Antidepressant Exposure and Risk of Fracture Among Medicaid-Covered Youth

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ABSTRACT

Objective: This study examines the association between antidepressant use and risk of fracture in depressed youth and assesses whether fracture incidence varies over the course of antidepressant treatment.

Method: A retrospective cohort analysis of Ohio Medicaid claims data was conducted for youth ages 6–17 years with a new episode of *ICD-9*–diagnosed depression from 2001–2009. The primary outcome variable was time to fracture. Fracture rates were compared between depressed youth treated with antidepressant medication and untreated depressed youth. Time categories of no use, past use, and current use were compared.

Results: Of 50,673 depressed youths, 5,872 (11.6%) experienced a fracture. Of those who had a fracture, 2,228 (37.9%) were exposed to antidepressants, 80% of which were selective serotonin reuptake inhibitors. The adjusted hazard ratio (HR) was 3% higher in those currently prescribed antidepressants (HR = 1.03; 95% CI, 1.00–1.06; $P = .03$). The risk ratio (RR) for adjusted fracture rates per 10,000 persons was twice as high during the first 30 days of antidepressant use compared to the other time periods (RR = 2.0; 95% CI, 1.2–3.3; $P = .007$). The number of fractures for those with past antidepressant use did not differ from those with no history of antidepressant use.

Conclusions: Antidepressant use may be associated with a small but significant increase in fracture risk, particularly within the first 30 days of treatment. Findings underscore a need for additional prospective and mechanistic research. Prescribers should consider other risks for fracture in antidepressant-treated youth, particularly disability and the concomitant use of other medications that increase fracture risk.

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Little is known about pediatric skeletal health risks from antidepressant treatment, although selective serotonin reuptake inhibitors (SSRIs) are linked to higher fracture rates and loss of bone mass in adults.[1] Following United States Food and Drug Administration (FDA) approval of several SSRIs for use in children 8 years and older, and practice parameters for major depressive and obsessive-compulsive disorders in youth, prescriptions for SSRIs dramatically rose.[2] Despite ~3 million prescriptions written for >6 million depressed US children from 1998–2001, phase IV safety reports focused primarily on suicidal ideation and attempts.[3,4]

SSRIs are implicated in altering skeletal development and remodeling in translational literature including basic and human case reports and series and epidemiologic cross-sectional, case-control, and cohort, including longitudinal, prospective studies. Findings include osteoblast and osteoclast inhibition,[5] impaired growth in animals and humans (including intrauterine growth),[6–8] and increased risk for bone loss, hip and vertebral fracture, and osteoporosis in adults.[1]

Childhood and adolescence are dominated by skeletal modeling as a core component of normal growth and development. Deleterious drug effects on bone formation and remodeling could place children, more mobile with smaller and more metabolically active bones than adults, at greater risk for poor bone quality and failure to meet full genetic potential for bone growth, density, and strength. We hypothesized that antidepressant use might also affect fracture rates in pediatric populations.

To clarify whether fracture risk screening and prevention may be warranted in youth taking antidepressants, this study sought to determine (1) any associations between antidepressant use and bone fractures in children and adolescents; and (2) whether fracture rates vary across the course of antidepressant treatment.

METHOD

Study Design and Population

A retrospective, longitudinal cohort analysis of state Medicaid claims data was conducted. Inclusion criteria included (1) age of 6–17 years, (2) a new episode of depression, and (3) continuous enrollment in Medicaid for at least a 1-year period, 6 months before and after the index claim for depression, July 1, 2001, to June 30, 2009 (N = 75,528). A new episode of depression was defined if there were no antidepressant prescriptions or depression claims during the 6 months prior to the index claim (*International Classification of Diseases*, Ninth Revision, Clinical Modification [*ICD-9-CM*] codes 296.2, 296.3, 300.4, and 311). Youth who (1) fractured in the 6 months before the index diagnosis (N = 8,383), (2) began antidepressant use ≥30 days after diagnosis (N = 11,668), or (3) had documented

Clinical Points

- Selective serotonin reuptake inhibitors are linked to higher fracture rates and bone loss in adults, but few studies have investigated pediatric skeletal health risks from antidepressant treatment.
- Assessment of and ongoing monitoring for fracture risk should be part of the standard of care for youth treated with antidepressants.
- Providers should reduce, when possible, medications with sedative or hypotensive or bone-suppressing properties, encourage and prescribe exercises to improve balance and leg strength, and counsel patients and families on environmental fall precautions.

antidepressant use within 6 months prior to depression diagnosis (N = 4,804) were excluded (total N = 24,855). The final analytic sample was 50,673.

