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# Neuroendocrine-Related Adverse Events Associated with Antidepressant Treatment in Children and Adolescents

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There is only limited community-based practice safety information available regarding antidepressant use in pediatric patients. This study identifies the factors associated with incident neuroendocrine-related metabolic, digestive, and sexual/reproductive adverse events in children and adolescents treated with antidepressants. A retrospective cohort design evaluating Medicaid medical and pharmacy claims between January, 1996 and December, 2005 was employed for 11970 children and adolescents prescribed an antidepressant medication, and a random sample of 4500 children not treated with psychotropic medications. Incident obesity/weight gain, Type 2 diabetes mellitus, and dyslipidemia were more likely for those prescribed selective serotonin reuptake inhibitors (SSRIs) (OR = 1.49; 1.37; 1.44), whereas Type 2 diabetes mellitus and dyslipidemia were more likely for those prescribed weight-inducing antidepressants (ORs = 1.26; 1.24), and those with pre-existing endocrinopathies (ORs = 3.96; 1.90), controlling for the effects of co-prescribed mood stabilizers or antipsychotics. Incident nausea/vomiting was less likely for those taking SSRIs (OR = 0.78). Females and children under 12 years of age were more likely to develop these adverse effects. Practitioners need to carefully consider the neuroendocrine- related adverse effects of SSRI antidepressant agents in particular, especially in individuals with comorbid endocrine conditions, and those co-prescribed other classes of psychotropic medications.

## Introduction

Various types of depressive disorders are common in children and adolescents, with rates increasing from childhood through late adolescence [1]. Antidepressants often form the cornerstone of treatment in affected individuals. As newer, safer, and easier-to-use agents have been developed and marketed, prescribing practices have shifted from tricyclic antidepressants (TCAs) and older agents toward selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and heterocyclic second-generation agents [2]. The cardiovascular and neurological adverse events associated with antidepressant treatment in pediatric populations have been previously addressed [3]. In light of intensifying general concern regarding the safety index of psychotropic agents, the growing obesity and diabetic epidemics in youth, and an increasing awareness of the pathophysiological overlap between mood disorders and metabolic syndromes [4], it is timely to evaluate the neuroendocrine-related safety profiles of antidepressants prescribed to children and adolescents in community-based care settings.

Early-onset, non-pharmacologic-induced obesity has a significant effect on the general health of the children affected: impaired glucose tolerance, hyperinsulinism, type 2 diabetes mellitus, polycystic ovary syndrome, dyslipidemia (hypercholesterolemia, hyperlipidemia, etc.), and hypothyroidism [5]. Serotonin, dopamine, and noradrenaline neurotransmitters inhibit prolactin secretion [6], regulate a wide variety of appetitive processes, and mediate feeding behavior, which are associated with obesity, insulin secretion/insulin resistance, and lipid homeostasis (through their linkage with body weight changes) [4]. Psychotropic agents, such as antidepressants and antipsychotics, may induce changes in endocrine-related

functions through their impact on neurotransmitters and neurohormones. Some serotonergic antidepressants (e.g., fluoxetine) reduce hyperglycemia, normalize glucose homeostasis, and increase insulin sensitivity, whereas some noradrenergic antidepressants (e.g., desipramine) exert the opposite effect [4]. Weight-inducing antidepressants (e.g., tricyclics and mirtazapine) exert an unfavorable effect on serum lipid parameters (i.e., triglycerides and low-density lipoprotein cholesterol), whereas weight-neutral agents (e.g., bupropion, duloxetine, and venlafaxine) are less likely to disrupt the lipid milieu [7].

Nausea, anorexia, weight gain, and metabolic disturbances are known side effects of some of the TCAs and many SSRIs, compared to the SNRI/other compounds [8–12]. Premarketing clinical trials indicate that SSRIs have a positive, often dose-related effect on a range of metabolic and digestive adverse events: nausea/vomiting (9–40%), anorexia/weight loss (1–15%), and obesity/weight gain (1–12%), whereas SNRIs have a somewhat more pronounced effect on nausea/vomiting (5–58%) and anorexia/weight loss (1–47%) [13]. Mirtazapine and venlafaxine have been found to increase hypercholesterolemia in 15 and 5% of patients, respectively, and mirtazapine is also associated with hyperglyceridemia in 3% of patients [13,14].

