Treating Pediatric Anxiety:
Initial Use of SSRIs and Other Antianxiety Prescription Medications

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ABSTRACT

Objective: Multiple pharmacotherapies for treating anxiety disorders exist, including selective serotonin reuptake inhibitors (SSRIs), the recommended first-line pharmacotherapy for pediatric anxiety. We sought to describe initial antianxiety medication use in children and estimate how long antianxiety medications were continued.

Methods: In a large commercial claims database, we identified children (3–17 years) initiating prescription antianxiety medication from 2004 to 2014 with a recent anxiety diagnosis (*ICD-9-CM* = 293.84, 300.0x, 300.2x, 300.3x, 309.21, 309.81, 313.23). We estimated the proportion of children initiating each medication class across the study period and used multivariable regression to evaluate factors associated with initiation with an SSRI. We evaluated treatment length for each initial medication class.

Results: Of 84,500 children initiating antianxiety medication, 70% initiated with an SSRI (63% [95% CI, 62%–63%] SSRI alone, 7% [95% CI, 7%–7%] SSRI + another antianxiety medication). Non-SSRI medications initiated included benzodiazepines (8%), non-SSRI antidepressants (7%), hydroxyzine (4%), and atypical antipsychotics (3%). Anxiety disorder, age, provider type, and comorbid diagnoses were associated with initial medication class. The proportion of children refilling their initial medication ranged from 19% (95% CI, 18%–20%) of hydroxyzine initiators and 25% (95% CI, 24%–26%) of benzodiazepine initiators to 81% (95% CI, 80%–81%) of SSRI initiators. Over half (55%, 95% CI, 55%–56%) of SSRI initiators continued SSRI treatment for 6 months.

Conclusions: SSRIs are the most commonly used first-line medication for pediatric anxiety disorders, with about half of SSRI initiators continuing treatment for 6 months. Still, a third began therapy on a non-SSRI medication, for which there is limited evidence of effectiveness for pediatric anxiety, and a notable proportion of children initiated with 2 antianxiety medication classes.

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Anxiety disorders are one of the most common mental illnesses in children in the United States,[1] with lifetime prevalence of pediatric anxiety disorders around 15%–20%.[2] Children with anxiety disorders have an increased risk for future additional anxiety disorders, depression, and substance use and experience academic impairments.[3–8] Pediatric anxiety disorders are likely to occur in association with somatic symptoms, including headaches, nausea, and trouble sleeping.[9] In 2010, anxiety disorders were the fifth leading contributor to years lived with disability in the United States,[10] demonstrating the sustained impact of unmanaged anxiety. Early diagnosis and effective treatment of anxiety disorders are essential to manage symptoms and improve quality of life and can reduce the persistence of anxiety into young adulthood and beyond.[8,11]

The American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters recommend psychotherapy as the first-line treatment for anxiety of mild severity.[8,12,13] AACAP recommends pharmacologic treatment when moderate to severe symptoms or comorbid psychiatric disorders are present, or when children are unable/unwilling to participate in or have a partial response to psychotherapy.[8,12,13] While there are a variety of pharmacologic approaches to treat anxiety, selective serotonin reuptake inhibitors (SSRIs) are considered the first-line pharmacotherapy for pediatric anxiety.[8,12,13] Randomized controlled trials (RCTs) showed efficacy of SSRIs over placebo in children with anxiety.[14,15] SSRIs are generally well tolerated and have a mild side effect profile compared to other drugs, and there is minimal empirical evidence to support use of other medications to treat pediatric anxiety.[8,12,13,16–18] However, since October 2004, antidepressants, including SSRIs, carry a black-box warning for an increased risk of suicidality in children,[19] and, while select SSRIs are approved by the US Food and Drug Administration (FDA) to treat obsessive-compulsive disorder (OCD), SSRIs are not approved for pediatric non-OCD

Clinical Points

- There are many potential prescription medications for treating anxiety disorders, and it has been unclear which antianxiety medications are used as first-line pharmacotherapy in pediatric anxiety.
- The majority of children initiating treatment with an antianxiety medication received an SSRI, the recommended first-line medication for pediatric anxiety disorders, although a third of children began pharmacotherapy with a non-SSRI antianxiety medication and a notable proportion of children initiated with 2 antianxiety medication classes.

anxiety. These factors may lead caregivers or providers to prefer non-SSRI medications for children beginning pharmacotherapy for anxiety.

Evidence on long-term efficacy and safety of antianxiety medications for children is limited, raising concern over the potential harms of routine pharmacologic anxiety treatment.[16,20] The 2007 AACAP guidelines caution that while RCTs have established the safety and efficacy of short-term SSRI treatment for pediatric anxiety, the benefits and risks of long-term SSRI use have not been studied.[8] Posttrial follow-up data have provided important evidence of continued SSRI response up to 36 weeks.[21,22] Benzodiazepines, another common antianxiety medication, are usually recommended for only short-term treatment given dependency concerns.[16]

There is little understanding of how often SSRIs and other pharmacotherapies are used and their duration of use when treating pediatric anxiety. Understanding treatment utilization can detail what, if any, changes in clinical practice are needed to improve treatment for pediatric anxiety disorders. Therefore, this study sought to estimate the initial medication class received by children diagnosed with anxiety beginning antianxiety medication, determine whether this varied across the study period and by patient characteristics, and estimate treatment continuation of the initial antianxiety medication.

METHODS

We used Truven Health Analytics' MarketScan Commercial Claims and Encounters database, containing individuals covered by employer-sponsored private health insurance across the United States. We utilized data from enrollment files, inpatient and outpatient services, and outpatient drug claims for reimbursed, dispensed prescriptions. We included children 3–17 years with an anxiety diagnosis who initiated an antianxiety medication between 2004 and 2014. An anxiety diagnosis was defined as an inpatient or outpatient *ICD-9-CM* code (293.84, 300.0x, 300.2x, 300.3x, 309.21, 309.81, 313.23). These codes roughly correspond to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, anxiety disorders[23] and additionally include posttraumatic stress disorder (PTSD) and OCD, as they share similar treatment recommendations and were previously classified under anxiety disorders.[24]

Table 1. Antianxiety Medications Included, Grouped by Medication Class

Medication Class	
Selective serotonin reuptake inhibitors	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone
Serotonin-norepinephrine reuptake inhibitors	Desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine
Tricyclic antidepressants	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine
Bupropion	
Other antidepressants	Atomoxetine, isocarboxazid, mirtazapine, nefazodone, phenelzine, selegiline transdermal, tranylcypromine, trazodone, vortioxetine
Benzodiazepines	Alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, halazepam, lorazepam, oxazepam, prazepam
Buspirone	
Anticonvulsants	Carbamazepine, gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, valproic acid
Atypical antipsychotics	Aripiprazole, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone
β-blockers	Acebutolol, atenolol, atenolol/chlorthalidone, bendroflumethiazide/nadolol, betaxolol, bisoprolol fumarate, carteolol, carvedilol, esmolol, metoprolol succinate, metoprolol tartrate, nadolol, nebivolol, penbutolol sulfate, pindolol, propranolol, sotalol, timolol maleate
Hydroxyzine	
Other	Clonidine, D-cycloserine, guanfacine, memantine, prazosin, riluzole

To identify initiators of antianxiety medications, we selected the initial antianxiety prescription based on records of dispensed prescriptions, defined as having no antianxiety prescription in the prior year. Children were required to have continuous insurance enrollment with prescription and mental health services coverage the year before medication initiation. We defined antianxiety medications as medications with trial evidence of efficacy in treating anxiety in adult or pediatric populations and also medications suggested as potential effective treatments for anxiety (Table 1, grouped into medication classes).[17,18,25,26] Children could have initiated antianxiety pharmacotherapy with 2 medication classes (eg, SSRI + benzodiazepine); children initiating with > 2 classes were excluded (0.3%). As these therapies have multiple indications, we required ≥ 1 anxiety diagnosis within 30 days prior to or on the date of the initial antianxiety prescription (Supplementary eFigure 1).

Each initial antianxiety prescription was grouped into one of 12 medication classes, but children were also broadly classified as initiating (1) SSRI with no other antianxiety medication (SSRI alone), (2) SSRI + another antianxiety medication, and (3) non-SSRI antianxiety medication. These mutually exclusive categories represented 3 treatment strategies.

