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Examining parental medication adherence as a predictor of child medication adherence in pediatric anxiety disorders

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Abstract

Background—Selective serotonin reuptake inhibitors (SSRIs) are the recommended first-line pharmacotherapy for pediatric anxiety disorders but adherence remains difficult to predict.

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Objectives—To estimate SSRI adherence in children with anxiety disorders and determine if prior parental medication adherence is predictive of child high SSRI adherence.

Methods—We identified children (3-17 years) initiating SSRI treatment after an anxiety disorder diagnosis in a commercial claims database (2005-2014). We evaluated parent SSRI, statin, and antihypertensive adherence (6-month proportion days covered, PDC, high adherence=PDC ≥ 0.80) in the year before child SSRI initiation. We estimated risk differences (RD) of high child SSRI adherence (6-month PDC) stratified by parent adherence and multivariable risk ratios (RR) using modified Poisson regression. We estimated change in c-statistic and risk reclassification when adding parent-level covariates with child-level covariates to predict child adherence.

Results—In 70,979 children with an anxiety disorder (59% = female, 14 = median age), the mean 6-month SSRI PDC was 0.72, with variation by anxiety disorder. Overall 64% of children had high adherence if their parent had high SSRI adherence vs. 53% of children with parents with low SSRI adherence (RD=12%, multivariable RR=1.17, 95% CI: 1.14-1.20). Findings were similar for parent statin (RD=10%) and antihypertensive adherence (RD=8%) and when stratified by child age and parent sex. There was minor improvement in risk reclassification and the c-statistic after adding parent adherence and parent-level covariates.

Conclusions—Parental medication adherence could help providers identify children at risk of non-adherence to inform the treatment decision, reduce unnecessary medication switches, and lead to broader effective interventions.

Keywords

medication adherence; antidepressant; anxiety disorders; child; parents

INTRODUCTION

The estimated lifetime prevalence of pediatric anxiety disorders is 15-20%¹ with 8% having an anxiety disorder with severe impairment.² Selective serotonin reuptake inhibitors (SSRIs) are the recommended and most commonly prescribed³ first-line pharmacotherapy for children with anxiety disorders.^{4,5} In randomized controlled trials SSRIs were effective over placebo in treating pediatric anxiety disorders with relatively mild side effects.^{4,6-9} In pooled estimates from randomized controlled trials approximately 50-70% of children with an anxiety disorder randomized to SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) responded to treatment.⁷

Poor medication adherence can be one cause of non-response to a medication.¹⁰ Antidepressant non-adherence is common among children with depression^{11,12} and in adults with anxiety disorders.¹³⁻¹⁵ However, research specifically on SSRI adherence in children with anxiety disorders is lacking.

Medication adherence is influenced by many factors, including medication-related (e.g., side-effects, lack of effectiveness), patient-related (e.g., views on medication importance), and provider- and system-related factors (e.g., pharmacy access, cost).^{16,17} For child medication adherence, parents and caregivers play an important role.¹⁶ Parents have a responsibility for storing their child's psychotropic medication and monitoring adherence,

benefits, and side effects.¹⁰ Accordingly, psychotropic medication may be a more challenging treatment option for children when there is limited family investment or adult supervision.¹⁰ Parent attitudes towards and involvement in a child's treatment have been associated with child psychotropic adherence^{18,19} Past medication adherence in adults predicts future adherence²⁰ and may predict his or her child's adherence, particularly given the role parents have in a child's treatment.

Identifying ways to assist patients in adhering to medications remains a research priority.^{16,21,22} Determining if parent adherence to their medications is predictive of child SSRI adherence could target interventions in children before and after SSRI initiation, help the provider determine an appropriate treatment plan, and reduce unnecessary medication switches. To address current research gaps, we sought to estimate SSRI adherence after initiation in commercially insured children with anxiety disorders and to determine if prior parental medication adherence was predictive of child SSRI adherence.

METHODS

Study population

We identified children from the MarketScan Commercial Claims database, which includes individuals covered by employer-sponsored insurance in the United States. We utilized enrollment files, inpatient and outpatient services, and outpatient, dispensed prescriptions. We included children (3-17 years) initiating an SSRI between 2005 and 2014. Included children had continuous prescription coverage with no SSRI claims in the year before SSRI initiation and an anxiety disorder diagnosis anytime in the month (30 days) before, or on, the date of SSRI initiation (index anxiety diagnosis) (Figure S1, digital supplement). An anxiety diagnosis was defined as an inpatient/outpatient ICD-9-CM code (293.84, 300.0x, 300.2x, 300.3x, 309.21, 309.81, 313.23),²³ including post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD).²⁴ To note, SSRIs are not FDA approved for non-OCD pediatric anxiety disorders. We excluded children with diagnostic codes for bipolar disorder, personality disorder, schizophrenia, or autistic disorder in the year before SSRI initiation. We required 6-months of insurance enrollment following SSRI initiation to evaluate adherence and excluded children when we could not identify a parent in the datasource.

