

# Benzodiazepine Treatment and Fracture Risk in Young Persons With Anxiety Disorders

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abstract

**BACKGROUND:** Benzodiazepines are commonly prescribed to treat anxiety disorders and have been associated with falls and fractures in older adults. It is unknown whether benzodiazepines increase fracture risk in youth. We examined whether youth with anxiety disorders initiating benzodiazepine treatment have an increased risk of fractures compared with youth initiating selective serotonin reuptake inhibitors (SSRIs).

**METHODS:** We used claims from commercially insured children (6–17 years) and young adults (18–24) with a recent anxiety disorder diagnosis, initiating benzodiazepines or SSRIs (2008–2016). Youth were followed until fracture, treatment discontinuation or switching, disenrollment, 3 months, or December 31, 2016. The primary end point was diagnostic codes for upper and lower limb fractures. Incident fracture rates, incident rate ratios (IRRs), and incident rate differences (IRDs) were estimated with propensity score inverse probability of treatment weighting.

**RESULTS:** The cohort included 120 715 children and 179 768 young adults. In children, crude fracture rates during treatment were 33.1 per 1000 person-years (PYs) for benzodiazepine initiators and 25.1 per 1000 PYs for SSRI initiators. Adjusted IRR and IRD were 1.53 (95% confidence interval [CI]: 0.94–2.50) and 13.4 per 1000 PYs. Risk was heightened in children initiating long-acting benzodiazepines versus SSRIs (adjusted IRR = 2.30 [95% CI: 1.08–4.91]). Fracture rates were lower in young adults, with minimal differences between treatments (adjusted IRR = 0.85 [95% CI: 0.57–1.27]; adjusted IRD = –1.3 per 1000 PYs).

**CONCLUSIONS:** An increased rate of fractures in children, but not young adults, with anxiety disorders initiating benzodiazepine treatment compared to SSRI treatment suggests a need for increased caution in the weeks after benzodiazepine initiation in children.



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**WHAT'S KNOWN ON THIS SUBJECT:** Benzodiazepine side effects include dizziness and slowed reaction time. Benzodiazepine treatment has been associated with an increased risk of fractures in older adults. It is unknown whether benzodiazepine treatment increases fracture risk in younger populations compared to alternative treatments.

**WHAT THIS STUDY ADDS:** We observed a heightened fracture rate in children with anxiety disorders initiating benzodiazepine treatment compared to selective serotonin reuptake inhibitor treatment, with no heightened rate in young adults. Increased caution after benzodiazepine initiation may be warranted in children.

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Benzodiazepines are a commonly prescribed medication class in the United States,<sup>1-3</sup> including in younger populations, with 2.8% of adolescents (12–17 years) and 6.3% of young adults (18–25 years) reporting a past-year prescription of benzodiazepine or tranquilizer use.<sup>4</sup> In mental health–related visits, 9% of adolescents and 21% of young adults were prescribed a benzodiazepine or other sedative-hypnotic medication.<sup>5</sup> Benzodiazepines are prescribed for psychiatric and nonpsychiatric conditions and are commonly used for anxiety disorders among youth<sup>6,7</sup> despite not being a recommended or Food and Drug Administration–approved pharmacotherapy for pediatric anxiety disorders.<sup>8-10</sup>

Side effects of benzodiazepine treatment can include slowed reaction time, drowsiness, dizziness, and weakness,<sup>11,12</sup> which can result in injury. Benzodiazepine treatment is associated with an increased risk of motor vehicle crashes, falls, and fractures.<sup>13-18</sup> Recent meta-analyses and studies support earlier findings that adult benzodiazepine users have an increased fracture risk compared with adults who do not use benzodiazepine, with most studies being focused on hip fractures in older adults.<sup>15,19-23</sup> The greatest risk of hip fracture was observed with short-term benzodiazepine use,<sup>19,24,25</sup> suggesting new users may be unaccustomed to benzodiazepine effects. In a case control study with stratified analyses of individuals ≤40 years of age, anxiolytic use remained associated with an increased fracture risk compared with never users.<sup>26</sup> We are unaware of a previous study that has been focused on benzodiazepines and fracture risk in young persons.

If benzodiazepine side effects contribute to unintentional falls, young persons may be susceptible to heightened fracture risk during benzodiazepine treatment. Pediatric

fractures are most often caused by falls.<sup>27,28</sup> Falls account for one-third of nonfatal injuries in children, with ~2.8 million children presenting to the emergency department (ED) for fall-related injuries annually.<sup>29</sup> Fractures can limit daily activities, negatively impact quality of life, and require medical procedures.<sup>30-32</sup>

We evaluated fracture risk in children and young adults with anxiety disorders initiating benzodiazepine treatment compared to selective serotonin reuptake inhibitors (SSRIs), a guideline-recommended pharmacotherapy for anxiety disorders.<sup>10</sup> Benzodiazepines and SSRIs are the most commonly prescribed medications for anxiety disorders, with similar prevalence in adults and with SSRIs prescribed more frequently than benzodiazepines in children.<sup>33-35</sup> By focusing on youth with anxiety disorders and employing an active comparator, we sought to directly inform treatment decisions while reducing confounding by indication.