Table 2. Selected[a] Characteristics of Children Initiating Antianxiety Medication and Factors Associated With Initiating With SSRI Plus Another Antianxiety Medication vs SSRI Alone and With Non-SSRI Antianxiety Medication vs SSRI Alone

Patient Characteristic	Children Initiating Antianxiety Medication (N = 84,500) n (%)	Initial Antianxiety Treatment Group				
		SSRI Alone (N = 53,009) n (%)	SSRI + Another Antianxiety Medication (N = 5,863)		Non-SSRI Antianxiety Medication (N = 25,628)	
			n (%)	vs SSRI Alone, Multivariable RR (95% CI)[a]	n (%)	vs SSRI Alone, Multivariable RR (95% CI)[a]
Female	49,255 (58)	31,688 (60)	3,771 (64)	Ref	13,796 (54)	Ref
Male	35,245 (42)	21,321 (40)	2,092 (36)	1.0 (0.9–1.0)	11,832 (46)	1.1 (1.1–1.1)
Age, median (IQR)	14 (11–16)	14 (11–16)	15 (13–16)		14 (10–16)	
Age, n (%)						
3–5 y	1,449 (2)	696 (1)	25 (< 1)	0.4 (0.2–0.5)	728 (3)	1.4 (1.3–1.5)
6–9 y	12,377 (15)	7,782 (15)	332 (6)	0.4 (0.4–0.5)	4,263 (17)	1.0 (1.0–1.1)
10–13 y	21,997 (26)	14,525 (27)	1,269 (22)	0.8 (0.7–0.8)	6,203 (24)	0.9 (0.9–1.0)
14–17 y	48,677 (58)	30,006 (57)	4,237 (72)	Ref	14,434 (56)	Ref
Anxiety disorder, index diagnosis						
Unspecified	42,652 (50)	26,037 (49)	2,417 (41)	Ref	14,198 (55)	Ref
Generalized anxiety disorder	20,508 (24)	13,812 (26)	1,417 (24)	1.1 (1.0–1.2)	5,279 (21)	0.8 (0.8–0.8)
OCD	6,194 (7)	4,773 (9)	353 (6)	0.9 (0.8–1.0)	1,068 (4)	0.5 (0.5–0.6)
Panic disorder	4,294 (5)	1,967 (4)	507 (9)	2.0 (1.9–2.2)	1,820 (7)	1.3 (1.3–1.4)
PTSD	3,531 (4)	1,683 (3)	492 (8)	1.5 (1.4–1.7)	1,356 (5)	1.2 (1.1–1.2)
Social phobia	1,972 (2)	1,465 (3)	156 (3)	1.0 (0.9–1.2)	351 (1)	0.6 (0.6–0.7)
Other[c]	3,530 (4)	1,993 (4)	279 (5)	1.6 (1.4–1.7)	1,258 (5)	1.1 (1.0–1.1)
Multiple	1,819 (2)	1,279 (2)	242 (4)	1.6 (1.5–1.9)	298 (1)	0.6 (0.6–0.7)
Provider type, index anxiety diagnosis						
Psychiatry	20,514 (24)	14,114 (27)	1,674 (29)	Ref	4,726 (18)	Ref
Psychologist, therapist	10,124 (12)	5,761 (11)	444 (8)	0.7 (0.7–0.8)	3,919 (15)	1.6 (1.6–1.7)
Family practice	11,136 (13)	7,004 (13)	788 (13)	0.9 (0.8–0.9)	3,344 (13)	1.0 (1.0–1.1)
Pediatrics	13,565 (16)	9,574 (18)	502 (9)	0.5 (0.5–0.6)	3,489 (14)	0.9 (0.8–0.9)
Other	20,980 (25)	12,109 (23)	1,768 (30)	1.0 (0.9–1.0)	7,103 (28)	1.3 (1.2–1.3)
Unknown	8,181 (10)	4,447 (8)	687 (12)	1.0 (0.9–1.1)	3,047 (12)	1.3 (1.3–1.4)
Psychiatric comorbidity details[d]						
Any recent nonanxiety psychiatric diagnosis[b]	38,363 (45)	23,841 (45)	3,188 (54)	–	11,334 (44)	–
Depression diagnosis (ref = no diagnosis)[b]						
Recent diagnosis	18,875 (22)	13,163 (25)	2,231 (38)	1.1 (1.0–1.2)	3,481 (14)	0.6 (0.6–0.6)
Prior diagnosis, no recent diagnosis	3,275 (4)	2,017 (4)	201 (3)	0.9 (0.8–1.1)	1,057 (4)	0.9 (0.9–1.0)
Attention deficit disorder (ref = no diagnosis)[b]						
Recent diagnosis	10,191 (12)	5,139 (10)	428 (7)	1.0 (0.9–1.2)	4,624 (18)	1.5 (1.5–1.6)
Prior diagnosis, no recent diagnosis	4,877 (6)	2,911 (5)	236 (4)	1.1 (0.9–1.2)	1,730 (7)	1.2 (1.1–1.2)
Other episodic mood disorder	4,073 (5)	2,036 (4)	455 (8)	1.2 (1.1–1.3)	1,582 (6)	1.3 (1.2–1.3)
Bipolar disorder	1,479 (2)	466 (1)	164 (3)	1.6 (1.4–1.8)	849 (3)	1.8 (1.7–1.9)
Index anxiety diagnosis in inpatient setting	4,313 (5)	1,981 (4)	938 (16)	2.1 (1.9–2.3)	1,394 (5)	1.2 (1.1–1.2)
Mental health diagnostic evaluation	45,051 (53)	29,917 (56)	3,294 (56)	1.1 (1.0–1.1)	11,840 (46)	0.8 (0.8–0.8)

[a]Multivariable RRs are from the full model that includes all variables in Supplementary eTable 1; the multivariable RRs (95% CI) for the comparison between SSRI + another antianxiety medication versus non-SSRI antianxiety medication are available in Supplementary eTable 1.
[b]Recent = 0–30 days before antianxiety medication initiation, prior = 31–365 days before antianxiety medication initiation.
[c]Anxiety disorders with < 1,000 children: other anxiety, separation anxiety, selective mutism, anxiety due to medical condition, agoraphobia, other/specific phobia.
[d]Definitions: depression (*ICD-9-CM*: 296.2x, 296.3x, 300.4x, 309.1x, 311.x), attention deficit disorder (*ICD-9-CM*: 314.0x), other episodic mood disorder (*ICD-9-CM*: 296.9x), bipolar disorder/cyclothymic (*ICD-9-CM*: 296.0x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x, 301.13).
Abbreviations: IQR = interquartile range, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, ref = reference category, RR = risk ratio, SSRI = selective serotonin reuptake inhibitor.
Symbol: – = variable not entered into the full multivariable model as specific indicators for psychiatric disorders were used.

Following initiation, treatment length per initial medication class was evaluated. A child was considered to have discontinued treatment in that medication class when there was no record of a dispensed prescription 30 days after the days' supply of the previous prescription ran out. Switching agents within a medication class was regarded as continuing that medication class. The primary measures for treatment continuation were (1) refilling a prescription in the initial medication class before discontinuation and (2) remaining on treatment for 6 months.

Patient characteristics were collected in the year prior to and on the date of medication initiation to describe the study cohort and identify factors associated with initial medication choice. Characteristics included age, sex, anxiety diagnosis details, anxiety-related symptoms, psychiatric comorbidities, nonpsychiatric comorbidities, health care utilization, region, and year of medication initiation. The anxiety diagnosis most prior to or on the date of antianxiety medication initiation (index diagnosis) was grouped into mutually exclusive categories. Patients with an unspecified and a specific anxiety diagnosis were assigned to the specific diagnosis; patients with ≥ 1 specific diagnosis were grouped under "multiple." The provider type of the index diagnosis was categorized as psychiatry, family practice, pediatrics, psychologist/therapist, all other types, and unknown/multiple providers. For common psychiatric comorbidities

Table 3. Initial Antianxiety Medication Class in Children With Diagnosed Anxiety Disorders Beginning Antianxiety Pharmacotherapy

	Primary Analysis: Full Cohort (N = 84,500)		Anxiety Diagnosis Same Day as Initial Antianxiety Prescription (N = 47,973)		2+ Anxiety Diagnoses, No Recent Comorbid Psychiatric Diagnosis[a] (N = 20,249)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
SSRI alone	53,009	63 (62–63)	32,044	67 (66–67)	13,492	67 (66–67)
SSRI + another antianxiety medication[b]	5,863	7 (7–7)	3,664	8 (7–8)	1,147	6 (5–6)
SSRI + benzodiazepine	2,528	3	1,890	4	652	3
SSRI + other antidepressant	926	1	475	1	113	1
SSRI + atypical antipsychotic	894	1	299	1	104	1
SSRI + hydroxyzine	761	1	511	1	132	1
Non-SSRI antianxiety medication	25,628	30 (30–31)	12,265	26 (25–26)	5,610	28 (27–28)
Benzodiazepine	7,125	8	4,038	8	1,735	9
Hydroxyzine	3,244	4	1,937	4	750	4
Other antidepressant	2,987	4	1,051	2	658	3
Other antianxiety[c]	2,967	4	1,090	2	519	3
Atypical antipsychotic	2,264	3	732	2	343	2
Bupropion	1,251	1	592	1	211	1
Buspirone	1,226	1	876	2	253	1
TCA	1,157	1	497	1	382	2
Anticonvulsant	988	1	289	1	294	1
SNRI	761	1	345	1	165	1
β-blocker	705	1	391	1	176	1
Non-SSRI + non-SSRI	953	1	427	1	124	1
Total	**84,500**	**100**	**47,973**	**100**	**20,249**	**100**

[a]At least 2 anxiety diagnoses in the prior year and no comorbid psychiatric diagnosis in the 30 days before antianxiety medication initiation.
[b]Primary analysis: SSRI + other antianxiety (n = 355), SSRI + buspirone (n = 133), SSRI + β-blocker (n = 110), SSRI + anticonvulsant (n = 83), SSRI + TCA (n = 55), SSRI + bupropion (n = 17).
[c]Of these prescriptions, 98% were clonidine or guanfacine.
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

(depression, adjustment disorder, attention-deficit/hyperactivity disorder [ADHD]), we created indicators for a recent diagnosis (within 30 days) or only a prior diagnosis (31–365 days prior). Any recent psychiatric diagnosis was defined as an *ICD-9-CM* code = 290–319 (excluding anxiety diagnoses).