Parent identification

We used child enrollment information to identify the primary and secondary beneficiaries on the insurance policy. We attempted to exclude potential siblings by only considering beneficiaries linked with the child's policy to be a parent if they were 15 years older than the child; results were consistent if requiring 20 years. We required parents have insurance enrollment with prescription coverage in the year before their child's SSRI initiation as we evaluated parent adherence during this time.

Child SSRI adherence measures

To capture SSRI adherence in the first months after initiation, the 6-month proportion of days covered (PDC) was the primary measure of child adherence. We calculated the PDC by

summing days supply for SSRI prescriptions dispensed in the first 180 days of treatment and dividing by 180 days, truncating at 1.00. In addition to the continuous PDC measure, we dichotomized the PDC consistent with prior adherence literature:²⁵ “low adherence”=PDC<0.80 and “high adherence”=PDC ≥ 0.80. We allowed switching between SSRI agents when calculating adherence measures. We included secondary measures to capture additional aspects of SSRI adherence: continuation/persistence for 6-months, modified medication possession ratio in the first 6-months, and 20-day gap in medication coverage between the first and second prescription fills; detailed definitions in supplement (Tables S1 and S4 footnotes).

Parent medication adherence measures

We examined parent adherence to SSRIs, statins, and antihypertensives (ACEs, ARBs, thiazides) during a 6-month window in the year before child SSRI initiation (Figure S1). We selected these drug classes as SSRIs are a common psychiatric medication and the drug studied in children and statins and antihypertensives are commonly prescribed chronic, preventative medications. Six-month PDCs were calculated for each medication class and dichotomized (“low adherence”=PDC <0.80, “high adherence”=PDC ≥ 0.80). Parents were required to have 1 prescription 6-12 months before their child’s SSRI initiation date to calculate the parent 6-month PDC before child SSRI initiation; PDC measures started with the parent’s first relevant prescription in the prior year. When both parents had a PDC measure in a medication class, parent PDCs were averaged per child; selecting the higher parent PDC value was also considered with consistent results. We used an adherence measure for each medication class in analyses (statins, SSRIs, antihypertensive), and, as a secondary measure, we created a summary parent adherence measure by averaging parent PDCs across classes.

Child and parent-level covariates

Given relevant psychotropic adherence research^{11,12,26,27} and limited research on SSRI adherence in pediatric anxiety using claims data, we included a variety of child-level characteristics measured in the year before SSRI initiation: age, sex, psychiatric co-morbidities, non-psychiatric co-morbidities, healthcare/medication utilization, and region. Index anxiety diagnosis was categorized by the specific anxiety disorder (1 specific diagnosis, categorized under ‘multiple’) or as unspecified anxiety if no specific anxiety diagnosis was recorded. The provider type of the index diagnosis was categorized: psychiatry, psychologist/therapist; pediatrics; family practice; multi-specialty physician group; other; unknown/multiple. For healthcare utilization, we included separate indicators for number of problem-oriented outpatient visits and well/preventative outpatient visits (each defined with CPT procedure codes), psychiatric-related inpatient admission and non-psychiatric-related inpatient admission, and ER visits. Medication utilization included a count of therapeutic classes prescribed, selected psychotropic medications, and opioids. Prior psychotherapy claims were identified through recorded CPT procedure codes.

For each child, we determined whether either parent had a psychiatric diagnosis (anxiety disorder, depression, adjustment disorder, substance use disorder, or other), preventative/well

outpatient visit, benzodiazepine prescription fill, or psychotherapy claim in the prior year and was aged 50 years or older, as adherence may vary by age.

Statistical analysis

In children, we described the mean 6-month PDC and the proportion with high adherence overall and stratified by age group, index anxiety diagnosis, and recent (30 days) co-morbid depression. Child SSRI adherence was stratified by parent adherence (low, high, no measure) to SSRIs, statins, and antihypertensives. We estimated the crude risk difference (RD) and risk ratio (RR) of child high adherence by parent adherence. Results were stratified by parent sex and child age, as parental treatment involvement varies by child age and mothers may have more regular involvement in child's treatment (mothers completed 87% of caregiver interviews in a pediatric anxiety disorders trial).²⁸ To determine if parent adherence independently predicted child adherence, we used modified Poisson regression²⁹ to estimate multivariable RRs of child high SSRI adherence in a model containing all child and parent-level covariates. We displayed results from the full multivariable model to inform future research; variable selection with least absolute shrinkage and selection operator (LASSO) regression, a machine-learning technique,³⁰ excluded few covariates.

