 (0.7) [0.2–2.8][a]	2 (1.6) [0.3–8.3][a]	0 (0.0)
Bronchodilators–NSAIDs	13 (1.1) [0.6–1.9]	1 (1.4) [0.2–9.3][a]	5 (3.0) [0.9–9.5][a]	1 (0.6) [0.1–4.8][a]	0 (0.0)	3 (1.3) [0.4–4.7][a]	3 (1.0) [0.3–3.3][a]
Penicillins–macrolides	5 (1.0) [0.2–4.2][a]	2 (6.0) [0.9–30.5][a]	1 (2.7) [0.4–16.7][a]***	1 (1.1) [0.1–8.3][a]	0 (0.0)	1 (0.5) [0.1–3.2][a]	0 (0.0)
Antidepressants–PPIs	5 (1.0) [0.3–3.1][a]	0 (0.0)	0 (0.0)	1 (0.7) [0.1–5.0][a]	1 (0.2) [0.0–1.5][a]	3 (3.3) [0.9–11.4][a]	0 (0.0)
Contraceptives–dermatological agents[b]	3 (2.1) [0.6–7.0][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.7) [1.1–12.0][a]	0 (0.0)
Penicillins–nasal preparations	6 (0.8) [0.3–2.4][a]	1 (5.6) [0.7–31.8][a]	0 (0.0)	3 (2.0) [0.4–8.5][a]	2 (0.8) [0.2–3.2][a]	0 (0.0)	0 (0.0)
Macrolides–nasal preparations	5 (0.6) [0.2–2.3][a]	1 (5.6) [0.7–31.8][a]	1 (0.3) [0.0–2.4][a]**	0 (0.0)	2 (0.5) [0.1–2.0][a]	1 (0.4) [0.0–2.8][a]	0 (0.0)
Bronchodilators–cephalosporins	6 (0.6) [0.2–1.5][a]	1 (1.0) [0.1–7.6][a]	4 (3.9) [1.2–11.8][a]	0 (0.0)	1 (0.2) [0.0–1.6][a]	0 (0.0)	0 (0.0)
Penicillins–cephalosporins	4 (0.5) [0.2–1.5][a]	2 (3.6) [0.6–18.5][a]	2 (2.1) [0.5–8.0][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Estimates are restricted to children who report the use of ≥2 prescription medications.

[a] Estimates are unreliable; relative SE >30%.

[b] Estimates are restricted to girls.

*** $P < .01$; ** $P < .05$; * $P < .10$ by using χ^2 tests to determine differences between girls and boys.

by 78 people, making the overall rate 0.7% (CI, 0.5%–1.0%). We found only 1 individual using a contraindicated DDI (aripiprazole–metoclopramide).

Among concurrent users of prescription medications, 8.2% [CI, 6.0%–11.1%] were at risk for potential major DDIs (Table 4). Nearly half of interacting regimens used involved psychotropic agents, primarily antidepressants, the most common adverse interaction effect being QT prolongation. The majority (68.0% [CI, 55.9%–78.0%]) of these interacting regimens involved the use of at least 1 acute medication.

The use of combinations with potential major DDIs was higher among adolescent girls (18.1% [CI, 11.0%–28.4%]) than among boys (6.6% [CI, 3.6%–11.9%], $P < .05$). This difference was largely due to the disproportionate use of tricyclic antidepressants in interacting combinations that involved acute medications, specifically nonsteroidal anti-inflammatory drugs (NSAIDs) (most commonly diclofenac–amitriptyline), antiemetics (ondansetron–nortriptyline), and albuterol (albuterol–amitriptyline) by adolescent girls. Atypical antipsychotics accounted for the vast majority of interacting drug combinations in boys ages 6 to 12, whereas antidepressants accounted for the majority in adolescent boys.

Whereas overall prevalence of potential major DDIs among concurrent users of prescription medications is similar to that reported during 2003–2008 (8.7% [95% CI, 6.5%–11.5%]), there was a significant increase among adolescent girls (11.8% [CI, 6.9%–19.7%] during 2003–2008 vs 18.1% [CI, 11.0%–28.4%] during 2009–2014; $P < .05$; Supplemental Table 8).

DISCUSSION

We used directly observed medication data from nationally representative samples to examine use and concurrent use of prescription medications among children and adolescents in the United States. During 2013–2014, one-fifth of children and adolescents used at least 1 prescription medication and ~1 in 10 concurrently used ≥2 prescription medications. Among children and adolescents concurrently using ≥2 prescription medications, 1 in 12 was at risk for a major DDI. Our findings are important because prescription medications are commonly used by children and adolescents in the United States, and population-level monitoring is needed to detect modifiable risk and optimize safe use.

Since 2003–2004, we observed a decline in the use of acute medications, corroborating findings from a previous analysis of pharmacy claims.[22] This decline was mainly attributable to lower rates of antibiotic use, which was also observed in previous research. We also found, however, that acute medications were commonly used in potentially life-threatening drug combinations, particularly among adolescent girls. More than three-quarters of potential major DDIs we identified involved prescription medications used acutely (eg, macrolide antibiotics, antiemetics, and albuterol), and nearly half of these interacting combinations also involved an antidepressant. The potential for QT prolongation is especially noteworthy given that it is often asymptomatic and unpredictable yet can develop quickly into a serious arrhythmia or sudden cardiac death,[23,24] a serious yet underreported problem in children and adolescents.[25,26] Instability in insurance coverage for children and fragmentation of health care (eg, use of retail clinics and emergency departments for episodic care) may increase the risk that a physician prescribing medication for an acute illness is unaware of a child's chronic medication regimen. Systemic strategies, including patient and provider access to accurate medication use data, are needed to reduce the risk of such major DDIs among children.