Data Source

Medicaid eligibility, fee-for-service claims, and managed care encounter data obtained from the Ohio Department of Job and Family Services included paid claims for prescription drugs and inpatient and outpatient services for enrollees. Eligibility information included monthly enrollment status, eligibility category, and demographic characteristics. Pharmacy files provided data on prescriptions filled by outpatient pharmacies, including dates written and dispensed, generic name and code, national drug code, dosage, number of days supplied, and quantity. Psychotropic medications were identified using dispense dates and generic name codes. Institutional and professional files provided service claims for inpatient hospitalizations, physician visits (office or hospital-based), and other outpatient services and included service dates, procedure codes, and up to 7 *ICD-9-CM* diagnoses. Data were followed until a last time point of December 31, 2009. The Ohio State Institutional Review Board approved all study procedures.

Measures

Outcome measure. The primary outcome measure was time in years to first fracture, including fractures of the upper and lower limb (*ICD-9-CM* 810–819, 820–829), spine and trunk (*ICD-9-CM* 805–809), and the skull (*ICD-9-CM* 800–804).

Antidepressant exposure. Pharmacy file antidepressants were classified by drug subclass as SSRIs, tricyclic antidepressants (TCAs), or other antidepressants, including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline (SSRIs); amoxapine, amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, and protriptyline (TCAs); and bupropion, duloxetine, mirtazapine, trazodone, and venlafaxine (others).

Associations between antidepressants and fracture were examined by separating depressed youth into 2 groups. Youth not prescribed antidepressants were classified as "none"; analysis time began at date of depression diagnosis and ended at date of fracture or end of study, whichever came first. Youth prescribed antidepressants had an individual cumulative duration of exposure calculated. *Current use* was defined as the number of consecutive days between their first antidepressant prescription start date and the end date of the last prescribed antidepressant, date of fracture, or end of study, whichever came first. *Past use* was defined as the number of consecutive days between the last antidepressant prescription's end date and fracture date or, if no fracture, end of study. As an individual's status (none, current, or past) could change during the analysis time period, a time-varying covariate was used to model the antidepressant variable.

Covariates. Table 1 lists demographic, clinical, and treatment characteristics considered as potential covariates. Demographic variables included age at diagnosis, race and ethnicity, sex, and Medicaid eligibility category (poverty, disabled, or foster care). Prescriptions for any antipsychotics, anticonvulsants, stimulants, anxiolytics, proton pump inhibitors, and steroids during the follow-up period were considered covariates and potential confounders, as they are typically controlled for in other fracture risk studies due to known associations with fractures. Comorbid physical and psychiatric disorders were identified as present or not present during follow-up, using *ICD-9* codes in the medical services claims files (see Table 1).

Data Analysis

Patient demographics, clinical characteristics, and specific antidepressant use patterns compared using Pearson χ^2 test across fracture status are presented as frequencies and percentages. There were 73,522 observations nested within 50,673 subjects, due to the time-varying nature of antidepressant use. Cox proportional time-varying hazard regression was performed, as an individual's antidepressant use could have 1 observation (none or current), 2 observations (none followed by current or current followed by past), or 3 observations (none followed by current followed by past). Antidepressant exposure was therefore entered into the model as a time-varying 3-level categorical variable.

For the primary study goal (antidepressant effects on fracture risk), the baseline regression model included subject age, sex, and race and a single indicator variable for use of any of the covariate comedications above, in addition to the time-varying antidepressant risk factor. Risk factor modeling was performed to determine if any additional covariates, acting as either confounder or effect modifier, should be added to the model.[9] A confounder was defined if, when added to the model, the hazard ratio (HR) associated with antidepressant administration changed by more than 10% in either direction, without considering statistical significance.[10] An effect modifier was defined as a covariate that had a significant interaction ($P \leq .05$) with antidepressant administration. A Kaplan-Meier curve was created to illustrate the relationship between antidepressant

Table 1. Demographic and Clinical Characteristics of Depressed Children and Adolescents by Fracture Status