Premarketing clinical trials also indicate that SSRIs have a positive, sometimes dose-related, effect on a range of sexual/reproductive events: menstrual disorders (<1–5%), hyperprolactinemia (<1–2%), ejaculation delay (2–28%), and impotence/erectile dysfunction (1–8%) [10,13,15,16]. Moreover, postmarketing clinical reports provide increasing evidence that treatment with SSRIs may induce sexual side effects at a much higher frequency than was reported during clinical trials [12]. The newer SNRIs, heterocyclics, trazadone, or bupropion are somewhat less likely to cause long-term reproductive dysfunction [11–13].

Depressed youths with comorbid conditions or aggressive/violent features may be co-prescribed antipsychotics, psychostimulants, or anticonvulsants, which are accompanied by their own safety and tolerability issues. For example, a diverse array of metabolic/sexual tolerability and safety concerns are attributable to conventional and second-generation antipsychotics (SGAs) in adult populations [17], and SGAs are associated with clinically significant weight gain and alterations in metabolic indices (e.g., type 2 diabetes mellitus and dyslipidemia) in pediatric populations [18–23]. While conventional antipsychotics, such as haloperidol, raise serum prolactin levels, SGAs are more variable in their effects, with some being more likely to elevate serum prolactin levels, namely risperidone, and the others being much less likely to change these levels or to reverse previous medication-induced elevations of prolactin, that is, ziprasidone and aripiprazole [24,25]. Valproic acid derivatives are also associated with the menstrual dysfunction, and hirsutism in polycystic ovary syndrome, especially in African Americans, and those with obesity, insulin resistance, and dyslipidemia [12]. Psychostimulants are the only major class of psychotropic agents frequently prescribed in pediatric populations but not generally associated with weight gain or metabolic disruption (e.g., methylphenidate and amphetamine salts) [13].

The primary aim of this analysis is to compare the long-term incidence/prevalence of metabolic, digestive, and sexual/reproductive adverse events in an antidepressant-treated cohort from South Carolina's Medicaid system, with the prevalence of these conditions in a random sample of children served through Medicaid with no exposure to psychotropic medications. The second objective is to identify the factors significantly related to prevalence of these adverse events in the treated cohort, for example, comorbid conditions, the co-prescription of other psychotropic medications, and individual risk factors of age, gender, and race.

## Methods

### Cohort Selection

Claims data for South Carolina's Medicaid program were obtained through the state's Office of Research and Statistics. Each Medicaid medical claim identifies a service encounter and gives the date of service, and the International Classification of Diseases (ICD), Ninth Revision Clinical Modification diagnosis codes related to that visit (visit file). Pharmacy claims identified the medication dispensed, and the date the prescription was filled (pharmacy file). A separate data file regarding eligibility was used to summarize the demographics for each patient (person file). The databases are frequently updated prior to being made available for analysis. This study was approved by the University of South Carolina Institutional Review Board as exempt from human subject research guidelines under 45 Code of Federal Regulations, part 46.

Medical and pharmacy claims for the calendar years January 1, 1996, through December 31, 2005, were used to identify a cohort of child and adolescent patients (ages 17 and under) enrolled in and eligible for Medicaid for a minimum of 9 months in each calendar year included in this analysis, who had a service encounter, and who were prescribed any of 27 antidepressants: amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxapram, doxepin, duloxetine, escitalopram, fluoxetine HCl, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline,

paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, or venlafaxine, between January 1, 1998, and December 31, 2003. The date of first prescription of an antidepressant medication in the Medicaid data set was defined as the selection encounter date.