Statistical Analyses

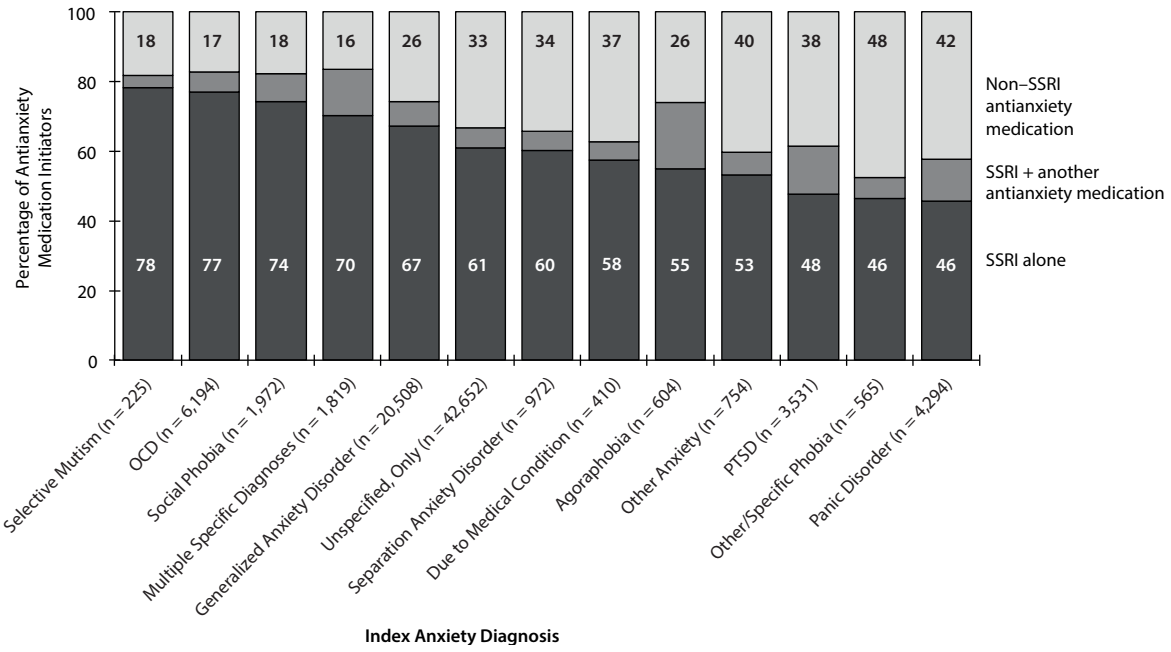
We determined the number and proportion of children initiating each antianxiety medication class overall and stratified by anxiety disorder and by year of initiation and age. As the proportion of children diagnosed with comorbid depression and comorbid ADHD increased across the study period, trends identified were examined in children without depression and without ADHD. We used multivariable Poisson regression with robust variance to estimate fully adjusted risk ratios (RRs) with 95% confidence intervals (CIs) to identify factors independently associated with initiating (1) SSRI + another antianxiety medication vs SSRI alone, (2) non-SSRI antianxiety medication vs SSRI alone, and (3) SSRI + another antianxiety medication vs non-SSRI antianxiety medication. We used Kaplan-Meier estimator to examine treatment continuation for each initial medication class up to 2 years, with censoring at insurance disenrollment and end of data (December 31, 2014). The proportion of children refilling their initial medication class was evaluated in children with ≥ 60 days of insurance enrollment after medication initiation. In an exploratory analysis, we estimated the proportion of children initiating with a non-SSRI antianxiety medication who subsequently filled an SSRI prescription within 3 months in children with ≥ 3 months of insurance enrollment.

Additional sensitivity analyses were completed. Given the multiple indications for antianxiety medications, we examined the proportion of children initiating each medication class in restricted cohorts: (1) children initiating antianxiety medication the same day as an anxiety diagnosis and (2) children with ≥ 2 anxiety diagnoses and no recent comorbid psychiatric diagnosis. We considered an interaction term between anxiety disorder and provider type in our multivariable model. When examining treatment continuation, analyses were repeated using 15- and 60-day grace periods to define discontinuation and stratified by 1 versus ≥ 2 prior anxiety diagnoses. The University of North Carolina Institutional Review Board approved this study.

RESULTS

We identified 84,500 children with diagnoses for anxiety who initiated antianxiety pharmacotherapy. The cohort had more girls (58%) and few children aged 3–5 years (2%), with the majority 14–17 years (58%), and 50% had an index anxiety diagnosis of unspecified anxiety (Table 2; Supplementary eTable 1). Approximately 24% were diagnosed with anxiety by a psychiatrist and 29% by a pediatrician or family practitioner. Fifty-seven percent of children had an anxiety diagnosis on the day of medication

Figure 1. Proportion of Children Initiating Antianxiety Pharmacotherapy With SSRI Alone, SSRI + Another Antianxiety Medication, or Non-SSRI Antianxiety Medication by Index Anxiety Diagnosis[a]



[a]Displayed by the anxiety disorder with the highest proportion of children initiating with an SSRI alone to the lowest proportion of children initiating with an SSRI alone.
Abbreviations: OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, SSRI = selective serotonin reuptake inhibitor.

initiation, resulting in a median number of days between the index anxiety diagnosis and antianxiety medication initiation of 0 (interquartile range, 0–3).

Overall, 63% of children initiated with an SSRI alone, and an additional 7% initiated with an SSRI + another antianxiety medication (Table 3). Benzodiazepines were the most commonly used non-SSRI medication (8% = benzodiazepine alone, 3% = SSRI + benzodiazepine), with the majority of use in children 14–17 years. Seven percent initiated with a non-SSRI antidepressant alone, and a small proportion initiated with an atypical antipsychotic, hydroxyzine, or clonidine/guanfacine. In sensitivity analyses with restricted cohorts, there was a slightly higher use of SSRIs alone, but overall findings were consistent (Table 3).

Across the study period, initiation with an SSRI remained fairly stable in children 3–13 years but increased in children 14–17 years (2004 = 55%, 2014 = 66%, Supplementary eFigure 2). The proportion of children 14–17 years initiating with a benzodiazepine decreased across the study period (2004 = 20%, 2014 = 10%) and approached the lower levels of use in younger children (Supplementary eFigure 3). This trend remained in children without a recent comorbid depression diagnosis. While few children 3–5 years with anxiety initiated an antianxiety medication (n = 1,449), the proportion that did so with guanfacine or clonidine increased, from 11% in 2007 to 18% in 2009 and further to 27% by 2014. The increase remained but stabilized (2007 = 8%, 2009 = 15%, 2014 = 18%) when restricted to children without a comorbid ADHD diagnosis.

The initial medication prescribed varied by anxiety disorder (Figure 1). Children with OCD (77%) and selective mutism (78%) were most likely to initiate with an SSRI alone, and children with panic disorder (46%), other/specific phobia (46%), and PTSD (48%) were least likely. In children with panic disorder, 24% initiated with a benzodiazepine alone and 8% with an SSRI + benzodiazepine (full cohort = 8% and 3%, respectively). In children with PTSD, 9% initiated with an atypical antipsychotic alone (19%, n = 66 in those with a recent comorbid disturbance of conduct or oppositional defiant disorder diagnosis vs 8%, n = 268 without this diagnosis) and 5% with an SSRI + atypical antipsychotic (full cohort = 3% and 1%, respectively).

