PEDIATRIC ANXIETY: INITIAL PHARMACOTHERAPY, ADHERENCE PREDICTION, AND BURDEN OF EVENTS

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ABSTRACT

Greta A. Bushnell: Pediatric Anxiety: Initial Pharmacotherapy, Adherence Prediction, and Burden of Events
(Under the direction of Til Stürmer)

Anxiety disorders are one of the most common mental illnesses in children. Multiple pharmacotherapies for treating anxiety exist; selective serotonin reuptake inhibitors (SSRIs) are the recommended first-line pharmacotherapy for pediatric anxiety. SSRI adherence is important to consider during care and parent adherence may help predict child SSRI adherence. The burden of serious events following an anxiety diagnosis has not been well characterized in children.

In children with anxiety, we aimed to: 1) describe the initial anti-anxiety medication prescribed and psychotherapy utilization, 2) estimate SSRI adherence and determine if parental medication adherence predicts child SSRI adherence, and 3) estimate the incidence of emergency room (ER) visits, mental health related hospitalizations, and treated self-harm events after a new anxiety diagnosis.

The research was completed in a large commercial claims database (2004-2014) in children (3-17 years) with diagnosed anxiety (ICD-9-CM code). We estimated the proportion of children initiating each medication class and factors independently associated with non-SSRI initiation. For adherence we measured the 6-month proportion of days covered; parent SSRI, statin, and antihypertensive adherence was evaluated prior to child SSRI initiation. We estimated the cumulative incidence of each event following the new anxiety diagnosis.

Among children initiating anti-anxiety medication (n=84,500), 70% initiated an SSRI followed by benzodiazepines (8%) and non-SSRI antidepressants (7%). Anxiety disorder, age, provider type, and co-morbid diagnoses were associated with the initial medication; less than a third had psychotherapy claims before medication initiation. In children initiating an SSRI, parent high adherence (risk ratio=1.16) independently predicted high child adherence compared to parents with low adherence. One-year after a

new anxiety diagnosis, 2.0% of children had a mental health related hospitalization, 8 per 10,000 an inpatient, treated self-harm event, and 1.4% an anxiety-related ER visit, with higher incidence in older children with co-morbid depression.

SSRIs are the most commonly used first-line medication for pediatric anxiety; yet, a third initiated a medication with limited evidence of effectiveness for pediatric anxiety. Parental adherence may help predict child SSRI adherence. Following a new anxiety diagnosis, a significant proportion of children experience a serious event, adding to understanding the burden of pediatric anxiety disorders.

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LIST OF ABBREVIATIONS

AACAP	American Academy of Child and Adolescent Psychiatry
ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blockers
ADHD	Attention-deficit/hyperactivity disorder
APA	American Psychiatric Association
CAMELS	Child/Adolescent Anxiety Multimodal Extended Long-term Study
CAMS	Child/Adolescent Anxiety Multimodal Study
CBT	Cognitive behavioral therapy
CI	Confidence interval
CPT/HCPCS	Current Procedural Terminology/Healthcare Common Procedure Coding System
DALYs	Disability-adjusted life years
DCS	D-cycloserine
DSM-VI	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth edition
ER	Emergency room
FDA	Food and Drug Administration
GAD	Generalized anxiety disorder
ICD-9-CM	International Classification of Diseases, Ninth Revision
IQR	Interquartile range
KM	Kaplan-Meier
LASSO	Least absolute shrinkage and selection operator
MAOI	Monoamine oxidase inhibitor
MEND	MENtal health-Diabetes
MEPS	Medical Expenditure Panel Survey
MDD	Major depressive disorder

MPR	Modified medication possession ratio
NAMCS	National Ambulatory Medical Care Survey
NDC	National drug code
NIMH	National Institute of Mental Health
NRI	Net reclassification index
OCD	Obsessive compulsive disorder
OR	Odds ratio
PDC	Proportion days covered
POTS	Pediatric OCD Treatment Study
PTSD	Posttraumatic stress disorder
RCT	Randomized controlled trial
RD	Risk difference
RR	Risk ratio
SAD	Separation anxiety disorder
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TADS	Treatment for Adolescents with Depression Study
TCA	Tricyclic antidepressant
US	United States
YLDs	Years lived with disability

CHAPTER 1: STATEMENT OF SPECIFIC AIMS

Anxiety disorders are one of the most common mental illnesses in children and adolescents with estimates of current worldwide prevalence from 2%[1] to 7%[2] and lifetime prevalence estimates in the United States (US) of pediatric anxiety ranging from 15-20%.[3] Anxiety disorders are associated with symptoms causing impairment and poor functioning, resulting in high disability-adjusted life years,[4] and are predictive of future depression and substance use.[5-9] Anxiety disorders typically begin during childhood,[10,11] making this an important age to consider.

Effective early treatment of anxiety may reduce its negative impact and reduce its persistence into young adulthood and beyond.[5] Selective serotonin reuptake inhibitors (SSRIs) are recommended as the first line medication treatment for children with functionally impairing anxiety disorders,[5] based on randomized controlled trial (RCT) evidence.[5,12-16] There are a variety of other prescription medications that can be used to treat anxiety and it is unclear what medication is typically first prescribed to children. The combination of cognitive behavioral therapy (CBT) and SSRIs has been shown to offer an advantage over SSRI and CBT mono-therapies in treating children with moderate to severe anxiety;[17,18] however, psychotherapy is often not received with medication treatment.[19,20]

Antidepressant non-adherence is common outside trial settings in children,[21,22] with limited information specifically on SSRI adherence in pediatric anxiety; determining ways to improve medication adherence remains a research priority.[23-25] Finally, describing the risk of serious, impactful events in children newly diagnosed with an anxiety disorder can help inform the patient and caregiver and contribute to the larger discussion on the importance of managing symptoms.

The overall goals of this dissertation were to, in a population of commercially insured children with anxiety, describe the initial anti-anxiety medication prescribed to children and psychotherapy claims surrounding medication initiation, estimate SSRI adherence and evaluate whether parent adherence can

serve as a predictor for child adherence, and estimate the incidence of treated self-harm, mental health related hospitalizations, and ER visits after a new anxiety diagnosis. To address the three aims, we utilized Truven Health Analytic's Marketscan Commercial Claims and Encounters database (2004-2014), which provides longitudinal data, adequate sample size, and a linkage to parent claims. The cohort varied for each aim, but each includes commercially insured children (3-17 years) with an anxiety disorder diagnosis (ICD-9-CM codes). The three dissertations aims are:

AIM 1. In children diagnosed with anxiety beginning prescription anti-anxiety medication: a) describe the initial medication class received and b) describe psychotherapy claims in the months surrounding medication initiation. This aim evaluated whether the initial pharmacotherapy prescribed (based on records of dispensed prescriptions) in a general population is concordant with recommendations and evidence and whether psychotherapy was used surrounding medication initiation. The duration of medication use and factors associated with non-SSRI initiation were also estimated.

AIM 2. In a population of commercially insured children with anxiety: a) estimate SSRI adherence after initiation and b) determine if prior parental medication adherence was predictive of child SSRI adherence. Multiple aspects of child SSRI adherence were considered. Parent adherence to statins, antihypertensives, and SSRIs was identified and evaluated in the year before child SSRI initiation.

AIM 3. In children newly diagnosed with anxiety in an office setting: a) estimate the risk of mental health related hospitalizations, inpatient treated self-harm, and ER visits overall and by age and psychiatric co-morbidities and b) estimate the incidence of events in a similar population of children without diagnosed anxiety.

Findings from the specific aims add to the understanding of current prescribing practices and treatment utilization in pediatric anxiety, determine if parent adherence can be used as a baseline predictor of child adherence, and expand the current understanding on the burden of anxiety disorders. Together this research can inform providers, patients, and caregivers in improving treatment and management of pediatric anxiety.

CHAPTER 2: REVIEW OF THE LITERATURE

2.1. EPIDEMIOLOGY OF PEDIATRIC ANXIETY DISORDERS

2.1.1 Anxiety disorders include disorders with features of excessive fear and anxiety. Symptoms of anxiety may include feelings of overwhelming panic and fear, painful memories, recurring nightmares, and physical symptoms.[26] This dissertation focuses on anxiety disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[27] These include separation anxiety disorder (SAD), selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder (GAD), anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder. Additionally posttraumatic stress disorder (PTSD), which is under 'Trauma- and Stressor-Related Disorders' in the DSM-5, and obsessive-compulsive disorder (OCD) under 'Obsessive-Compulsive Disorders' are included as they were previously under 'Anxiety Disorders' in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The diagnostic criteria for anxiety disorders consider a patient's presence and severity of symptoms, functional impairment, length of symptoms, and other co-morbid conditions.