To determine if the addition of parent-level adherence and covariates improved the prediction of child adherence over only child-level predictors, we estimated change in c-statistic using LASSO regression and examined clinical risk reclassification.³¹ In both analyses, we compared a model with child-level covariates to a model adding 1) parent adherence alone and 2) all parent-level covariates. The average change in c-statistic was reported from random validation (20%) datasets based on results using LASSO regression in training datasets run with and without the parent-level covariates. For risk reclassification, we used logistic regression to estimate predicted probabilities of high child adherence (classified into strata: <40%, 40-70%, >70% for high, moderate, and low probability of adherence). Results from the models with and without parent-level covariates were cross-classified and summarized with the net reclassification index (NRI): sum of net proportion of events (high adherence) assigned higher probability category and net proportion of nonevents assigned lower probability category.³²⁻³⁴

In sensitivity analyses we examined adherence among children who had at least two SSRI fills before discontinuation and child adherence stratified by parent adherence using the secondary measures of child adherence. We also examined child adherence stratified by whether one or two parents per child were identified in the database. The University of North Carolina Institutional Review Board approved this study.

RESULTS

The cohort included 70,979 children with a diagnosed anxiety disorder initiating an SSRI (Figure S2). The median age was 14 years (interquartile range, IQR:11-16), 41% were male, and 25% had a recent depression diagnosis (Table 1). Thirty-nine percent of children initiated on sertraline followed by fluoxetine (27%), escitalopram (15%), and citalopram (13%). The majority (88%) had an initial SSRI days supply of 30 days and 6% had <30 days; <1% filled multiple SSRI prescriptions at initiation.

Child SSRI adherence

The mean 6-month SSRI PDC was 0.72 (median=0.83); 42% had low adherence and 58% high adherence (77% of whom had a PDC ≥ 0.95 , Table 2). Children had a median of 5 fills before SSRI discontinuation (IQR:2-10) and 14% had no second SSRI fill within 6-months. The average PDC was higher in younger children (3-13 years=0.76) compared to older children (14-17 years=0.70) and similar in children with and without co-morbid depression. Children with an index anxiety diagnosis of OCD (0.79) or social phobia (0.77) had the highest mean PDC and children with panic disorder (0.68) and PTSD (0.65) the lowest. Results were largely consistent across secondary adherence measures (Table S1).

Prior parent medication adherence

Overall, 70% of children had two parents identified in the data; half (49%) of children had 1 parent PDC measure in the year before SSRI initiation. There were 20,268 children (29%) with a parent SSRI PDC, 12,987 children (18%) with a parent statin PDC, and 15,344 children (22%) with a parent antihypertensive PDC. The mean 6-month parent PDCs were: SSRI=0.81, statins=0.85, and antihypertensives=0.88.

Child SSRI adherence by parent adherence

The child mean SSRI PDC was higher in children who had parents with high SSRI adherence than in children who had parents with low SSRI adherence (mean PDC=0.77 vs. 0.70). Overall, 64% of children had high adherence if their parent had high SSRI adherence vs. 53% of children with parents with low SSRI adherence, RD=12% (95% confidence interval, CI:10-13%, RR=1.23, 95% CI:1.19-1.26). Findings were similar, but slightly attenuated, for parent statin and antihypertensive adherence (Table 3). When stratified by child age at SSRI initiation and sex of parent with a PDC measure, results were largely consistent (Figure 1).

In the multivariable model, parent high adherence independently predicted child high adherence for SSRIs (RR=1.17, 95% CI:1.14-1.20), statins (RR=1.11, 95% CI:1.07-1.14), and antihypertensives (RR=1.08, 95% CI:1.05-1.13) compared to parent low adherence (Table 3, Figure 2). Considering parent-level covariates, parent substance use disorder diagnosis (RR=0.86) and parent well visit (RR=1.05) were also identified as independent predictors of high child SSRI adherence (Figure 2).

The average c-statistic increase when parent-level covariates were added to child-level covariates as potential predictors was 0.013 (highest c-statistic=0.654); when adding only parent adherence, the average c-statistic increase was 0.008. For risk reclassification, when parent-level covariates were added 8% of children saw improved reclassification and 6% worsened, resulting in a positive, low NRI=0.040 (Table S2); NRI=0.024 when only adding parent adherence.

