Simultaneous Benzodiazepine and SSRI Initiation in Young People With Anxiety Disorders

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ABSTRACT

Objective: There are potential risks and benefits of combining benzodiazepine (BZD) and selective serotonin reuptake inhibitor (SSRI) therapy at anxiety disorder treatment onset. We investigated how often adolescents and young adults with anxiety disorders simultaneously initiate BZD treatment with SSRI treatment and examined whether SSRI treatment duration varies by simultaneous BZD initiation.

Methods: In a United States commercial claims database (January 2008–December 2016), we identified adolescents (10–17 years) and young adults (18–24 years) with *ICD-9-CM*/*ICD-10-CM* anxiety disorder diagnoses initiating SSRI treatment, without past-year SSRI and BZD treatment. We defined simultaneous initiation as filling a new BZD prescription on the date of SSRI initiation. We estimated time to SSRI treatment discontinuation and used stabilized inverse probability of treatment weighting for adjusted estimates.

Results: The study included 94,399 adolescents and 130,971 young adults initiating SSRI treatment with an anxiety disorder. Four percent of adolescents and 17% of young adults simultaneously initiated BZD treatment, varying by age, anxiety disorder, comorbidities, health care utilization, and provider type. Simultaneous BZD initiation among SSRI initiators declined from 2008 to 2016. SSRI treatment duration was similar in initiators of simultaneous therapy vs SSRI monotherapy: ≥ 6 months in adolescents (55% vs 56%, respectively) and in young adults (39% vs 40%). Nine percent of simultaneous initiators continued BZDs for ≥ 6 months.

Conclusions: Simultaneous initiation of BZD and SSRI treatment is relatively common in young adults with anxiety disorders and was not associated with longer SSRI persistence. Given risks of BZD treatment, potential benefits and risks of adding a BZD at SSRI treatment initiation must be carefully weighed.

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Antidepressants are typically recommended as the first-line pharmacotherapy for anxiety disorders in children and adults.[1–6] Benzodiazepines (BZDs) are prescribed alone or with antidepressants for acute treatment to rapidly reduce moderate to severe anxiety symptoms or as an augmentation strategy to treat residual anxiety symptoms.[1,7,8] In children, there is no evidence that BZDs are efficacious in treating anxiety disorders, with only a few trials having been conducted.[5,9] The recently released 2020 American Academy of Child and Adolescent Psychiatry guideline for pediatric anxiety calls for more research on the benefits and harms of BZDs given insufficient information.[6]

The coprescribing of BZDs in combination with antidepressants at treatment onset has become a pharmacologic treatment practice for adult depression. An estimated 11% of adults with depression starting antidepressant treatment simultaneously initiated BZD treatment (2001–2014).[10] For adults, there are limited studies on the benefits of combination BZD and antidepressant therapies at treatment onset. In a review of randomized trials in adults with depression, those with combination therapy were less likely to drop out and had improved short-term response than those on antidepressants alone.[11] In patients with panic disorder, one study found greater improvement in symptoms in the first weeks of treatment with combined treatment.[8] In patients with comorbid anxiety and depression, it has been suggested that adding a BZD to selective serotonin reuptake inhibitor (SSRI) treatment may reduce SSRI-induced anxiety or agitation or improve SSRI adherence.[7] It is unknown how common the practice of coprescribing is in children and young adults with anxiety disorders.

Whether SSRI treatment duration is longer in those simultaneously initiating BZD treatment is unclear but could inform decisions around coprescribing. After initiating antidepressant treatment for an anxiety disorder, it is recommended that a trial period of 8–10 weeks, if effective, be followed by maintenance treatment for 9–12 months.[3] However, SSRI adherence is often low; 43% of adults[12] and 58% of children[13] with anxiety disorders were adherent at 6 months.

While BZDs may offer benefit in managing anxiety disorder symptoms, they are recommended less

Clinical Points

- Simultaneous initiation of benzodiazepine and SSRI treatment, and its effect on SSRI treatment duration, had not been detailed in young people with anxiety disorders.
- Simultaneous benzodiazepine and SSRI initiation was relatively common in young adults but not associated with longer SSRI treatment.
- Potential benefits and risks of adding a benzodiazepine at SSRI initiation should be carefully considered.

frequently than SSRIs because of potential harms including side effects, such as drowsiness or memory problems, risk of dependency, risk of overdose, and misuse.[1,14–17] Young adults commonly misuse BZDs, or take them outside medical direction, with approximately 5% reporting past-year misuse.[18] Further, many use BZDs with other depressants, such as alcohol or opioids,[18,19] raising increased safety concerns for prescribing BZD treatment. In September 2020, the US Food and Drug Administration announced an anticipated update to the Boxed Warning for BZDs on the potential for abuse, addiction, and other serious risks.[20]

Among adolescents (10–17 years) and young adults (18–24 years) with anxiety disorders initiating SSRI treatment, we aimed to (*a*) estimate how many patients simultaneously initiate prescription BZD treatment and whether this varied from 2008 to 2016 and (*b*) estimate whether SSRI treatment duration varies by whether a patient simultaneously initiates BZD treatment and how long BZD treatment is continued in simultaneous initiators.

METHOD

Dataset and Study Population

We used the 2008–2016 MarketScan Commercial Claims and Encounters database, which covers individuals with employer-sponsored health insurance and their dependents across the United States. The MarketScan dataset is owned by IBM and can be accessed for research.[21,22] Patient-level details were available on insurance enrollment, outpatient and inpatient services, and outpatient dispensed prescriptions.