Evaluating the association between benzodiazepine treatment and fracture risk compared to therapeutic alternatives (ie, SSRIs) in young people can inform clinicians, parents, and patients in treating anxiety disorders. We therefore aimed to determine if children and young adults with anxiety disorders initiating benzodiazepine treatment have a short-term increased risk of fractures compared with SSRI initiators. Children (6–17 years) and young adults (18–24 years) were examined separately given differences in injury and fracture rates<sup>36-38</sup> and prescribing guidelines.<sup>10,39-41</sup>

## METHODS

### Data Source and Study Population

We used MarketScan Commercial Claims and Encounters data from January 1, 2007, through December

31, 2016. The database covers individuals with employer-sponsored health insurance and their dependents across the United States. Patient-level details were available on insurance enrollment, outpatient and inpatient services, and outpatient dispensed prescriptions. Service visits contained information on the date, provider type, diagnostic codes, and procedure codes.

We identified privately insured children (6–17 years) and young adults (18–24) newly initiating benzodiazepine or SSRI treatment (Table 1 footnotes). We used records of dispensed prescriptions to identify new benzodiazepine and SSRI treatment episodes, defined as no benzodiazepine or SSRI prescriptions in the year before treatment initiation with continuous insurance enrollment during that year (Supplemental Fig 2). We required an anxiety disorder diagnosis within the 30 days before or the day of treatment initiation. Anxiety disorders were defined with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) or *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) codes (Supplemental Table 4).

We excluded new users with diagnoses for bipolar disorder, schizophrenia, personality disorder, other psychosis, autistic disorder, substance use disorder, or epilepsy and/or convulsions in the previous year and an inpatient admission in the previous 30 days. We excluded persons with any fracture diagnosis in the 3 months before treatment initiation to reduce misclassification of follow-up fracture visits as an outcome. For youth with >1 new benzodiazepine or SSRI treatment episode meeting inclusion criteria, we selected the first episode. Lastly, we excluded youth initiating benzodiazepine and SSRI treatment on the same day.

**TABLE 1** Children and Young Adults Initiating Benzodiazepine or SSRI Treatment of an Anxiety Disorder, 2008–2016: Selected Patient Characteristics