Highlighted in our findings is also an important opportunity to improve the safe use of medications among adolescent girls given that nearly 1 in 5 adolescent girls who concurrently used prescription medications was at risk for a DDI. The threefold higher prevalence of these interacting drug regimens among adolescent girls, when compared with adolescent boys, was largely due to a higher rate of tricyclic antidepressant use in combination with acute medications, most commonly macrolide antibiotics, antiemetics, NSAIDs, and proton pump inhibitors (PPIs). These acute medications may be prescribed to treat sexually transmitted infections (eg, azithromycin) or gastrointestinal symptoms (eg, ondansetron, omeprazole) from eating disorders.[27,28] Some are also available over-the-counter (OTC), specifically NSAIDs and PPIs. Product labeling for OTC medications does not always include comprehensive information on adverse effects, including DDIs. For example, in the labeling for OTC omeprazole, the DDI between citalopram and omeprazole is not mentioned.[29] Many adolescent girls and their parents may therefore not be aware of the cardiovascular risks associated with use.

We also found that prescription medications associated with an increased risk of suicidality are commonly used in children and adolescents and are often used together. For example, more than half of adolescent girls taking antidepressants concurrently use at least 2 additional psychotropic medications or hormonal contraceptives. Although there is some evidence that the combined use of these drugs may increase the onset and severity of suicidal thoughts and behavior,[19,30] we found no cases of DDIs associated with suicidality. This finding is expected because suicidality, in contrast to serotonin

TABLE 4 Potentially Major DDIs Among Children and Adolescents Concurrently Using Prescription Medications Overall and by Gender and Age Group in the United States (2009–2014)

	Prevalence of DDIs, No. (%) [95% CI]							
	Overall, *n* = 993	0–5 y		6–12 y		13–19 y		Adverse Interaction Effect
		Girls (*n* = 112)	Boys (*n* = 159)	Girls (*n* = 156)	Boys (*n* = 244)	Girls (*n* = 170)	Boys (*n* = 152)	
Any major DDI	78 (8.2) [6.0–11.1]	4 (3.0) [1.0–8.2][a]	6 (3.0) [1.0–8.6][a]	7 (3.0) [1.2–7.0][a]	19 (5.7) [3.3–9.6]	30 (18.1) [11.0–28.4]	12 (6.6) [3.6–30.2] [a**]	
Psychotherapeutic agents	48 (5.6) [3.6–8.6]	0 (0.0)	0 (0.0)	5 (2.2) [0.9–5.0][a]	14 (4.4) [2.3–8.2][a]	20 (12.5) [6.2–23.6] [a]	9 (5.4) [2.5–37.0][a*]	
Antidepressants	33 (3.9) [2.5–6.1]	0 (0.0)	0 (0.0)	5 (2.2) [0.9–5.0][a]	7 (2.2) [1.0–5.2][a]	15 (9.1) [4.9–16.1]	6 (3.9) [1.5–46.5][a]	
SSRIs	21 (2.3) [1.4–3.9]	0 (0.0)	0 (0.0)	3 (1.5) [0.4–3.0][a]	2 (0.7) [0.2–2.8][a]	11 (4.9) [2.2–10.6][a]	5 (3.7) [1.3–49.4][a*]	
Citalopram–omeprazole[b]	1 (0.4) [0.1–3.2][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7) [0.2–11.5][a]	0 (0.0)	QT prolongation
Fluoxetine–trazodone	4 (0.4) [0.2–1.0][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4) [0.1–3.0][a]	2 (0.8) [0.2–3.2][a]	1 (0.5) [0.1–96.4][a]	QTprolongation and/or serotonin syndrome
Escitalopram–amphetamines	1 (0.3) [0.0–2.3][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6) [0.2–98.0][a]	Serotonin syndrome
Sertraline–amphetamines	3 (0.3) [0.1–0.9][a]	0 (0.0)	0 (0.0)	1 (0.4) [0.1–1.0][a]	0 (0.0)	1 (0.4) [0.1–2.7][a]	1 (0.7) [0.1–100.0][a]	Serotonin syndrome
Escitalopram–hydroxyzine[b]	2 (0.2) [0.1–1.1][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3) [0.0–2.0][a]	1 (0.7) [0.1–4.7][a]	0 (0.0)	QT prolongation
Sertraline–trazodone	2 (0.1) [0.0–0.5][a]	0 (0.0)	0 (0.0)	2 (0.8) [0.2–2.0][a]	0 (0.0)*	0 (0.0)	0 (0.0)	Serotonin syndrome
Fluoxetine–amphetamines	1 (0.1) [0.0–0.7][a]	0 (0.0)	0 (0.0)	1 (0.7) [0.1–1.0][a]	0 (0.0)	0 (0.0)	0 (0.0)	Serotonin syndrome
Tricyclics	8 (1.4) [0.6–3.3][a]	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0) [0.2–4.3][a]	5 (4.5) [1.6–11.8][a]	0 (0.0)*	
Amitriptyline–albuterol[b]	1 (0.3) [0.0–2.5][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3) [0.2–9.1][a]	0 (0.0)	Cardiovascular effects
Nortriptyline–ondansetron[b]	1 (0.3) [0.0–1.9][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0) [0.1–6.9][a]	0 (0.0)	QT prolongation
Imipramine–quetiapine	1 (0.2) [0.0–1.1][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7) [0.1–5.1][a]	0 (0.0)	0 (0.0)	QT prolongation
Atypical antipsychotics	21 (1.8) [1.1–3.1]	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.3) [1.4–7.4][a*]	8 (2.8) [1.3–5.9][a]	4 (1.9) [0.7–49.2][a]	
Quetiapine–aripiprazole	3 (0.3) [0.1–1.3][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8) [0.2–3.4][a]	1 (0.4) [0.1–98.0][a]	QT prolongation
Risperidone–lithium	3 (0.3) [0.1–0.9][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3) [0.0–2.3][a]	0 (0.0)	2 (1.1) [0.3–69.8][a]	Extrapyramidal symptoms
Quetiapine–trazodone	3 (0.2) [0.1–0.8][a]	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5) [0.1–2.2][a]	1 (0.5) [0.1–3.5][a]	0 (0.0)	QT prolongation
Quetiapine–risperidone	2 (0.2) [0.0–0.7][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5) [0.1–3.2][a]	1 (0.3) [0.0–2.1][a]	0 (0.0)	QT prolongation
Risperidone–hydroxyzine[b]	2 (0.1) [0.0–0.7][a]	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4) [0.1–3.1][a]	0 (0.0)	0 (0.0)	QT prolongation
CNS stimulants	14 (1.7) [0.8–3.5][a]	0 (0.0)	0 (0.0)	4 (1.8) [0.6–4.0][a]	3 (1.0) [0.3–3.2][a]	4 (2.8) [0.7–10.8][a]	3 (2.5) [0.6–67.9][a]	
Atomoxetine–albuterol[b]	2 (0.6) [0.1–3.2][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5) [0.1–3.2][a]	1 (1.9) [0.3–12.9][a]	0 (0.0)	Cardiovascular effects
Amphetamines–trazodone	4 (0.2) [0.1–0.6][a]	0 (0.0)	0 (0.0)	2 (0.7) [0.2–2.0][a]	2 (0.5) [0.1–2.2][a]	0 (0.0)	0 (0.0)	Serotonin syndrome
Methylphenidate–bupropion	3 (0.2) [0.0–0.5][a]	0 (0.0)	0 (0.0)	1 (0.4) [0.1–1.0][a]	0 (0.0)	1 (0.2) [0.0–1.5][a]	1 (0.2) [0.0–99.2][a]	Seizures
Analgesics	11 (1.4) [0.5–3.4][a]	0 (0.0)	2 (0.6) [0.1–2.4][a]	0 (0.0)	1 (0.2) [0.0–1.3][a]	8 (4.9) [1.8–12.6][a]	0 (0.0)*	
Narcotics	7 (0.8) [0.3–1.9][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2) [0.0–1.3][a]	6 (3.0) [1.2–7.2][a]	0 (0.0)*	
Hydrocodone[b]–oxycodone[b]	2 (0.4) [0.1–1.7][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5) [0.4–6.5][a]	0 (0.0)	CNS depression
Hydrocodone[b]–cyclobenzaprine[b]	2 (0.2) [0.1–0.9][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9) [0.2–3.5][a]	0 (0.0)	CNS depression