We identified adolescents (10–17 years) and young adults (18–24 years) initiating SSRI treatment who had not filled BZD or SSRI prescriptions for at least 1 year. Continuous insurance enrollment was required during the prior year, and SSRI treatment was defined with records of dispensed prescriptions for citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vilazodone. We required SSRI initiators to have a recent anxiety disorder diagnosis (≤ 30 days) defined with *ICD-9-CM* and *ICD-10-CM* codes (Tables 1 and 2 footnotes). We excluded SSRI new users with diagnoses for bipolar disorder, schizophrenia, other psychoses, personality disorder, epilepsy/convulsions, or autistic disorder in the prior year or with an inpatient admission in the prior 30 days. Adolescents and young adults with any other comorbid diagnosis were allowed.

Simultaneous BZD Initiation

We defined simultaneous SSRI and BZD initiation as SSRI initiators who filled a BZD prescription on the same date as SSRI initiation. BZD treatment was defined with records of dispensed prescriptions for alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, prazepam, quazepam, temazepam, and triazolam. For a secondary analysis, we examined how many youths filled a BZD prescription up to 90 days following SSRI initiation.

Treatment Duration

We estimated SSRI treatment duration based on prescription refill dates and prescription days' supply. If there was no prescription refill 30 days after the previous prescription's days' supply ended, the individual was considered to have discontinued treatment. In simultaneous initiators, we also estimated BZD treatment duration.

Additional Measures

Patient characteristics were identified from inpatient and outpatient records (*ICD-9-CM*, *ICD-10-CM* codes, CPT codes) and records of dispensed prescriptions in the year before SSRI initiation. We included measures for age, sex, anxiety disorder, comorbid depression, other mental health diagnoses, provider type on the anxiety diagnosis, psychotherapy claims, health care utilization, prescription medication, and non-psychiatric diagnoses (Tables 1 and 2).

Analysis

We described adolescents and young adults by simultaneous BZD initiation status. Per year, we estimated the proportion of SSRI initiators who simultaneously initiated BZD treatment. For a sensitivity analysis, we standardized trends by age, sex, and geographical region (New England, Middle Atlantic, South Atlantic, East South Central, West North Central, West South Central, Mountain, Pacific) to account for possible changes in the underlying source population. We estimated the survival function of SSRI treatment persistence at 3, 6, and 9 months with Nelson-Aalen estimator stratified by simultaneous BZD initiation status, censoring at insurance disenrollment or end of data. For adjusted analyses of treatment persistence, we estimated propensity scores for simultaneous BZD initiation with logistic regression including factors associated with treatment type and adherence[12,23–25] and applied stabilized inverse probability of treatment weights. Analyses were completed separately in adolescents and young adults. Results were consistent under limited and more inclusive variable selection; we present results from the more inclusive propensity score model (sex, age, year of SSRI initiation, mental health diagnoses, provider type diagnosing anxiety, psychotherapy claims, other medication use, other medical diagnoses, inpatient admissions, emergency department visits, outpatient visits, geographical region; Table 3 footnote).

Table 1. Adolescents (10–17 Years) With Anxiety Disorders Initiating SSRI Treatment by Simultaneous Initiation With Benzodiazepine (BZD) Treatment[a]