Characteristic	No Fracture (n = 44,801), n (%)	Fracture (n = 5,872), n (%)	Total (N = 50,673), N (%)	*P* Value
Demographics				
Age, y				< .001
6–10	4,191 (9.4)	304 (5.2)	4,495 (8.9)	
11–13	6,783 (15.1)	753 (12.8)	7,536 (14.9)	
14–17	33,827 (75.5)	4,815 (82.0)	38,642 (76.3)	
Sex				< .001
Male	18,381 (40.9)	3,408 (58.0)	21,749 (42.9)	
Female	26,420 (59.0)	2,464 (42.0)	28924 (57.1)	
Race				< .001
White	30,797 (68.7)	4,616 (78.6)	35,413 (69.9)	
Black	13,507 (30.2)	1,208 (20.6)	14,715 (29.0)	
Other	497 (1.1)	48 (0.8)	545 (1.1)	
Ethnicity				< .001
Non-Hispanic	43,548 (97.2)	5,760 (98.1)	49,308 (97.3)	
Hispanic	1,253 (2.8)	112 (1.9)	1,365 (2.7)	
Eligibility category				< .001
Poverty	38,753 (86.5)	4,881 (83.1)	43,634 (86.1)	
Disabled	2,349 (5.2)	560 (9.6)	2,909 (5.7)	
Foster care	3,699 (8.3)	431 (7.3)	4,130 (8.2)	
Clinical				
Any antidepressants	15,463 (34.5)	2,228 (37.9)	17,691 (34.9)	< .001
Any psychiatric comorbidity				
Anxiety	6,831 (15.3)	1,122 (19.1)	7,953 (15.7)	< .001
Conduct	12,921 (28.8)	2,140 (36.4)	15,061 (29.7)	< .001
ADHD	12,357 (27.6)	2,231 (38.0)	14,588 (28.8)	< .001
Substance abuse	4,677 (10.4)	922 (15.7)	5,599 (11.1)	< .001
Autism	99 (0.2)	13 (0.2)	112 (0.2)	.995
Mental retardation	9,717 (21.7)	1,567 (26.7)	11,284 (22.3)	< .001
Any medical condition				
Diabetes	712 (1.6)	133 (2.3)	845 (1.7)	< .001
Sickle cell anemia	70 (0.2)	12 (0.2)	82 (0.2)	.39
Cerebral palsy	190 (0.4)	26 (0.4)	216 (0.4)	.84
Seizures	907 (2.0)	194 (3.3)	1,101(2.2)	< .001
Asthma	6,812 (15.2)	1,221 (20.8)	8,037 (15.9)	< .001
Congenital heart disease	456 (1.0)	88 (1.5)	544 (1.1)	.001
Cancer	2,001 (4.5)	346 (5.9)	2,347 (4.6)	< .001
Immunocompromised	227 (0.5)	35 (0.6)	262 (0.5)	.37
Major organ disease	232 (0.5)	49 (0.8)	281 (0.6)	.002
Anorexia nervosa	39 (0.09)	4 (0.07)	43 (0.08)	.81
Comedication				
Any antipsychotic	10,630 (23.7)	1,794 (30.5)	12,424 (24.5)	< .001
Any anticonvulsant	6,705 (15.0)	1,259 (21.4)	7,964 (15.7)	< .001
Any stimulant	11,419 (25.5)	1,900 (32.4)	13,319 (26.3)	< .001
Any anxiolytic	2,475 (5.5)	542 (9.2)	3,107 (6.0)	< .001
Any proton pump inhibitors	9,330 (20.8)	2,124 (36.2)	11,454 (22.6)	< .001
Any steroids	10,161 (22.7)	2,149 (36.6)	12,310 (24.3)	< .001
Any comedication	27,361 (61.1)	4,526 (77.1)	31,887 (62.9)	< .001

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

use (none, current, or past) and fracture risk. The proportional hazards assumption was tested by running the Cox proportional time-varying regression and verifying graphically that the 3 hazard plots (none vs current vs past) were parallel.