TABLE 4 Continued

	Prevalence of DDIs, No. (%) [95% CI]								
	Overall, $n = 993$	0–5 y		6–12 y		13–19 y		Adverse Interaction Effect
		Girls ($n = 112$)	Boys ($n = 159$)	Girls ($n = 156$)	Boys ($n = 244$)	Girls ($n = 170$)	Boys ($n = 152$)	
NSAIDs	4 (0.5) [0.1–2.5][a]	0 (0.0)	2 (0.6) [0.1–2.4][a]	0 (0.0)	0 (0.0)	2 (1.9) [0.3–9.6][a]	0 (0.0)	
Naproxen[b]–amitriptyline	1 (0.1) [0.0–0.6][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3) [0.0–2.3][a]	0 (0.0)	Bleeding
Antiemetic or antibiotics	14 (1.6) [0.9–2.8]	0 (0.0)	1 (1.1) [0.2–7.9][a]	1 (0.4) [0.1–1.0][a]	2 (0.5) [0.1–2.0][a]	7 (4.0) [1.7–9.4][a]	3 (1.2) [0.4–58.8][a]	
Promethazine[b]–azithromycin[b]	3 (0.3) [0.1–1.1][a]	0 (0.0)	1 (1.1) [0.2–7.9][a]	1 (0.4) [0.1–1.0][a]	0 (0.0)	0 (0.0)	1 (0.3) [0.0–99.4][a]	QT prolongation
Ondansetron[b]–erythromycin	2 (0.2) [0.0–0.7][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6) [0.1–2.6][a]	0 (0.0)	QT prolongation
Ondansetron[b]–clarithromycin	1 (0.1) [0.0–0.9][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5) [0.1–3.2][a]	0 (0.0)	QT prolongation

Estimates are weighted to account for differential probabilities of selection and differential nonresponse. Micromedex was used to determine potential contraindicated and major DDIs among all medications used by children or adolescents who report using ≥2 medications during 2013–2014 (with Supplemental Table 6, we provide a list of these medications, and with Supplemental Table 7 , we provide a list of all DDIs found). Aripiprazole–metoclopramide is considered a contraindicated DDI; all other DDIs were considered potentially major DDIs. DDI, contraindicated or major DDI; SSRI, selective serotonin reuptake inhibitor.