Patient characteristic	SSRI + BZD (n = 4,068)[b]	SSRI alone (n = 90,331)[b]	Standard difference	SSRI + BZD, row % (of total)
Male	1,450 (35.6)	32,415 (35.9)	0.0	4.3
Female	2,618 (64.4)	57,916 (64.1)	0.0	4.3
Age at SSRI initiation, mean (SD)	15.2 (1.9)	14.4 (2.2)	0.4	
10–13 y	757 (18.6)	27,785 (30.8)	−0.3	2.7
14–17 y	3,311 (81.4)	62,546 (69.2)	0.3	5.0
Anxiety disorder diagnosis (prior 30 d)[c]				
Unspecified anxiety	1,464 (36.0)	37,867 (41.9)	−0.1	3.7
Generalized anxiety disorder	950 (23.4)	24,251 (26.8)	−0.1	3.8
Panic disorder	562 (13.8)	3,622 (4.0)	0.3	13.4
Adjustment disorder with anxiety	318 (7.8)	11,977 (13.3)	−0.2	2.6
Acute stress disorder	59 (1.5)	1,194 (1.3)	0.0	4.7
Social phobia	93 (2.3)	2,530 (2.8)	0.0	3.5
Other anxiety disorder	116 (2.9)	3,040 (3.4)	0.0	3.7
Multiple specific diagnoses	506 (12.4)	5,850 (6.5)	0.2	8.0
Provider of anxiety diagnosis				
Psychiatry	957 (23.5)	19,438 (21.5)	0.0	4.7
Psychology	359 (8.8)	13,780 (15.3)	−0.2	2.5
Family practitioner	898 (22.1)	14,528 (16.1)	0.2	5.8
Pediatrician	532 (13.1)	17,138 (19.0)	−0.2	3.0
Other general provider[d]	436 (10.7)	7,913 (8.8)	0.1	5.2
Other provider type	479 (11.8)	10,664 (11.8)	0.0	4.3
Unknown or multiple	407 (10.0)	6,870 (7.6)	0.1	5.6
Any comorbid psychiatric diagnosis, 1 y	2,011 (49.4)	54,846 (60.7)	−0.2	3.5
Depression				
Recent (0–30 d)	1,062 (26.1)	27,820 (30.8)	−0.1	3.7
Past (31–365 d), no recent	156 (3.8)	4,023 (4.5)	0.0	3.7
Sleep disorder				
Recent (0–30 d)	172 (4.2)	2,790 (3.1)	0.1	5.8
Past (31–365 d), no recent	92 (2.3)	2,311 (2.6)	0.0	3.8
ADHD				
Recent (0–30 d)	224 (5.5)	11,978 (13.3)	−0.3	1.8
Past (31–365 d), no recent	145 (3.6)	5,348 (5.9)	−0.1	2.6
PTSD, 1 y	67 (1.6)	1,211 (1.3)	0.0	5.2
Adjustment disorder, 1 y	281 (6.9)	7,476 (8.3)	−0.1	3.6
Conduct disorder, 1 y	90 (2.2)	4,088 (4.5)	−0.1	2.2
OCD, 1 y	123 (3.0)	2,911 (3.2)	0.0	4.1
Substance use disorder, 1 y	103 (2.5)	1,887 (2.1)	0.0	5.2
Tobacco/nicotine dependence, 1 y	28 (0.7)	467 (0.5)	0.0	5.7
Suicidal ideation, self-harm, 1 y	54 (1.3)	1,588 (1.8)	0.0	3.3
Recent (90 d) prescriptions				
Stimulant	225 (5.5)	11,442 (12.7)	−0.3	1.9
Antidepressant (excludes SSRIs)	190 (4.7)	4,618 (5.1)	0.0	4.0
Hydroxyzine	77 (1.9)	3,014 (3.3)	−0.1	2.5
Hypnotic	38 (0.9)	355 (0.4)	0.1	9.7
Anticonvulsant	52 (1.3)	1,386 (1.5)	0.0	3.6
Opioid	314 (7.7)	4,576 (5.1)	0.1	6.4
Psychotherapy claims, recent (0–30 d)	1,420 (34.9)	38,918 (43.1)	−0.2	3.5
Inpatient admissions, 31–365 d[e]				
Psychiatric-related	30 (0.7)	794 (0.9)	0.0	3.6
Non-psychiatric related	98 (2.4)	1,252 (1.4)	0.1	7.3
ED visit, recent (0–30 d)	662 (16.3)	9,688 (10.7)	0.2	6.4
Preventative outpatient visit, 1 y	2,071 (50.9)	49,757 (55.1)	−0.1	4.0

[a]Sample includes adolescents (10–17 years) identified from a commercial claims database (2008–2016); BZD + SSRI row percent by geographical region: Northeast = 5.4%, North Central = 4.0%, South = 3.7%, West = 4.9%.
[b]Values expressed as n (%) unless otherwise noted.
[c]Anxiety disorder diagnoses: *ICD-9-CM*: 293.84, 300.0, 300.2, 308, 309.21, 309.24, 309.28, 313.23, 799.21; *ICD-10-CM*: F06.4, F40, F41, F43.0, F43.22, F43.23, F93.0, F94.0, R45.0, R45.7.
[d]Other general provider categories, BZD + SSRI row percent: internal medicine = 5.9%, nurse practitioner = 3.2%, physician assistant = 5.6%.
[e]Adolescents with a recent inpatient admission (0–30 days) were excluded.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, d = day, ED = emergency department, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor.

In simultaneous initiators, we also estimated the survival function of BZD treatment persistence in the same manner. Further, in simultaneous users with 6 months of follow-up, we examined the percent with long-term BZD treatment overall and by specific patient factors (initial BZD agent, SSRI agent, BZD days' supply, age, sex, mental health diagnoses, psychotropics and opioid prescriptions, provider type, psychotherapy claims). Long-term BZD use was defined as at least 6 months of continued BZD use. We used logistic regression to examine whether factors were independently associated with long-term BZD use. Adolescents and young adults were combined for this analysis given the limited number of adolescents with long-term BZD use. The study was approved by the Rutgers University Institutional Review Board.

RESULTS

Simultaneous BZD Initiation

The study cohort included 94,399 adolescents and 130,971 young adults initiating SSRI treatment with a recent anxiety disorder diagnosis. Overall, 4.3% of adolescents and 16.7% of young adults simultaneously initiated BZD treatment, with a monotonic increase by age (Figure 1). Alprazolam was the most common BZD dispensed to simultaneous initiators (adolescents: 37%, young adults: 49%) with a median 15 days' supply on the initial prescription (Supplementary Table 1). An additional 4% of adolescents and 7% of young adults started BZD treatment 1 to 90 days after SSRI initiation.