Selected Patient Characteristic	Children (6–17 y)		Young Adults (18–24 y)	
	Benzodiazepine <sup>a</sup>	SSRI <sup>b</sup>	Benzodiazepine <sup>a</sup>	SSRI <sup>b</sup>
	<i>n</i> = 12 840	<i>n</i> = 107 875	<i>n</i> = 57 684	<i>n</i> = 122 084
Male sex, <i>n</i> (%)	4774 (37.2)	41 311 (38.3)	19 836 (34.4)	39 939 (32.7)
Age, mean (SD)	14.6 (2.63)	13.6 (3.03)	21.3 (1.94)	20.7 (1.97)
Anxiety disorder (previous 30 d), <i>n</i> (%)				
Unspecified anxiety	5997 (46.7)	45 929 (42.6)	31 986 (55.5)	63 050 (51.6)
Generalized anxiety disorder	2097 (16.3)	29 604 (27.4)	8446 (14.6)	29 010 (23.8)
Panic disorder	1614 (12.6)	3885 (3.6)	7413 (12.9)	6092 (5.0)
Adjustment disorder with anxiety	1360 (10.6)	13 326 (12.4)	2664 (4.6)	9097 (7.5)
Acute stress disorder	406 (3.2)	1293 (1.2)	2207 (3.8)	2811 (2.3)
Phobic disorder	288 (2.2)	686 (0.6)	1032 (1.8)	689 (0.6)
Social phobia	110 (0.9)	2794 (2.6)	432 (0.7)	2451 (2.0)
Other anxiety	399 (3.1)	3425 (3.2)	1624 (2.8)	4463 (3.7)
Multiple diagnoses	569 (4.4)	6933 (6.4)	1880 (3.3)	4421 (3.6)
Provider on recent anxiety diagnosis, <i>n</i> (%)				
Psychiatry	1419 (11.1)	24 611 (22.8)	3907 (6.8)	12 405 (10.2)
Psychology	1872 (14.6)	15 988 (14.8)	2589 (4.5)	8784 (7.2)
Pediatrician	1992 (15.5)	21 536 (20.0)	1346 (2.3)	5456 (4.5)
Family practitioner	2248 (17.5)	15 811 (14.7)	19 595 (34.0)	46 877 (38.4)
Other general (nurse practitioner, internal medicine)	1136 (8.8)	9159 (8.5)	10 830 (18.8)	22 831 (18.7)
Other provider type	2168 (16.9)	12 663 (11.7)	10 022 (17.4)	14 576 (11.9)
Unknown or multiple provide types	2005 (15.6)	8107 (7.5)	9395 (16.3)	11 155 (9.1)
Recent psychiatric diagnoses (0–30 d), <i>n</i> (%)				
ADHD	1006 (7.8)	16 775 (15.6)	3142 (5.4)	7751 (6.3)
Depression	1286 (10.0)	29 418 (27.3)	5698 (9.9)	30 622 (25.1)
Sleep disorder	519 (4.0)	3234 (3.0)	3130 (5.4)	5944 (4.9)
Conduct disorder	151 (1.2)	3310 (3.1)	100 (0.2)	366 (0.3)
OCD	144 (1.1)	3085 (2.9)	218 (0.4)	1356 (1.1)
PTSD	87 (0.7)	1036 (1.0)	372 (0.6)	945 (0.8)
Any psychiatric comorbidity (1 y), <i>n</i> (%)	4829 (37.6)	65 353 (60.6)	17 719 (30.7)	53 090 (43.5)
Nonpsychiatric diagnoses (1 y), <i>n</i> (%)				
Asthma	1656 (12.9)	11 044 (10.2)	4608 (8.0)	8368 (6.9)
Chest pain, palpitations	1908 (14.9)	6886 (6.4)	10 893 (18.9)	12 645 (10.4)
Dizziness, fainting	1098 (8.6)	5565 (5.2)	4504 (7.8)	6991 (5.7)
Muscle spasm	420 (3.3)	1964 (1.8)	1844 (3.2)	2933 (2.4)
Injury-related diagnoses (1 y unless specified), <i>n</i> (%)				
Fracture (91 d–1 y)	500 (3.9)	3462 (3.2)	1089 (1.9)	2075 (1.7)
Injury diagnosis (excluding fracture)	3242 (25.2)	22 896 (21.2)	10 918 (18.9)	20 830 (17.1)
Fall diagnosis	168 (1.3)	1422 (1.3)	453 (0.8)	959 (0.8)
Joint disorder, nontraumatic	2143 (16.7)	14 316 (13.3)	6903 (12.0)	13 929 (11.4)
Recent prescriptions (0–90 d), <i>n</i> (%)				
Stimulant	1266 (9.9)	15 714 (14.6)	4445 (7.7)	8576 (7.0)
Antidepressant (baseline SSRI use excluded)	1085 (8.5)	5204 (4.8)	6677 (11.6)	8163 (6.7)
Anticonvulsant	426 (3.3)	1599 (1.5)	1319 (2.3)	1997 (1.6)
Antipsychotic, lithium	364 (2.8)	2411 (2.2)	659 (1.1)	1054 (0.9)
Hypnotic	110 (0.9)	361 (0.3)	1390 (2.4)	2196 (1.8)
Opioid	1422 (11.1)	4770 (4.4)	7590 (13.2)	10 555 (8.6)
Psychotherapy claims (recent, 0–30 d), <i>n</i> (%)	3796 (29.6)	46 604 (43.2)	6359 (11.0)	21 226 (17.4)
ED visits (recent, 0–30 d), <i>n</i> (%)	3627 (28.2)	10 191 (9.4)	14 766 (25.6)	12 462 (10.2)
Preventive outpatient visit (1 y), <i>n</i> (%)	6527 (50.8)	59 937 (55.6)	23 394 (40.6)	53 053 (43.5)

OCD, obsessive compulsive disorder; PTSD, posttraumatic stress disorder.

<sup>a</sup> Benzodiazepine treatment included prescriptions for alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, prazepam, quazepam, temazepam, or triazolam.

<sup>b</sup> SSRI treatment included dispensed prescription for citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, or vilazodone.

## Measures

### Incident Fracture Event

We identified fracture events using ICD-9-CM or ICD-10-CM diagnostic

codes from inpatient and outpatient records beginning the day after benzodiazepine or SSRI initiation and ending at 3 months. The primary outcome was incidence of upper or

lower limb fractures (shoulder, upper arm, forearm, wrist, femur, lower leg, ankle) because these fractures are more likely than other fracture locations to be caused by

falls.<sup>27,28,42–45</sup> For a secondary outcome, we included all fracture locations. Fracture definitions are presented in Supplemental Table 5.

### Treatment Duration

We estimated benzodiazepine and SSRI treatment duration with prescription refill dates and days' supply. If there was no prescription refill within 20 days (grace period) after the days' supply ended for the previous prescription, the individual was considered to have discontinued treatment. In sensitivity analyses, 10- and 30-day grace periods were used.

### Additional Measures

Patient characteristics were identified from inpatient and outpatient records (ICD-9-CM, ICD-10-CM, or *Current Procedural Terminology* codes) and dispensed prescription records in the year before or day of treatment initiation. Broadly, these included age, sex, anxiety disorder diagnosis, provider type of anxiety diagnosis, psychotherapy claims, psychiatric diagnoses, health care use measures, nonpsychiatric medical diagnoses, pediatric chronic complex condition scale,<sup>46</sup> injuries, and psychotropic and other medications dispensed in the previous 90 days.