To determine whether timing of antidepressant use affected fracture risk, data were divided into 2 groups: group 1, current observations; group 2, past observations. A Cox proportional hazard regression was run separately for each group, with fractures per 10,000 youths expressed over 30-day increments up to 1 year. This regression used the same final model developed in the risk factor analysis above. All analyses were run using Stata, version 13.1 (StataCorp LP, College Station, TX).[11]

Table 2. Pattern of Antidepressant Use Among Depressed Children and Adolescents

Description of Antidepressants	No Fracture, n (%)	Fracture, n (%)	Total, N (%)
Total	44,801 (88.4)	5,872 (11.6)	50,673 (100.0)
Any antidepressants	15,463 (34.5)	2,228 (37.9)	17,691 (34.9)
Any SSRIs	12,329 (27.5)	1,694 (28.9)	14,023 (27.7)
Citalopram	2,833 (23.0)	468 (27.6)	3,301 (23.5)
Escitalopram	2,849 (23.1)	438 (25.9)	3,287 (23.4)
Fluoxetine	4,673 (37.9)	591 (34.9)	5,264 (37.5)
Fluvoxamine	139 (1.1)	32 (1.9)	171 (1.2)
Paroxetine	2,228 (18.1)	452 (26.7)	2,680 (19.1)
Sertraline	6,151 (49.9)	941 (55.6)	7,092 (50.6)
Any other	4,042 (9.0)	709 (12.1)	4,751 (9.4)
Bupropion	2,321 (57.4)	415 (58.5)	2,736 (57.6)
Duloxetine	159 (3.9)	20 (2.8)	179 (3.8)
Mirtazapine	841 (20.8)	209 (29.5)	1,050 (22.1)
Trazodone	1,528 (37.8)	300 (42.3)	1,828 (38.5)
Venlafaxine	877 (21.7)	189 (26.7)	1,066 (22.4)
Any TCA	442 (1.0)	70 (1.2)	512 (1.0)
Amoxapine	0 (0.0)	0 (0.0)	0 (0.0)
Amitriptyline	265 (60.0)	35 (50.0)	300 (58.6)
Clomipramine	6 (1.4)	1 (1.4)	7 (1.4)
Desipramine	9 (2.0)	3 (4.3)	12 (2.3)
Doxepin	28 (6.3)	8 (11.4)	36 (7.0)
Imipramine	177 (40.1)	37 (52.9)	214 (41.8)
Maprotiline	0 (0.0)	0 (0.0)	0 (0.0)
Nortriptyline	0 (0.0)	0 (0.0)	0 (0.0)
Protriptyline	0 (0.0)	0 (0.0)	0 (0.0)
No antidepressant use	29,338 (65.5)	3,644 (62.1)	32,982 (65.1)
Monotherapy	14,133 (31.5)	1,989 (33.9)	16,122 (31.8)
Polytherapy[a]	1,330 (3.0)	239 (4.0)	1,569 (3.1)

[a]Polytherapy is defined as 2 or more antidepressants prescribed and filled simultaneously.
Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

RESULTS

Demographic and Clinical Covariates

Table 1 describes demographics and clinical characteristics by fracture status. Of 50,673 individual youth, 17,691 (34.9%) were prescribed antidepressants, and 5,872 (11.6%) experienced a fracture. Those who experienced fracture(s) tended to be older (14–17 years), male, white, non-Hispanic, or disabled. Fracture types and frequencies experienced by the total number of individuals were upper limb, 6.5% (n = 3,286); lower limb, 3.4% (n = 1,726); skull, 1.2% (n = 615); and spine and trunk, 0.7% (n = 365). Percentages of the total number of fracture incidents (5,992) were sustained in the upper limb, 54.8%; lower limb, 28.8%; skull, 10.3%; and spine and trunk, 6.1%. Psychiatric comorbidities were all greater in the fracture group except for autism. Youth who suffered a fracture were also more likely to have medical comorbidities and to have exposure to all concomitant medications previously reported to raise fracture risk (Table 1).