The highest prevalence of simultaneous initiation among SSRI initiators was in adolescents (13%) and young adults (35%) with panic disorder (row percents, Tables 1 and 2). The prevalence of simultaneous initiation was similar in adolescents (5%, 6%) and young adults (17%, 18%) diagnosed by a psychiatrist or family practitioner, with lower prevalence of simultaneous initiation seen in adolescents (3%) and young adults (8%) diagnosed by a pediatrician. Considering region, simultaneous prescribing was more common in young adults treated in the

Table 2. Young Adults (18–24 Years) With Anxiety Disorders Initiating SSRI Treatment by Simultaneous Initiation With Benzodiazepine (BZD) Treatment[a]

Patient characteristic	SSRI + BZD (n = 21,902)[b]	SSRI alone (n = 109,069)[b]	Standard difference	SSRI + BZD, row % (of total)
Male	7,578 (34.6)	37,974 (34.8)	0.0	16.6
Female	14,324 (65.4)	71,095 (65.2)	0.0	16.8
Age at SSRI initiation, mean (SD)	21.1 (1.9)	20.7 (2.0)	0.2	
18–20 y	8,710 (39.8)	55,188 (50.6)	−0.2	13.6
21–24 y	13,192 (60.2)	53,881 (49.4)	0.2	19.7
Anxiety disorder diagnosis (prior 30 d)[c]				
Unspecified anxiety	10,653 (48.6)	56,185 (51.5)	−0.1	15.9
Generalized anxiety disorder	4,466 (20.4)	25,702 (23.6)	−0.1	14.8
Panic disorder	3,025 (13.8)	5,541 (5.1)	0.3	35.3
Adjustment disorder with anxiety	1,019 (4.7)	8,321 (7.6)	−0.1	10.9
Acute stress disorder	468 (2.1)	2,580 (2.4)	0.0	15.4
Social phobia	226 (1.0)	2,210 (2.0)	−0.1	9.3
Other anxiety disorder	675 (3.1)	4,496 (4.1)	−0.1	13.1
Multiple specific diagnoses	1,370 (6.3)	4,034 (3.7)	0.1	25.4
Provider of anxiety diagnosis				
Psychiatry	2,271 (10.4)	11,096 (10.2)	0.0	17.0
Psychology	725 (3.3)	7,956 (7.3)	−0.2	8.4
Family practitioner	9,150 (41.8)	41,392 (38.0)	0.1	18.1
Pediatrician	400 (1.8)	4,959 (4.5)	−0.2	7.5
Other general provider[d]	4,433 (20.2)	20,257 (18.6)	0.0	18.0
Other provider type	2,529 (11.5)	13,195 (12.1)	0.0	16.1
Unknown or multiple	2,394 (10.9)	10,214 (9.4)	0.1	19.0
Any comorbid psychiatric diagnosis, 1 y	8,536 (39.0)	48,908 (44.8)	−0.1	14.9
Depression				
Recent (0–30 d)	4,846 (22.1)	27,581 (25.3)	−0.1	14.9
Past (31–365 d), no recent	568 (2.6)	3,643 (3.3)	0.0	13.5
Sleep disorder				
Recent (0–30 d)	1,415 (6.5)	5,361 (4.9)	0.1	20.9
Past (31–365 d), no recent	408 (1.9)	2,380 (2.2)	0.0	14.6
ADHD				
Recent (0–30 d)	641 (2.9)	6,613 (6.1)	−0.2	8.8
Past (31–365 d), no recent	636 (2.9)	3,766 (3.5)	0.0	14.4
PTSD, 1 y	279 (1.3)	1,113 (1.0)	0.0	20.0
Adjustment disorder, 1 y	560 (2.6)	3,470 (3.2)	0.0	13.9
Conduct disorder, 1 y	70 (0.3)	631 (0.6)	0.0	10.0
OCD, 1 y	245 (1.1)	1,439 (1.3)	0.0	14.5
Substance use disorder, 1 y	854 (3.9)	4,509 (4.1)	0.0	15.9
Tobacco/nicotine dependence, 1 y	1,064 (4.9)	4,458 (4.1)	0.0	19.3
Suicidal ideation, self-harm, 1 y	93 (0.4)	656 (0.6)	0.0	12.4
Recent (90 d) prescriptions				
Stimulant	867 (4.0)	7,299 (6.7)	−0.1	10.6
Antidepressant (excludes SSRIs)	907 (4.1)	6,984 (6.4)	−0.1	11.5
Hydroxyzine	362 (1.7)	4,779 (4.4)	−0.2	7.0
Hypnotic	419 (1.9)	1,980 (1.8)	0.0	17.5
Anticonvulsant	240 (1.1)	1,724 (1.6)	0.0	12.2
Opioid	2,517 (11.5)	9,852 (9.0)	0.1	20.3
Psychotherapy claims, recent (0–30 d)	2,472 (11.3)	19,380 (17.8)	−0.2	11.3
Inpatient admissions, 31–365 d[e]				
Psychiatric-related	66 (0.3)	536 (0.5)	0.0	11.0
Non–psychiatric-related	777 (3.5)	3,614 (3.3)	0.0	17.7
ED visit, recent (0–30 d)	3,228 (14.7)	12,059 (11.1)	0.1	21.1
Preventative outpatient visit, 1 y	8,580 (39.2)	46,949 (43.0)	−0.1	15.5

[a]Sample includes young adults (18–24 years) identified from a commercial claims database (2008–2016); BZD + SSRI row percent by geographical region: Northeast = 16.3%, North Central = 16.5%, South = 16.0%, West = 19.1%.
[b]Values expressed as n (%) unless otherwise noted.
[c]Anxiety disorder diagnoses: *ICD-9-CM*: 293.84, 300.0, 300.2, 308, 309.21, 309.24, 309.28, 313.23, 799.21; *ICD-10-CM*: F06.4, F40, F41, F43.0, F43.22, F43.23, F93.0, F94.0, R45.0, R45.7.
[d]Other general provider categories, BZD + SSRI row percent: internal medicine = 19.3%, nurse practitioner = 13.1%, physician assistant = 13.5%.
[e]Young adults with a recent inpatient admission (0–30 d) were excluded.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BZD = benzodiazepine, d = day, ED = emergency department, OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, y = year.