### Analysis

We described children and young adults with anxiety disorders initiating benzodiazepine or SSRI treatment and estimated treatment duration and switching between therapies (eg, SSRI initiator filling a benzodiazepine). Primary analyses were as treated given investigation of a safety concern with hypothesized effect during drug use.<sup>47</sup> Youth contributed person-time beginning the day after treatment initiation until the first of the following: incident fracture, treatment discontinuation, treatment switching, insurance disenrollment, 3 months, or the end of data.

Our primary measures of adverse effect included crude and propensity score-adjusted incident fracture rates, incident rate differences (IRDs), and incident rate ratios (IRRs). We estimated propensity scores of benzodiazepine treatment separately in children and young adults; variables included potential confounders or predictors of fracture, including year of treatment initiation to account for temporal shifts in prescribing and fracture diagnoses. We used inverse probability of treatment weighting (IPTW) and applied asymmetric trimming,<sup>48</sup> excluding those with a propensity score below the first percentile of benzodiazepine initiators and above the 99th percentile of SSRI initiators, to select youth with greater treatment equipoise. In secondary analyses, we estimated results using stabilized inverse probability of treatment weighting (SIPTW) without trimming, restricting follow-up to 30 days, and by duration of action for the initial benzodiazepine (long acting, short acting).

### Sensitivity Analyses

We completed intention-to-treat analyses with no censoring at treatment discontinuation or switching and as-treated estimates using 10- and 30-day grace periods to define treatment discontinuation. We examined results in youth with an initial benzodiazepine or SSRI days' supply value  $\geq 3$ , excluding youth with baseline antidepressant use, and censoring at September 30, 2015, given the shift to ICD-10-CM codes. We stratified results by sex and common comorbid psychiatric diagnoses (attention-deficit/hyperactivity disorder [ADHD], depression) and restricted the data to youth without previous injury diagnostic codes given hypothesized differing baseline fracture rates in these subgroups. We additionally examined results in youth without recent psychotropic prescriptions and we examined results stratified by any

psychiatric comorbidity diagnosis. Propensity scores were re-created with trimming applied to each subgroup. For exploratory analyses in benzodiazepine initiators, we examined fracture rates by a high versus lower initial benzodiazepine dose per day. A high dose per day was defined empirically as a dose greater than the third quartile on the basis of the distributions in children (diazepam  $>10$  mg/day, alprazolam  $>1$  mg/day, clonazepam  $>1$  mg/day, lorazepam  $>2$  mg/day) and in young adults (diazepam  $>15$  mg/day, alprazolam  $>1.25$  mg/day, clonazepam  $>1.1$  mg/day, lorazepam  $>2.1$  mg/day). The exploratory analyses included 92% of children and 94% of young adults initiating benzodiazepine treatment; expanded details are in the Supplemental Information.

## RESULTS

The final child cohort included 12 840 benzodiazepine initiators and 107 875 SSRI initiators with anxiety disorders, and the young adult cohort included 57 684 benzodiazepine initiators and 122 084 SSRI initiators. Unspecified anxiety disorder and generalized anxiety disorder were the most common anxiety diagnoses, and benzodiazepine initiators were older, more likely to have panic disorder and recent ED visits, and less likely to have comorbid mental health diagnoses (Table 1). Alprazolam and lorazepam were the most common initial benzodiazepine agents (Supplemental Table 6).

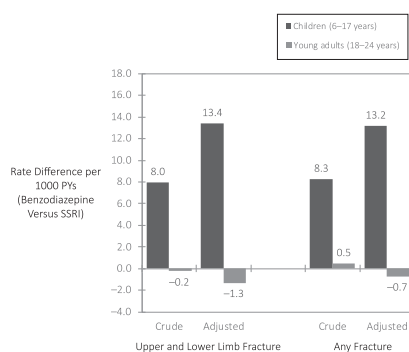
### Treatment Duration and Switching

Most children (82%) and young adults (77%) initiating benzodiazepine treatment did not have a second prescription fill before discontinuation. Three months after initiation, 8% of child and 11% of young adult benzodiazepine initiators remained on treatment, compared with more than half of SSRI initiators (Supplemental Table 6). In addition,

22% of child and 17% of young adult benzodiazepine initiators filled an SSRI prescription in the 3 months after, and fewer SSRI initiators filled a benzodiazepine during follow-up.

### Children: Incident Fractures

In children, the incident upper and lower limb fracture rate during the first months of treatment was 25.5 per 1000 person-years (PYs), with 33.1 per 1000 PYs in benzodiazepine initiators and 25.1 per 1000 PYs in SSRI initiators (Table 2). After weighting and trimming, benzodiazepine and SSRI initiators were well balanced (Supplemental Table 7). The adjusted fracture rate was elevated in benzodiazepine initiators compared with SSRI initiators: adjusted IRR = 1.53 (95% confidence interval [CI]: 0.94–2.50) and IRD = 13.4 per 1000 PYs (Table 2, Fig 1). The association was



**FIGURE 1** Incident fracture rate difference in benzodiazepine versus SSRI initiators in children and young adults. Subjects were followed for a maximum of 3 months; upper and lower limb fractures include fractures of the shoulder, upper arm, forearm, wrist, femur, lower leg, and/or ankle.

stronger for long-acting benzodiazepine initiators versus SSRI initiators: adjusted IRD = 32.9 and IRR = 2.30 (CI: 1.08–4.91).