Antidepressant Treatments

Table 2 describes the sample's antidepressant exposure. About one-third were prescribed at least 1 antidepressant. The fracture group had higher use for all antidepressant classes (SSRIs, other antidepressants, and TCAs). This relationship was also observed for

Figure 1. Kaplan-Meier Curve of Fracture Risk by Antidepressant Use

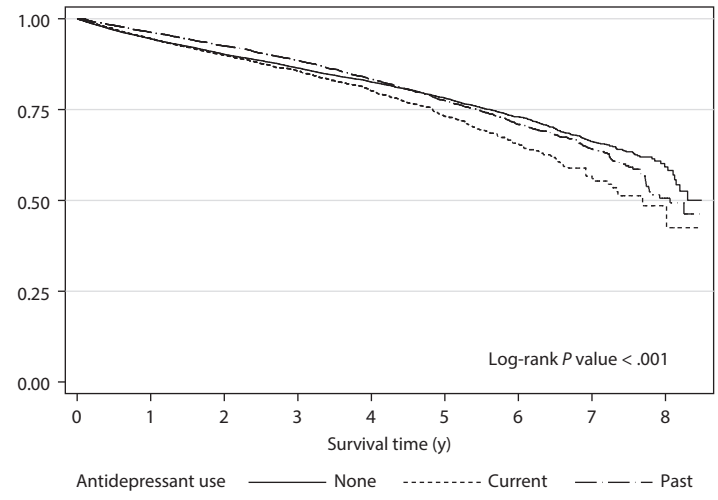

Table 3. Estimated Hazard Ratio (HR) and 95% Confidence Interval (CI) of Fracture Risk Associated With Antidepressant Exposure in Depressed Children and Adolescents

	HR	95% CI		*P* Value
Unadjusted				
None (referent)	1.00	…	…	…
Past	1.04	1.01	1.06	.002
Current	1.09	1.06	1.12	<.001
Adjusted[a]				
None (referent)	1.00	…	…	…
Past	0.99	0.97	1.01	.38
Current	1.03	1.00	1.06	.03

[a]Regression adjusted for subject age, race, gender, and prescriptions for any of the following comedications during the study: antipsychotic, anticonvulsant, stimulant, proton pump inhibitor, or steroids.

individual antidepressants except fluoxetine and duloxetine. The vast majority of antidepressant-treated youth (91%) were prescribed a single antidepressant; 9% were prescribed 2 or more antidepressants simultaneously.

Time Course

Fracture hazard was highest for current antidepressant exposure (Figure 1, Kaplan-Meier curve). The hazard for past antidepressant exposure was similar to no exposure. Table 3 displays unadjusted and adjusted HRs for past and current exposure, with the no exposure group as referent, based on Cox proportional hazard regression. The adjusted hazard of fracture was 3% higher for those currently prescribed antidepressants compared to those never-prescribed (HR = 1.03; 95% CI, 1.00–1.06; $P = .03$). There were no differences in fracture hazard between untreated and past treated youth (HR = 0.99; 95% CI, 0.97–1.01; $P = .38$). Supplementary eTable 1 (available at PSYCHIATRIST.COM) lists the percent change in unadjusted current and past HRs with possible confounders added to the regression model individually. None rose to the level of a confounder (change of 10% or more in either direction). Accordingly, comorbid physical and psychiatric disorders were not included in the model. Final results were adjusted by age, race, sex, and comedications, as these variables associate with fracture. None of the interaction *P* values were significant for variables in Supplementary eTable 1 at the .05 level. Thus, no variables modified the relationship between antidepressant exposure and fracture occurrence.

Table 4 presents the unadjusted and adjusted fractures per 10,000 persons for current and past use of prescribed antidepressants. In the first half of the table, the first 30-day increment represents the first 30 days after starting antidepressants, while the second 30-day increment represents days 30 to 60 after starting antidepressants. In the second half, the first 30-day increment represents the first 30 days after stopping the antidepressant. The risk ratio (RR), based on adjusted fractures per 10,000 persons during the first 30 days of current antidepressant use, was compared to the other time periods. The first 30 days after starting an antidepressant appear to be associated with greater fracture risk: the adjusted fracture rate per 10,000 persons is 44, compared with 19 to 28 for the remaining increments after 30 days (RR = 2.0, 95% CI, 1.2–3.3, $P = .007$). There was no difference in fracture risk across time for past antidepressant use (RR first 30 days past = 1.1; 95% CI, 0.5–2.2; $P = .85$). The median follow-up period for participants was 1.66 years (interquartile range: 0.73–3.25 years).

DISCUSSION

To our knowledge, this is the first study of fracture risk associated with antidepressant use in children and adolescents. The primary finding is that active antidepressant treatment of depressed children and adolescents is associated with a small but significant increase in fracture risk within the first 30 days of treatment. We found that for those youth aged 6–17 years who were prescribed antidepressants, fractures occurred at an annual rate of 1.5%. This is within the range of reported overall pediatric fracture rates of 1.2%–3.5% per year.[12] Increased fracture risk is likely to be associated with use of any class of antidepressant, including SSRIs, other novel antidepressants, and TCAs, though risk may vary by class and by specific agent. An association was not found between past pediatric antidepressant use and fracture risk.