The initial antianxiety medication also varied by age, provider type, comorbid psychiatric diagnoses, and other patient factors (Table 2; Supplementary eTable 1). Children with a recent depression diagnosis were less likely (RR: 0.57; 95% CI, 0.56–0.59) and children with a recent ADHD diagnosis were more likely (RR: 1.53; 95% CI, 1.48–1.59) to initiate a non-SSRI medication than SSRI alone. Children 3–13 years were less likely to initiate with an SSRI + another antianxiety medication vs SSRI alone, as were children diagnosed with anxiety by a pediatrician (RR: 0.53; 95% CI, 0.48–0.59) compared to a psychiatrist. Inferences were limited for the interaction between anxiety disorder and provider type given sample size. However, the primary variation was with social phobia where family practice providers were more likely to prescribe an SSRI + another antianxiety medication and panic disorder where pediatricians and family practice

Table 4. Proportion of Children Refilling Their Initial Antianxiety Medication Class and Continuing That Medication Class for 6 Months

Initial Medication Class[a]	n	Refilled Initial Prescription,[b] % (95% CI)	Continued Medication for 6 Months, % (95% CI)
SSRI	58,872	81 (80–81)	55 (55–56)
Benzodiazepine	10,005	25 (24–26)	5 (4–7)
Hydroxyzine	4,165	19 (18–20)	3 (1–7)
Other antidepressant	4,151	58 (56–59)	28 (26–31)
Atypical antipsychotic	3,501	71 (69–72)	41 (38–43)
Other antianxiety[c]	3,424	64 (62–66)	38 (35–40)
Buspirone	1,474	49 (46–51)	19 (15–23)
Bupropion	1,459	69 (66–71)	37 (33–40)
Tricyclic antidepressant	1,279	55 (52–57)	27 (23–32)
Anticonvulsant	1,218	64 (61–66)	35 (30–39)
β-blocker	887	32 (29–35)	14 (9–20)
SNRI	881	66 (63–69)	38 (33–43)

[a]Each medication class evaluated separately for patients initiating 2 classes.
[b]Calculated from the 93% of children with ≥ 60 days of continuous insurance in follow-up.
[c]Of these prescriptions, 98% were clonidine or guanfacine.
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

providers were more likely to prescribe a non-SSRI than psychiatry.

SSRI prescriptions were most likely to be refilled (81%), followed by atypical antipsychotics (71%) and bupropion (69%) (Table 4). Over half (55%) of children initiating with an SSRI continued SSRI treatment for 6 months, 34% for 1 year, and 17% for 2 years. Benzodiazepine and hydroxyzine initiators were least likely to refill (25% and 19%, respectively) and continue treatment for 6 months (5% and 3%, respectively). Children initiating a benzodiazepine or hydroxyzine were more likely to receive a shorter days' supply: 54% of initial benzodiazepine prescriptions and 42% of hydroxyzine prescriptions were for ≤ 10 days compared with only 6% of initial SSRI prescriptions with a days' supply < 30 days. We observed similar patterns when varying the grace period to define treatment continuation and when stratified by ≥ 2 prior anxiety diagnoses, with higher continuation in children with ≥ 2 prior diagnoses (Supplementary eTables 2 and 3).

Eighteen percent (n = 4,121) of children initiating with a non-SSRI antianxiety medication subsequently filled an SSRI prescription within 3 months. This pattern varied by medication class (range, 11%–24%), with 24% of benzodiazepine initiators and 20% of atypical antipsychotic initiators later filling an SSRI prescription (Supplementary eTable 4).

DISCUSSION

Concordant with the majority of evidence and recommendations, SSRIs were the most commonly used first-line antianxiety medication in children diagnosed with anxiety disorders. By 2007, there was convincing evidence that SSRIs were efficacious in treating pediatric anxiety, summarized in a meta-analysis of RCTs[14] with findings upheld in updated meta-analyses.[15,27] There are appropriate reasons for a child to initiate with a non-SSRI medication; however, those reasons likely do not account for the third of children who began pharmacotherapy with an antianxiety medication with limited evidence of efficacy or no trial evidence.

There is evidence demonstrating efficacy of SNRIs for some anxiety disorders,[14] and duloxetine was recently approved for pediatric generalized anxiety disorder.[28] SNRIs are not recommended first-line therapy and were rarely used as the initial antianxiety medication in our study. Benzodiazepines, while used much less frequently than SSRIs, were the second most commonly used initial antianxiety medication. Conversely, in US adults with anxiety disorders, where benzodiazepines are approved for several anxiety disorders, SSRIs and benzodiazepines are used at more comparable frequencies.[29,30] While the proportion of children initiating with an atypical antipsychotic remained low across the study period, given the potential harms of antipsychotics, they should not be considered as first-line treatment for anxiety.[31] Our finding that 18% of non-SSRI initiators filled an SSRI prescription in the following months highlights that some children could have avoided being exposed to potential side effects from medications lacking evidence of effectiveness.

In adult guidelines for panic disorder, SSRIs, SNRIs, tricyclic antidepressants, and benzodiazepines are said to be roughly comparable in efficacy,[32] possibly explaining the higher observed benzodiazepine use in children with panic disorder. Relatedly, while SSRIs are approved to treat PTSD in adults,[12] there is less evidence supporting SSRIs for pediatric PTSD, likely explaining the lower proportion of children with PTSD initiating with an SSRI alone.[12,26] The variation observed in initial medication class by comorbid psychiatric diagnoses was expected and potentially appropriate as medication selection should consider comorbidities.[8] Still, almost a third of children with no recent comorbid psychiatric diagnosis initiated with a non-SSRI antianxiety medication. Variation in initial medication class by provider type is likely influenced by familiarity with treatment guidelines and clinical experience or potentially due to unmeasured differences in anxiety and comorbidity severity between providers.

The large increase in the proportion of young children initiating antianxiety pharmacotherapy with guanfacine or clonidine occurred following the medications' FDA approval for pediatric ADHD. In the United States, guanfacine and clonidine use increased from 11% of children receiving any psychotropic medication in 2009 to 14% in 2011, with the majority of use for ADHD.[33] The trend we observed with guanfacine and clonidine could be related to caregiver preferences for selecting treatment with pediatric FDA approval.[34] Relatedly, caregivers may prefer that their child initiate treatment with a non-antidepressant medication given the antidepressant black-box warning. In a small chart review of children with anxiety who were offered a trial of antidepressants, the percentage of caregivers refusing antidepressant treatment increased after the black-box warning.[35]

AACAP practice parameters state that prescribers should have a clear rationale for prescribing medication combinations.[36] In our cohort, 7% initiated with an SSRI + another antianxiety medication. Half of those children initiated an SSRI + benzodiazepine, which is sometimes done to achieve rapid reduction in severe anxiety symptoms.[8] The practice of concurrent antianxiety medication initiation was less common in younger children and children diagnosed by a provider outside psychiatry but occurred across provider types, similar to findings from broader psychotropic polypharmacy in children.[37] Despite some exceptions, beginning pharmacotherapy with an SSRI + another antianxiety medication raises concern given limited data on psychotropic polypharmacy in regards to effectiveness and possible increased adverse event burden, especially for treatment-naive children.[38]

Pediatric OCD guidelines state that treatment should typically be continued for 6–12 months and then gradually withdrawn.[13] For non-OCD anxiety, a medication-free period has been recommended in children who experienced anxiety symptom reduction for a year,[39] but there are no formal guidelines on recommended SSRI treatment length.[8,12] In our study, just over half of commercially insured children with anxiety continued SSRI treatment for 6 months. This was similar to 6-month SSRI estimates in children with major depressive disorder (46%),[40] for whom guidelines are more specific, recommending ≥ 6 months of continued medication.[4]

The previously described gap between the amount of provider contact required by evidence-based treatments and the amount received in children with anxiety[41] could influence early medication discontinuation. Medication discontinuation may be appropriate, including if the child responded to concurrent cognitive behavioral therapy. As such, we cannot discern whether medication was discontinued due to nonresponse, side effects, or other reasons, and whether a clinician advised discontinuation. In certain instances, the initial antianxiety medication was likely intended for short-term use (ie, benzodiazepine and hydroxyzine with short initial days' supply values). It is reassuring that the recommended medication class with the most evidence of efficacy for pediatric anxiety disorders had the highest continuation and that benzodiazepines were used primarily for short-term treatment.[16]

Around 44% of children with severe mental health impairment receive outpatient mental health services,[42] and 31% of children with anxiety report receiving treatment; 9% receive medication.[43] These estimates highlight that our findings apply to a subset of children with anxiety, children who were diagnosed and initiated an antianxiety pharmacotherapy. With our additional requirements of continuous private insurance coverage, our results are likely not generalizable to all US children. Future research could explore whether the initial prescription antianxiety medication differs in children covered by Medicaid given prior research on differences in psychotropic and antipsychotic use in children on public and private insurance.[44,45]

Almost half of children in our population had an unspecified anxiety diagnosis given most prior to, or on, the date of antianxiety medication initiation. The use of unspecified anxiety diagnoses has increased in youth, rising from 45% (1999–2002) to 58% (2007–2010) of anxiety diagnoses in ambulatory settings.[46] Children classified as having an unspecified anxiety diagnosis prior to medication initiation likely include children with a more specific anxiety disorder diagnosis that was not evaluated or not recorded, resulting in misclassification. However, in some cases, children with an unspecified anxiety diagnosis may represent those with subthreshold anxiety that do not meet the criteria for a specific anxiety disorder. These factors limit our ability to interpret the associations between unspecified anxiety and treatment choice.