West (19% vs 16%) and was similar by region in adolescents (4%–5%; footnotes Tables 1 and 2).

Overall, simultaneous BZD initiators were older, more likely to have panic disorder, a recent ED visit, or sleep disorder, and to have been recently prescribed an opioid (adolescents: Table 1, young adults: Table 2). Simultaneous BZD initiators were less likely to have an ADHD diagnosis, a psychotherapy claim, or hydroxyzine prescriptions. Comorbid depression was slightly less common in simultaneous initiators vs SSRI monotherapy in adolescents (26% vs 31%, respectively) and young adults (22% vs 25%).

Trends in Simultaneous BZD Initiation

In adolescents, there was a steady decline over time in the proportion of SSRI initiators simultaneously initiating BZD treatment from 6% in 2008 to 3% in 2016 (Figure 2). From 2008 to 2012, 19%–20% of young adult SSRI initiators simultaneously initiated BZD treatment, which declined to 12% by 2016. Trends were consistent after standardizing by age, sex, and geographical region.

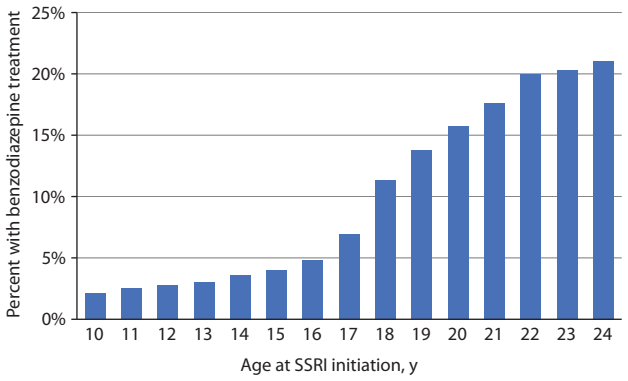
SSRI Treatment Duration

Seventy-eight percent of adolescents (BZD + SSRI: 75%, SSRI: 78%) and 64% of young adults (BZD + SSRI: 63%, SSRI: 65%) refilled their SSRI prescription. Overall, SSRI treatment duration was similar between SSRI initiators with or without simultaneous BZD initiation (Table 3). After weighting, in adolescents, 55% (95% CI, 53–57) of simultaneous BZD initiators and 56% (95% CI, 56–57) of SSRI monotherapy initiators remained on SSRI treatment after 6 months. In young adults, after weighting, 39% (95% CI, 39%–40%) of simultaneous BZD initiators and 40% (95% CI, 40%–40%) of SSRI monotherapy initiators remained on SSRI treatment after 6 months.

BZD Treatment Duration

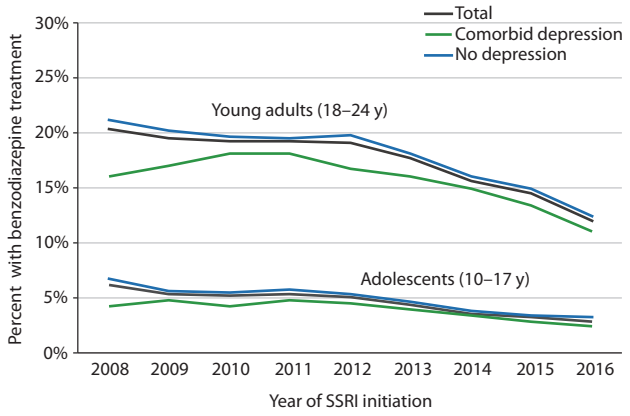
Approximately one third of adolescent (32%) and young adult (30%) simultaneous initiators refilled the initial BZD prescription. From

Figure 1. Percentage of SSRI Initiators With Anxiety Disorders Simultaneously Initiating Benzodiazepine Treatment Stratified by Age at SSRI Initiation[a]



[a]Privately insured adolescents (10–17 years) and young adults (18–24 years) newly initiating SSRI treatment after an anxiety disorder diagnosis, identified from a commercial claims database (2008–2016).
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 2. Percentage of Adolescent and Young Adult SSRI Initiators Simultaneously Initiating Benzodiazepine Treatment Stratified by Year and Comorbid Depression[a]



[a]Privately insured adolescents (10–17 years) and young adults (18–24 years) newly initiating SSRI treatment after an anxiety disorder diagnosis, identified from a commercial claims database (2008–2016).
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 3. SSRI Treatment Persistence by Simultaneous BZD Initiation Status

	Adolescents (10–17 years)		Young adults (18–24 years)	
	SSRI + BZD (N = 4,068	SSRI alone (n = 90,331	SSRI + BZD N = 21,902	SSRI alone N = 109,069
Proportion remaining on SSRI treatment at:				
3 months	74% (73–75)	78% (78–79)	64% (63–65)	66% (66–67)
6 months[a]	52% (50–54)	57% (56–57)	38% (37–38)	40% (40–41)
9 months	40% (38–42)	43% (43–43)	25% (25–26)	28% (28–28)
Weighted[b]				
3 months	76% (75–78)	78% (78–78)	65% (65–66)	66% (66–66)
6 months	55% (53–57)	56% (56–57)	39% (39–40)	40% (40–40)
9 months	43% (41–45)	43% (43–43)	27% (26–27)	28% (27–28)
Proportion remaining on BZD treatment at:				
3 months	25% (23–26)	—	23% (23–24)	—
6 months[c]	9% (9–11)	—	9% (9–10)	—
9 months	6% (5–6)	—	6% (5–6)	—