Out of the same population and from the same period, medical and pharmacy claims were also used to identify a randomly selected group of child and adolescent patients (0–17 years old) eligible for Medicaid, 9 of 12 months in all calendar years under study, who had service encounters, but *no* prescriptions in the database for *any* class of psychotropic medications (antipsychotics, antidepressants, anticonvulsants used as mood stabilizers, or psychostimulants) and no psychiatric diagnoses. This process resulted in the identification of 40,660 patients who met the criteria. From this group, a random sample of 4500 patients was selected to use as a representative control/comparison group.

### Adverse Event Coding

Metabolic, digestive, or sexual/reproductive medical conditions that were detected in the 24 months prior to each patient's selection encounter date were coded as "preexisting" for this study. If the patient developed a medical condition subsequent to the prescription of the antidepressant medication, new variables were created for these "incident" events. In the control group, detection of *any* of the metabolic, sexual/reproductive, or digestive medical conditions in a service billing record was coded for analysis. The following categories of conditions and events were evaluated: obesity or excessive weight gain (ICD-9 codes: 278; 278.00; 278.01; 783.1, 783.2), dyslipidemia (ICD-9 codes: 272; 272, 288.0, 285.9), type 2 diabetes mellitus (ICD-9 codes 250, 250.00–251.92 with 5th digit = 0, 2), anorexia or weight loss (ICD-9 codes 780.52, 783.0, 783.21), nausea/vomiting (ICD-9 codes 787.01, 787.02, 787.03), amenorrhea (ICD-9 code 626.0), oligomenorrhea (ICD-9 code 626.1), erectile dysfunction (ICD-9 codes 302.72, 607.84), pituitary disorders including hyperprolactinemia (ICD-9 code 253.xx), irregular menses (ICD-9 code 626.4), gynecomastia (ICD-9 codes 611.1, 611.6), or galactorrhea (ICD-9 code 676).

### Statistical Analysis

To address research questions regarding differences in incidence/prevalence of the metabolic, digestive, and sexual/reproductive conditions/events in the treated versus control groups, six multiple logistic regression equations were constructed to assess the relative odds associated with developing each adverse event, using the control group as the primary comparator, and controlling for three individual risk factors (i.e., gender, ethnicity, and age), dichotomously coded as male/female, African American/other, and age $\leq$12/age $\geq$13.

Then, to identify factors associated with the metabolic, digestive, and sexual/reproductive events in the treated cohort of pediatric patients prescribed antidepressants, including the role of comorbid medical conditions and concomitant psychotropic medications on the development of these conditions, six separate multiple logistic regression equations were constructed to assess the relative odds associated with developing each adverse event under scrutiny, using the SSRI, SNRI, and "antidepressants likely to induce weight gain" as the main covariates, and co-prescriptions of anticonvulsants/mood stabilizers, psychostimulants, or antipsychotics as additional covariates of interest, controlling for three dichotomously coded individual risk factors (i.e., gender, ethnicity, and age). Antidepressants were categorized as SSRIs for citalopram, escitalopram, fluoxetine HCl, fluvoxamine, paroxetine, and sertraline. The antidepressants coded for "likely to cause weight gain" were amitriptyline, nortriptyline, mirtazapine, and paroxetine [4]. Mood stabilizers coded in the regression equations were divalproex/valproic acid derivatives, lithium, and carbamazepine. Psychostimulants coded in the analyses were methylphenidate, dextroamphetamine, amphetamine salts, and atomoxetine. Antipsychotics coded in the analyses were aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine, or haloperidol.

Time elapsed between the prescription of an antidepressant medication and the first diagnosis of one of the metabolic, digestive, or sexual/reproductive conditions was assessed using Kaplan-Meier survival analysis. A Cox proportional hazards (PH) model regression (SAS PROC PHREG) was then employed to determine whether there were differences in time elapsed to adverse event, using the SSRI agents as the main covariates, controlling for the three individual risk factors (i.e., gender, ethnicity, and age).