Although mechanisms cannot be determined by observational data, the association between current use and elevated fracture risk early in treatment suggests that a greater propensity to falls and accidents may contribute. SSRIs can cause behavioral disinhibition, increasing risk for physical trauma. TCAs can increase body sway (decreased postural balance) in adults,[13] possibly due to anticholinergic or cardiovascular effects. Although there are no similar pediatric studies on whether or how SSRIs might affect postural stability or falls, SSRI use in adults also appears to increase fall risk.[14,15]

Falls have been postulated as contributory in the adult literature on antidepressants and fracture risk, due to greater

Table 4. Fractures per 10,000 Persons Over 30-Day Increments for Current and Past Antidepressant Use

Time Period (d)	Fractures per 10,000 Persons	
	Unadjusted	Adjusted[a]
Probabilities for those currently on an antidepressant at the index date		
0–30	91	44
30–60	44	21
60–90	51	24
90–120	49	24
120–150	45	22
150–180	41	20
180–210	58	28
210–240	48	24
240–270	41	20
270–300	40	20
300–330	38	19
330–360	40	20
Probabilities for those with past use of antidepressants		
0–30	41	14
30–60	31	11
60–90	33	12
90–120	30	11
120–150	34	12
150–180	37	13
180–210	42	15
210–240	51	18
240–270	46	16
270–300	33	12
300–330	28	10
330–360	43	15

[a]Adjusted for subject age, race, gender, and prescriptions for any of the following comedications during the study: antipsychotic, anticonvulsant, stimulant, proton pump inhibitor, or steroids.

risk immediately after starting SSRIs. Elevated hip fracture rates in elderly Canadians using SSRIs were first reported in 1998, via a case-control design ($OR_{adj} = 2.4$ for a 1-year period; 95% CI, 2.0–2.7).[16] Fracture risk was higher in new current SSRI users compared to past and continuous users, consistent with our findings in children. At least 12 subsequent epidemiologic studies have confirmed greater fracture risk in adults taking SSRIs. The population-based Canadian Multicentre Osteoporosis Study (CaMoS) found an adjusted HR of 1.68 (95% CI, 1.32–2.14).[17] In the Women's Health Initiative Observational Study (1994–1998), fracture risk in women ≥ 65 years was increased by depressive symptoms (HR = 1.08; 95% CI,1.02- 1.14) and by antidepressant therapy (HR = 1.22; 95% CI, 1.15-1.30), particularly for vertebral fractures, suggesting that trabecular bone may be more sensitive to antidepressant effects (HR = 1.36; 95% CI, 1.14- 1.16).[18] Two controlled studies, one prospective, described lower bone mineral density (BMD) in adults taking SSRIs, consistent with direct negative effects on bone.[19,20] Depression itself is associated with lower BMD in premenopausal adult women,[21] elderly men,[22] and adolescent girls.[23] Several meta-analyses have confirmed depression is related to osteoporosis, but cannot confirm causality. The relationship between depression and lower BMD was significant only for women with *DSM*-criteria major depression diagnosed by a psychiatrist ($d = -0.36$); lower bone mass was found in the spine, hip, and forearm on meta-analysis.[24] Bone mass (anterior-posterior spine, total femur, and femoral neck) was significantly lower in depressed women versus controls, likely raising fracture risk.[25] A third meta-analysis supported an association between depression, elevated fracture risk, and bone loss, noting that these associations may be mediated by antidepressants, as the hazard ratio (HR) for studies adjusted for antidepressant treatment was 1.05 (95% CI, 0.86–1.29; $P = .06$) versus 1.3 (95% CI, 1.11–1.52; $P = .01$) for those not adjusted.[26] One study to date has described lower bone mass density (BMD) in youth taking SSRIs. In a cross-sectional naturalistic cohort of risperidone-treated boys, risperidone-induced hyperprolactinemia and concomitant SSRI use were associated with lower radial trabecular BMD via peripheral quantitative computed tomography (pQCT; $P = .03$), and lower lumbar spine BMD *z*-score via dual-energy x-ray absorptiometry (DXA) ($P < .05$).[27] A study of SSRI treatment for vasomotor symptoms associated with perimenopause in women without mental disorders found higher fracture rates compared to a demographically similar cohort who started treatment with H_2 antagonists or proton pump inhibitors.[28]