Additional limitations should be considered. While we aimed to describe antianxiety medication utilization in children with anxiety, including children with comorbid conditions, we cannot be certain that medications were initiated to treat anxiety. It is possible that when an anxiety diagnosis was recorded on the same day as medication initiation the 2 events were unrelated. Additionally, little is known about the validity of *ICD-9-CM* anxiety diagnostic codes for children in administrative data, and *ICD-9-CM* codes for anxiety disorders do not perfectly correspond with *DSM* diagnoses. Selected symptoms that may guide antianxiety medication selection are not available in our data source. The study design excluded children with baseline antianxiety medication use, and, given the multiple indications of these medications, we thereby excluded children with an array of previously treated conditions. We do not have information on if and when dispensed medications were taken, including if medications filled the same day were taken concurrently, and whether adequate dosing was achieved. Treatment length estimates rely on correct days' supply values for dispensed prescriptions. We lack details on whether antianxiety medications were intended for short-term or as-needed use and on prescriptions provided in-hospital or obtained outside insurance (ie, paid out-of-pocket, free samples), which could result in misclassification of antianxiety medication initiation or continuation.

While the majority of children with anxiety initiated antianxiety pharmacotherapy with an SSRI, as recommended by current guidelines, a third of children initiated with a non-SSRI antianxiety medication, and a notable proportion of children initiated with 2 antianxiety medication classes. By describing the initial antianxiety pharmacotherapy utilized in children with anxiety, our study can inform efforts to better tailor medication use in pediatric anxiety disorders.

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Potential conflicts of interest: **Dr Bushnell** received support from the National Institute of Mental Health as a Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellow (F31MH107085). Dr Bushnell also held a graduate research assistantship with GlaxoSmithKline and was the Merck fellow for the Center for Pharmacoepidemiology (both ended December 2015). **Dr Compton** receives research support from the National Institute of Mental Health, NC GlaxoSmithKline Foundation, and Mursion; has

been a consultant for Shire; received honoraria from the *Journal of Consulting and Clinical Psychology*, Nordic Long-Term OCD Treatment Study Research Group, and The Centre for Child and Adolescent Mental Health, Eastern and Southern Norway; and has given expert testimony for Duke University. **Dr Brookhart** has received investigator-initiated research funding from the National Institutes of Health and through contracts with the Agency for Healthcare Research and Quality's DEcIDE program and the Patient-Centered Outcomes Research Institute; within the past 3 years, has received research support from Amgen and AstraZeneca and has served as a scientific advisor for Amgen, Merck, GSK, Genentech, TargetPharma, and RxAnte; and owns equity in NoviSci, a data sciences company. **Dr Walkup** has received past research support for federally funded studies including free drug and placebo from Pfizer in 2007 to support the Child Adolescent Anxiety Multimodal study, free medication from Abbott in 2005 for the Treatment of Early Age Mania study, and free drug and placebo from Eli Lilly in 2003 for the Treatment of Adolescents with Depression study; currently receives research support from the Tourette's Association of America and the Hartwell Foundation; and receives royalties from Guilford Press and Oxford Press for multiauthored books about Tourette syndrome. **Dr Rynn** has received grant support from Eunice Kennedy Shriver National Institute of Child Health and Human Development and National Institute of Mental Health; has received research support from Eli Lilly, National Institute of Mental Health, and Shire; and has received royalties from the American Psychiatric Association Publishing, Oxford University Press, and UpToDate. **Dr Stürmer** receives investigator-initiated research funding from the National Institutes of Health (principal investigator, R01 AG023178; coinvestigator: R01 CA174453, R01 HL118255, R21-HD080214); receives salary support as Director of the Comparative Effectiveness Research Strategic Initiative, NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR001111) and as Director of the Center for Pharmacoepidemiology, Department of Epidemiology UNC Gillings School of Global Public Health (current members: GlaxoSmithKline, UCB BioSciences, Merck); receives research support from pharmaceutical companies (Amgen, AstraZeneca) to the Department of Epidemiology, University of North Carolina at Chapel Hill; does not accept personal compensation of any kind from any pharmaceutical company; and owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk. **Drs Gaynes** and **Dusetzina** report no financial interests or potential conflicts of interest.

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Additional information: MarketScan Commercial Claims and Encounters Database is owned by Truven Health Analytics an IBM Company. Information on acquiring access to the database can be found at http://truvenhealth.com/.

Supplementary material: See accompanying pages.

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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.

Supplementary material follows this article.

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Supplementary Material

Article Title: Treating Pediatric Anxiety: Initial Use of SSRIs and Other Antianxiety Prescription Medications

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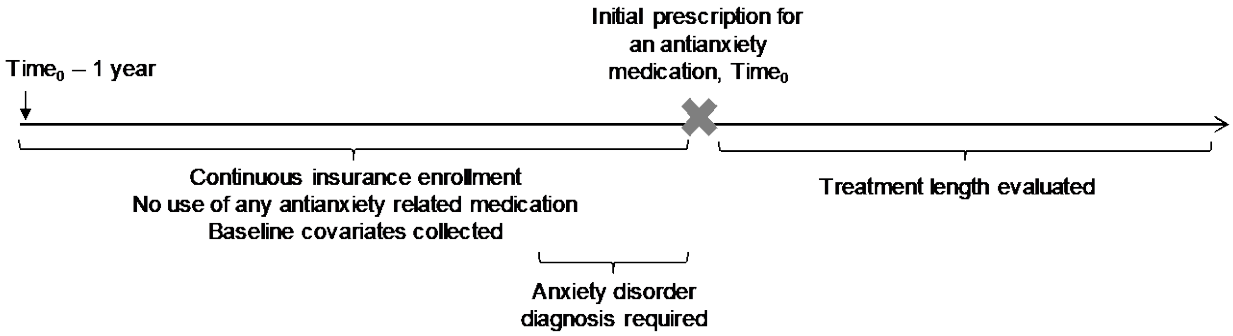
List of Supplementary Material for the article

Disclaimer

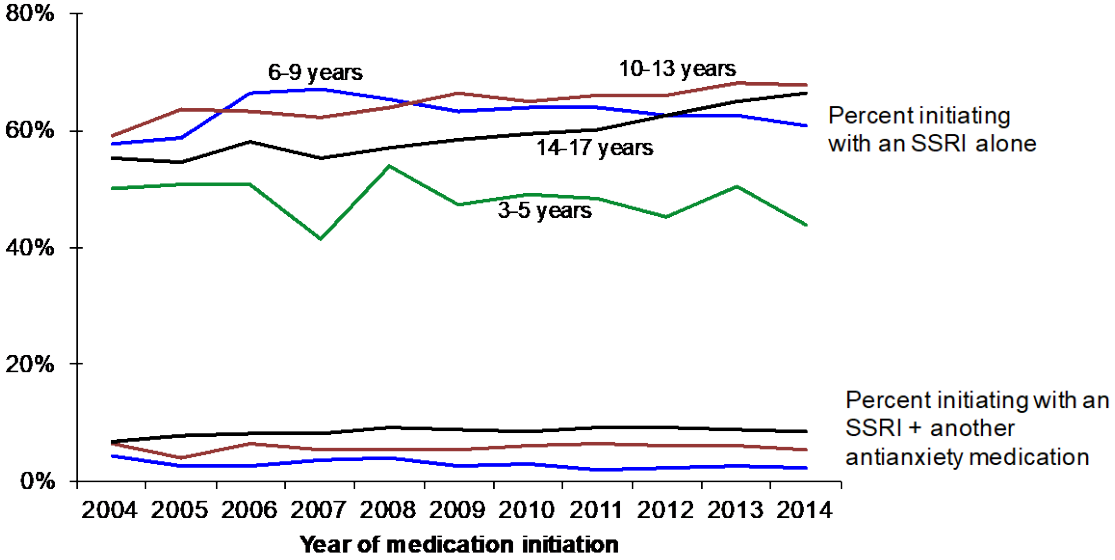
This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

SUPPLEMENTARY MATERIAL

Supplementary eFigure 1. Study design, cohort of children with anxiety disorders initiating antianxiety medication