Considering initial benzodiazepine dose, the crude fracture rate was 52.7 (CI: 25.2–96.8) per 1000 PYs in initiators of high dose-per-day benzodiazepine compared to 30.3 (CI: 19.8–44.5) per 1000 PYs in initiators of lower dose-per-day benzodiazepine.

Under the any fracture outcome definition, the incident fracture rate approximately doubled (49.7 per 1000 PYs) and the IRR approached null, whereas the IRD remained similar to our primary fracture definition (Table 2). Results were consistent when restricting follow-up to a maximum of 1 month, in children without a previous injury, and in children without recent psychotropic prescriptions (Table 3). We observed a heightened fracture rate in benzodiazepine initiators when using a stricter 10-day grace period to

**TABLE 2** Incident Fracture Rates in Children and Young Adults Initiating Benzodiazepine or SSRI Treatment Over a Maximum of 3 Months on Treatment

	No. Persons	Primary Fracture (Upper and Lower Limb) <sup>a</sup>				Any Fracture <sup>b</sup>		
		No. Fracture Events	PY	Rate per 1000 PYs	IRR (95% CI)	No. Fracture Events	Rate per 1000 PYs	IRR (95% CI)
<b>Children (6–17 y)</b>								
Crude	120 715	598	23 441	25.5	—	1162	49.7	—
Benzodiazepine initiators	12 840	38	1148	33.1	1.32 (0.95–1.83)	66	57.6	1.17 (0.91–1.50)
SSRI initiators	107 875	560	22 293	25.1	Referent	1096	49.3	Referent
Adjusted <sup>c</sup>								
Benzodiazepine	10 864	380	9871	38.5	1.53 (0.94–2.50)	618	62.7	1.27 (0.88–1.82)
SSRI	95 991	553	22 046	25.1	Referent	1088	49.5	Referent
Stratified analysis, adjusted <sup>c</sup>								
Long-acting <sup>d</sup> benzodiazepine	3480	562	9634	58.3	2.30 (1.08–4.91)	884	92.0	1.84 (1.09–3.13)
SSRI <sup>e</sup>	98 596	535	21 071	25.4	Referent	1049	49.9	Referent
Short-acting benzodiazepine	7184	279	9399	29.7	1.21 (0.54–2.70)	443	47.2	0.96 (0.53–1.75)
SSRI <sup>e</sup>	94 565	517	21 009	24.6	Referent	1029	49.1	Referent
<b>Young adults (18–24 y)</b>								
Crude	179 768	254	28 827	8.8	—	775	26.9	—
Benzodiazepine initiators	57 684	51	5896	8.7	0.98 (0.72–1.33)	161	27.3	1.02 (0.86–1.21)
SSRI initiators	122 084	203	22 931	8.9	Referent	614	26.8	Referent
Adjusted <sup>c</sup>								
Benzodiazepine	51 912	130	17 007	7.6	0.85 (0.57–1.27)	447	26.4	0.97 (0.78–1.21)
SSRI	109 690	269	30 084	8.9	Referent	814	27.1	Referent
Stratified analysis, adjusted <sup>c</sup>								
Long-acting <sup>d</sup> benzodiazepine	11 288	116	13 845	8.4	0.95 (0.49–1.84)	372	26.9	0.99 (0.67–1.46)
SSRI <sup>e</sup>	110 569	202	22 766	8.9	Referent	620	27.3	Referent
Short-acting benzodiazepine	39 974	111	15 255	7.3	0.80 (0.52–1.25)	388	25.5	0.94 (0.73–1.23)
SSRI <sup>e</sup>	108 959	252	27 779	9.1	Referent	748	27.0	Referent

—, not applicable.

<sup>a</sup> Upper and lower limb fracture: fractures of the shoulder, upper arm, forearm, wrist, femur, lower leg, and/or ankle.

<sup>b</sup> PYs under any fracture definition are not displayed and are similar to PYs under primary fracture definition.

<sup>c</sup> Adjusted results: IPTW applied in trimmed cohort; total person count displayed is unweighted, and remaining displayed results are weighted.

<sup>d</sup> Long-acting benzodiazepine is defined as initial prescription for clordiazepoxide, clobazam, clorazepate, clonazepam, diazepam, or flurazepam.

<sup>e</sup> SSRI reference group varies given reweighting or trimming in each stratified cohort.