Strengths and Limitations

Study strengths include population data, an internal comparison group of depressed youth without antidepressant exposure, and control for multiple clinical confounders. Limitations include observational results (precluding determination of causality), lack of standardized diagnostic assessment, and inability to assess or control for direct effects of depression or other illnesses or exposures on fracture rates and bone characteristics (density, mass, strength, or quality). Additionally, we lack information comparing lifestyle risks for poor bone health between the fracture versus the no-fracture groups, including dietary calcium, omega-3 fatty acid and vitamin D intake, weight-bearing physical activity, and exposure to tobacco and other substances of abuse. Compliance, dose, and changes between antidepressant types are unknown, as is depressive illness duration. Over half of antidepressant-treated youth may be nonadherent, thus biasing results toward the null hypothesis and potentially increasing significance in the compliant group.[29]

Clinical Implications

Current recommendations for pediatric depression are unlikely to change dramatically in the foreseeable future, necessitating antidepressant treatment for youth with moderate to severe depression. Our results, with the literature to date, underscore the need for a proactive approach to reduce antidepressant-associated fracture risk, particularly at treatment initiation and at antidepressant class or dose changes. Assessment for fracture risk should be part of a standard of care for youth who are being considered for treatment with antidepressants. Lowest doses of antidepressants should be used for the shortest period of time possible. Clinical strategies to reduce fracture risk in youth currently taking antidepressants include monitoring closely for baseline conditions or side effects that increase fall risk, such as dizziness or drowsiness, of central or cardiovascular origin. Checking orthostatic blood pressure

and pulse and assessing gait and balance via a Timed Get Up and Go test are helpful screening strategies in the office or at the bedside.[30] In youth with a fracture history, clinicians should also review nutrition, physical activity, pubertal stage and growth patterns, illness severity, family fracture history, and medication and substance abuse exposures. Fall risk reduction strategies, particularly for those with neuromuscular or orthopedic conditions, or taking anticonvulsants or analgesics, include reducing concomitant medications with sedative or hypotensive properties or that are known to suppress bone metabolism (eg, proton pump inhibitors, oral steroids, and some forms of hormonal contraception), prescribing exercises to improve balance and leg strength, and counseling patients and families on environmental fall precautions (eg, removing throw rugs and using night lights). Weight-bearing exercise along with adequate dietary calcium and vitamin D intake may improve bone and muscle strength, although whether these steps moderate any adverse SSRI effects on bone mineralization is unknown.

Screening is indicated for youth with multiple fracture risks, as low bone mass raises fracture risk above the rate of 33%–50% in healthy childhood, already similar to osteoporotic adults.[31] The Pediatric Position Development Conference of the International Society for Clinical Densitometry[32] endorses a baseline dual-energy X-ray absorptiometry (DXA) for conditions such as cystic fibrosis, anorexia nervosa, and inflammatory bowel disease,[33] but does not address all disorders present in this Ohio Medicaid database. Youth with low bone mass for age or a significant fracture history should be evaluated by a specialist with bone expertise appropriate to the clinical presentation, such as a pediatric endocrinologist, nephrologist, geneticist, rheumatologist, or gynecologist.[34] A call has been made to acknowledge SSRIs as a medication class that contributes to osteoporosis, leading to consideration for DXA testing in those taking SSRIs who have additional fracture risks or prolonged exposure.[35]

CONCLUSIONS

Prospective controlled trial research is needed on antidepressant exposures and their mechanisms and effects on bone quality, density, and biomarkers (including short- and long-term fracture risk), examining bone imaging and metabolism in youth newly treated with SSRI/other novel antidepressants. Whether clinical monitoring of bone biomarkers in youth is helpful is unclear but requires study, given that in depressed older adults 12 weeks of venlafaxine increased bone resorption.[36] More intensive screening, prevention, and intervention are indicated in this population, especially for those with a prior fracture history, to modify lifestyle factors such as vitamin D status, dietary calcium intake, and physical activity, to promote bone mass and quality. Genetic screening for serotonin transporter gene variants should be examined to determine its use in predicting pediatric bone vulnerability to antidepressant effects.[37] DXA use to estimate fracture risk in depressed multiply comorbid and/or comedicated pediatric populations should be examined, with historical risk models generated for high-risk subgroups and the general pediatric population, similar to the World Health Organization FRAX online fracture risk assessment tool for adults,[38] to provide families and clinicians with better information.