## Results

### Patients

The treated cohort (N = 11,970) was primarily male and white (Table 1), being treated for depression (30.0%), bipolar disorder (11.6%), major depressive disorder (14.4%), attention-deficit hyperactivity disorder (ADHD; 62.1%), conduct/oppositional defiant disorders (48.0%), organic brain syndrome/developmental disabilities (51.8%), or psychotic disorders (11.2%), with a

**Table 1** Descriptive analysis of the cohort of 11,970 youths prescribed antidepressant medications

| Indicator | Number of treated cohort (%) | Number of control sample (%) |
|---|---|---|
| Gender | | |
| Male | 6789 (56.2) | 1972 (43.8) |
| Female | 5292 (43.8) | 2528 (56.2) |
| Race | | |
| Caucasian | 6064 (50.2) | 842 (18.7) |
| African American | 4758 (39.4) | 3405 (75.7) |
| Other | 1259 (10.4) | 253 (5.6) |
| Age | | |
| ≤12 | 3698 (30.6) | 375 (8.3) |
| ≥13 | 8383 (69.4) | 4125 (91.7) |
| Psychiatric diagnoses | | |
| Major affective disorders | 3813 (26.9) | |
| Schizophrenia, other psychotic disorders | 1341 (11.2) | |
| Attention-deficit hyperactivity disorder | 7506 (62.1) | |
| Psychotropic medications | | |
| SSRIs | 7606 (53.7) | |
| SNRI, other | 9817 (69.3) | |
| Weight-inducing antidepressants | 5384 (38.0) | |
| Psychostimulants | 9360 (66.1) | |
| Mood stabilizers | 2634 (18.6) | |
| Antipsychotics | 3491 (24.6) | |
| Long-term treatment (6 months or more) | 1433 (15.0) | |

mean age of 10.3 (SD = 3.4) years at the time of antidepressant initiation (selection date into the cohort). The newest antidepressant agents (SNRIs and others) were prescribed to the highest numbers of youth (69%), along with psychostimulants (66%), with much smaller percentages being prescribed mood stabilizers (19%) or antipsychotic agents (25%). Only 15% of the antidepressant-treated cohort was treated long term (i.e., 6 months or more), likely due to a more clinically complex presentation for bipolar or psychotic disorders.

The control sample (representing the general Medicaid population of 0–17 years) demographics were different: 43.8% male, 75.7% African American, and 18.7% Caucasian, with a mean age of 7.6 years at selection into the random sample. Although the clients in the treated cohort were about 3 years older at selection into the cohort (start date of antidepressant medication) than those in the control sample, data were compiled on the treated cohort for 2 years prior to their selection date for analysis of the preexisting conditions, making their average age at start date in the data set more comparable to the control group (8.4 years). Furthermore, the control sample was in the Medicaid data set for an average of 7.6 years, compared to the treated group being in it, on average, 7.4 years. Therefore, the "unmatched" treated cohort and control sample provide an adequate period for examining differences in types of conditions developing over time and the opportunity to examine the individual risk factors associated with these incident conditions.

## Comparison of Treated Cohort and Untreated Control Sample

The incidence/prevalence rates for the metabolic, digestive, and sexual/reproductive conditions are presented in Table 2, along with the prevalence rates of these conditions in the untreated control sample. Since the preexisting and incident categories are mutually exclusive, they can be tallied to represent a cumulative prevalence of each condition as the youths are transitioning into treatment as adults. That is, 15.8% would have diagnosed obesity, 5.6% type 2 diabetes mellitus, 13.6% dyslipidemia, 44.6% nausea/vomiting, 8.8% anorexia/weight loss, and 13.5% sexual/reproductive problems.