Sensitivity analyses

Results were similar, with higher 6-month PDCs, when restricted to children with a second SSRI fill before discontinuation.(Table 2, Table 3) The overall predictive relation between child and parent adherence remained across the secondary measures of child SSRI

adherence (Tables S3, S4). Results were consistent stratified by whether one (N=21,250) or two (N=49,729) parents were identified per child (crude RR high vs. low adherence: 1 parent=1.21 vs. 2 parents=1.19) with lower adherence in children with 1 parent identified (high adherence=52% vs. 60%).

DISCUSSION

In commercially insured children with anxiety disorders beginning an SSRI, adherence was poor and early discontinuation common. SSRI adherence was higher in children with parents highly adherent to SSRIs, statins, or antihypertensives. While adherence is difficult to predict at baseline, parental adherence and parent-level covariates offer slight improvement in predicting child SSRI adherence even after accounting for available child-level predictors. Parent adherence may help providers distinguish non-responders from non-adherers, identify targets for adherence interventions, and ultimately improve SSRI adherence in children.

Child SSRI adherence

In the Child/Adolescent Anxiety Multimodal Study over 90% of children had high adherence to an SSRI at 12 weeks;³⁵ however, this estimate was based on pills returned and over a shorter time period and adherence in trials is typically higher than a general population. To our knowledge, there are no published SSRI adherence estimates for pediatric anxiety disorders in standard care. In adults with anxiety disorders, less than half were adherent to antidepressant treatment at 6 months, with adherence measured similar to our research;^{13,15} these estimates highlight the prevalence of non-adherence when treating anxiety disorders.

We observed the highest adherence in children with an OCD diagnosis. This may be related to more specific guidelines on SSRI treatment length for children with OCD than non-OCD anxiety disorders.^{4,36} The lowest adherence was in children with a PTSD diagnosis, which could be partially because there is less evidence of SSRI effectiveness for pediatric PTSD than other pediatric anxiety disorders.^{37,38} Though, an important consideration for our study is that we cannot disentangle instances when non-adherence led to non-response or when non-response led to non-adherence or when discontinuation was clinically advised, perhaps due to perceived lack of effectiveness. If a child does not respond to SSRI treatment, another SSRI agent is recommended before switching medication classes.³⁹ However, when poor adherence is the reason for non-response, poor adherence will likely remain with the new medication,⁴⁰ supporting the need to assess adherence before altering dosing or exposing a child to a new and potentially unnecessary class of medication.

Parent adherence predicting child adherence

Parent adherence to SSRIs, statins, or antihypertensives was predictive of future SSRI adherence in children with diagnosed anxiety disorders. Family history of SSRI response can influence SSRI selection for a child.^{41,42} If family SSRI response is associated with child SSRI response, we may expect higher child SSRI adherence in parents with higher SSRI adherence; this assumes correlation between SSRI response and high adherence. Further, parent high SSRI adherence may signify more favorable views on SSRIs, which

could translate to improved child SSRI adherence. However, parallel associations with parent statin and antihypertensive adherence and child SSRI adherence point to other, or additional, explanations for observed predictability.

Larger unmeasured contextual factors such as pharmacy access, insurance coverage and co-payments, refill reminders, relationship with provider, or family socio-economic status^{16,17,26,43} affecting both parent and child adherence may contribute to our observed link between parent and child adherence. Parent views or behaviors influencing their own adherence may directly influence their child's adherence, or indirectly if the child shares/models parent views or behaviors. Adherence in children was previously associated with parent report of perceived psychosocial benefits of medication,⁴⁴ parent belief medication was necessary and outweighed concerns,⁴⁵ and parent negative views on medication.⁴⁶ Statins and antihypertensives are often used as preventative medications, parents initiating and adhering to these medications may be more likely to partake in healthy behaviors^{47,48} that could influence involvement in their child's treatment. Additionally, adherent parents may be accustomed to taking daily medications and making trips to the pharmacy. Shared behaviors or contextual factors likely contribute to the observed predictability of parent adherence on child adherence since associations held across age groups, even though older children may manage their own medication.^{19,49}

Clinical utility of parent adherence as a predictor

Without identifying the specific mechanisms causing parent adherence to be predictive of child SSRI adherence, parental adherence can help providers predict child SSRI adherence. Adherence is one of many factors considered in treatment selection; before pharmacotherapy initiation, a psychiatric evaluation involving interviews with the child and parent is recommended.¹⁰ Providers can discuss the parent's reasons for non-adherence and whether this may translate to the child and if they could overcome any barrier to adherence for the child. The clinical utility of using parent adherence, without an objective source (i.e. electronic health records), is lessened as self-reported adherence is often higher than actual adherence.⁵⁰ Nevertheless, parent adherence represents an additional factor to help predict child adherence and target interventions aimed at improving child adherence.