2.1.2 Anxiety disorders are highly prevalent in children with the causes of anxiety disorders largely unknown.[26] The current thought is that mental illnesses, including anxiety, are likely caused by genetic, environmental, psychological, and developmental factors; ongoing research aims to learn more about what makes the brain create excessive fear and anxiety.[28] Anxiety disorders are one of the most common mental illnesses in children; estimates of the lifetime prevalence of pediatric anxiety range from 15-20%.[3,28] A meta-analysis estimating the global prevalence of any anxiety disorder based on data from 1980-2009, estimated the adjusted current global prevalence in children (3-17 years) to be 7% (95% CI: 5%-11%).[2] The adjusted prevalence estimates for all ages varied by country's economic status (developing: 5%, emerging: 9%, developed: 8%) and culture (range: 10% in Western Europe/North

America/Australia to 5% in Indonesia/Asia and Africa).[2] The Global Burden of Disease 2013 Study estimated that globally 2.2% of children 0-19 years have an anxiety disorder, also with variation by developed (3.4%) countries vs. non-developed (2.1%)[1]

In the United States (US) anxiety disorders have a predicted lifetime prevalence of 32% by age 75.[11] Prevalence estimates for current anxiety vary depending on age and diagnostic criteria. From a large review, an estimated 4.6% of children have an anxiety disorder.[1] Three percent of surveyed parents reported current diagnosed anxiety in their child (3-17 years).[29] In older children (13-18 years), who were interviewed and given DSM-IV diagnoses, 32% met the criteria for an anxiety disorder, 8% of whom had severe anxiety.[10] The National Comorbidity Survey Replication-Adolescent Supplement 2001-2004, looked at one specific anxiety disorder, GAD, and found 3% of adolescents (13-18 years) met the DSM-IV/5 criteria for GAD.[30] There is a lot of variation in prevalence by specific anxiety disorder, exemplified in the Early Developmental Stages of Psychopathology study in children and young adults (14-24 years) in Germany, prevalence estimates varying from 1.6% for panic disorder to 16.2% for specific phobia.[8]

When adolescents and adults with anxiety were retrospectively interviewed, the median age of onset for anxiety disorder symptoms was reported to be 6[10] and 11[11] years, making childhood an important age to consider treatment utilization and impactful events.

2.1.3. Anxiety disorders are associated with current and future impairment, including social, family, and academic impairments; children with anxiety disorders are at risk for developing additional anxiety disorders along with future depression and substance use.[6-9,31] Pediatric anxiety disorders are likely to occur in association with somatic symptoms that can include headache, nausea, trouble sleeping, dizziness, and stomachache.[32] Mental and substance use disorders overall account for 7% of all global disability-adjusted life years (DALYs) and 23% of the years lived with disability (YLDs).[33] Anxiety disorders constituted 15% of those mental health related DALYS and YLDs, with anxiety related DALYs rising through childhood and adolescence.[33] In the US, anxiety was the 5th leading contributor to YLD in 2010 behind low back pain, major depressive disorder, other musculoskeletal disorders, and neck pain.[34]

The Global Burden of Diseases, Injuries, and Risk Factors 2015 Study, specifically for children and adolescents, anxiety disorders ranked 23rd in global disability-adjusted life years (DALYs)[4]

A meta-analysis of 29 studies (the vast majority in adult populations) found mortality to be higher in persons with anxiety (RR: 1.43, 95% CI: 1.24, 1.64) compared to the general population with no details on heterogeneity by age,[35] demonstrating the impairment and poorer health often present in the population with an anxiety disorder. Anxiety disorders in adults have been found to be predictive of chronic conditions, such as incident hypertension[36] and the escalation of symptoms of social phobia in childhood have been linked to adolescent alcohol use.[37] Retrospectively, 35% of adults treated for anxiety reported their worries and feelings related to anxiety as children had caused them to stay home from school for an extended period of time,[38] demonstrating the impact anxiety can have on daily childhood life.

Despite the impairment associated with anxiety, not all patients seek treatment. In a survey of children with a current clinical level anxiety disorder (n=32), 31% of children ever received medication or counseling compared to 40% of children with depression and 79% of children with attention-deficit/hyperactivity disorder (ADHD).[39] In a more general population (Medical Expenditure Panel Survey, MEPS) of children (6-17 years) with more severe mental health impairment (all diagnoses, not restricted to anxiety) only 44% had used any outpatient mental health service (outpatient visit with a mental disorder diagnosis, use of psychotherapy, or use of psychotropic medications) in 2010-2012 up from 36% in 2003-2005.[40]

2.1.4. Effective early treatment of anxiety may reduce its negative impact and reduce its persistence into young adulthood and beyond.[5] As written by Katzman et al. "because anxiety is highly prevalent and associated with chronic morbidity and comorbidities, effective treatment is essential to help patients manage their symptoms and improve their quality of life."[41] There is a need for studies focused on improving outcomes for children with anxiety as they can have important public health implications.[17,42]

***Summary**: Given that anxiety disorders are prevalent in children, can cause impairing symptoms, and appropriate treatment can lessen the impact, there is a heightened importance to learn more about treatment and impact of anxiety disorders during childhood.*

2.2. PSYCHOTHERAPY FOR ANXIETY DISORDERS

2.2.1. Psychotherapy, particularly cognitive behavioral therapy (CBT), is an effective treatment for pediatric anxiety.[43,44] The American Academy of Child and Adolescent Psychiatry (AACAP) recommends that psychotherapy be considered as part of the treatment for children with anxiety.[5,45] AACAP guidelines for PTSD and for anxiety disorders state that treatment should, until more evidence from comparative trials is available, begin with psychotherapy for conditions of mild severity with pharmacotherapy added when there is a need for acute reduction of moderate/severe symptoms, comorbid conditions requiring treatment, and partial or unsatisfactory response to psychotherapy with possibility of improved outcome with combined treatment.[5,45]

CBT for the treatment of pediatric anxiety disorders often involves the following steps as described by James et al.: "(1) recognize anxious feelings and bodily or somatic reactions to anxiety, (2) clarify thoughts or cognitions in anxiety-provoking situations (e.g. unrealistic or negative attributions and expectations), (3) develop coping skills (e.g. modifying anxious self-talk into coping self-talk) and (4) evaluate outcomes."[43] A recent literature review surmised that approximately two-thirds of children with anxiety responded favorably to CBT.[46] A Cochrane Collaboration that reviewed CBT for anxiety disorders in children (5-18 years) found that CBT was more likely to result in remission of anxiety diagnosis (ITT analysis, 59% CBT vs. 18% waitlist, OR=0.1, 26 studies).[43] Of importance, given the nature of the therapy, there was no blinding of treatment for the patient or clinician, for the majority of studies it was unclear if bias was present in the randomization process, and it was unclear when the outcome was evaluated in each arm.[43]

2.2.2. The combination of medication and psychotherapy was shown to offer increased benefits for children with anxiety.[17,18] The Child/Adolescent Anxiety Multimodal Study (CAMS) randomized 488 children, 7-17 years with moderate to severe anxiety to CBT (14 sessions), sertraline (an

SSRI), combination therapy (CBT+sertraline), or placebo for 12 weeks.[17] The proportion of children very improved or much improved at 12 weeks was 81% (95% CI: 73-86) combination therapy, 60% (95% CI: 51-68%) CBT mono-therapy, 55% (95% CI: 46-63%) sertraline mono-therapy, and 24% (95% CI: 16-35%) placebo group. CBT demonstrated superior improvement to placebo and a similar response to sertraline[17] with combination therapy offering an advantage over CBT and sertraline mono-therapies up to 9 months after treatment initiation.[17,18] Similar results were found in the Treatment for Adolescents with Depression Study (TADS) and the Pediatric OCD Treatment Study (POTS);[47-49] with the exception that in TADS, SSRI (fluoxetine) mono-therapy was more similar to combination therapy and superior to CBT mono-therapy.[49] Further, in a naturalistic study of children (7-18 years) with separation anxiety disorder (SAD) who were referred to a hospital and treated with an SSRI, patients also receiving psychotherapy were more likely to respond to treatment than those receiving medication only (73% vs. 51%).[50] Additional randomized controlled trials (RCTs) have also considered the efficacy of combination therapy compared to mono-therapy or mono-therapies in adults with major depressive disorder,[51] PTSD,[52] and panic disorder.[53]

2.2.3. Despite recommendations, adequate psychotherapy is often not implemented in the treatment of mental health disorders.[19,20,54-57] There are difficulties accessing psychotherapy (i.e. shortage of pediatric mental health specialists, convenience) that may result in underutilization.[57] The choice on the use of psychotherapy and medication can be influenced by preference and views of the family.[58] Based on the 2007 MEPS, 9% of children and adults treated for an anxiety disorder received psychotherapy alone (down from 20% in 1998), 35% psychotherapy and medication (down from 42% in 1998), and 56% medication alone (up from 38% in 1998).[54] While the estimate combined children and adults, it suggests that psychotherapy mono-therapy may be becoming a less common treatment choice.