**Table 2** Overall prevalence and incidence rates for pediatric patients prescribed antidepressant (AD) medications (N = 11,970) and the control sample (N = 4500)

| Condition | Number of control sample prevalence rate (%) | Number of preexisting prevalence (24 months prior to AD Medications) rate (%) | Number of newly developed incidence (after AD medications) rate (%) |
|---|---|---|---|
| Obesity, weight gain | 388 (8.6) | 791 (6.6) | 1038 (9.2) |
| Type 2 diabetes mellitus | 85 (1.9) | 264 (2.1) | 363 (3.1) |
| Dyslipidemia | 486 (10.8) | 829 (6.9) | 756 (6.7) |
| Nausea, vomiting | 1174 (26.1) | 2561 (26.0) | 2226 (18.6) |
| Anorexia, weight loss | 80 (1.8) | 398 (3.5) | 639 (5.3) |
| Sexual/reproductive | 296 (6.6) | 399 (3.7) | 1169 (9.8) |

**Table 3** Comparison of prevalence of medical conditions in the treated cohort and untreated control samples controlling for individual risk factors

| Dependent variable | Treated cohort OR[a] (95% CI[b]) | Female OR (95% CI) | African American OR (95% CI) | Age ≤12 OR (95% CI) | LR[c] chi-square *P* |
|---|---|---|---|---|---|
| Obesity, weight gain | 2.02 | 1.74 | 1.15 | 1.25 | 322.46 |
| | (1.79–2.29) | (1.58–1.91) | (1.04–1.26) | (1.13–1.38) | <0.0001 |
| Type 2 diabetes mellitus | 2.74 | 1.69 | | 1.63 | 202.82 |
| | (2.15–3.50) | (1.44–1.98) | | (1.39–1.92) | <0.0001 |
| Dyslipidemia | 1.43 | 1.42 | 1.67 | 1.43 | 251.58 |
| | (1.27–1.61) | (1.29–1.56) | (1.52–1.85) | (1.30–1.59) | <0.0001 |
| Anorexia, weight loss | 1.89 | 1.19 | 0.83 | | 50.99 |
| | (1.47–2.43) | (1.01–1.41) | (0.70–0.99) | | <0.0001 |
| Nausea, vomiting | 1.62 | 1.39 | 0.60 | | 584.26 |
| | (1.49–1.75) | (1.30–1.49) | (0.56–0.64) | | <0.0001 |
| Sexual/reproductive | 1.83 | 8.64 | | 4.13 | 2435.04 |
| | (1.59–2.13) | (7.48–9.98) | | (3.70–4.61) | <0.0001 |

All reported ORs and CIs are significant at $P < 0.001$.
[a]Odds ratio.
[b]Confidence interval.
[c]Likelihood ratio.

Table 3 presents statistical comparisons of the treated cohort and untreated control sample, controlling for the statistically significant influence of individual risk factors (i.e., age, gender, and ethnicity). All the conditions were more prevalent in the treated cohort: obesity/weight gain (OR = 2.02), type 2 diabetes mellitus (OR = 2.74), dyslipidemia (OR = 1.43), anorexia (OR = 1.89), nausea/vomiting (OR = 1.62), and sexual/reproductive (OR = 1.35).

### *Obesity/Weight Gain*

As shown in Table 4, the likelihood of incident obesity/excessive weight gain was higher for those prescribed SSRIs (OR = 1.49), mood stabilizers (OR = 1.34), and antipsychotics (OR = 1.41), but lower for those taking psychostimulants (OR = 0.80). The mean time elapsed between initiation of an antidepressant and diagnosed obesity/weight gain was 29.5 months. There was a significantly longer time period between the initiation of the antidepressant agent and incident obesity/weight gain for adolescents (Wald $\chi^2 = 7.97$; p = .005; Hazard Ratio = 1.23; CI = 1.07, 1.42) but no medication group difference.

### *Type 2 Diabetes Mellitus*

The odds of developing type 2 diabetes mellitus were higher for those taking SSRIs (OR = 1.47), weight-inducing antidepressants (OR = 1.26), antipsychotics (OR = 1.43), and those with comorbid endocrinopathies (OR = 3.87) (Table 5).

**Table 4** Adjusted odds ratios for incident obesity/weight gain

| Parameter | Odds ratio | 95% Confidence intervals |
|---|---|---|
| Female | 1.92** | 1.69–2.17 |
| Age 13 and over | | |
| African American | 1.30** | 1.15–1.47 |
| SSRIs | 1.34** | 1.17–1.54 |
| SNRI, other | | |
| Weight-inducing | | |
| Mood stabilizer | 1.30** | 1.11–1.52 |
| Stimulant | 0.80** | 0.69–0.92 |
| Antipsychotic | | |
| Long-term treatment | 1.26* | 1.00–1.58 |

*Significant at $P = 0.05$ or less; **significant at $P = 0.0001$ or less.