[a] Estimates are unreliable; relative SE >30%.

[b] Acute medications (used ≤30 days).

** $P < .05$; * $P < .10$ by using χ^2 tests to determine differences between girls and boys.

syndrome and QT prolongation, is not captured as a potential DDI in existing drug interaction software,[31] including Micromedex. Therefore, health care professionals, including psychiatrists, may not be fully aware of the suicidal risks associated with the concurrent use of prescription medications in the evaluation and treatment of depressive symptoms in younger patients.

With these findings, it is suggested that preventive efforts used to improve the safe use of medications by children should promote public and health professional awareness of the increased risks associated with concurrent use of prescription and OTC medications, particularly suicidality and QT prolongation. Such efforts may include incorporation of a list of commonly used medications and interacting combinations associated with increases in QT prolongation and suicidal risks in treatment guidelines and screening tools for depression. Efforts should be used to target both consumers and health professionals, including those involved in acute or episodic care. Such efforts are particularly important among adolescents considering suicide and cardiovascular events, as well as unintentional drug overdoses, are persistently leading causes of death.[16,32] Nonmedical use of prescription drugs, including opioids, is also more prevalent in adolescents than in younger children[33] and is known to increase risk for both suicide and sudden death.

This study has several limitations. We examined the potential for DDIs rather than actual adverse drug events. Prescribers might have been aware of the risks and benefits of coprescribing the medications, established an appropriate monitoring plan, and determined in discussion with the patient and/or caregiver that the potentially interacting regimen may be the best option for the patient.

Second, our medication data were limited to prescription medications and were not used to capture information on OTC products. Therefore, we likely underestimate the rates of use, and potential DDIs, for several therapeutic classes (eg, antihistamines, PPIs, NSAIDs) that are widely available without a prescription. Moreover, OTC products, including acetaminophen and cough and cold medicines, are key contributors to adverse drug events in children.[34] Third, we used the Micromedex drug interaction software to identify potentially major DDIs in our sample, and other drug interaction software may yield different estimates. However, the accuracy, including sensitivity and specificity, comprehensiveness, and usefulness of Micromedex has been previously established.[35,36]For example, authors of a study in which the various software for DDIs were evaluated ranked Micromedex the highest in accuracy.[35] Fourth, the estimates for DDIs are for 30-day point prevalence. Therefore, it is possible that over a longer period of time, the concurrent use of potential DDIs is greater than our estimates.

In addition, the distinction between acute and chronic is not absolute; some medications initiated <30 days before data collection, yet intended for chronic use, may have been misclassified as acute. Last, for children <16 years old, a parent or guardian answered questions on their child's use of prescription medications. Therefore, underreporting is possible, particularly for prescription medications surreptitiously used by the child. Finally, NHANES may be underpowered to examine the prevalence of medication use, resulting in unreliable nationwide estimates.

CONCLUSIONS

Using nationally representative data, we found that many children and adolescents use and concurrently use prescription medications in the United States. Among concurrent users of prescription medications, nearly 1 in 12 was at risk for a major DDI. Largely because of their higher rate of acute medication use, adolescent girls were at a higher risk of using interacting drug regimens than other subgroups. Treatment and prevention efforts to reduce the burden of adverse drug events in younger populations should be used to consider the role of interacting drug combinations, especially among these individuals.

ABBREVIATIONS

CI: confidence interval
CNS: central nervous system
DDI: drug–drug interaction
NSAID: nonsteroidal anti-inflammatory drug
OTC: over-the-counter
PPI: proton pump inhibitor

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Supplemental Information

SUPPLEMENTAL TABLE 5 Trends of Commonly Used Prescription Medication Therapeutic Classes in the Previous 30 Days Among Children and Adolescents in the United States (2003–2014)