**TABLE 3** Secondary and Sensitivity Analyses: Benzodiazepine and SSRI (Referent) Initiators and Rate of Fractures (Primary Definition: Upper and Lower Limb)

	Crude				Adjusted <sup>a</sup>	
	Benzodiazepine Users	SSRI Users	IRR (95% CI)	IRD per 1000 PYs	IRR (95% CI)	IRD per 1000 PYs
	Fracture Rate per 1000 PYs	Fracture Rate per 1000 PYs				
Children (6–17 y), % of cohort	33.1	25.1	1.32 (0.95–1.83)	8.0	1.53 (0.94–2.50)	13.4
SIPTW estimate	—	—	—	—	1.36 (0.84–2.19)	9.0
Maximum of 30 d follow-up	35.3	25.7	1.37 (0.94–2.00)	9.6	1.54 (0.88–2.69)	14.0
Intention-to-treat analysis	23.9	24.4	0.98 (0.77–1.25)	–0.5	1.16 (0.81–1.66)	3.9
Treatment duration grace period						
10 d	36.0	25.0	1.44 (1.00–2.08)	11.0	1.83 (1.07–3.14)	20.5
30 d	30.0	24.9	1.21 (0.89–1.65)	5.2	1.35 (0.84–2.15)	8.5
Initial d supply 3+ d (98%)	30.5	25.1	1.21 (0.85–1.74)	5.4	1.34 (0.79–2.27)	8.4
Fracture outcomes by ICD-9-CM only (81%)	31.3	26.0	1.20 (0.84–1.72)	5.3	1.32 (0.84–2.89)	8.1
No previous injury (67%)	21.1	19.7	1.07 (0.64–1.80)	1.4	1.58 (0.79–3.15)	11.3
No baseline antidepressant use (95%)	33.3	25.0	1.33 (0.94–1.89)	8.3	1.43 (0.83–2.44)	10.6
No psychotropic use (78%)	27.9	24.6	1.14 (0.75–1.71)	3.3	1.44 (0.69–3.00)	10.4
No depression diagnosis <sup>b</sup> (70%)	34.0	27.0	1.26 (0.88–1.80)	7.0	1.44 (0.83–2.50)	11.6
Stratification by ADHD diagnosis						
ADHD (21%)	58.8	27.2	2.16 (1.14–4.11)	31.6	2.00 (0.86–4.66)	27.2
No ADHD (79%)	28.6	24.5	1.17 (0.80–1.71)	4.1	1.56 (0.84–2.89)	13.6
Stratification by psychiatric comorbidity						
Psychiatric comorbidity (58%)	39.7	25.6	1.55 (0.97–2.50)	14.2	1.89 (1.03–3.46)	22.8
No comorbidity (42%)	28.8	24.4	1.18 (0.75–1.86)	4.4	0.86 (0.45–1.66)	–3.2
Stratification by sex						
Male (38%)	45.0	33.4	1.35 (0.86–2.12)	11.7	1.40 (0.76–2.58)	13.5
Female (62%)	25.6	20.0	1.28 (0.79–2.09)	5.5	1.34 (0.66–2.69)	6.5
Young adults (18–24 y), % of cohort	8.7	8.9	0.98 (0.72–1.33)	–0.2	0.85 (0.57–1.27)	–1.3
SIPTW estimate	—	—	—	—	0.90 (0.61–1.35)	–0.9
Maximum of 30 d follow-up	7.9	8.9	0.88 (0.59–1.32)	–1.0	0.79 (0.47–1.33)	–2.0
Intention-to-treat analysis	8.6	8.7	0.99 (0.79–1.23)	–0.1	0.83 (0.64–1.08)	–1.5
Treatment duration grace period						
10 d	8.9	8.6	1.03 (0.73–1.46)	0.3	0.97 (0.62–1.52)	–0.3
30 d	8.9	8.9	1.00 (0.76–1.32)	0.0	0.84 (0.59–1.20)	–1.4
Initial d supply 3+ d (98%)	8.6	8.8	0.98 (0.72–1.34)	–0.2	0.86 (0.57–1.28)	–1.3

**TABLE 3** Continued

	Crude			Adjusted <sup>a</sup>		
	Benzodiazepine Users	SSRI Users	IRR (95% CI)	IRD per 1000 PYs	IRR (95% CI)	IRD per 1000 PYs
	Fracture Rate per 1000 PYs	Fracture Rate per 1000 PYs				
Fracture outcomes by ICD-9-CM only (80%)	8.0	9.3	0.87 (0.61–1.22)	–1.2	0.68 (0.45–1.03)	–2.9
No previous injury (72%)	6.0	7.1	0.85 (0.55–1.31)	–1.0	0.68 (0.41–1.12)	–2.3
No baseline antidepressant use (92%)	8.8	9.1	0.98 (0.71–1.35)	–0.2	0.85 (0.55–1.31)	–1.4
No psychotropic use (82%)	8.2	8.7	0.93 (0.65–1.34)	–0.6	0.75 (0.48–1.18)	–2.3
No depression diagnosis <sup>b</sup> (76%)	9.0	9.0	1.00 (0.72–1.39)	0.0	0.85 (0.58–1.26)	–1.3
No ADHD diagnosis <sup>b</sup> (90%)	8.5	8.6	1.00 (0.72–1.38)	0.0	0.83 (0.56–1.24)	–1.4
Stratification by psychiatric comorbidity						
Psychiatric comorbidity (39%)	8.8	9.0	0.98 (0.58–1.65)	–0.2	0.98 (0.49–1.95)	–0.2
No comorbidity (61%)	8.6	8.8	0.98 (0.67–1.44)	–0.2	0.85 (0.55–1.32)	–1.2
Stratification by sex						
Male (33%)	10.8	12.2	0.89 (0.56–1.40)	–1.4	0.62 (0.37–1.06)	–4.6
Female (67%)	7.4	7.3	1.02 (0.68–1.55)	0.2	1.04 (0.61–1.77)	0.3

—, not applicable.