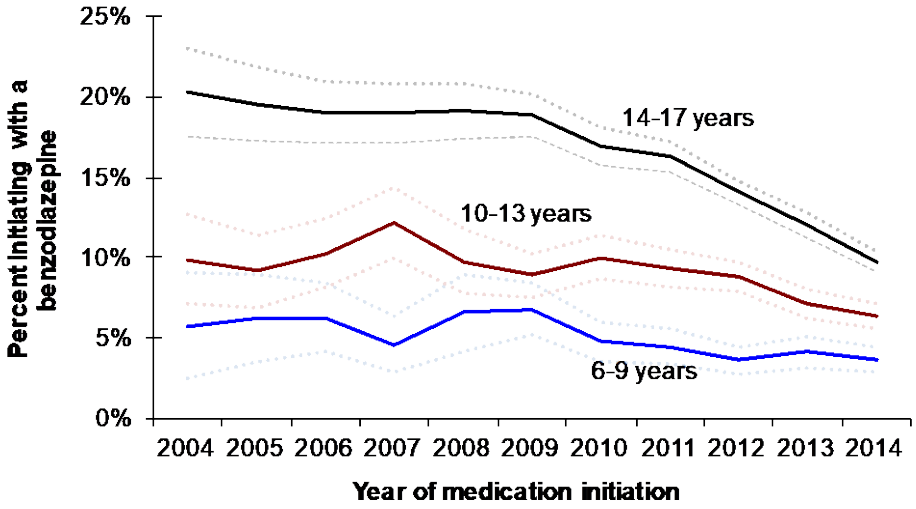
Supplementary eFigure 2. Proportion of children with anxiety initiating antianxiety medication with an SSRI alone and with an SSRI + another antianxiety medication by age group[a]



Results standardized internally by US census division (children with unknown division, n=799, excluded); imprecise estimates for children 3-5 years (SSRI alone, ex. 2005: 95% CI: 36%-65%, 2014: 37%-51%); widest confidence interval range for SSRI alone in children 6-9 years 13%, 10-13 years 9%, 14-17 years 7%)

[a]Uncommon initiation with an SSRI + another antianxiety medication in children 3-5 years, results not displayed

Supplementary eFigure 3. Proportion of children with anxiety initiating antianxiety medication with a benzodiazepine by age group[a,b]



Results standardized internally by US census division (children with unknown division, n=799, excluded); dotted lines represent 95% confidence intervals

[a]Includes children initiating with a benzodiazepine alone or with SSRI + benzodiazepine

[b]Uncommon benzodiazepine initiation in children 3-5 years, results not displayed

Supplementary eTable 1. Full list of patient characteristics of children initiating an antianxiety medication and factors associated with initiation of each treatment group[a]

	Children initiating antianxiety medication (N=84,500)	Initial antianxiety treatment group					
		SSRI alone (N=53,009)	SSRI + another antianxiety medication (N=5,863)		Non-SSRI antianxiety medication (N=25,628)		SSRI + another antianxiety medication vs. Non-SSRI Multivariable RR (95% CI)
	No. (%)	No. (%)	No. (%)	Vs. SSRI alone Multivariable RR (95% CI)	No. (%)	Vs. SSRI alone Multivariable RR (95% CI)	
Female	49,255 (58)	31,688 (60)	3,771 (64)	Ref	13,796 (54)	Ref	Ref
Male	35,245 (42)	21,321 (40)	2,092 (36)	1.0 (0.9-1.0)	11,832 (46)	1.1 (1.1-1.1)	0.9 (0.8-0.9)
Age, median (IQR)	14 (11, 16)	14 (11, 16)	15 (13, 16)		14 (10, 16)		
3-5 years	1,449 (2)	696 (1)	25 (<1)	0.4 (0.2-0.5)	728 (3)	1.4 (1.3-1.5)	0.2 (0.2-0.3)
6-9 years	12,377 (15)	7,782 (15)	332 (6)	0.4 (0.4-0.5)	4,263 (17)	1.0 (1.0-1.1)	0.5 (0.4-0.5)
10-13 years	21,997 (26)	14,525 (27)	1,269 (22)	0.8 (0.7-0.8)	6,203 (24)	0.9 (0.9-1.0)	0.9 (0.8-0.9)
14-17 years	48,677 (58)	30,006 (57)	4,237 (72)	Ref	14,434 (56)	Ref	Ref
Anxiety disorder, index diagnosis							
Unspecified	42,652 (50)	26,037 (49)	2,417 (41)	Ref	14,198 (55)	Ref	Ref
Generalized anxiety disorder	20,508 (24)	13,812 (26)	1,417 (24)	1.1 (1.0-1.2)	5,279 (21)	0.8 (0.8-0.8)	1.4 (1.3-1.5)
OCD	6,194 (7)	4,773 (9)	353 (6)	0.9 (0.8-1.0)	1,068 (4)	0.5 (0.5-0.6)	1.8 (1.7-2.0)
Panic disorder	4,294 (5)	1,967 (4)	507 (9)	2.0 (1.9-2.2)	1,820 (7)	1.3 (1.3-1.4)	1.3 (1.2-1.4)
PTSD	3,531 (4)	1,683 (3)	492 (8)	1.5 (1.4-1.7)	1,356 (5)	1.2 (1.1-1.2)	1.3 (1.2-1.4)
Social phobia	1,972 (2)	1,465 (3)	156 (3)	1.0 (0.9-1.2)	351 (1)	0.6 (0.6-0.7)	1.7 (1.5-1.9)
Other[c]	3,530 (4)	1,993 (4)	279 (5)	1.6 (1.4-1.7)	1,258 (5)	1.1 (1.0-1.1)	1.3 (1.2-1.5)
Multiple	1,819 (2)	1,279 (2)	242 (4)	1.6 (1.5-1.9)	298 (1)	0.6 (0.6-0.7)	2.1 (1.9-2.3)
Provider type, index anxiety diagnosis							
Psychiatry	20,514 (24)	14,114 (27)	1,674 (29)	Ref	4,726 (18)	Ref	Ref
Psychologist, therapist	10,124 (12)	5,761 (11)	444 (8)	0.7 (0.7-0.8)	3,919 (15)	1.6 (1.6-1.7)	0.5 (0.4-0.5)
Family practice	11,136 (13)	7,004 (13)	788 (13)	0.9 (0.8-0.9)	3,344 (13)	1.0 (1.0-1.1)	0.9 (0.8-0.9)
Pediatrics	13,565 (16)	9,574 (18)	502 (9)	0.5 (0.5-0.6)	3,489 (14)	0.9 (0.8-0.9)	0.7 (0.7-0.8)
Other	20,980 (25)	12,109 (23)	1,768 (30)	1.0 (0.9-1.0)	7,103 (28)	1.3 (1.2-1.3)	0.8 (0.7-0.8)
Unknown	8,181 (10)	4,447 (8)	687 (12)	1.0 (0.9-1.1)	3,047 (12)	1.3 (1.3-1.4)	0.7 (0.7-0.8)
Anxiety diagnosis details							
Index anxiety diagnosis in inpatient setting	4,313 (5)	1,981 (4)	938 (16)	2.1 (1.9-2.3)	1,394 (5)	1.2 (1.1-1.2)	1.6 (1.5-1.7)
Prior anxiety diagnosis	27,639 (33)	17,809 (34)	1,454 (25)	0.8 (0.8-0.9)	8,376 (33)	1.0 (1.0-1.0)	0.8 (0.8-0.9)
Acute reaction to stress diagnosis[f]	861 (1)	474 (1)	79 (1)	1.1 (0.9-1.3)	308 (1)	1.1 (1.0-1.2)	1.0 (0.8-1.2)
Anxiety-related symptoms, prior 3 months[d]	15,688 (19)	8,651 (16)	1,248 (21)	1.1 (1.1-1.2)	5,789 (23)	1.2 (1.2-1.2)	0.9 (0.8-0.9)