	Prevalence of Use, %						*P*
	2003–2004 (*n* = 5064)	2005–2006 (*n* = 5367)	2007–2008 (*n* = 4212)	2009–2010 (*n* = 4315)	2011–2012 (*n* = 4194)	2013–2014 (*n* = 4404)	
Respiratory agents	9.13	9.54	9.57	7.62	8.59	6.79	<.001
Bronchodilators	4.52	4.85	5.57	5.09	5.03	3.50	.085
Antihistamines	2.74	2.91	2.00	1.36	1.56	1.83	<.001
Leukotriene modifiers	1.38	2.35	2.90	1.59	2.17	1.71	.918
Respiratory inhalant products	0.47	0.95	0.75	1.14	1.54	1.27	<.001
Psychotherapeutic agents[a]	4.37	4.51	6.42	4.71	5.40	5.02	.337
CNS stimulants	2.87	2.75	4.47	3.42	3.19	3.34	.476
Antidepressants	1.25	1.41	2.18	0.95	1.66	1.16	.720
Antipsychotics	0.43	0.66	0.74	0.47	0.40	0.90	.244
Anticonvulsants	0.44	0.83	0.98	0.39	0.77	0.79	.611
Anxiolytics, sedatives, and hypnotics	0.29	0.26	0.30	0.22	0.40	0.27	.735
Anti-infective agents	7.92	8.10	6.20	7.03	5.55	4.80	<.001
Penicillins	3.23	4.13	2.87	3.63	2.57	2.22	.025
Macrolide derivatives	0.85	1.08	0.69	0.71	0.85	0.85	.719
Cephalosporins	1.55	1.23	1.04	1.08	0.64	0.51	.008
Topical agents	3.38	4.38	3.20	3.45	3.90	2.98	.229
Nasal preparations	1.67	2.15	1.58	1.21	1.75	1.49	.301
Dermatological agents	1.33	1.68	0.87	1.54	1.37	1.17	.605
Hormones and/or hormone modifiers	2.30	2.96	4.00	3.02	3.71	2.06	.984
Contraceptives[b]	1.29	1.14	1.71	1.19	2.24	1.24	.302
Adrenal cortical steroids	0.93	1.37	1.78	1.42	1.25	0.62	.151
Gastrointestinal agents	1.49	1.77	1.75	1.83	1.20	1.47	.550
PPIs	0.53	0.43	0.57	0.83	0.69	0.62	.371
H_2 antagonist	0.49	0.33	0.64	0.64	0.38	0.53	.770
Antiadrenergic agents, centrally acting	0.25	0.40	0.50	0.36	0.60	1.11	<.001
Analgesics	1.91	1.55	1.68	1.37	1.57	1.09	.090
Nonsteroidal anti-inflammatory	0.92	0.38	0.76	0.65	0.77	0.72	.991
Narcotics	0.75	0.93	0.56	0.63	0.65	0.43	.116
Anti-vertigo agents	0.49	0.27	0.32	0.23	0.29	0.72	.347
Antidiabetic agents	0.25	0.24	0.35	0.35	0.34	0.51	.172

Estimates are weighted to account for differential probabilities of selection and differential nonresponse. H_2, xxx.

[a] Derived from Multum classification of psychotherapeutic agents, CNS stimulants, anticonvulsants, and anxiolytics, sedatives, and hypnotics.

[b] Among girls only.

SUPPLEMENTAL TABLE 6 Prescription Medications Used by Concurrent Medication Users (2013–2014)

Prescription Medication	Unweighted, No.
1. Albuterol	140
2. Amoxicillin	89
3. Montelukast	67
4. Methylphenidate	53
5. Cetirizine	46
6. Fluticasone nasal	39
7. Fluticasone	34
8. Lisdexamfetamine	28
9. Ranitidine	27
10. Ibuprofen	26
11. Beclomethasone	25
12. Clonidine	24
13. Amphetamine and dextroamphetamine	21
14. Azithromycin	21
15. Loratadine	20
16. Budesonide	17
17. Guanfacine	16
18. Mometasone nasal	15
19. Ondansetron	15
20. Levalbuterol	14
21. Risperidone	14
22. Fluoxetine	13
23. Polyethylene glycol 3350	12
24. Dexmethylphenidate	10
25. Ethinyl estradiol and norethindrone	10
26. Omeprazole	10
27. Amoxicillin and clavulanate	9
28. Aripiprazole	9
29. Diphenhydramine	9
30. Griseofulvin	9
31. Levothyroxine	9
32. Prednisolone	9
33. Atomoxetine	8
34. Ethinyl estradiol and norgestimate	8
35. Fluticasone and salmeterol	8
36. Lansoprazole	8
37. Minocycline	8
38. Sulfamethoxazole and trimethoprim	8
39. Topiramate	8
40. Acetaminophen and hydrocodone	7
41. Cefdinir	7
42. Cyproheptadine	7
43. Hydroxyzine	7
44. Oseltamivir	7
45. Quetiapine	7
46. Cephalexin	6
47. Insulin lispro	6
48. Prednisone	6
49. Sertraline	6
50. Amphetamine	5
51. Escitalopram	5
52. Metformin	5
53. Naproxen	5
54. Penicillin versus potassium	5
55. Budesonide and formoterol	4
56. Dextromethorphan and promethazine	4
57. Divalproex sodium	4
58. Doxycycline	4
59. Esomeprazole	4
60. Ethinyl estradiol and levonorgestrel	4
61. Fexofenadine	4
62. Hydrocodone	4

TABLE 6 Continued

Prescription Medication	Unweighted, No.
63. Isotretinoin	4
64. Lamotrigine	4
65. Promethazine	4
66. Acetaminophen and oxycodone	3
67. Amitriptyline	3
68. Brompheniramine, dextromethorphan, and pseudoephedrine	3
69. Bupropion	3
70. Cyclobenzaprine	3
71. Desmopressin	3
72. Erythromycin	3
73. Formoterol and mometasone	3
74. Insulin aspart	3
75. Insulin glargine	3
76. Lacosamide	3
77. Levetiracetam	3
78. Levocetirizine	3
79. Lisinopril	3
80. Nitrofurantoin	3
81. Oxycodone	3
82. Propranolol	3
83. Trazodone	3
84. Amlodipine	2
85. Brompheniramine and pseudoephedrine	2
86. Carbamazepine	2
87. Cefprozil	2
88. Ciprofloxacin	2
89. Clonazepam	2
90. Dextroamphetamine	2
91. Diclofenac	2
92. Enalapril	2
93. Ethinyl estradiol and norelgestromin	2
94. Furosemide	2
95. Mometasone	2
96. Oxcarbazepine	2
97. Oxybutynin	2
98. Phenobarbital	2
99. Rifampin	2
100. Sumatriptan	2
101. Triamcinolone	2
102. Adalimumab	1
103. Albuterol and ipratropium	1
104. Baclofen	1
105. Balsalazide	1
106. Buspirone	1
107. Ceftriaxone	1
108. Chlorpheniramine, dextromethorphan, and pseudoephedrine	1
109. Chlorpheniramine and hydrocodone	1
110. Ciclesonide	1
111. Ciclesonide nasal	1
112. Clarithromycin	1
113. Codeine, phenylephrine, and promethazine	1
114. Docusate	1
115. Drospirenone, ethinyl estradiol, and levomefolate	1
116. Famotidine	1
117. Fentanyl	1
118. Fluconazole	1
119. Gabapentin	1
120. Glycopyrrolate	1
121. Hydrocortisone	1
122. Imipramine	1
123. Infliximab	1
124. Insulin aspart and/or insulin aspart protamine	1
125. Insulin isophane	1