<sup>a</sup> Adjusted results: IPTW applied in trimmed cohort (except when noted for SIPTW results).

<sup>b</sup> Results from strata with <10 fracture events in a treatment group are not displayed.

define treatment discontinuation (IRR = 1.83 [CI: 1.07–3.14]). Fracture rates were higher in boys and children with ADHD; the association between benzodiazepine versus SSRI treatment and fractures was stronger in children with ADHD, although estimates are less precise.

### Young Adults: Incident Fractures

In young adults, the incident upper and lower limb fracture rate was 8.8 per 1000 PYs, approximately one-third of the rate in children. The fracture rate was similar in benzodiazepine (8.7 per 1000 PYs) and SSRI initiators (8.9 per 1000 PYs) (Table 2). After weighting and trimming, benzodiazepine and SSRI initiators were well balanced (Supplemental Table 8). The adjusted fracture rate was 7.6 per 1000 PYs in benzodiazepine initiators and 8.9 per 1000 PYs in SSRI initiators, with an adjusted IRR of 0.85 (CI: 0.57–1.27)

and IRD of –1.3 per 1000 PYs (Table 2, Fig 1). The crude fracture rate was similar in young adults initiating benzodiazepine treatment on a high or low dose per day, that of 8.3 (CI: 4.0–15.3) and 8.8 (CI: 6.2–12.1) per 1000 PYs, respectively.

Under the any fracture definition, the young adult incident fracture rate tripled to 26.9 per 1000 PYs with no association between treatment type and fracture (Table 2). Most findings from additional analyses were similar to the primary analysis (Table 3). Incident upper and lower limb fracture rates were lower in male benzodiazepine versus SSRI initiators; however, under the any fracture definition (results not shown), the association was null (IRR = 0.94). Similarly, when restricting follow-up to outcomes under ICD-9-CM fracture codes, the estimate was null under the any fracture definition.

### DISCUSSION

With our findings, we provide novel comparative estimates of fracture rates during benzodiazepine and SSRI treatment in children and young adults with anxiety disorders. In children initiating benzodiazepines, we observed a heightened rate of upper and lower limb fractures compared to SSRI treatment, with no heightened rate in young adult benzodiazepine initiators. Increased caution may be warranted at benzodiazepine initiation in children with anxiety disorders, particularly with initiation of long-acting benzodiazepines. These findings add to the limited understanding of benzodiazepine treatment safety in youth.

The elevated upper and lower limb fracture rate in children initiating benzodiazepine treatment compared to SSRI treatment (IRR = 1.53) is

similar to estimates from older adult benzodiazepine users compared with nonusers with pooled meta-analysis effect estimates of risk ratios of 1.25 to 1.52.<sup>15,19,21,22</sup> We focused on short-term fracture risk because benzodiazepine treatment is typically for short durations in youth with anxiety disorders and authors of literature regarding older adults have observed greater fall and fracture risk in the first weeks after initiation.<sup>19,24,25,49</sup> However, not all study authors observed this short-term effect.<sup>20</sup>

Fracture rates were higher in children initiating long-acting benzodiazepines. In adults, there is evidence suggesting benzodiazepines with longer half-lives have a higher relative risk of fractures and motor vehicle crashes than benzodiazepines with shorter half-lives<sup>13,50,51</sup>; however, findings are mixed.<sup>18,24,25,52</sup> In meta-analyses, authors observed similar fracture risk in short-acting and long-acting adult benzodiazepine users.<sup>15,21</sup> Preferential prescribing of short-acting benzodiazepines to adults at increased fall or fracture risk may have contributed to observations of no elevated risk with long-acting benzodiazepines.<sup>25</sup> Relatedly, children prescribed long-acting benzodiazepines for anxiety could have a baseline elevated fracture risk beyond what we controlled for and may also have greater benzodiazepine exposure if prescribed for regular, daily use versus as-needed use. In our exploratory analysis, we observed an elevated fracture rate in children initiating a high benzodiazepine dose per day versus lower dose per day. In older adults, higher benzodiazepine doses are associated with a heightened fracture risk.<sup>25,26,50</sup> It is suggested in our crude estimates that a closer examination of benzodiazepine dose on fracture risk and the interaction of dose and half-life will further inform prescribing decisions.

The estimated rate difference for fractures in children receiving benzodiazepine versus SSRI treatment was moderately small (13 per 1000 PYs), yet notable because alternative treatments are available; these fractures thus represent potentially preventable adverse outcomes. The heightened fracture rate difference in boys and children with ADHD may be related to greater activity levels and thus increased opportunities for treatment-related adverse effects that result in fracture-causing falls. Most falls in children and young adults are without incident; however, falls can result in fracture including severe, life-threatening injuries, particularly if falls occur from elevated heights.<sup>29,53</sup> Clinicians could advise caution in activities that increase the likelihood of a severe injury until it is clear how benzodiazepine treatment will affect the child.