[a]SSRI continuation at 6 months in persons with comorbid depression: adolescents: SSRI + BZD: 56% (53–59); SSRI alone: 58% (58–59) and young adults: SSRI + BZD: 39% (37–40); SSRI alone: 42% (42–43).
[b]Stabilized inverse probability of treatment weighting, variables in propensity score model: sex, age, year of SSRI initiation, anxiety disorder diagnosis, provider type diagnosing anxiety, psychiatric and non-psychiatric diagnoses, psychotropic and other prescription medication use, psychotherapy claims, treated injuries, suicidality, provider contact, inpatient admissions, emergency department visits, outpatient visits, geographical division.
[c]BZD continuation at 6 months in persons with comorbid depression: adolescents: 12% (10–15) and young adults: 11% (10–12).
Abbreviations: BZD: benzodiazepine; SSRI: selective serotonin reuptake inhibitor.

2008 to 2016, the proportion of simultaneous initiators refilling the initial BZD prescription was highest in 2011 for adolescents (36%) and in 2012 for young adults (33%), followed by declines to 29% in adolescents and 30% in young adults in 2015 (the last year with full follow-up data).

Among simultaneous initiators, 9% (95% CI, 9–11) of adolescents and 9% (95% CI, 9–10) of young adults continued BZD treatment for 6+ months (Table 3). In the analysis of factors associated with long-term BZD use among simultaneous initiators, females were less likely to become long-term BZD users than males (adjusted OR = 0.60, Supplementary Table 2). Simultaneous initiators with a longer days' supply value were more likely to become long-term BZD users as were those initiating with clonazepam, seen by a psychiatrist, with a prior substance use disorder diagnosis, and with recent use of other psychotropics.

DISCUSSION

Among adolescents and young adults with anxiety disorders initiating SSRI treatment, the simultaneous initiation of prescription BZD and SSRI treatment has declined but remained relatively common in young adults and was not associated with lengthened SSRI treatment. Given risks of BZD treatment, the potential benefit and risk of adding BZD treatment to SSRI treatment should be carefully weighed. While the practice of BZD and SSRI coprescribing became less frequent among SSRI initiators

from 2008 through 2016, detailing this practice will hopefully encourage dialogue and development of specific recommendations for coprescribing in young populations.

The proportion of SSRI initiators simultaneously initiating BZD treatment was higher with increasing age from 10 to 24 years (2%–21%), with the largest increase from age 17 to 18 years. This mirrors broader BZD prescribing distributions in young adults and adolescents.[26] Several factors may explain the age difference, including variation in evidence and guidelines between children and adults.[1,2,5] There is evidence that BZDs are efficacious in treating anxiety disorders in adults.[27] In the limited trials in children, BZDs were not efficacious in treating anxiety disorders.[5,9,28] However, few trials in young populations exist, and there are no trials with BZDs as adjunctive treatment with SSRIs at treatment onset. While simultaneous prescribing was more common in young adults across provider types, provider types more commonly seen by young adults (ie, family practitioners) had higher prevalence of simultaneous initiation. Simultaneous BZD initiation may also be more common in young adults due to increased comorbidity, presentation acuity, or for targeting of specific symptoms.

We observed a decline in the proportion of SSRI initiators simultaneously initiating BZD treatment. One reason for the decline may be increasing concerns surrounding BZD-related overdoses, particularly when combined with opioids or alcohol, which may limit BZD prescribing.[29] The FDA added a Boxed Warning to BZDs in 2016 for a risk of death when combining BZDs and opioids.[30] Additionally, in findings from a study of adolescents with treatment-resistant depression, adjunctive BZD treatment (non-randomly assigned) was associated with suicidal adverse events (n = 6/10) compared to adolescents without adjunctive BZD treatment (n = 42/324).[31] Observed associations between BZD treatment and suicide attempts could be related to confounding by indication,[32,33] yet these concerns may have nevertheless affected BZD coprescribing in youth with anxiety disorders. Rates of substance use in young people[34] may have also raised concerns for prescribing physicians. Further, the decline could be, at least in part, a function of the base population (adolescents and young adults starting SSRI treatment for anxiety) shifting over the study period. For example, this could include a decline in the average severity of SSRI initiators.

Other concerns surrounding BZDs such as dependency, misuse, or side effects may influence prescribing practices. Given dependency concerns, BZDs are not recommended for routine use,[27] and adolescents receiving BZD treatment should be monitored for BZD misuse.[16] In our study, the majority of simultaneous initiators discontinued BZD treatment early, as recommended. However, 9% of simultaneous initiators continued BZD treatment for at least 6 months. The factors associated with long-term BZD use apply specifically to simultaneous initiators with anxiety disorders and likely differ from factors associated with long-term BZD use in general. While persistent BZD treatment may be a key component of treatment for certain patients,[3] and it may reflect severity of psychiatric symptoms and an evolving course of clinical presentation, the subset progressing to long-term BZD treatment warrants closer examination.