TABLE 6 Continued

Prescription Medication	Unweighted, No.
126. Ipratropium	1
127. Isoniazid	1
128. Ketorolac	1
129. Lactulose	1
130. Lithium	1
131. Lorazepam	1
132. Megestrol	1
133. Methotrexate	1
134. Methylprednisolone	1
135. Metoclopramide	1
136. Metronidazole	1
137. Mirtazapine	1
138. Morphine	1
139. Multivitamin	1
140. Nortriptyline	1
141. Olopatadine nasal	1
142. Oxygen	1
143. Pantoprazole	1
144. Phenytoin	1
145. Polymyxin B sulfate	1
146. Pseudoephedrine	1
147. Simvastatin	1
148. Somatropin	1
149. Sorafenib	1
150. Tiotropium	1
151. Tizanidine	1
152. Triamcinolone nasal	1
153. Ursodiol	1
154. Valproic acid	1
155. Venlafaxine	1
156. Verapamil	1
157. Anti-infectives, unspecified[a]	7
158. Triamcinolone topical[b]	9
159. Clindamycin topical[b]	4
160. Hydrocortisone topical[b]	4
161. Olopatadine ophthalmic[b]	4
162. Tretinoin topical[b]	4
163. Ciprofloxacin and dexamethasone otic[b]	3
164. Fluoride topical[b]	3
165. Adapalene and benzoyl peroxide topical[b]	2
166. Antipyrine and benzocaine otic[b]	2
167. Betamethasone topical[b]	2
168. Desonide topical[b]	2
169. Fluticasone topical[b]	2
170. Lidocaine and prilocaine topical[b]	2
171. Mometasone topical[b]	2
172. Mupirocin topical[b]	2
173. Nystatin topical[b]	2
174. Ofloxacin otic[b]	2
175. Tacrolimus topical[b]	2
176. Benzoyl peroxide topical[b]	1
177. Clobetasol topical[b]	1
178. Desoximetasone topical[b]	1
179. Emollients topical[b]	1
180. Erythromycin ophthalmic[b]	1
181. Fluorometholone ophthalmic[b]	1
182. Moxifloxacin ophthalmic[b]	1
183. Pimecrolimus topical[b]	1
184. Prednisolone ophthalmic[b]	1
185. Silver sulfadiazine topical[b]	1

[a] Excluded from DDI analysis because specific medication used is unknown.

[b] Excluded from DDI analysis because it represented a topical, ophthalmic, or otic formulation.

SUPPLEMENTAL TABLE 7 Number of DDIs Found Among Children and Adolescents in the United States (2003–2014)

	n		
	2003–2008	2009–2014	Overall
Contraindicated or major DDI	80	78	158
Contraindicated interaction	1	1	2
1. Aripiprazole–metoclopramide	0	1	1
2. Promethazine–metoclopramide	1	0	1
Major interaction	79	77	156
3. Albuterol–levalbuterol	10	13	23
4. Atomoxetine–albuterol	5	2	7
5. Sertraline–amphetamines and dextroamphetamine	3	3	6
6. Sertraline–trazodone	4	2	6
7. Fluoxetine–trazodone	1	4	5
8. Promethazine–azithromycin	2	3	5
9. Quetiapine–trazodone	2	3	5
10. Risperidone–sertraline	3	2	5
11. Methylphenidate–bupropion	1	3	4
12. Quetiapine–aripiprazole	1	3	4
13. Disdexamfetamine–trazodone	2	2	4
14. Aripiprazole–escitalopram	2	2	4
15. Amphetamine and dextroamphetamine–fluoxetine	3	1	4
16. Risperidone–lithium	0	3	3
17. Aripiprazole–fluoxetine	1	2	3
18. Fluticasone and salmeterol–azithromycin	2	1	3
19. Escitalopram–quetiapine	2	1	3
20. Ibuprofen–prednisolone	2	1	3
21. Aripiprazole–trazodone	2	1	3
22. Amphetamine and dextroamphetamine–trazodone	0	2	2
23. Divalproex sodium–lamotrigine	0	2	2
24. Cyclobenzaprine–hydrocodone	0	2	2
25. Erythromycin–ondansetron	0	2	2
26. Escitalopram–hydroxyzine	0	2	2
27. Risperidone–hydroxyzine	0	2	2
28. Quetiapine–risperidone	0	2	2
29. Hydrocodone–oxycodone	0	2	2
30. Fluticasone nasal–clarithromycin	1	1	2
31. Amitriptyline–albuterol	1	1	2
32. Fluoxetine–sulfamethoxazole and trimethoprim	1	1	2
33. Hydrocodone–promethazine	1	1	2
34. Fluoxetine–bupropion	1	1	2
35. Clonidine–imipramine	1	1	2
36. Azithromycin–clarithromycin	2	0	2
37. Amphetamine and dextroamphetamine–carbamazepine	2	0	2
38. Promethazine–erythromycin	2	0	2
39. Amphetamine and dextroamphetamine–bupropion	2	0	2
40. Ibuprofen–sertraline	2	0	2
41. Aripiprazole–carbamazepine	0	1	1
42. Clarithromycin–ondansetron	0	1	1
43. Escitalopram–amphetamine	0	1	1
44. Amitriptyline–ondansetron	0	1	1
45. Nortriptyline–ondansetron	0	1	1
46. Amitriptyline–sumatriptan	0	1	1
47. Amitriptyline–diclofenac	0	1	1
48. Carbamazepine–fluoxetine	0	1	1
49. Fluticasone and salmeterol–trazodone	0	1	1
50. Albuterol–nortriptyline	0	1	1