### *Dyslipidemia*

The likelihood of developing lipids dysregulation was higher for those taking SSRIs (OR = 1.60; CI = 1.36–1.89; $P < 0.0001$), weight-inducing antidepressants (OR = 1.31; CI = 1.13–1.52; $P = 0.0003$), and those with comorbid endocrinopathies (OR = 1.91; CI = 1.45–2.51; $P < 0.0001$).

### *Anorexia/Weight Loss or Nausea/Vomiting*

The odds of developing incident anorexia or weight loss that required medical intervention were higher for those taking stimulant medications (OR = 1.48; CI = 1.01–2.15; $P = 0.04$), whereas the odds of developing nausea or vomiting that required medical intervention were

**Table 5** Adjusted odds ratios for type 2 diabetes mellitus

| Parameter | Odds ratio | 95% Confidence intervals |
|---|---|---|
| Female | 1.82** | 1.49–2.27 |
| African American | 1.22* | 1.00–1.47 |
| Age 13 and over | 1.33* | 1.10–1.63 |
| SSRIs | 1.37* | 1.10–1.71 |
| SNRI, other | | |
| Weight-inducing | 1.26* | 1.04–1.52 |
| Antipsychotic | 1.41* | 1.06–1.88 |
| Preexisting obesity/weight gain | | |
| Comorbid endocrine disorders | 3.96** | 2.98–5.27 |
| Long-term treatment | | |

*Significant at $P = 0.05$ or less; **significant at $P = 0.0001$ or less.

higher for those taking mood stabilizers (OR = 1.14; CI = 1.01–1.31; $P = 0.04$), but lower for those taking SSRIs (OR = 0.78; CI = 0.70–0.86; $P < 0.0001$).

### *Sexual/Reproductive*

The likelihood of developing hyperprolactinemia and its ensuing reproductive/sexual adverse events were higher for those with comorbid type 2 diabetes mellitus and dyslipidemia (ORs = 1.86 and 1.34) and those with other comorbid endocrine disorders (OR = 6.78) (Table 6). The mean time elapsed between initiation of antidepressant medication and incident hyperprolactinemia and reproductive/sexual adverse events was 29.2 months. Results from the Cox PH regression model demonstrated a significantly shorter time elapsed from start of the antidepressant to onset of hyperprolactinemia and reproductive/sexual adverse events for adolescents (Wald chi-square = 37.35; $P < 0.0001$; HR = 1.73; CIs = 1.45, 2.07), females (Wald chi-square = 105.35; $P < 0.0001$; HR = 8.33; CIs = 3.13, 25.00), and those prescribed SSRIs (Wald chi-square = 5.05; $P = 0.02$; HR = 1.29; CIs = 1.03, 1.61).

**Table 6** Adjusted odds ratios for incident sexual/reproductive events related to medications and comorbid conditions

| Parameter | Odds ratio | 95% Confidence intervals |
|---|---|---|
| Female | 3.15** | 2.43–4.10 |
| African American | 0.77* | 0.62–0.96 |
| Age 13 and over | 6.90** | 5.35–8.93 |
| SSRIs | | |
| Antipsychotics | | |
| Preexisting metabolic condition | 1.86** | 1.40–2.48 |
| Incident metabolic condition | 1.34* | 1.01–1.78 |
| Endocrine condition | 6.78** | 5.10–9.01 |
| Long-term treatment | | |

*Significant at $P = 0.05$ or less; **significant at $P < 0.0001$.

Females and children were at higher risk of experiencing and reporting all the adverse events examined. Long-term treatment of 6 months or more with an antidepressant was significantly associated with only an increased risk of developing obesity/weight gain.