The c-statistic and risk reclassification results yielded a similar conclusion that parent adherence and parent-level covariates provided small improvement over only child-level measures when predicting child SSRI adherence. The c-statistic increase, while minimal, was comparable to risk prediction in other settings, including adding high-sensitivity C-reactive protein to cardiovascular risk prediction models,⁵¹ and is notable given the variety of child-level covariates included in the base prediction model. Our ability to predict adherence was modest (0.65) and similar to prior research predicting adherence at baseline within claims.^{52,53} Regarding risk reclassification, research in other settings has yielded higher NRIs than our results, for example, adding biological markers to predict atrial fibrillation resulted in NRIs=0.10-0.14.⁵⁴ It was suggested that an NRI of at least 0.04-0.06 was needed to consider a new marker promising, with acknowledgement that true determination depends on the specific situation.⁵⁴ While the addition of parent adherence was below this range and all parent-level covariates resulted in an NRI=0.04, our results

show some improvement, further, in the multivariable model, the predictive association of parent adherence was comparable to the strongest available child-level predictors. Therefore, we believe further research is warranted.

Currently, the no parent adherence category essentially represents missing information, combining children with parents who started and discontinued the medication, were prescribed but never filled the prescription, do not need the medication, or need but were never prescribed the medication. Additionally, conclusions are limited to parent SSRI, statin, and antihypertensive adherence. Future research with medication use spanning further in the parent history and across additional medication classes would increase the sample with parent adherence information and extend the potential implications of the research.

More broadly, results highlight the role parents have in children's treatment and demonstrate the value of parent-level measures in pediatric epidemiologic treatment utilization studies. Research with a wider variety of parent-level covariates could further inform the value parent information has in predicting child adherence. Further, contingent on additional research in the area, parent adherence and parent-level measures could potentially be used for adjustment in pharmacoepidemiologic studies to proxy for contextual factors and familial-level behaviors not captured through child-level claims.

Limitations

In some instances, low adherence values are blended with discontinuation, which may have been appropriate and clinically advised. A PDC of 0.80 may not be a clinically relevant adherence cut-point for all cases. Our focus was SSRI adherence after initiation; therefore, adherence calculations did not include switching to non-SSRI anti-anxiety medications and future research is needed to evaluate longer term adherence in pediatric anxiety. Parent adherence was relatively high, partially because we included prevalent users given our interest in recent parent adherence; however, incident parent medication use is an area to explore further along with the indication for use (i.e. parent SSRI for anxiety). Estimates from the multivariable prediction model are not meant to be interpreted causally as we evaluate prediction rather than direct causal relationships.⁵⁵ Our measures of adherence might be incorrect for reasons including: patients taking prescriptions concurrently or taking multiple medications within a medication class; incorrect days supply values; measures based on dispensed prescriptions, not actual use; patients obtaining medication not captured through insurance, such as free medication samples, inpatient prescriptions, paying out-of-pocket.^{56,57} Reasons for incorrect adherence measures may be shared by child and parent. Two-percent of children were identified as a potential sibling to another child (same insurance plan) who separately met cohort inclusion requirements; we assume correlation with high child adherence to remain low given infrequent occurrence of siblings and that adherence is associated with many factors. Risk reclassification results are sensitive to selected predicted probability strata. Our findings are based on children with a parent identified in the database, possibly limiting generalizability. The beneficiary in the child's insurance policy we label 'parent' may not be and may be uninvolved in the child's treatment; we are unaware of a validation study on the linkage of family members under the same insurance policy.

Conclusion

Low SSRI adherence in a large population of commercially insured children with an anxiety disorder was relatively common, indicating that adherence should be prioritized and evaluated during follow-up visits. Parent medication adherence at baseline was predictive of SSRI adherence in children with anxiety disorders; a predictive association that could be caused by a variety of mechanisms. Parent adherence and parent-level measures offer another tool to assist in predicting pediatric adherence and help providers make treatment decisions to ultimately improve care in pediatric anxiety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Percent difference in child high SSRI adherence by parent high vs. low adherence: Stratified
by parent medication, parent sex, and child age

Figure 2. Predictors of child high SSRI adherence (PDC 0.80): Multivariable model with child and parent characteristics^a

PDC=proportion days covered; Ref.=reference; dx=diagnosis; OCD=obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; GAD=generalized anxiety disorder; y=years