TABLE 7 Continued

	n		
	2003–2008	2009–2014	Overall
51. Lorazepam–phenobarbital	0	1	1
52. Amitriptyline–naproxen	0	1	1
53. Fentanyl–oxcarbazepine	0	1	1
54. Amphetamine and dextroamphetamine–oxycodone	0	1	1
55. Fluoxetine–risperidone	0	1	1
56. Famotidine–hydroxyzine	0	1	1
57. Quetiapine–hydroxyzine	0	1	1
58. Fluoxetine–quetiapine	0	1	1
59. Imipramine–quetiapine	0	1	1
60. Ondansetron–sorafenib	0	1	1
61. Budesonide–ibuprofen	0	1	1
62. Clonazepam–fentanyl	0	1	1
63. Clonazepam–morphine	0	1	1
64. Fentanyl–morphine	0	1	1
65. Lithium–trazodone	0	1	1
66. Sertraline–mirtazapine	0	1	1
67. Omeprazole–citalopram	0	1	1
68. Amoxicillin–tetracycline	0	1	1
69. Prednisone–nifedipine	0	1	1
70. Fluticasone and salmeterol–clarithromycin	1	0	1
71. Clarithromycin–sulfamethoxazole and trimethoprim	1	0	1
72. Amitriptyline–sulfamethoxazole and trimethoprim	1	0	1
73. Erythromycin–sulfamethoxazole and trimethoprim	1	0	1
74. Promethazine–fluticasone and salmeterol	1	0	1
75. Amitriptyline–promethazine	1	0	1
76. Escitalopram–esomeprazole	1	0	1
77. Ciprofloxacin–quetiapine	1	0	1
78. Aripiprazole–risperidone	1	0	1
79. Escitalopram–risperidone	1	0	1
80. Amphetamine and dextroamphetamine–sumatriptan	1	0	1
81. Dextroamphetamine–venlafaxine	1	0	1
82. Azithromycin–hydroxyzine	1	0	1
83. Carbamazepine–clonazepam	1	0	1
84. Amoxicillin–doxycycline	1	0	1
85. Imipramine–risperidone	1	0	1
86. Escitalopram–trazodone	1	0	1
87. Diclofenac–venlafaxine	1	0	1
88. Quetiapine–venlafaxine	1	0	1
89. Dextroamphetamine–buspirone	1	0	1
90. Hydrocodone–topiramate	1	0	1
91. Fluticasone nasal–bupropion	1	0	1
92. Promethazine–morphine	1	0	1
93. Fluoxetine–sertraline	1	0	1
94. Trazodone–venlafaxine	1	0	1
95. Sertraline–bupropion	1	0	1
96. Hydrocodone–morphine	1	0	1
97. Ibuprofen–prednisone	1	0	1
98. Morphine–hydroxyzine	1	0	1
99. Budesonide–naproxen	1	0	1
100. Ibuprofen–naproxen	1	0	1
101. Ibuprofen–digoxin	1	0	1

SUPPLEMENTAL TABLE 8 Potentially Major DDIs Among Children and Adolescents Concurrently Using Prescription Medications Overall and by Gender and Age Group in the United States (2003–2008) (*N* = 1192)