Psychiatric co-morbidity details[f]							
Depression diagnosis (ref=no diagnosis)[b]							
Recent diagnosis	18,875 (22)	13,163 (25)	2,231 (38)	1.1 (1.0-1.2)	3,481 (14)	0.6 (0.6-0.6)	1.9 (1.8-2.1)
Prior diagnosis, no recent diagnosis	3,275 (4)	2,017 (4)	201 (3)	0.9 (0.8-1.1)	1,057 (4)	0.9 (0.9-1.0)	1.0 (0.9-1.2)
Self-harm related behavior[e]	438 (1)	284 (1)	69 (1)	0.8 (0.6-1.0)	85 (<1)	0.8 (0.6-0.9)	1.1 (0.9-1.3)
Adjustment disorder (ref=no diagnosis)[b]							
Recent diagnosis	6,826 (8)	4,729 (9)	561 (10)	1.0 (0.9-1.1)	1,536 (6)	0.9 (0.9-0.9)	1.1 (1.0-1.2)
Prior diagnosis, no recent diagnosis	6,159 (7)	4,048 (8)	381 (6)	0.9 (0.8-1.0)	1,730 (7)	1.0 (0.9-1.0)	0.9 (0.8-1.0)
Attention deficit disorder (ref=no diagnosis)[b]							
Recent diagnosis	10,191 (12)	5,139 (10)	428 (7)	1.0 (0.9-1.2)	4,624 (18)	1.5 (1.5-1.6)	0.6 (0.5-0.7)
Prior diagnosis, no recent diagnosis	4,877 (6)	2,911 (5)	236 (4)	1.1 (0.9-1.2)	1,730 (7)	1.2 (1.1-1.2)	0.9 (0.8-1.0)
Disturbance of conduct, oppositional defiant disorder	5,341 (6)	2,876 (5)	385 (7)	1.1 (1.0-1.2)	2,080 (8)	1.1 (1.1-1.2)	0.9 (0.8-1.0)
Other episodic mood disorder	4,073 (5)	2,036 (4)	455 (8)	1.2 (1.1-1.3)	1,582 (6)	1.3 (1.2-1.3)	0.8 (0.8-0.9)
Sleep disorder	3,948 (5)	1,918 (4)	400 (7)	1.6 (1.5-1.8)	1,630 (6)	1.3 (1.3-1.4)	1.1 (1.0-1.2)
Substance use disorder	2,785 (3)	1,308 (2)	391 (7)	1.3 (1.1-1.4)	1,086 (4)	1.2 (1.2-1.3)	1.0 (0.9-1.0)
Pervasive developmental disorder	2,502 (3)	1,516 (3)	96 (2)	0.9 (0.7-1.1)	890 (3)	1.0 (1.0-1.1)	0.8 (0.7-1.0)
Developmental delay, learning disability	2,235 (3)	1,287 (2)	76 (1)	0.8 (0.7-1.0)	872 (3)	1.0 (0.9-1.0)	0.8 (0.7-1.0)
Bipolar disorder	1,479 (2)	466 (1)	164 (3)	1.6 (1.4-1.8)	849 (3)	1.8 (1.7-1.9)	0.6 (0.5-0.7)
Eating disorder	1,373 (2)	994 (2)	132 (2)	0.9 (0.8-1.1)	247 (1)	0.8 (0.7-0.8)	1.1 (1.0-1.3)
Tic	999 (1)	493 (1)	45 (1)	1.2 (0.9-1.6)	461 (2)	1.4 (1.3-1.5)	0.7 (0.6-1.0)
Personality disorder	614 (1)	320 (1)	77 (1)	1.1 (0.9-1.4)	217 (1)	1.1 (1.0-1.2)	1.0 (0.9-1.3)
Schizophrenia	103 (<1)	28 (<1)	*	1.4 (0.8-2.3)	65 (<1)	1.7 (1.5-2.0)	0.5 (0.3-0.9)
Non-psychiatric co-morbidities							
Allergic rhinitis	10,608 (13)	6,452 (12)	681 (12)	1.0 (0.9-1.1)	3,475 (14)	1.0 (1.0-1.1)	1.0 (0.9-1.0)
Asthma	8,423 (10)	4,915 (9)	627 (11)	1.1 (1.0-1.2)	2,881 (11)	1.1 (1.0-1.1)	1.0 (0.9-1.1)
Fainting, dizziness	4,374 (5)	2,342 (4)	384 (7)	1.1 (1.0-1.2)	1,648 (6)	1.1 (1.1-1.1)	1.0 (0.9-1.1)
Cardiac disorder	2,373 (3)	1,137 (2)	215 (4)	1.2 (1.0-1.3)	1,021 (4)	1.2 (1.1-1.2)	0.9 (0.8-1.0)
Migraine, chronic headache	2,371 (3)	1,144 (2)	182 (3)	1.1 (1.0-1.3)	1,045 (4)	1.3 (1.2-1.3)	0.8 (0.7-0.9)
Overweight, obesity	1,792 (2)	1,067 (2)	145 (2)	1.0 (0.9-1.2)	580 (2)	1.0 (1.0-1.1)	0.9 (0.8-1.1)
Visual disturbance/loss	1,495 (2)	806 (2)	88 (2)	1.0 (0.8-1.2)	601 (2)	1.1 (1.0-1.2)	0.8 (0.7-1.0)
Convulsions	1,123 (1)	451 (1)	68 (1)	1.3 (1.0-1.6)	604 (2)	1.2 (1.1-1.3)	0.8 (0.6-1.0)
Urinary incontinence, encopresis, enuresis	1,032 (1)	599 (1)	40 (1)	0.9 (0.7-1.2)	393 (2)	1.1 (1.0-1.2)	0.8 (0.6-1.1)
Diabetes	591 (1)	356 (1)	47 (1)	1.0 (0.7-1.3)	188 (1)	1.0 (0.9-1.1)	1.0 (0.8-1.2)
Epilepsy, recurrent seizers	550 (1)	205 (<1)	23 (<1)	0.9 (0.6-1.3)	322 (1)	1.2 (1.1-1.3)	0.6 (0.4-0.8)
Hypertension	546 (1)	271 (1)	47 (1)	1.0 (0.8-1.4)	228 (1)	1.1 (1.0-1.2)	1.0 (0.7-1.2)
Cancer, any diagnosis	328 (<1)	135 (<1)	27 (<1)	1.5 (1.1-2.1)	166 (1)	1.2 (1.1-1.3)	0.9 (0.7-1.3)
Injury events							

Fracture, dislocation, sprain (non-skull)	12,776 (15)	7,568 (14)	980 (17)	1.1 (1.0-1.1)	4,228 (16)	1.1 (1.0-1.1)	1.0 (0.9-1.0)
Head/brain injury, concussion, skull fracture	3,047 (4)	1,728 (3)	221 (4)	0.9 (0.8-1.1)	1,098 (4)	1.0 (1.0-1.1)	0.9 (0.8-1.0)
Poisoning from drug, biologic	1,211 (1)	713 (1)	176 (3)	0.9 (0.7-1.0)	322 (1)	0.9 (0.8-1.0)	1.1 (0.9-1.2)
Other injury	17,618 (21)	10,318 (19)	1,353 (23)	1.0 (1.0-1.1)	5,947 (23)	1.0 (1.0-1.1)	1.0 (0.9-1.0)
Family difficulties[g]	1,551 (2)	958 (2)	153 (3)	0.9 (0.8-1.1)	440 (2)	1.0 (0.9-1.0)	1.0 (0.9-1.1)
Child trauma, neglect[h]	654 (1)	332 (1)	106 (2)	1.0 (0.8-1.2)	216 (1)	1.0 (0.9-1.1)	1.0 (0.9-1.2)
Healthcare utilization							
Preventative, well visit	45,235 (54)	29,208 (55)	2,890 (49)	0.9 (0.9-1.0)	13,137 (51)	1.0 (0.9-1.0)	1.0 (1.0-1.1)
Outpatient problem-oriented visits, median (IQR)	4 (2, 6)	4 (2, 6)	3 (2, 6)		4 (2, 6)		
0-1	15,976 (19)	10,107 (19)	1,320 (23)	Ref	4,549 (18)	Ref	Ref
2-5	43,041 (51)	27,556 (52)	2,849 (49)	0.9 (0.9-1.0)	12,636 (49)	0.9 (0.9-1.0)	1.0 (0.9-1.0)
6+	25,483 (30)	15,346 (29)	1,694 (29)	0.9 (0.8-1.0)	8,443 (33)	0.9 (0.9-1.0)	1.0 (0.9-1.1)
Non-psychiatric inpatient admission[i]	1,801 (2)	825 (2)	158 (3)	1.1 (1.0-1.3)	818 (3)	1.1 (1.1-1.2)	0.9 (0.8-1.0)
Psychotherapy, recent (ref=no recorded claims)[b]							
1-2	22,511 (27)	14,727 (28)	1,353 (23)	0.8 (0.8-0.9)	6,431 (25)	0.9 (0.9-0.9)	1.0 (0.9-1.0)
3+	12,063 (14)	8,109 (15)	873 (15)	0.9 (0.9-1.0)	3,081 (12)	0.9 (0.8-0.9)	1.1 (1.0-1.2)
Mental health diagnostic evaluation	45,051 (53)	29,917 (56)	3,294 (56)	1.1 (1.0-1.1)	11,840 (46)	0.8 (0.8-0.8)	1.4 (1.3-1.4)
Medication utilization							
Prescriptions by therapeutic group, median (IQR)[j]	2 (1, 3)	2 (1, 3)	2 (1, 4)		2 (1, 4)		
0 or 1	35,031 (41)	22,654 (43)	2,455 (42)	Ref	9,922 (39)	Ref	Ref
2-5	42,639 (50)	26,568 (50)	2,863 (49)	1.0 (0.9-1.0)	13,208 (52)	1.0 (1.0-1.0)	1.0 (0.9-1.1)
6+	6,830 (8)	3,787 (7)	545 (9)	1.1 (1.0-1.2)	2,498 (10)	1.0 (1.0-1.1)	1.0 (0.9-1.1)
ADHD medication dispensed	11,703 (14)	6,506 (12)	441 (8)	0.7 (0.6-0.8)	4,756 (19)	1.1 (1.0-1.1)	0.7 (0.6-0.7)
Opioid medication dispensed	10,769 (13)	6,032 (11)	901 (15)	1.1 (1.0-1.2)	3,836 (15)	1.1 (1.0-1.1)	1.0 (0.9-1.0)
Region							
Northeast	14,682 (17)	9,309 (18)	1,007 (17)	0.9 (0.9-1.0)	4,366 (17)	1.0 (1.0-1.0)	0.9 (0.9-1.0)
North Central	26,131 (31)	17,345 (33)	1,674 (29)	0.8 (0.8-0.9)	7,112 (28)	0.9 (0.8-0.9)	0.9 (0.9-1.0)
South	27,238 (32)	16,496 (31)	2,019 (34)	Ref	8,723 (34)	Ref	Ref
West	15,649 (19)	9,331 (18)	1,122 (19)	0.9 (0.9-1.0)	5,196 (20)	1.1 (1.0-1.1)	0.9 (0.8-0.9)
Unknown	800 (1)	528 (1)	41 (1)	0.8 (0.6-1.1)	231 (1)	0.9 (0.8-1.0)	0.8 (0.6-1.1)
Year of treatment initiation							
2004-2006	7,539 (9)	4,390 (8)	460 (8)	1.0 (0.9-1.1)	2,689 (10)	1.3 (1.2-1.3)	0.7 (0.7-0.8)
2007-2009	14,892 (18)	8,968 (17)	1,023 (17)	1.1 (1.0-1.2)	4,901 (19)	1.2 (1.1-1.2)	0.9 (0.8-0.9)
2010-2012	32,334 (38)	20,213 (38)	2,310 (39)	1.1 (1.0-1.1)	9,811 (38)	1.1 (1.0-1.1)	1.0 (0.9-1.0)
2013-2014	29,735 (35)	19,438 (37)	2,070 (35)	Ref	8,227 (32)	Ref	Ref