Appendix 2 contains more information on estimates of psychotherapy use. Even if psychotherapy is initiated, it may not be continued sufficiently long enough. Many studies/surveys have defined psychotherapy use as 1 visit, often during a year period. A study in children with depression defined 'minimally adequate psychotherapy' as at least 4 visits within a 12 week period following a depressive

episode, of which approximately two-thirds of children received this amount of psychotherapy.[56] The Cochrane review of CBT for pediatric anxiety was limited to RCTs with 9+ CBT sessions (mean 13).

Summary: *In children with anxiety, psychotherapy, specifically CBT, is an effective treatment; however, it is often underutilized in children, the extent of underutilization surrounding medication initiation is unknown.*

2.3. PHARMACOLOGICAL TREATMENT FOR ANXIETY DISORDERS

2.3.1. There are many potential pharmacotherapies for anxiety; SSRIs are the recommended first-line prescription medication for treating anxiety in children.

The National Institute of Mental Health (NIMH) lists antidepressants (SSRIs, serotonin norepinephrine reuptake inhibitors, SNRIs, tricyclic antidepressants, TCAs, monoamine oxidase inhibitors, MAOIs), anti-anxiety medications (benzodiazepines, buspirone), and beta-blockers among the most common medications for anxiety.[59] Atypical antipsychotics, anticonvulsants, antihistamines, and other medications have also been suggested as alternative treatments for anxiety.[59-65] However, SSRIs are considered the first line pharmacotherapy. This recommendation is based on RCT evidence in children with anxiety where SSRIs had increased treatment efficacy over placebo and were well tolerated.[5,12-16] In a meta-analysis of RCTs in children with non-OCD anxiety (6 studies: 4 SSRIs, 2 SNRIs) the risk difference of treatment efficacy was 37 per 100 (95% CI: 23-52) and 20 per 100 (95% CI: 13-27) in children with OCD, higher than in children with major depressive disorder (11, 7-15).[16] The AACAP practice parameter for pediatric anxiety, which was published in 2007 following the black-box warning, recommends SSRIs be prescribed when moderate/severe symptoms of anxiety are present, if the condition makes it difficult for the child to participate in psychotherapy, or in cases of partial treatment response with psychotherapy.[5] SSRIs are often preferred over other medications because they are generally well-tolerated, have a mild side effect profile compared to other treatments, do not have the concern for dependency compared to benzodiazepines, and there is little or no clinical trial evidence to support the use of other medications to treat anxiety in children.[12,15,66-70] Most of the medications lack evidence because no trials have been done in a pediatric anxiety population.

The non-SSRI medications that can be prescribed for anxiety are listed in Table 3.1. Appendix 1 contains specific details on the evidence and reasoning behind the inclusion of each pharmacotherapy (ex. non-SSRI antidepressants, benzodiazepines, buspirone, anticonvulsants, antipsychotics, hydroxyzine).

2.3.2. It is unknown what proportion of children initiating pharmacotherapy for anxiety initiate on SSRIs. To date no SSRI has been approved by the US Food and Drug Administration (FDA) to treat non-OCD anxiety in children,[13] possibly resulting in treatment ambiguity as the first line pharmacotherapy for pediatric anxiety is not FDA approved for non-OCD anxiety in children. There is evidence that some SNRI antidepressants are effective in treating pediatric anxiety and duloxetine, a SNRI, was recently approved for pediatric generalized anxiety disorder.[71] However, SNRIs are not recommended as first-line anti-anxiety medication. There is limited evidence for the long-term efficacy and safety of pharmacotherapy for children with anxiety and there are concerns over the potential harms of routine pharmacological treatment.[12,72,73] Trial results for pharmacotherapies in adults with anxiety may not be equivalent to children, as evidence has suggested a difference between children and adults in the absorption, distribution, metabolism, and safety of some medications.[74,75]

Additionally, as of October 2004 SSRIs carry a black-box warning for an increased risk in suicidality in children (<18 years), a potentially lethal side effect.[74] This decision was based on a meta-analysis of RCTs in children that found children randomized to antidepressants had twice the rate of suicidal ideation and behavior when compared to placebo.[74,76,77] Through 2006 there were 6 placebo controlled RCTs with newer antidepressants in children (<19 years) with non-OCD anxiety; suicide ideation or suicide attempt/preparatory actions in the group treated with antidepressants (6/573) vs. placebo (1/582) resulted in a risk difference of 1 (-0 to 2) per 100 children.[16] Because of the black-box warning, non-antidepressant medications may be preferred by caregivers or providers when prescribing pharmacotherapy for pediatric anxiety. This was highlighted in a chart-review of children offered a trial of antidepressants, the percentage of caregivers refusing antidepressant treatment in children (4-12 years) with anxiety was 8% (n=5) prior to the black-box warning and increased to 33% (n=17) after the black-box warning, higher than the change in refusal for children with depression (11% to 25%). There were

also high changes in refusal for older children (13-17 years) with anxiety (14% to 44%) and with depression (4% to 25%) following the black-box warning. [78]

There is evidence that children are commonly treated with antidepressants and other psychotropics for anxiety and other mental illnesses: Among children 0-19 years who filled an antidepressant prescription in 2010, 49% had an anxiety diagnosis;[79] the percentage of antipsychotic medication prescriptions at outpatient psychiatrist visits (based on mostly adults in the National Ambulatory Medical Care Survey, NAMCS) for anxiety disorders doubled from 1996-1999 (11%) to 2004-2007 (21%);[80] the prevalence of antidepressant use from 2007-2010 was 3% of commercially insured children and 4% of children insured under Medicaid;[81] in Medicaid 9% of enrolled children (6-17 years) receiving antipsychotics had an anxiety or depression diagnosis.[82] Prior studies have shown that, following concerns of the risk of suicidality associated with antidepressants and the subsequent black-box warning, antidepressant use decreased in youth.[83-88] Aim 1 determines which pharmacotherapies are prescribed to treatment naïve children. Children as young as 3 years old are included in the study as anxiety symptoms present early in childhood[10,11] and prior literature has shown that young, preschool aged children do receive psychotropic medications for mental illnesses.[89,90] There is limited evidence for the long-term efficacy and safety of pharmacotherapy for children with anxiety.[5,12,72] Therefore, it is unclear how long children remain on these medications when used in standard care.

Summary: *SSRIs are effective in treating pediatric anxiety and are considered the recommended first-line treatment. It is unknown how often other pharmacotherapies are used as the initial treatment in pediatric anxiety.*

2.4. SSRI ADHERENCE AND PARENT ADHERENCE AS A PREDICTOR

2.4.1. Adherence to SSRIs in children with anxiety is unclear. Adherence can be defined as the process by which patients take medications as prescribed.[91] Antidepressant non-adherence is common among children[21,22] and among adults with anxiety disorders.[92-94] Sertraline adherence in CAMS was based on the extra pills returned during visits; sertraline adherence among patients without missing adherence data was over 90% at 12 weeks.[70] However, adherence in RCTs is usually much higher than

the general population.[25] This is likely due to the selection of participants (e.g., able to consent and willing to be randomized) and effort research investigators put into sample maintenance that is not part of real world clinical care. Our observational study is able to examine SSRI adherence in a general population of children.

In some scenarios medication discontinuation may be appropriate (i.e. medication is ineffective, side effects). However, it is important to optimize adherence early in treatment to determine if SSRIs are effective and to maintain adherence if the child responds to treatment. When poor adherence is the reason for lack of medication effectiveness (non-response), poor adherence will likely remain a problem with the new medication.[95] Given that recommendations suggest that if a child does not respond to SSRI treatment it is recommended the provider try another SSRI agent before switching to another medication class,[13] adherence is important to evaluate as the cause for SSRI non-response before dose alterations and changing medications.