	Prevalence of DDIs, No. (%) [95% CI][a]						
	Overall, *n* = 993	0–5 y		6–12 y		13–19 y	
		Girls (*n* = 112)	Boys (*n* = 159)	Girls (*n* = 156)	Boys (*n* = 244)	Girls (*n* = 170)	Boys (*n* = 152)
Any major DDI	80 (8.7) [6.5–11.5]	6 (4.2) [1.2–14.0][a]	7 (2.9) [1.2–6.7][a]	8 (6.2) [2.5–14.7][a]	14 (8.4) [4.8–14.5]	26 (11.8) [6.9–19.7]	19 (12.7) [7.7–20.1]
Psychotherapeutic agents	52 (6.3) [4.5–8.8]	2 (2.9) [0.5–15.7][a]	0 (0.0)	5 (4.3) [1.4–12.5][a]	9 (4.9) [2.2–9.3][a]	23 (11.1) [6.2–19.1]	13 (8.5) [4.6–15.1]
Antidepressants	39 (5.5) [3.6–8.3]	0 (0.0)	0 (0.0)	5 (4.3) [1.4–12.5][a]	7 (4.1) [1.7–7.6][a]	17 (9.7) [5.1–17.7][a]	10 (8.1) [4.3–14.9][a]
SSRIs	23 (3.4) [2.1–5.5]	0 (0.0)	0 (0.0)	2 (1.4) [0.2–7.7][a]	4 (1.8) [0.5–4.9][a]	12 (7.0) [3.6–13.0][a]	5 (5.7) [2.1–14.3][a]
Citalopram–omeprazole[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fluoxetine–trazodone	1 (0.0) [0.0–0.2][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1) [0.0–0.7][a]	0 (0.0)
Escitalopram–amphetamines	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sertraline–amphetamines	3 (0.2) [0.0–1.2][a]	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0) [0.1–2.9][a]	1 (0.1) [0.0–0.5][a]	0 (0.0)
Escitalopram–hydroxyzine[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sertraline–trazodone	4 (0.8) [0.2–2.7][a]	0 (0.0)	0 (0.0)	1 (1.1) [0.1–8.7][a]	0 (0.0)	3 (2.3) [0.5–9.4][a]	0 (0.0)
Fluoxetine–amphetamines	3 (0.6) [0.2–2.1][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.2) [0.6–7.5][a]	0 (0.0)
Tricyclics	5 (0.6) [0.3–1.5][a]	0 (0.0)	0 (0.0)	2 (2.1) [0.4–11.2][a]	1 (1.1) [0.2–1.2][a]	1 (0.1) [0.0–0.9][a]	1 (0.6) [0.1–4.3][a]
Amitriptyline–albuterol[b]	1 (0.1) [0.0–0.8][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6) [0.1–4.3][a]
Nortriptyline–ondansetron[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imipramine–quetiapine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atypical antipsychotics	17 (1.8) [1.0–3.2]	0 (0.0)	0 (0.0)	2 (1.1) [0.2–5.2][a]	3 (1.5) [0.4–3.0][a]	9 (4.1) [2.2–7.6][a]	3 (1.3) [0.3–5.6][a]
Quetiapine–aripiprazole	1 (0.0) [0.0–0.1][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1) [0.0–0.4][a]	0 (0.0)
Risperidone–lithium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quetiapine–trazodone	2 (0.2) [0.0–0.9][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2) [0.0–1.3][a]	1 (0.5) [0.1–3.8][a]	0 (0.0)
Quetiapine–risperidone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Risperidone–hydroxyzine[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CNS stimulants	16 (2.1) [1.0–4.1][a]	1 (2.5) [0.3–16.8][a]	0 (0.0)	0 (0.0)	5 (2.8) [0.9–5.5][a]	6 (2.7) [0.9–7.6][a]	4 (3.2) [1.0–10.1][a]
Atomoxetine–albuterol[b]	5 (0.5) [0.2–1.5][a]	1 (2.5) [0.3–16.8][a]	0 (0.0)	0 (0.0)	2 (0.7) [0.1–2.6][a]	2 (0.4) [0.1–2.2][a]	0 (0.0)
Amphetamines–trazodone	2 (0.4) [0.1–1.7][a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1) [0.1–1.0][a]	0 (0.0)	1 (1.2) [0.2–7.9][a]
Methylphenidate–bupropion	1 (0.3) [0.0–2.2][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7) [0.2–11.0][a]
Analgesics	11 (0.7) [0.3–1.7][a]	1 (0.3) [0.0–2.0][a]	2 (0.7) [0.1–3.7][a]	0 (0.0)	2 (0.7) [0.1–2.1][a]	3 (1.2) [0.2–5.8][a]	3 (0.6) [0.1–2.4][a]
Narcotics	3 (0.1) [0.0–0.3][a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2) [0.1–1.0][a]	1 (0.1) [0.0–0.8][a]
Hydrocodone[b]–oxycodone[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydrocodone[b]–cyclobenzaprine[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NSAIDs	8 (0.6) [0.2–1.6][a]	1 (0.3) [0.0–2.0][a]	2 (0.7) [0.1–3.7][a]	0 (0.0)	2 (0.7) [0.1–2.1][a]	1 (0.9) [0.1–6.6][a]	2 (0.5) [0.1–2.4][a]
Naproxen[b]–amitriptyline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antiemetic or antibiotics	17 (2.4) [1.3–4.3][a]	2 (0.7) [0.2–3.0][a]	1 (0.4) [0.1–3.2][a]	2 (3.0) [0.7–12.2][a]	3 (3.1) [0.9–3.4][a]	3 (0.8) [0.2–3.4][a]	6 (5.9) [2.3–13.9][a**]
Promethazine[b]–azithromycin[b]	2 (0.4) [0.1–2.0][a]	0 (0.0)	1 (0.4) [0.1–3.2][a]	0 (0.0)	1 (1.7) [0.3–1.7][a]	0 (0.0)	0 (0.0)
Ondansetron[b]–erythromycin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ondansetron[b]–clarithromycin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Estimates are weighted to account for differential probabilities of selection and differential nonresponse. Micromedex was used to determine potential contraindicated and major DDIs among all medications used by children or adolescents who report using ≥2 medications during 2013–2014 (With Supplemental Table 6, we provide a list of these medications, and with Supplemental Table 7, we provide a list of all DDIs found). Aripiprazole–metoclopramide is considered a contraindicated DDI; all other DDIs were considered potentially major DDIs. SSRI, selective serotonin reuptake inhibitor.

[a] Estimates are unreliable; relative SE >30%.

[b] Acute medications (used ≤30 days).

** $P < .05$ by using χ^2 tests to determine differences between girls and boys.