Abbreviations: IQR=interquartile range, ref=referent category

*Number not displayed due to small sample

[a]Table represents the expanded, full version of manuscript Table 2

[b]Recent=0-30 days before antianxiety medication initiation, prior=31-365 days before antianxiety medication initiation

[c]Anxiety disorders with <1000 children: other anxiety, separation anxiety, selective mutism, anxiety due to medical condition, agoraphobia, other/specific phobia

[d]Any ICD-9-CM diagnostic code for abdominal pain, unspecified chest pain, headache, hyperventilation, malaise/fatigue, nausea, palpations, or weight loss in the prior 3 months

[e]Self-harm event, ICD-9-CM=E950-E959

[f]ICD-9-CM codes used to define co-morbidities: acute stress (308.x); adjustment disorder (309.0x, 309.3x, 309.4x, 309.9x, 309.22, 309.23, 309.24, 309.28, 309.29, 309.82, 309.83, 309.89); attention deficit disorder (314.0x); pervasive developmental disorder (299.x); bipolar disorder (296.0x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x, 301.13); disturbance of conduct, oppositional defiant disorder (312.x, 313.81); depression (296.2x, 296.3x, 300.4x, 309.1x, 311.x); developmental delay, learning disability (315.x, 784.61, V40.0x); eating disorder (307.1x, 307.5x); other episodic mood disorder (296.9x); personality disorder (301.x); schizophrenia (295.x); sleep disorder (327.x, 347.x, 307.4x, 780.5x); substance use disorder (291.x, 292.x, 303.x, 304.x, 305.x); tic (307.2x)

[g]Family difficulties, ICD-9-CM=V61.0x, V61.20, V61.23-V61.29, V61.4x, V61.8x, V61.9x

[h]Child neglect/trauma, ICD-9-CM=V15.4x, V61.21, V71.81, 995.5x, 995.80-995.85, E967.x

[i]Non-psychiatric inpatient admission excludes inpatient admissions with an ICD-9-CM code=290-319 as the primary or secondary diagnosis; variable for psychiatric hospitalizations not included due to high correlation with inpatient index anxiety diagnosis

[j]Number of medication therapeutic classes, at least one dispensed prescription per Anatomical Therapeutic Chemical (ATC) Classification System therapeutic subgroup

Supplementary eTable 2. Treatment continuation sensitivity analysis: Proportion of children who refilled the initial antianxiety medication and continued treatment for 6 months, by anxiety diagnoses in the prior year

	Children with at least 2 anxiety diagnoses in the prior year (n=39,613)[a]		Children with one anxiety diagnosis in the prior year (n=44,887)[a]	
Initial medication class	Refilled initial prescription[a]	Continued medication for 6 months	Refilled initial prescription[a]	Continued medication for 6 months
SSRI	84% (83-84)	61% (60-61)	78% (78-79)	50% (49-51)
Benzodiazepine	28% (26-29)	7% (4-9)	23% (22-24)	4% (3-6)
Hydroxyzine	22% (20-25)	4% (1-10)	17% (16-19)	3% (1-7)
Other antidepressant	61% (59-63)	32% (28-35)	54% (51-56)	24% (20-28)
Atypical antipsychotic	72% (70-74)	43% (40-47)	69% (67-72)	38% (34-41)
Other antianxiety	66% (63-68)	39% (35-42)	62% (59-64)	36% (31-40)
Buspirone	57% (53-62)	26% (19-33)	45% (41-48)	15% (11-21)
Bupropion	68% (64-72)	40% (34-45)	69% (66-72)	33% (28-39)
TCA	58% (54-62)	30% (24-36)	52% (48-56)	25% (20-31)
Anticonvulsant	64% (61-68)	35% (30-41)	63% (58-67)	34% (27-41)
Beta-blocker	38% (33-44)	21% (12-30)	28% (24-32)	10% (5-18)
SNRI	67% (62-72)	41% (34-49)	66% (61-70)	36% (29-42)

[a]Restricted to the 93% of children with at least 60 days of continuous insurance enrollment

Supplementary eTable 3. Treatment continuation sensitivity analysis: Varying the grace period to define treatment discontinuation to 15 and 60 days

	15 day grace period		60 day grace period	
Initial medication class	Refilled initial prescription[a]	Continued medication for 6 months	Refilled initial prescription[a]	Continued medication for 6 months
SSRI	75% (75-75)	41% (41-42)	83% (83-84)	67% (67-68)
Benzodiazepine	20% (20-21)	3% (1-5)	29% (28-30)	10% (9-12)
Hydroxyzine	15% (14-16)	2% (0-6)	23% (21-24)	8% (5-11)
Other antidepressant	51% (49-53)	19% (17-22)	61% (60-63)	39% (37-41)
Atypical antipsychotic	64% (63-66)	28% (26-31)	74% (73-76)	54% (51-56)
Other antianxiety	57% (55-58)	28% (25-30)	68% (66-70)	49% (46-51)
Buspirone	43% (40-46)	12% (8-16)	52% (50-55)	28% (24-32)
Bupropion	63% (61-66)	25% (21-29)	70% (68-73)	48% (44-52)
TCA	49% (47-52)	19% (15-23)	58% (55-61)	36% (32-41)
Anticonvulsant	57% (54-60)	25% (21-29)	67% (64-70)	46% (42-50)
Beta-blocker	28% (25-31)	9% (5-15)	35% (32-39)	19% (14-24)
SNRI	60% (56-63)	27% (22-32)	68% (64-71)	49% (44-54)

[a]Restricted to the 93% of children with at least 60 days of continuous insurance enrollment

Supplementary eTable 4. Proportion of children initiating with a non-SSRI antianxiety medication with a subsequent SSRI fill within 3 months

Non-SSRI antianxiety medication at initiation	Total non-SSRI prescription No.	Children with 3 months enrollment[a] No.	SSRI prescription filled within 3 months No.	% (95% CI)
Benzodiazepine	7,477	6,810	1,649	24% (23-25)
Hydroxyzine	3,404	3,006	486	16% (15-18)
Other antidepressant	3,225	2,889	459	16% (15-17)
Other antianxiety	3,069	2,668	349	13% (12-14)
Atypical antipsychotic	2,607	2,353	470	20% (18-22)
Bupropion	1,442	1,273	227	18% (16-20)
Buspirone	1,341	1,191	200	17% (15-19)
TCA	1,224	1,092	140	13% (11-15)
Anticonvulsant	1,135	987	130	13% (11-15)
SNRI	880	789	109	14% (12-16)
Beta-blocker	777	676	73	11% (9-13)
All non-SSRI initiators	25,628	22,884	4,121	**18% (18-19)**

Each medication class evaluated separately for patients initiating two classes (4%)

[a]Overall 89% of non-SSRI initiators had 3 months continuous insurance enrollment