BZDs are typically used at the initiation of antidepressant treatment for rapid, short-term relief of symptoms and SSRI-induced agitation, and it has been suggested that they may improve antidepressant adherence by ameliorating these troublesome symptoms.[7] In randomized trials for adult depression, simultaneous users were less likely to drop out due to side effects than antidepressant monotherapy users.[11] However, in older adults with GAD, those prescribed BZDs with escitalopram treatment were more likely to drop out of the study than those without BZD treatment, with no difference in treatment response or adherence.[35] We cannot evaluate symptoms or adherence in the first days and weeks, when BZD treatment may have the largest potential for benefit. However, our results suggest that improving SSRI treatment persistence after 3 months may not be a benefit of simultaneous treatment, as we did not observe longer SSRI treatment in adolescents and young adults who simultaneously initiated BZD treatment. This was also observed in a similar study of adults with depression, where simultaneous antidepressant and BZD initiation was not associated with longer antidepressant treatment.[10] Other modifiable factors[12,24,25] may be more effective in improving SSRI persistence with lower risk than BZDs.

Simultaneous BZD treatment initiation was highest in adolescents (13%) and young adults (35%) with panic disorder initiating SSRI treatment. This is consistent with stronger evidence for BZDs as a treatment for panic disorder.[1] A small trial of adults with moderate to severe panic disorder observed greater improvement in symptoms in the first weeks of treatment with combined clonazepam and sertraline treatment compared with sertraline monotherapy; still, both groups had similar levels of clinical improvement by study end (12 weeks).[8] Practice guidelines for adult panic disorder state that combined BZD and antidepressant treatment can help with rapid symptom control[1]; however, not all guidelines recommend BZDs for treating panic disorder given risks of BZD treatment.[4]

In addition to age and anxiety disorder, simultaneous initiation varied by comorbidity, prescription medications, and health care utilization and was slightly less common in adolescents and young adults with comorbid depression. There is limited information on the potential benefits to BZD and SSRI coprescription for adults with major depressive disorder[11] or comorbid anxiety and depression.[7] In adults with anxiety disorders, psychiatrists are more likely to prescribe BZDs than primary care providers.[36] As compared to youth seen by psychiatrists, we found youth diagnosed by family practitioners were more likely and those diagnosed by pediatricians were less likely to receive BZD and SSRI treatment. Adolescents and young adults who received psychotherapy prior to SSRI initiation were less likely to be coprescribed BZD treatment, perhaps an indication of an alternative treatment strategy. Individuals receiving

psychotherapy prior to SSRI initiation may be less likely to have an acute need for rapid symptom reduction, which is a situation in which BZD treatment may be more likely to be prescribed. In our sample, there was an increased prevalence of simultaneous BZD initiation in youth with a recent ED visit; research examining ED visits in which anxiety was the primary diagnosis (all ages), found anxiolytics and BZDs to be commonly prescribed (53% of visits when medication was provided).[37] The higher coprescribing could be related to a greater need for acute symptom remission in individuals recently presenting to the ED. Overall, the variation in simultaneous BZD initiation by psychotherapy receipt, provider type, and ED visit is likely at least in part related to anxiety disorder severity. Data resources with more detailed anxiety symptom measures can inform the role of severity in the decision to coprescribe.

Despite recommendations that BZD treatment should be avoided in persons with substance use,[3,5] 3% of adolescents and 4% of young adults simultaneously initiating BZD and SSRI treatment had a recorded substance use disorder diagnosis within the past year. These individuals were also more likely to become long-term BZD users. While we cannot determine if the prescriber knew of the prior diagnosis, this suggests prescribing improvements are needed in youth with substance use disorders. A closer examination of alcohol and drug use prior to SSRI initiation could direct future efforts, particularly as substance use disorders are almost certainly underdiagnosed in our sample and we lack details on alcohol and drug use.

Limitations of this work should be considered. BZD and SSRI prescriptions could have been prescribed by separate providers and not intended for concurrent use; we do not have details on the prescriber, but instead the provider who diagnosed the anxiety disorder. We have access only to dispensed prescriptions and do not know how many patients were coprescribed BZD treatment but did not fill the BZD prescription; primary adherence to new antianxiety medications was estimated to be 77%, with higher primary adherence (94%) in children.[38] Further, we cannot determine whether the BZD was intended for as-needed or regular use and the setting in which the SSRI or BZD was prescribed. While we required an anxiety disorder diagnosis at least 30 days prior to SSRI initiation, we cannot be certain the SSRI or BZD was prescribed for anxiety, especially in patients with comorbid diagnoses. Psychiatric diagnoses were based on diagnostic codes. We examined treatment length adjusting for potential confounders; however, we lack clinical measures, such as anxiety severity, that may influence treatment duration. We detailed BZD and SSRI simultaneous initiation in a commercially insured population; findings may not generalize to adolescents and young adults who are uninsured or insured by Medicaid. Further, race and ethnicity data are unavailable in the dataset. Our study design focused on same-day BZD and SSRI initiation; concurrent SSRI and BZD use at any point during the treatment course will be higher. Our study focused on SSRI initiators; results may differ for treatment initiation with SNRIs or other antidepressants.

The decision to coprescribe BZD and SSRI treatment for anxiety disorders is multifactorial, and there is limited evidence on potential benefits of, or the subpopulation of adolescents and young adults who will benefit the most from, this treatment approach. While these data show that the practice of simultaneous prescribing has declined, in everyday clinical practice in those seen by both generalists and specialty care providers, BZD and SSRI treatments continue to be simultaneously prescribed to young people with anxiety disorders, particularly to young adults. Still, it remains unclear if simultaneous BZD treatment improves SSRI treatment persistence.