2.4.2. A variety of factors influence adherence and parents play an important role in child adherence.[25] In addition to medication related factors that may affect adherence, there are also factors related to the patient, such as remembering to take a medication each day or whether they value the medication, and there are factors related to the larger healthcare system, such as copayment or pharmacy access.[25,96] In child adherence, there is an additional factor related to parents and caregivers. As stated by Osterberg and Blaschke, "Achieving full adherence in pediatric patients requires not only the child's cooperation but also a devoted, persistent, and adherent parent or caregiver."[25] Especially for young children when parents are responsible for storing the child's psychotropic medication and have responsibility for monitoring medication adherence, benefits, and side effects.[97] Parent behaviors and views have been shown to influence child adherence; in Australia lack of parental involvement in medication routines and monitoring was associated with poor psychotropic adherence in children (n=84).[98] There was higher adherence in children with ADHD (n=33) when they had parents reporting higher perceived psychosocial benefits of the medication.[99] In children with ADHD in Sweden (n=79),

negative parent views on stimulant medication was related to the child's willingness to discontinue medication.[100]

2.4.3. Parent adherence may serve as a predictor for child SSRI adherence. It remains a research priority to identify ways to assist patients in adhering to medications.[23-25] In adults with depression, past medication adherence to non-psychiatric chronic medications predicted future antidepressant adherence,[101] demonstrating the consistent influence of adherence related behaviors across medication classes. Parent adherence may also be associated with their child's medication adherence. Determining if parent prior adherence is predictive of child adherence could help target intervention efforts before SSRI initiation and during SSRI treatment, help the provider determine an appropriate treatment plan, and encourage conversations on a family's barriers to adherence.

Summary: *SSRI adherence in pediatric anxiety has not been well described and parent adherence may represent a way to predict future child SSRI adherence.*

2.5. SERIOUS EVENTS IN PEDIATRIC ANXIETY

2.5.1. The burden of serious events children newly diagnosed with anxiety is unknown. Serious events include hospitalizations and events that are life threatening or incapacitating.[17] Adults with anxiety disorders have high rates of health care service use,[32,102-104] but findings are less definitive for children as there have been few studies conducted in that population.[32] Events evaluated include treated self-harm events, mental health related hospitalizations, and emergency room (ER) visits. These events place a significant burden on the patient, caregivers, and the healthcare system.[105-107] The incidence of these events in children with newly diagnosed anxiety is unknown and whether the incidence varies by age and by co-morbid depression. There are few longitudinal studies describing the risk following a new diagnosis, a time especially useful to inform the patient and caregiver.

2.5.2. Mental health related hospitalizations. In 2011 the rate of mental health related inpatient hospitalizations in children was 26/10,000 (37% admitted through the ER) with anxiety disorders accounting for 2.7% of the inpatient hospitalizations.[108] The mean cost of each mental health related

hospitalization in children was $5,805 with a mean length of stay of 7 days.[108] Mental health related hospitalizations occurred in 7% of Medicaid enrolled children with a mental health diagnosis.[106]

2.5.3. Treated self-harm events. In 2010, suicide was the 4th leading cause of death in children 5-14 years (n=274 deaths) and the 3rd leading cause of death in children 15-24 years (n=4,600 deaths) based on death certificate data published by the National Center for Health Statistics.[109] Suicide attempts are associated with future death by suicide; suicide risk in adults following self-poisoning was strikingly increased relative to persons without a prior self-poisoning episode (hazard ratio=42).[110] Suicide attempts and suicide ideations are common. In the 2011 Youth Risk Behavior Survey of students in grades 9-12, 16% reported they had seriously considered suicide, which was down from 19% in 2001, and 8% reported they had attempted suicide one or more times during the prior year.[29,111] In a 7-19 year follow-up study of a small sample of children (n=66) treated with CBT for anxiety, 9% had made at least 1 suicide attempt and 27% reported experiencing suicidal ideation, treatment responders were less likely to report lifetime suicide ideation than non-responders.[112] A review of the literature by Hill et al. on the relationship between anxiety disorders and suicide related behaviors concluded: "It is clear that anxiety is a risk marker for suicide-related behaviors in children and adolescents. Even so, there is not yet sufficient evidence to confirm anxiety as a causal risk factor for suicide-related behaviors in this age group."[113] While the causal association between anxiety and suicide may not be clear, children with anxiety are often at an increased risk.

2.5.4. Emergency room visits. In 2012, 18% of children had an ER visit[109] and in 2011, 10.5% of treat-and-release ER visits for mental health conditions in children were due to anxiety disorders.[108] In the US from 2009-2011, there were an estimated 1,498 annual ER visits due to an adverse event from antidepressants in children 0-10 years and 8,250 in children 11-18 years.[114] Injury (including adverse effects) was the reason for 21% of ER visits for children (<18 years) from 2009-2010 in the US.[111] Anxiety disorders have been found to be predictive of unintentional burns, poisonings, and head injuries,[107] events that often result in an ER visit. Patients (16+ years) in Denmark with PTSD had a

higher baseline prevalence of traumatic events, including accidents and injuries from external causes, than did members of the comparison cohort.[115]

Summary: *The burden of events (treated self-harm events, mental health related hospitalizations, and ER visits) following a new anxiety disorder diagnosis has not been characterized in children.*

2.6. DATASOURCE

To address the study aims, we utilized a secondary datasource that provided adequate sample size, longitudinal data, a general population, and parent linkage. The aims all center on having a general population of children to see how medications are prescribed and utilized in standard care. Aim 1 examines how anti-anxiety medications are prescribed in children as it is unclear how often medication treatment recommendations are followed. Aim 2 assesses adherence patterns in children initiating SSRI treatment. The ability to link parents with children in Aim 2 and collect parent adherence details was another major benefit of the datasource. The large sample size of the datasource allows for stratification of results by anxiety disorder and other clinically relevant characteristics and allows incidence estimates for events with a low event rate. The datasource also provides longitudinal follow-up to evaluate medication adherence and events. The datasource has been previously used to evaluate healthcare utilization, antidepressant and psychotropic use, medication adherence, and self-harm related behaviors in adults and children.[116-124]

CHAPTER 3: TREATING PEDIATRIC ANXIETY: INITIAL USE OF SSRIS AND OTHER ANTI-ANXIETY PRESCRIPTION MEDICATIONS AND PSYCHOTHERAPY UTILIZATION[1]

3.1. INTRODUCTION

Anxiety disorders are one of the most common mental illnesses in children in the United States (US),[10] with lifetime prevalence of pediatric anxiety around 15-20%.[3] Children with anxiety have an increased risk of developing additional anxiety disorders, depression, and substance abuse and experience academic impairments.[7,8,31,37,38] Pediatric anxiety disorders are likely to occur in association with somatic symptoms, including headaches, nausea, and trouble sleeping.[32] In 2010, anxiety disorders were the fifth leading contributor to years lived with disability in the US,[34] demonstrating the sustained impact of unmanaged anxiety. Early diagnosis and treatment of anxiety can reduce the negative impact and persistence of anxiety into young adulthood and beyond[5] and is essential to manage symptoms and improve quality of life.[41]

The American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters recommend psychotherapy as the first-line treatment for anxiety of mild severity.[5,45,125] AACAP recommends pharmacological 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.[5,45,125] While there are a variety of pharmacological approaches to treat anxiety, selective serotonin reuptake inhibitors (SSRIs) are considered the first-line pharmacotherapy for pediatric anxiety.[5,45,125] Randomized controlled trials (RCTs) showed efficacy of SSRIs over placebo in children with anxiety.[16,126] 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.[5,12,45,125,127,128] However, since 2004, antidepressants, including SSRIs, carry a black-box warning for an increased risk of suicidality in children[74] and, while select SSRIs are approved by the US Food and

[1] Parts of this chapter were accepted to appear as an article in the Journal of Clinical Psychiatry

Drug Administration (FDA) to treat obsessive-compulsive disorder (OCD), SSRIs are not approved for pediatric non-OCD 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 anti-anxiety medications for children is limited, raising concern over the potential harms of routine pharmacological anxiety treatment.[12,73] 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.[5] Post-trial follow-up data have provided important evidence of continued SSRI response up to 36 weeks.[18,129] Benzodiazepines, another common anti-anxiety medication, are usually recommended for only short-term treatment given dependency concerns.[12]

Psychotherapy is a recommended part of treatment for pediatric anxiety.[130] However, in the US there is an increasing trend for mental illness to be treated with medication alone, rather than psychotherapy alone or the combination of psychotherapy and medication.[54] Further, adequate treatment is often not received for children with anxiety including underutilization of cognitive behavioral therapy (CBT).[57]

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

3.2 METHODS

We used Truven Health Analytics' MarketScan Commercial Claims and Encounters database, containing individuals covered by employer-sponsored private health insurance across the US, with over-representation of large employers. We utilized data from enrollment files, inpatient and outpatient services, and outpatient drug claims for reimbursed, dispensed prescriptions. The outpatient drug claims contains records on mail and retail reimbursed, dispensed prescriptions; providing the days covered by the prescription, number of units dispensed, the National Drug Code (NDC) Classification, and the therapeutic class.[131,132] The NDC, a system of classification by the FDA, provides specific details of the dispensed medication including the brand name.[132]

We included children 3-17 years with an anxiety diagnosis who initiated an anti-anxiety medication between 2004 and 2014. An anxiety diagnosis was defined as an inpatient or outpatient ICD-9-CM code (293.84, 300.0x-300.3x, 309.21, 309.81, 313.23). These codes roughly correspond to the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 anxiety disorders[27] and additionally post-traumatic stress disorder (PTSD) and OCD were included, as they share similar treatment recommendations and were previously classified under anxiety disorders.[133]

To identify initiators of anti-anxiety medications we selected the initial anti-anxiety prescription based on records of dispensed prescriptions, defined as having no anti-anxiety prescription in the prior year (Figure 3.1). Children were required to have continuous insurance enrollment with prescription and mental health services coverage the year before medication initiation. We defined anti-anxiety medications as medications with trial evidence of effectiveness in treating anxiety in adult or pediatric populations and also medications suggested as potential effective treatments for anxiety (Table 3.1, grouped into medication classes).[127,128,134,135] A detailed reasoning for the inclusion of each medication is provided in Appendix 1. Children could have initiated anti-anxiety pharmacotherapy with two medication classes (e.g. 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 anti-anxiety prescription (Supplementary eFigure 1). When evaluating psychotherapy

utilization we also required continuous insurance enrollment with mental health services coverage in the 3 months after medication initiation.