^aMultivariable model contains all child and parent-level covariates; estimates from the multivariable prediction model are not meant to be interpreted causally; Variables with less than 5% change in multivariable RR (i.e. $0.952 < RR < 1.05$) not displayed: female=1.04; prior contact with psychiatrist=1.03; 3+ baseline anxiety diagnoses=1.04; ICD-9-CM diagnosis for: potential anxiety-related symptoms=0.97, adjustment disorder=1.00, attention deficit hyperactivity disorder=0.96, development delay/learning disability=1.03, disruptive behavior/oppositional defiant disorder=0.96, other episodic mood disorder=1.00, sleep disorder=0.97, allergic rhinitis=1.02, asthma=0.98, cardiac disorder=1.03, dysthymia=1.00, fainting/dizziness=1.00, gastroesophageal reflux disease=1.01, migraine=1.01, scoliosis=1.05, fracture/sprain=0.99, head injury=0.95, other injury=0.98; dispensed

prescription: antidepressant=0.97, benzodiazepine=0.99, ADHD medication=0.98, antipsychotic=1.02, hydroxyzine=0.95, opioid=0.97, therapeutic medication groups (4+=0.98, 2-3=1.00, 0-1=reference); problem-oriented outpatient visit count (6+=1.04, 2-5=1.02, 0-1=reference); psychiatric-related inpatient admission=0.98; non-psychiatric-related inpatient admission=0.99; parent aged 50+ years=1.04, parent anxiety diagnosis=0.99, parent depression diagnosis=0.98, parent adjustment disorder diagnosis=0.99, other parent psychiatric diagnosis=1.01, parent benzodiazepine prescription=0.97, parent psychotherapy claims=1.00

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Table 1

Characteristics of children initiating an SSRI stratified by high vs. low SSRI adherence

	Total N=70,979	High adherence (PDC 0.80) N=40,982	Low adherence (PDC<0.80) N=29,997
Child-level characteristics ^a	No.(%)	No.(%)	No.(%)
Male	29,339 (41.3)	16,782 (40.9)	12,557 (41.9)
Age, Median(IQR)	14 (11-16)	14 (11-16)	15 (12-16)
3-9 years	11,192 (15.8)	7,113 (17.4)	4,079 (13.6)
10-13 years	19,070 (26.9)	11,986 (29.2)	7,084 (23.6)
14-17 years	40,717 (57.4)	21,883 (53.4)	18,834 (62.8)
Anxiety disorder, index diagnosis			
Unspecified anxiety	34,220 (48.2)	18,985 (46.3)	15,235 (50.8)
Generalized anxiety disorder	18,094 (25.5)	10,879 (26.5)	7,215 (24.1)
OCD	6,251 (8.8)	4,184 (10.2)	2,067 (6.9)
Panic disorder	3,221 (4.5)	1,688 (4.1)	1,533 (5.1)
PTSD	2,808 (4.0)	1,267 (3.1)	1,541 (5.1)
Social phobia	1,743 (2.5)	1,112 (2.7)	631 (2.1)
Multiple specific diagnoses	1,742 (2.5)	1,139 (2.8)	603 (2.0)
Other specific diagnosis ^b	2,900 (4.1)	1,728 (4.2)	1,172 (3.9)
3+ anxiety diagnoses, prior year	25,694 (36.2)	16,573 (40.4)	9,121 (30.4)
Provider type of index anxiety diagnosis			
Psychiatry	19,918 (28.1)	12,544 (30.6)	7,374 (24.6)
Pediatrics	11,221 (15.8)	6,408 (15.6)	4,813 (16.0)
Family practice	9,370 (13.2)	4,299 (10.5)	5,071 (16.9)
Psychologist, therapist	7,695 (10.8)	4,876 (11.9)	2,819 (9.4)
Multi-specialty physician group	2,325 (3.3)	1,385 (3.4)	940 (3.1)
Other	14,479 (20.4)	8,052 (19.6)	6,427 (21.4)
Unknown, multiple	5,971 (8.4)	3,418 (8.3)	2,553 (8.5)
Anxiety related symptoms, prior 90 days ^c	13,360 (18.8)	7,176 (17.5)	6,184 (20.6)
Psychotherapy claims, prior year ^d			
None	33,322 (46.9)	16,928 (41.3)	16,394 (54.7)
1-4	17,318 (24.4)	10,693 (26.1)	6,625 (22.1)
5+	20,339 (28.7)	13,361 (32.6)	6,978 (23.3)
Psychiatric co-morbidities ^e			
Any psychiatric diagnosis, recent	33,550 (47.3)	19,759 (48.2)	13,791 (46.0)
Depression diagnosis			
Inpatient diagnosis	3,943 (5.6)	2,136 (5.2)	1,807 (6.0)
Specific diagnosis	9,586 (13.5)	5,711 (13.9)	3,875 (12.9)
General diagnosis	7,496 (10.6)	4,186 (10.2)	3,310 (11.0)
No diagnosis	49,954 (70.4)	28,949 (70.6)	21,005 (70.0)
Adjustment disorder	11,863 (16.7)	7,352 (17.9)	4,484 (14.9)