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Supplementary material: Available at PSYCHIATRIST.COM

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Supplementary Material

Article Title: Simultaneous Benzodiazepine and SSRI Initiation in Young People With Anxiety Disorders

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List of Supplementary Material for the article

1. Table 1 — BZD prescription details in adolescents and young adults simultaneously initiating BZD and SSRI treatment
2. Table 2 — Clinical factors associated with long-term BZD use (6+ months) in adolescents and young adults simultaneously initiating BZD+SSRI treatment

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Supplementary Table 1. BZD prescription details in adolescents and young adults simultaneously initiating BZD and SSRI treatment

Initial BZD prescription details	**Adolescents (10-17 years),** N=4,068	**Young adults (18-24 years),** N=21,902
BZD, No. (%)		
Alprazolam	1,511 (37.1)	10,782 (49.2)
Clonazepam	1,253 (30.8)	5,022 (22.9)
Lorazepam	1,160 (28.5)	5,480 (25.0)
Diazepam	87 (2.1)	266 (1.2)
Other	57 (1.4)	352 (1.6)
Days supply, median (IQR)	15 (10-30)	15 (10-30)
Quantity dispensed, median (IQR)	30 (15-30)	30 (20-40)

BZD: benzodiazepine; IQR: interquartile range

Supplementary Table 2. Clinical factors associated with long-term BZD use (6+ months) in adolescents and young adults simultaneously initiating BZD+SSRI treatment

	Simultaneous initiators with 6+ months follow-up, N=20,301	
Clinical factor	Long-term BZD use, Row %	aOR (95% CI)[a]
Overall long-term BZD use (N=1,684)	8.3%	-
Initial BZD agent		
Alprazolam	7.2%	REF
Clonazepam	13.4%	1.32 (1.17-1.49)
Lorazepam	5.3%	0.67 (0.58-0.78)
Other	10.1%	0.97 (0.72-1.29)
BZD days supply, initial prescription		
1-10 days	3.4%	0.52 (0.44-0.61)
11-20 days	6.9%	REF
21+ days	14.8%	2.03 (1.78-2.32)
Initial SSRI agent		
Citalopram	7.9%	0.98 (0.85-1.13)
Escitalopram	7.6%	0.83 (0.72-0.96)
Fluoxetine	9.1%	0.97 (0.83-1.15)
Sertraline	8.6%	REF
Other	8.8%	0.99 (0.82-1.19)
Female (Ref: male)	6.6%	0.60 (0.54-0.67)
Age at SSRI initiation		
10-17 y	8.4%	REF
18-20 y	8.1%	1.19 (1.01-1.40)
21-24 y	8.4%	1.24 (1.06-1.46)
Anxiety disorder diagnosis (prior 30d)		
Unspecified anxiety	7.0%	REF
Generalized anxiety disorder	9.7%	1.13 (0.98-1.30)
Panic disorder	9.5%	1.12 (0.95-1.31)

Adjustment disorder with anxiety	7.9%	0.91 (0.70-1.19)
Acute stress disorder	6.0%	0.87 (0.57-1.33)
Social phobia	12.7%	1.08 (0.73-1.60)
Other anxiety disorder	7.8%	1.11 (0.81-1.54)
Multiple specific diagnoses	10.5%	1.07 (0.87-1.31)
Provider of anxiety diagnosis		
Psychiatry	16.3%	REF
Psychology	9.5%	0.64 (0.49-0.83)
Family practitioner	6.6%	0.57 (0.49-0.67)
Pediatrician	4.1%	0.44 (0.30-0.65)
Other general provider	7.3%	0.60 (0.50-0.72)
Other provider type	8.2%	0.69 (0.57-0.83)
Unknown or multiple	7.6%	0.64 (0.52-0.78)
Depression, 1y	10.1%	1.09 (0.97-1.23)
Sleep disorder, 1y	10.0%	1.01 (0.84-1.22)
ADHD, 1y	11.0%	0.83 (0.64-1.08)
PTSD, 1y	10.7%	1.00 (0.66-1.52)
Adjustment disorder, 1y	8.6%	0.89 (0.66-1.21)
OCD, 1y	12.2%	1.20 (0.83-1.73)
Other episodic mood disorder	14.1%	1.38 (0.97-1.97)
Substance use disorder, 1y	17.4%	1.76 (1.41-2.19)
Tobacco/nicotine dependence, 1y	13.5%	1.44 (1.15-1.79)
Poisoning event, 1y	11.2%	1.07 (0.66-1.75)
Recent (0-90d) prescriptions		
Stimulant	12.8%	1.57 (1.17-2.10)
Antidepressant (excludes SSRIs)	15.6%	1.63 (1.32-2.01)
Hydroxyzine	14.3%	1.57 (1.13-2.17)
Hypnotic	16.6%	1.79 (1.31-2.44)
Anticonvulsant	12.2%	0.96 (0.63-1.47)
Opioid	12.5%	1.66 (1.43-1.92)
Psychotherapy claims		
Recent (0-30d)	11.3%	1.18 (1.01-1.38)
Past (31-365d), no recent	9.9%	1.06 (0.83-1.35)
None	7.6%	REF

ADHD: attention-deficit/hyperactivity disorder; aOR: adjusted odds ratios; d: days; OCD: obsessive compulsive disorder; PTSD: post-traumatic stress disorder; Ref: Reference group; SSRI: Selective Serotonin Reuptake Inhibitor; y: years

[a] Presented aORs are from a single logistic regression model; the reference groups for diagnoses and recent prescriptions are those without that diagnosis or prescription