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

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 previous prescription's days supply 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.

We examined psychotherapy claims (CPT codes in Appendix 4) billed through insurance in inpatient or outpatient medical settings in the three months before and in the three months after a child initiated an anti-anxiety medication. Children with at least 2 recorded psychotherapy claims in that three-month period were considered psychotherapy "users."

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 co-morbidities, non-psychiatric co-morbidities, healthcare utilization, region, and year of medication initiation. The anxiety diagnosis most prior to or on the date of anti-anxiety 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 co-morbidities (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). Appendix 5 contains detailed definitions for the included covariates.

3.2.1. Statistical analyses

We determined the number and proportion of children initiating each anti-anxiety medication class overall and stratified by anxiety disorder and by year of initiation and age. As the proportion of children diagnosed with co-morbid depression and co-morbid 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 estimation to estimate fully adjusted risk ratios (RR) with 95% confidence intervals (CI) to identify factors independently associated with initiating 1) SSRI+another anti-anxiety medication vs. SSRI alone, 2) non-SSRI anti-anxiety medication vs. SSRI alone, and 3) SSRI+another anti-anxiety medication vs. non-SSRI anti-anxiety medication. We used Kaplan-Meier (KM) estimator to examine treatment continuation for each initial medication class up to 2 years, with censoring at insurance disenrollment and end of data (12/31/2014). 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 anti-anxiety medication who subsequently filled an SSRI prescription within three months. This was restricted to children with ≥3 months of insurance enrollment.

Additional sensitivity analyses were completed. Given the multiple indications for anti-anxiety medications, we examined the proportion of children initiating each medication class in restricted cohorts: 1) children initiating anti-anxiety medication the same day as an anxiety diagnosis and 2) children with ≥2 anxiety diagnoses and no recent co-morbid 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 vs. ≥2 prior anxiety diagnoses.

Based on recorded psychotherapy claims, we estimated the proportion of children who were psychotherapy users before and after medication initiation. Among children who did not have psychotherapy claims before medication initiation, we estimated how had psychotherapy claims after medication initiation by the provider specialty recording the anxiety diagnosis most prior to anti-anxiety medication initiation. This was further stratified by year of medication initiation and internally standardized by age group, sex, and region. In a sensitivity analysis, we examined psychotherapy claims in children without any co-morbid psychiatric diagnosis in the prior year.

3.3. RESULTS

We identified 84,500 children with diagnoses for anxiety who initiated anti-anxiety pharmacotherapy. The cohort had more girls (58%), 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 3.2). Approximately 24% were diagnosed with anxiety by a psychiatrist and 25% by a pediatrician. Fifty-seven percent of children had an anxiety diagnosis on the day of medication initiation, resulting in a median number of days between the index anxiety diagnosis and anti-anxiety medication initiation of 0 (interquartile range, IQR=0-3).

Overall, 63% of children initiated with an SSRI alone and an additional 7% initiated an SSRI+another anti-anxiety medication (Table 3.3). 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. Eight-percent initiated with a non-SSRI antidepressant 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 3.3).

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%, Figure 3.2). The proportion of children 14-17 years initiating with a benzodiazepine decreased across the study period (2004=20%, 2014=10%) and approached the low levels of use in younger children (Figure 3.3). This trend remained in children

without a recent co-morbid depression diagnosis. While few children 3-5 years with anxiety initiated an anti-anxiety medication (n=1,449), the proportion that did so on guanfacine or clonidine increased, from 11% in 2007 to 18% in 2009 and further to 27% by 2014. The increase remained but stabilized (2007=10%, 2009=15%, 2014=18%) when restricted to children without a co-morbid ADHD diagnosis.

The initial medication prescribed varied by anxiety disorder (Figure 3.4). 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 co-morbid 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 anti-anxiety medication also varied by age, provider type, co-morbid psychiatric diagnoses, and other patient factors (Table 3.2). Children with a recent depression diagnosis were less likely (RR:0.57, 95% CI:0.55-0.59) 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 anti-anxiety 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 anti-anxiety medication and panic disorder where pediatrics and family practice 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 3.4). 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 diagnoses (Tables 3.4 and 3.5).

Eighteen percent (n=4,121) of children initiating with a non-SSRI anti-anxiety medication subsequently filled an SSRI prescription within 3 months. This varied by medication class including 24% of benzodiazepine initiators and 20% of atypical antipsychotic initiators later filling an SSRI prescription (Table 3.6).

Of the 75,024 children with 3 months of follow-up, 50% (n=37,480) had at least one psychotherapy claim in the year prior to medication initiation. A third (35%, n=26,085) of children were psychotherapy users before initiating an anti-anxiety medication (2+ claims in prior 3 months), with a median of 4 psychotherapy claims (IQR=3-7) during those 3 months. This proportion of children who were psychotherapy users before anti-anxiety medication initiation remained relatively stable across the study period (2004-2014, range: 31-37%). An additional 10% of children had just one psychotherapy claim in the three months before medication initiation. The majority of children who were psychotherapy users before medication initiation remained psychotherapy users after anti-anxiety medication initiation (80%, n=20,881/26,085).

Among children who did not have psychotherapy claims before medication initiation, 30% (n=14,688/48,939) became psychotherapy users after medication initiation (median claims=4, IQR=3-6). An additional 9% of children had only one recorded psychotherapy claim in the three months after medication initiation. In children diagnosed by a psychiatrist before medication initiation 44% became psychotherapy users after medication initiation and 21% of children diagnosed by a pediatrician (Figure 3.5). Within each provider, there was no increase in the proportion of children becoming psychotherapy

users after medication initiation from 2004 to 2014. Overall 54% of children were psychotherapy users before or after medication initiation based on recorded psychotherapy claims.

When restricted to children without any recorded co-morbid psychiatric diagnosis in the year before anti-anxiety medication initiation (n=32,309), results were fairly consistent with slightly lower psychotherapy use. Twenty-percent were psychotherapy users before medication start (20%, n=6,562) and 79% remained psychotherapy users after medication initiation. In those without psychotherapy claims prior to medication start, 24% became psychotherapy users after starting a medication.

3.4. DISCUSSION

Concordant with the majority of evidence and recommendations, SSRIs were the most commonly used first-line anti-anxiety medication in children with anxiety diagnoses. By 2007 there was convincing evidence that SSRIs were effective in treating pediatric anxiety, summarized in a meta-analysis of RCTs[16] with findings upheld in an updated meta-analysis.[126] 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 anti-anxiety medication with limited evidence of effectiveness, or no trial evidence. Additionally, our findings based on recorded psychotherapy claims, suggest that psychotherapy utilization can be improved surrounding anti-anxiety medication initiation in children with anxiety.

There is evidence demonstrating efficacy of SNRIs for some anxiety disorders,[16] and duloxetine was recently approved for pediatric generalized anxiety disorder.[71] SNRIs are not recommended first-line therapy and were rarely used as the initial anti-anxiety medication in our study. Benzodiazepines, while used much less frequently than SSRIs, were the second most commonly used initial anti-anxiety medication. Conversely, in US adults with anxiety, where benzodiazepines are approved for several anxiety disorders, SSRIs and benzodiazepines are used at more comparable frequencies.[136,137] 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.[138] 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,[139] possibly explaining the higher observed benzodiazepine use in children with panic disorder. Relatedly, while SSRIs are approved to treat PTSD in adults,[45] there is less evidence supporting SSRIs for pediatric PTSD, likely explaining the lower proportion of children with PTSD initiating with an SSRI alone.[45,135] The variation observed in initial medication class by co-morbid psychiatric diagnoses was expected and potentially appropriate as medication selection should consider co-morbidities.[5] Still, 31% of children with no recent co-morbid psychiatric diagnosis initiated with a non-SSRI anti-anxiety 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 co-morbidity severity between providers.