	Total	High adherence (PDC 0.80)	Low adherence (PDC<0.80)
	N=70,979	N=40,982	N=29,997
ADHD	14,042 (19.8)	8,037 (19.6)	6,005 (20.0)
Disruptive behavior, conduct disorder	4,637 (6.5)	2,664 (6.5)	1,973 (6.6)
Other episodic mood disorder	3,653 (5.1)	2,088 (5.1)	1,565 (5.2)
Substance use disorder	2,223 (3.1)	895 (2.2)	1,328 (4.4)
Prescription medication use, prior year			
Count of therapeutic groups, Median(IQR)	3 (2-5)	3 (2-5)	3 (2-5)
Non-SSRI antidepressant	5,558 (7.8)	3,006 (7.3)	2,552 (8.5)
Benzodiazepine	7,306 (10.3)	4,010 (9.8)	3,296 (11.0)
Psychiatric diagnostic evaluation ^f	40,815 (57.5)	25,671 (62.6)	15,144 (50.5)
Parent-level characteristics (either parent) ^a			
Two parents identified	49,729 (70.1)	29,965 (73.1)	19,764 (65.9)
Parent age, Median(IQR)	45 (40-49)	45 (41-49)	44 (39-49)
Parent 50+ years	20,130 (28.4)	11,976 (29.2)	8,154 (27.2)
Psychiatric diagnoses			
Anxiety disorder	13,391 (18.9)	7,741 (18.9)	5,650 (18.8)
Depression	14,943 (21.1)	8,629 (21.1)	6,314 (21.0)
Adjustment disorder	6,336 (8.9)	3,790 (9.2)	2,546 (8.5)
Substance use disorder	4,147 (5.8)	1,942 (4.7)	2,205 (7.4)
Other diagnosis, not above	2,747 (3.9)	1,631 (4.0)	1,116 (3.7)
Benzodiazepine prescription	17,423 (24.5)	9,836 (24.0)	7,587 (25.3)
Psychotherapy claim	13,820 (19.5)	8,374 (20.4)	5,446 (18.2)
Outpatient well/preventative visit	29,724 (41.9)	18,284 (44.6)	11,440 (38.1)

IQR=interquartile range; OCD=obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; ADHD=attention deficit hyperactivity disorder; 'recent'=30-day period before SSRI initiation

^a Defined from inpatient/outpatient diagnoses and procedures and outpatient dispensed prescriptions

^b Total population=separation anxiety disorder=1.2%, agoraphobia=0.9%, other anxiety=0.7%, other/specific phobia=0.5%, due to medical condition=0.5%, selective mutism=0.3%

^c Diagnostic code for abdominal pain, unspecified chest pain, headache, hyperventilation, malaise/fatigue, nausea, palpitations, or weight loss in prior 3 months

^d Recorded psychotherapy CPT codes=90804-90819, 90821-90824, 90826-90829, 90832-90834, 90836-90839, 90847, 90849, 90853, 90857

^e Psychiatric co-morbidity definitions=ICD-9-CM codes: Any psychiatric diagnosis=290-319.x; specific depression diagnosis=296.2x-.3x, 300.4x, 309.1x; general depression diagnosis=311.x; adjustment disorder=309.0x, 309.22-.29, 309.3x-.4x, 309.82-.89, 309.9x; ADHD=314.x; disruptive behavior/conduct disorder=312.x, 313.81; other episodic mood disorder=296.9x; substance use disorder=291-292, 303-305

^f Defined with recorded CPT codes=90801-2, 90791-2

SSRI adherence in children with an anxiety disorder: Six-month proportion days covered (PDC)

Table 2

	No. Children	6-month mean PDC (95% CI)	High adherence (PDC 0.80)	Children with 2 nd fill: High adherence (PDC 0.80) ^b
	No.		%	%
Overall	70,979	0.72 (0.72-0.73)	58%	70%
Age group				
3-9 years	11,192	0.76 (0.76-0.77)	64%	76%
10-13 years	19,070	0.76 (0.76-0.77)	63%	74%
14-17 years	40,717	0.70 (0.69-0.70)	54%	67%
Anxiety disorder				
Unspecified anxiety	34,220	0.71 (0.70-0.71)	55%	69%
GAD	18,094	0.74 (0.74-0.75)	60%	72%
OCD	6,251	0.79 (0.78-0.79)	67%	78%
Panic disorder	3,221	0.68 (0.67-0.69)	52%	68%
PTSD	2,808	0.65 (0.63-0.66)	45%	58%
Social phobia	1,743	0.77 (0.76-0.78)	64%	73%
Multiple/other diagnosis	4,642	0.75 (0.74-0.76)	62%	74%
Co-morbid recent depression ^a				
Depression	17,942	0.73 (0.72-0.73)	58%	69%
No depression	53,037	0.72 (0.72-0.73)	58%	71%