## Discussion

These findings indicate that the antidepressant-treated cohort was more likely to demonstrate all the adverse events examined. Females were more likely to experience all these adverse effects, and childhood (preadolescence) was usually the period when the event was first reported or diagnosed. Incident obesity/excessive weight gain, type 2 diabetes mellitus, and dyslipidemia adverse events were more likely for those individuals prescribed SSRIs, controlling for the effects of co-prescribed mood stabilizers or antipsychotics, and comorbid endocrinopathies. The results generally comport with findings from previous controlled studies and clinical reports in both adult and pediatric populations [8–11,14].

In the treated cohort, co-prescribed antipsychotic medications were associated with obesity/excessive weight gain and type 2 diabetes mellitus, as also found in previous adult and child studies [17–23], but not with the development of dyslipidemia, as the existing literature would predict. This finding may be due to the low percentage of youths in the treated cohort who were co-prescribed antipsychotic medications and the high percentage that were treated for less than 6 months with these psychotropic agents.

Reproductive/sexual adverse events were more likely to occur in those with comorbid metabolic and endocrine disorders, as others have found [8,10,11,13,15], but were not associated with the prescription of SSRIs or the co-prescription of antipsychotic or mood-stabilizing medications, as would be expected based on previous studies [14,15,23]. These findings may be due to practitioners' switching from SSRIs (54%) to SNRI or newer agents (69%) over time, the brief average duration of antidepressant treatment of less than 6 months, or to the low percentage of youth in the treated cohort taking mood stabilizers (19%) or antipsychotic medications (25%), as well as to the likelihood that newer, prolactin-sparing SGAs were used.

Co-prescribed anticonvulsant/mood-stabilizing medications were also associated with obesity/weight gain, while incident anorexia/weight loss was more likely for those taking psychostimulant medications. These findings would be expected due to the previously published

adverse event profiles for mood stabilizing and psychostimulant medications [13,16].

The perspective provided by this longitudinal database has several strengths: the cohort represents a large, heterogeneous group of children and adolescents with varying periods of exposure to antidepressants and other psychotropics; (2) this observational data set can be mined without putting children at risk beyond what they would normally experience in routine clinical practice; (3) there is sufficient power in the treated cohort size to detect somewhat low-incidence medical conditions, and determine the relative safety of the medications; (4) the average treatment length in this study of about 5–6 months provides a longer treatment window during which to determine the incident adverse events, compared to an average length of treatment in randomized clinical trials of 6–12 weeks; (5) previous studies have found that although Medicaid databases provide much less detailed information on individuals than a structured research interview, the physician diagnoses and utilization data are more reliable than client or family self-reports [26,27]; and (6) the outcomes of disparate neuroendocrine-related adverse events associated with antidepressant and co-prescribed medication use are clinically relevant and of substantial public health importance.

These results also need to be interpreted with several limitations in mind: (1) the data were not based on controlled trial methods but, instead, a secondary administrative data set and observational techniques were used in a retrospective cohort design; (2) structured research and clinical interviews were not employed to confirm any of the assigned medical disorders; (3) the reporting of adverse events was based on spontaneous reporting to a physician and is, consequently, likely to be an underestimate; (4) these results report associations and, as a result, *directions of causality cannot be inferred*; (5) key risk factors, such as family history of obesity and metabolic disorders, were not available in the database and are not modeled in these analyses; and (6) there is no way to estimate the representativeness of this Medicaid cohort in relation to those in other states or service systems.

The purpose of this analysis is to draw attention to the safety profile of antidepressants in young populations and the need for expanded empirical foundation to support clinical decisions. These results indicate that antidepressants are associated with neuroendocrine-related (as well as cardiovascular and neurological) adverse events in community-based care settings, and are important in the overall appraisal of the benefits and risks of this class of agents. When evaluating the overall benefit–risk ratio of antidepressants in children and adolescents, the practitioner needs to give careful consideration to possible metabolic disruptions or sexual/reproductive side effects of these agents, especially in individuals with comorbid metabolic/endocrine conditions and those co-prescribed other classes of psychotropic medications.

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## Conflict of Interest

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