The large increase in the proportion of young children initiating anti-anxiety pharmacotherapy with guanfacine or clonidine occurred following the medications' FDA approval for pediatric ADHD. In the US, 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.[140] The trend we observed with guanfacine and clonidine could be related to caregiver preferences for selecting treatment with pediatric FDA approval.[141] Relatedly, caregivers may prefer initiating a child on a non-antidepressant 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.[78]

AACAP practice parameters state that prescribers should have a clear rationale for prescribing medication combinations.[97] In our cohort 7% initiated with an SSRI+another anti-anxiety medication. Half of those children initiated an SSRI+benzodiazepine, which is sometimes done to achieve rapid reduction in severe anxiety symptoms.[5] The practice of concurrent anti-anxiety 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.[142] Despite some exceptions, beginning pharmacotherapy with an SSRI+another anti-anxiety medication raises concern given limited data on psychotropic polypharmacy in regards to effectiveness and possible increased adverse event burden, especially for treatment naïve children.[143]

Pediatric OCD guidelines state that treatment should typically be continued for 6-12 months then gradually withdrawn.[125] For non-OCD anxiety a medication free period has been recommended in children who experienced anxiety symptom reduction for a year,[144] but there are no formal guidelines on recommended SSRI treatment length.[5,45] 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%),[101] where guidelines are more specific, recommending ≥6 months of continued medication.[31]

The previously described gap between the amount of provider contact required by evidence-based treatments and the amount received in children with anxiety[145] 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 anti-anxiety medication was likely intended for short-term use (i.e. 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 had the highest continuation and that benzodiazepines were used primarily for short-term treatment.[12]

Only a third of children had psychotherapy claims in the months before starting an anti-anxiety medication. In Medicaid enrolled children aged 0-20 years only half received a psychosocial service in the three months before antipsychotic initiation, demonstrating that psychotherapy and behavioral interventions are not consistently used as a first-line treatment option.[146] In many areas the need for qualified practitioners to deliver quality, evidence-based psychotherapy, often makes medication the default treatment.[57,130,146] For pediatric anxiety specifically, the benefits of treating children with an SSRI

and CBT compared to an SSRI alone have been described,[17] highlighting the public health importance of having access to psychotherapy. The advent of online and electronic sources of therapy[147-149] may increase access to psychotherapy for children unable to access traditional office-based face-to-face therapy. Additionally, therapy delivered in primary care settings such as brief behavioral therapy for pediatric anxiety and depression may provide another means to increase access.[150,151]

Around 44% of children with severe mental health impairment receive outpatient mental health services[40] and 31% of children with anxiety report receiving treatment, 9% treated with medication.[39] These estimates highlight that our findings apply to a subset of children with anxiety, children who were diagnosed and initiated an anti-anxiety pharmacotherapy. With our additional requirements of continuous private insurance coverage, our results are likely not generalizable to all US children. Given prior reports of treatment differences by insurance type,[152] future research could explore whether the initial prescription anti-anxiety medication differs in children covered by Medicaid.

Almost half of children in our population had an unspecified anxiety diagnosis given most prior to, or on, the data of anti-anxiety medication initiation. The use of unspecified anxiety diagnoses has increased, rising from 45% (1999-2002) to 58% (2007-2010) of all anxiety diagnoses in ambulatory settings.[153] Children classified as having an unspecified anxiety diagnosis prior to medication initiation likely include children with a specific anxiety disorder who were not evaluated or the diagnosis was not recorded, resulting in misclassification. However, in some cases, children with an unspecified anxiety diagnosis may represent those with sub-threshold anxiety that does 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 anti-anxiety medication utilization in children with anxiety, including children with co-morbid 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 two 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 codes

for anxiety disorders do not perfectly correspond with DSM diagnoses. Selected symptoms that may guide anti-anxiety medication selection are not available in our datasource. The study design excluded children with baseline anti-anxiety 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. Additionally, we lack details on whether anti-anxiety medications were intended for short-term or prn (as-needed) use. Treatment length estimates rely on correct days supply values for dispensed prescriptions. The datasource lacks information on prescriptions provided in-hospital or obtained outside insurance (i.e. paid out-of-pocket, free samples), possibly resulting in misclassification of anti-anxiety medication initiation or continuation.

Regarding psychotherapy utilization, we are only able to evaluate psychotherapy that is billed through insurance claims and cannot identify therapy obtained outside of insurance; therefore, we may underestimate the use of psychotherapy. We may also be more likely to underestimate psychotherapy use in children diagnosed with anxiety outside mental health providers. In 1999, an estimated 34% of outpatient psychotherapy visits for anxiety disorders were reported to be self-paid.[154] In 2005-2006, 72% of psychiatrists accepted private non-capitated insurance, which decreased to 55% in 2009-2010.[155] However, it is unclear how often psychotherapy is paid for out-of-pocket and not entered through insurance in privately insured children with anxiety. The varying patterns of psychotherapy claims surrounding medication initiation observed in our study may all be appropriate depending on the clinical situation; we cannot know whether a child would have benefited from using psychotherapy prior to or after anti-anxiety medication initiation. Relatedly, we sought to describe psychotherapy utilization and did not attempt to account for differences in anxiety severity and psychiatric co-morbidities, which likely influence the provider type seen and psychotherapy use.

While the majority of children with anxiety initiated anti-anxiety pharmacotherapy with an SSRI, as recommended by current guidelines, a third of children initiated with a non-SSRI anti-anxiety medication and a notable proportion of children initiated with two anti-anxiety medication classes. By

describing the initial anti-anxiety pharmacotherapy and psychotherapy claims surrounding medication initiation in children with anxiety, our study provides insight into existing practices and can inform future research and efforts to better tailor treatment for pediatric anxiety.

Table 3.1. Anti-anxiety medications included grouped by medication class

Medication class	**Generic names included**
Selective serotonin reuptake inhibitors	Citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline, vilazodone
Serotonin norepinephrine reuptake inhibitors	Desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine
Tricyclic antidepressants	Amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine, amoxapine*
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, valporic acid
Atypical antipsychotics	Aripiprazole, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone
Hydroxyzine	-
Beta-blockers	Acebutolol, atenolol, atenolol/chlorthalidone, bendroflumethiazide/nadolol, betaxolol, bisoprolol fumarate, carteolol, carvedilol, esmolol, metoprolol succinate, metoprolol tartrate, propranolol, timolol maleate, nadolol, nebivolol, penbutolol sulfate, pindolol, sotalol
Other	Clonidine, D-cycloserine, guanfacine, memantine, prazosin, riluzole

*Dibenzoxazepinederivative tricyclic antidepressant

Table 3.2. Patient characteristics of children initiating anti-anxiety medication and factors associated with SSRI initiation[a]

	Children initiating anti-anxiety medication (N=84,500)	Initial anti-anxiety treatment group					
		SSRI alone (N=53,009)	SSRI + another anti-anxiety medication (N=5,863)		Non-SSRI anti-anxiety medication (N=25,628)		SSRI + another anti-anxiety 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	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)

setting							
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	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[b]							
No recorded diagnosis	62,350 (74)	37,829 (71)	3,431 (59)	REF	21,090 (82)	REF	REF
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 (any)[b]							
No recorded diagnosis	71,515 (85)	44,232 (83)	4,921 (84)	REF	22,362 (87)	REF	REF
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 (0.8-0.9)	1,730 (7)	1.0 (0.9-1.0)	0.9 (0.8-1.0)
Attention deficit disorder (ADD/ADHD)[b]							
No recorded diagnosis	69,432 (82)	44,959 (85)	5,199 (89)	REF	19,274 (75)	REF	REF
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)
Disruptive behavior, conduct 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)
Autism spectrum, 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, burn	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[b]							
No recorded sessions	49,619 (59)	29,980 (57)	3,627 (62)	REF	16,012 (62)	REF	REF
1-2	22,520 (27)	14,725 (28)	1,353 (23)	0.8 (0.8-0.9)	6,442 (25)	0.9 (0.9-0.9)	1.0 (0.9-1.0)
3+	12,361 (15)	8,304 (16)	883 (15)	0.9 (0.9-1.0)	3,174 (12)	0.9 (0.8-0.9)	1.1 (1.0-1.2)
Mental health diagnostic/evaluation visit	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

IQR: Interquartile range, REF: Referent category

*Number not displayed due to small sample

[a]All variables were used to calculate multivariable RRs; 'Any recent non-anxiety psychiatric diagnosis' was not entered into the full multivariable model as specific indicators for psychiatric disorders were used instead