In young adults with anxiety disorders, we did not observe an elevated fracture rate in benzodiazepine initiators versus SSRI initiators. Several factors may contribute to this finding. Young adults are generally less active and experience fewer fall-related injuries than do children.<sup>54,55</sup> Therefore, there may be less opportunity for benzodiazepine adverse effects to cause a fall that could result in fracture. Young adults may receive increased warnings surrounding benzodiazepine side effects given this age group drives and benzodiazepine drug labels state that individuals should not drive or engage in dangerous activities until they know how the medication will affect them. Relatedly, young adults likely have more awareness of symptoms and side effects and autonomy over when medication is taken. Benzodiazepines are more commonly prescribed to young adults than children<sup>56</sup>; children who receive benzodiazepines may, on average, have higher anxiety severity than young adults,

a potential source of residual confounding. Subthreshold or undiagnosed conduct disorder is another potential source of residual confounding more prevalent in children. Young adults may be more likely to have previous medical or nonmedical exposure to benzodiazepine<sup>4,57</sup> that lessens their risk of benzodiazepine-related fractures. Alcohol and drug use are potential unmeasured confounders that can increase accidental injury and fall risk<sup>58-60</sup> and could increase the likelihood of receiving SSRIs given concerns related to benzodiazepine misuse. This could lead to attenuated fracture risk effect, particularly in young adults for whom substance use is more prevalent; however, there is uncertainty because patient treatment preferences could differ by substance use. In addition, our primary fracture outcome was uncommon in young adults and perhaps less clinically relevant than for children.

As previously recognized, the observed association between benzodiazepines and fractures in older adults could be biased by confounding by indication.<sup>15,18,22</sup> Our restriction to youth with anxiety disorders, active comparator design, and implementation of IPTW sought to reduce the potential for confounding by indication while addressing a clinically relevant question. Despite our study design, unmeasured confounding may persist. Antidepressants (including SSRIs, our active comparator) have been associated with an elevated fracture risk compared to no antidepressant use.<sup>22,61,62</sup> The proposed mechanism of fracture risk with benzodiazepine treatment is related to adverse effects such as sedation or dizziness leading to a fall, whereas for SSRIs, the hypothesized mechanisms are an increased fall risk or decreased bone mineral density.<sup>63,64</sup> However, findings are inconsistent on the association



between SSRIs and fractures<sup>26,65</sup> and studies may be susceptible to confounding by indication.<sup>62,66</sup> Whether our observed associations between benzodiazepines and fractures hold across benzodiazepine indications and compared with other alternative pharmacotherapies remains unclear.

Limitations of the work should be considered. We cannot be certain the primary treatment indication was an anxiety disorder and whether, and when, filled prescriptions were consumed. We lack clinical severity measures; it is unclear how much unmeasured differences in psychiatric condition severity exist between youth initiating a benzodiazepine versus SSRI and how anxiety severity impacts fracture risk. Further research is needed to evaluate whether elevated fracture risk with benzodiazepine treatment is concentrated in children with a psychiatric comorbidity or if this observation is a result of differences in prescribing and/or patient characteristics between children with and without psychiatric comorbidities. Benzodiazepine treatment is typically shorter than SSRI treatment; however, our results restricting to 30 days of treatment compare outcomes over a similar

denominator. Many subgroup analyses were limited by sample size; future research will determine if findings remain across populations. Although the primary fracture definition intended to capture fractures more likely to be caused by a fall, fractures could be caused by any mechanism and be unrelated to treatment. We do not expect differential misclassification of fracture coding by treatment; however, fracture events were based on diagnostic codes and may not represent true events. The validity of fracture diagnostic codes varies by fracture type, with positive predictive values typically estimated at >80%.<sup>67-69</sup> Our data overlapped the transition to ICD-10-CM codes; authors of future analyses could examine this research question strictly under ICD-10-CM codes.

## CONCLUSIONS

We observed a heightened rate of fractures in children with anxiety disorders initiating benzodiazepine treatment compared to SSRI treatment but not in young adults. Increased caution in the weeks after benzodiazepine initiation in children with anxiety disorders may be

warranted. Moreover, given the lack of efficacy evidence and limited safety data for benzodiazepine treatment of pediatric anxiety disorders, this safety signal is an important consideration in the benefit-harm evaluation for prescribing benzodiazepines to youth with anxiety disorders.

## ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder  
CI: confidence interval  
ED: emergency department  
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*  
ICD-10-CM: *International Classification of Diseases, 10th Revision, Clinical Modification*  
IPTW: inverse probability of treatment weighting  
IRD: incident rate difference  
IRR: incident rate ratio  
PY: person-year  
SIPTW: stabilized inverse probability of treatment weighting  
SSRI: selective serotonin reuptake inhibitor

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