GAD=generalized anxiety disorder; OCD=obsessive-compulsive disorder; PTSD=Post-traumatic stress disorder; PDC=proportion days covered; CI=confidence interval

^aDepression diagnosis (ICD-9-CM=296.2x-.3x, 300.4x, 309.1x, 311.x) within 30 days before SSRI initiation^bAdherence in children (n=56,914) with a second SSRI fill before discontinuation (30-day grace period)

Table 3

Child SSRI adherence stratified by parent prior medication adherence (6-month PDC)^{a,b}

	No. Children	Mean child PDC (95% CI)	No.	% ^c	Child high SSRI adherence (PDC 0.80)			Multivariable prediction ^d RR(95% CI)
					Crude RD(95% CI)	Crude prediction RR(95% CI)	Crude prediction RR(95% CI)	
Parent SSRI adherence								
Low	6,585	0.70 (0.69-0.70)	3,463	53%	REF	REF	REF	REF
High	13,683	0.77 (0.77-0.78)	8,823	64%	12% (10-13)	1.23 (1.19-1.26)	1.17 (1.14-1.20)	1.17 (1.14-1.20)
No use	50,711	0.72 (0.71-0.72)	28,696	57%	4% (3-5)	1.08 (1.05-1.10)	1.05 (1.02-1.07)	1.05 (1.02-1.07)
Parent statin adherence								
Low	3,323	0.70 (0.69-0.71)	1,817	55%	REF	REF	REF	REF
High	9,664	0.77 (0.76-0.78)	6,231	64%	10% (8-12)	1.18 (1.14-1.22)	1.11 (1.07-1.14)	1.11 (1.07-1.14)
No use	57,992	0.72 (0.72-0.72)	32,934	57%	2% (0-4)	1.04 (1.01-1.07)	1.02 (0.98-1.05)	1.02 (0.98-1.05)
Parent antihypertensive adherence								
Low	2,958	0.69 (0.67-0.70)	1,530	52%	REF	REF	REF	REF
High	12,386	0.74 (0.73-0.74)	7,424	60%	8% (6-10)	1.16 (1.12-1.20)	1.08 (1.05-1.13)	1.08 (1.05-1.13)
No use	55,635	0.72 (0.72-0.73)	32,028	58%	6% (4-8)	1.11 (1.07-1.15)	1.06 (1.02-1.09)	1.06 (1.02-1.09)
Parent adherence (overall)								
Low	10,312	0.69 (0.69-0.70)	5,429	53%	REF	REF	REF	REF
High	24,167	0.76 (0.76-0.76)	15,258	63%	10% (9-12)	1.20 (1.17-1.22)	1.16 (1.13-1.18)	1.16 (1.13-1.18)
No adherence measure	36,500	0.71 (0.71-0.71)	20,295	56%	3% (2-4)	1.06 (1.03-1.08)	1.03 (1.01-1.05)	1.03 (1.01-1.05)

PDC=proportion days covered; REF=reference; CI=confidence interval; RD=risk difference; RR=risk ratio

^aParent low adherence=6-month PDC<0.80, high adherence=PDC 0.80, no use=neither parent had a prescription in that medication class 6-12 months before the child initiated an SSRI (6-month PDC could not be calculated)^bAlternative parent adherence definition (selecting higher parent PDC value when both parents had available PDC), parent SSRI adherence: RD=13% (95%CI:1.1-14), crude RR=1.24(95%CI:1.21-1.28); parent statin adherence: RD=10% (95%CI:8-12), RR=1.19(95%CI:1.15-1.23); parent antihypertensive adherence: RD=8% (95%CI:6-10), RR=1.15(95%CI:1.11-1.20)^cPercent of children with high adherence in the subset of children with a second SSRI fill before discontinuation (n=56,914): Per strata of parent low, high, no adherence, respectively, parent SSRI adherence=66%, 75%, 70%, parent statin adherence=68%, 76%, 70%, parent antihypertensive adherence=65%, 72%, 70%^dMultivariable model includes all child and parent-level covariates; Estimates from the multivariable prediction model are not meant to be interpreted causally