[b]Recent=0-30 days before anti-anxiety medication initiation, prior=31-365 days before anti-anxiety 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 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); autism spectrum, pervasive developmental disorder (299.x); bipolar disorder, cyclothymic (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 disorders (327.x, 347.x, 307.4x, 780.5x); substance use disorder (291.x, 292.x, 303.x, 304.x, 305.x); tics (307.2x)

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

[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 admissions excludes inpatients admissions with an ICD-9-CM code=290-319 as the primary or secondary diagnosis; separate 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

Table 3.3. Initial anti-anxiety medication class in children with diagnosed anxiety beginning anti-anxiety pharmacotherapy

	Primary analysis: Full cohort		Anxiety diagnosis same day as initial anti-anxiety prescription		2+ Anxiety diagnoses, no recent comorbid psychiatric diagnosis[a]	
	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
SSRI alone	53,009	63% (62-63)	32,044	67% (66-67)	13,492	67% (66-67)
SSRI+another anti-anxiety 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 anti-anxiety 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 anti-anxiety[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%*
Beta-blocker	*705*	*1%*	*391*	*1%*	*176*	*1%*
Non-SSRI + Non-SSRI	*953*	*1%*	*427*	*1%*	*124*	*1%*
	84,500	100%	47,973	100%	20,249	100%

[a]At least two anxiety diagnoses in the prior year and no comorbid psychiatric diagnosis in the 30 days before anti-anxiety medication initiation

[b]Primary analysis: SSRI+other anxiety (n=355), SSRI+buspirone (n=133), SSRI+beta-blocker (n=110), SSRI+anticonvulsant (n=83), SSRI+TCA (n=55), SSRI+bupropion (n=17), SSRI+SNRI (not reported due to small sample)

[c]98% of prescriptions were clonidine or guanfacine

Table 3.4. The proportion of children refilling their initial anti-anxiety medication class and continuing that medication class for six months

Initial medication class[a]	Total No.	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 anti-anxiety[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)
TCA	1,279	55 (52-57)	27 (23-32)
Anticonvulsant	1,218	64 (61-66)	35 (30-39)
Beta-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 two classes

[b]Calculated from the 93% of children with ≥60 days of continuous insurance in follow-up

[c]98% of prescriptions were clonidine or guanfacine

Table 3.5. Treatment continuation sensitivity analysis: Proportion of children who refilled the initial anti-anxiety 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%	61%	78%	50%
Benzodiazepine	28%	7%	23%	4%
Hydroxyzine	22%	4%	17%	3%
Other antidepressant	61%	32%	54%	24%
Atypical antipsychotic	72%	43%	69%	38%
Other anti-anxiety	66%	39%	62%	36%
Buspirone	57%	26%	45%	15%
Bupropion	68%	40%	69%	33%
TCA	58%	30%	52%	25%
Anticonvulsant	64%	35%	63%	34%
Beta-blocker	38%	21%	28%	10%
SNRI	67%	41%	66%	36%

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

Table 3.6. 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%	41%	83%	67%
Benzodiazepine	20%	3%	29%	10%
Hydroxyzine	15%	2%	23%	8%
Other antidepressant	51%	19%	61%	39%
Atypical antipsychotic	64%	28%	74%	54%
Other anti-anxiety	57%	28%	68%	49%
Buspirone	43%	12%	52%	28%
Bupropion	63%	25%	70%	48%
TCA	49%	19%	58%	36%
Anticonvulsant	57%	25%	67%	46%
Beta-blocker	28%	9%	35%	19%
SNRI	60%	27%	68%	49%

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

Table 3.7. Proportion of children initiating with a non-SSRI anti-anxiety medication with a subsequent SSRI fill within 3 months

Non-SSRI anti-anxiety medication at initiation	Total with non-SSRI prescription No.	Children with 3 months enrollment[a] No.	SSRI prescription filled within 3 months No.	SSRI prescription filled within 3 months % (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 anti-anxiety	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)
Anticonvulsants	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

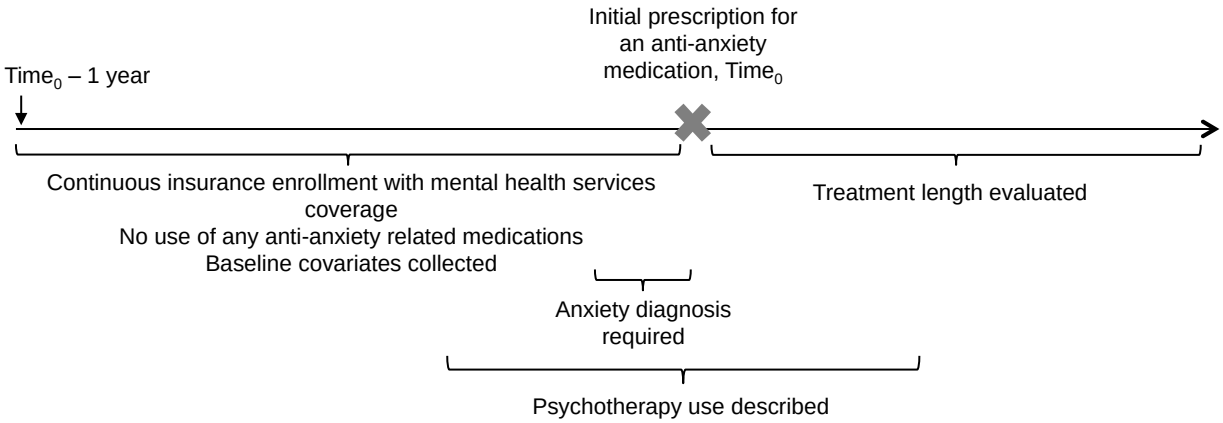
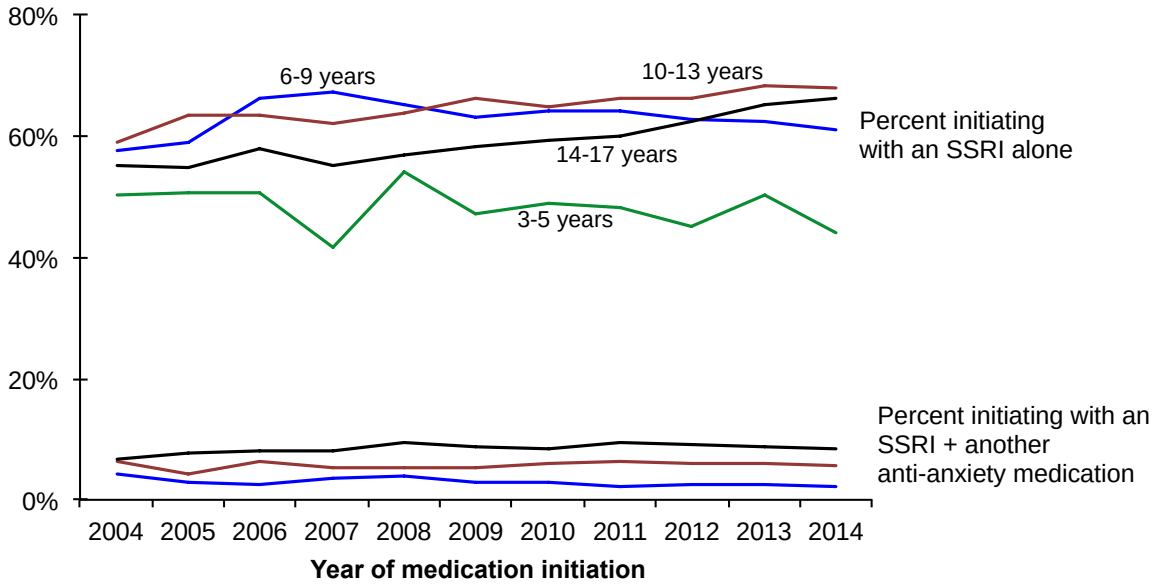
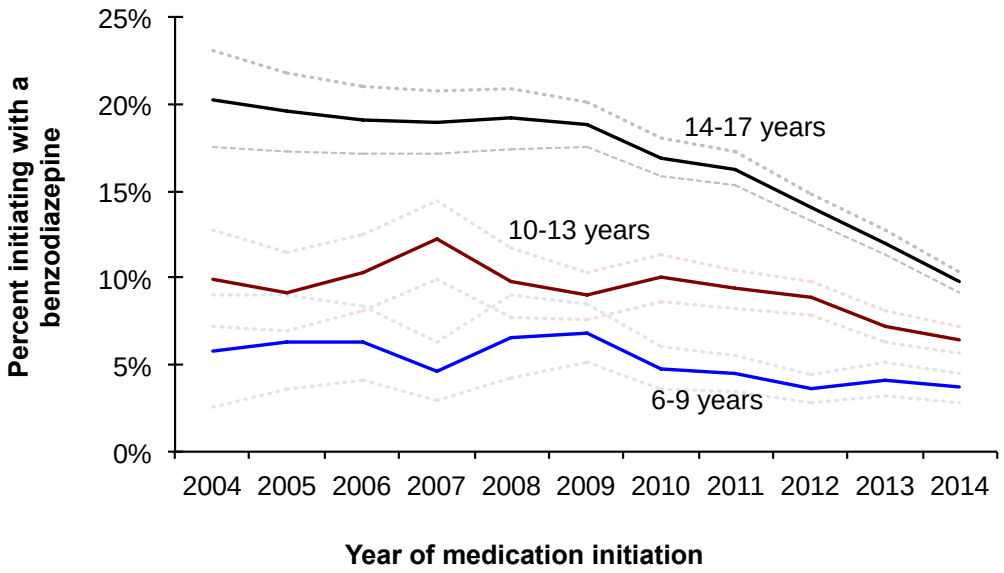