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Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Silenor and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), maprotiline, mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), protriptyline (Vivactil and others), risperidone (Risperdal and others), sertraline (Zoloft and others).

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Additional information: For information on the database, contact Helen Anne Sweeney from the Department of Mental Health and Addiction Services, helenanne.sweeney@mha.ohio.gov.

Supplementary material: Available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Antidepressant Exposure and Risk of Fracture Among Medicaid-Covered Youth

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List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1: Confounding analysis of time-varying Cox proportional hazard regression

Potential Confounders	HR	95% CI		*p*-value	Change
Unadjusted					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Categorical age					
Current	1.07	1.04	1.10	<0.001	-1.8%
Past	1.02	1.00	1.05	0.03	-1.9%
Gender					
Current	1.10	1.07	1.13	<0.001	0.9%
Past	1.03	1.01	1.06	0.003	-1.0%
Race					
Current	1.06	1.03	1.09	<0.001	-2.8%
Past	1.02	1.00	1.04	0.09	-1.9%
Ethnicity					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Eligibility					
Current	1.08	1.05	1.11	<0.001	-0.9%
Past	1.03	1.01	1.06	0.003	-1.0%
Anxiety disorder					
Current	1.08	1.05	1.11	<0.001	-0.9%
Past	1.03	1.01	1.06	0.005	-1.0%
Substance abuse					
Current	1.08	1.05	1.11	<0.001	-0.9%
Past	1.03	1.01	1.05	0.009	-1.0%
Conduct disorder					
Current	1.08	1.05	1.11	<0.001	-0.9%
Past	1.03	1.01	1.05	0.005	-1.0%
ADHD					
Current	1.08	1.05	1.11	<0.001	-0.9%
Past	1.03	1.01	1.05	0.01	-1.0%
MR					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Autism					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Diabetes					
Current	1.08	1.06	1.11	<0.001	-0.9%
Past	1.04	1.01	1.06	0.002	0.0%
Sickle cell					

Potential Confounders	HR	95% CI		*p*-value	Change
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Cerebral palsy					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Seizures					
Current	1.08	1.06	1.11	<0.001	-0.9%
Past	1.03	1.01	1.06	0.002	-1.0%
Asthma					
Current	1.08	1.05	1.11	<0.001	-0.9%
Past	1.03	1.01	1.06	0.003	-1.0%
Congenital heart					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Cancer					
Current	1.08	1.06	1.11	<0.001	-0.9%
Past	1.03	1.01	1.06	0.002	-1.0%
Immunocompromised					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Auto immune					
Current	1.08	1.05	1.11	<0.001	-0.9%
Past	1.04	1.01	1.06	0.002	0.0%
Major organ					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Anorexia					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.002	0.0%
Anti-psychotic					
Current	1.08	1.05	1.11	<0.001	-0.9%
Past	1.03	1.01	1.06	0.005	-1.0%
Anti-convulsant					
Current	1.07	1.04	1.10	<0.001	-1.8%
Past	1.03	1.01	1.05	0.01	-1.0%
Stimulant					
Current	1.09	1.06	1.12	<0.001	0.0%
Past	1.04	1.01	1.06	0.001	0.0%
Anti-anxiety					
Current	1.07	1.04	1.10	<0.001	-1.8%
Past	1.03	1.01	1.05	0.006	-1.0%
PPI					

Potential Confounders	HR	95% CI		*p*-value	Change
Current	1.05	1.02	1.07	0.002	-3.7%
Past	1.02	1.00	1.04	0.09	-1.9%
Steroid					
Current	1.07	1.04	1.10	<0.001	-1.8%
Past	1.03	1.01	1.05	0.005	-1.0%
Any medication					
Current	1.05	1.02	1.08	< 0.001	-3.7%
Past	1.01	0.99	1.04	0.21	-2.9%

Abbreviations: Attention Deficit Hyperactivity Disorder (ADHD); Mental Retardation (MR); Proton Pump Inhibitors (PPI)