Figure 3.1. Study design, cohort of children with anxiety initiating anti-anxiety medication



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 and another anti-anxiety medication in children 3-5 years, results not displayed

Figure 3.2. Proportion of children with anxiety initiating anti-anxiety medication with an SSRI alone and with an SSRI+another anti-anxiety medication by age group[a]

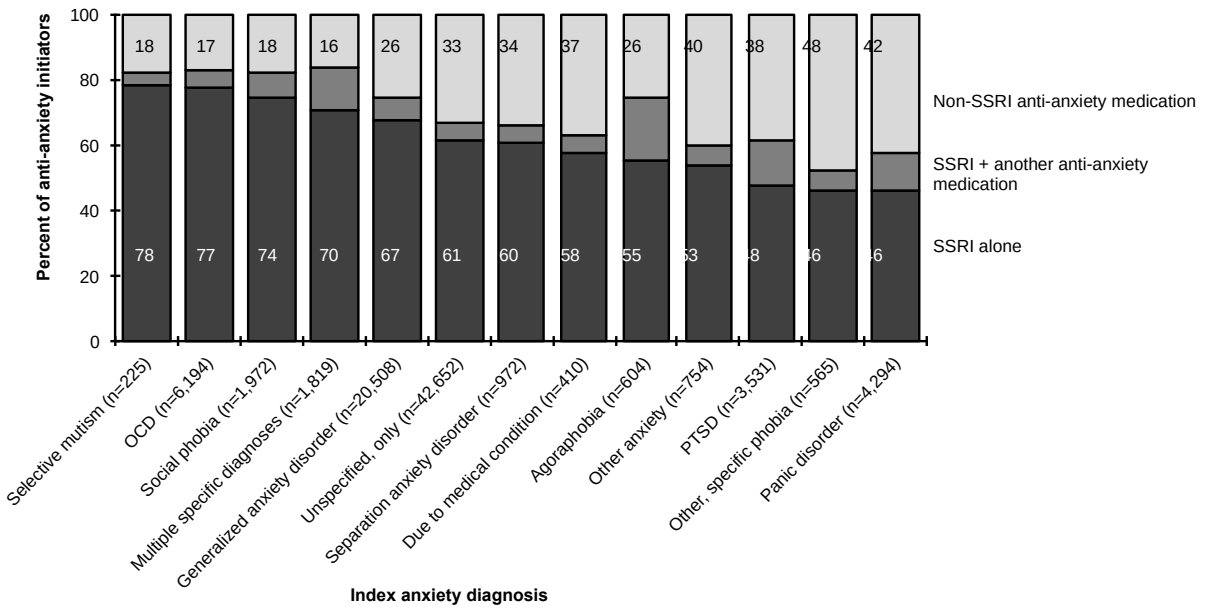


Results standardized internally by US census division (children with unknown division, n=799, excluded); dotted lines represent 95% confidence intervals

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

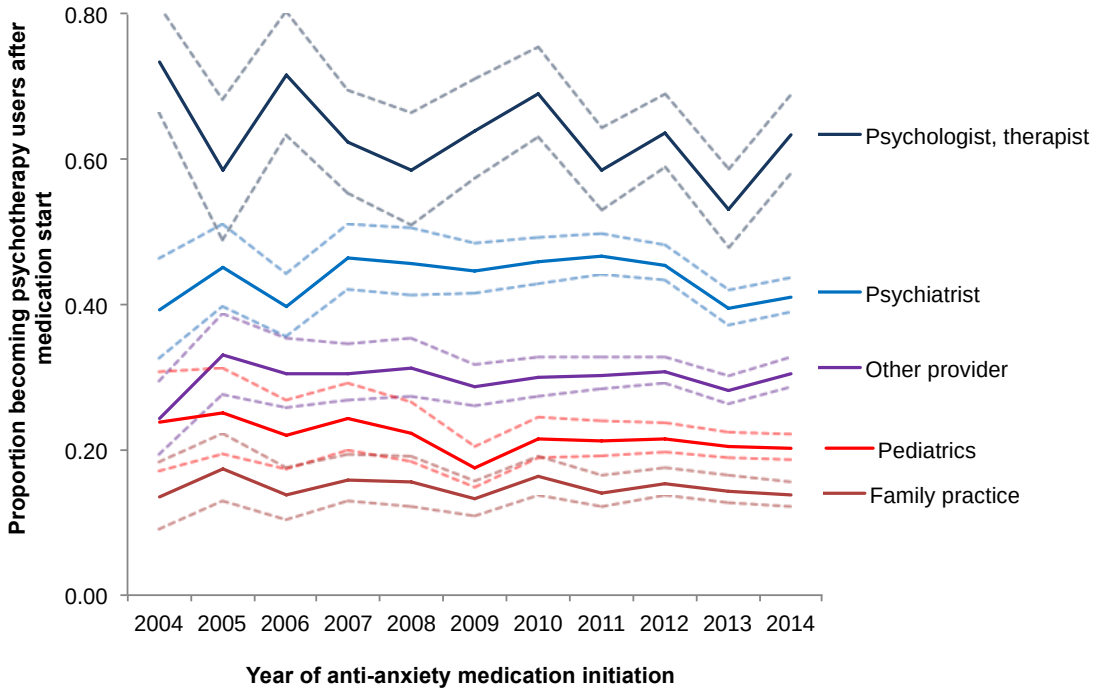
[b]Uncommon benzodiazepine initiation in children 3-5 years, results not displayed

Figure 3.3. Proportion of children with anxiety initiating anti-anxiety medication with a benzodiazepine by age group[a,b]



[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

Figure 3.4. The proportion of children initiating anti-anxiety pharmacotherapy with SSRI alone, SSRI+another anti-anxiety medication, or non-SSRI anti-anxiety medication by index anxiety diagnosis[a]



Dotted lines represent 95% confidence intervals

[a]Restricted to non-psychotherapy users (<2 sessions in 3 months) before anti-anxiety medication initiation; psychotherapy use after medication initiation defined as 2+ sessions in the following 3 months; the majority of children with an anxiety diagnosis from a psychologist/therapist were psychotherapy users before anti-anxiety medication initiation and therefore were excluded from this figure

[b]Standardized internally (reference year=2012) by sex, age group (3-9, 10-13, 14-17 years), and region to account for shifts in the population covered across the study period; children with an unknown region or provider specialty and prior psychotherapy users were excluded (included n=43,809)

[c]Primary values under 'other' provider specialty include acute care hospital, medical doctor-not elsewhere classified, multispecialty physician group, internal medicine-not elsewhere classified, nurse practitioner, and mental health facilities; the remaining third includes 80+ different values.

Figure 3.5. Proportion of children becoming psychotherapy users after anti-anxiety medication initiation who were not users of psychotherapy prior to medication initiation by provider specialty [a,b,c]

CHAPTER 4: EXAMINING PARENTAL MEDICATION ADHERENCE AS A PREDICTOR OF CHILD SSRI ADHERENCE IN PEDIATRIC ANXIETY

4.1. INTRODUCTION

The estimated lifetime prevalence of pediatric anxiety disorders is 15-20%[3] and 8% for anxiety disorders with severe impairment.[10] Selective serotonin reuptake inhibitors (SSRI) are the recommended, and most commonly prescribed,(Aim 1) first-line pharmacotherapy for children with anxiety.[31,156] Randomized controlled trials have shown SSRIs to be effective in treating pediatric anxiety over placebo with relatively mild side effects.[16,31,126] In pooled estimates from randomized controlled trials approximately 50-70% of children with anxiety randomized to SSRIs or serotonin–norepinephrine reuptake inhibitor (SNRIs) responded to treatment.[16]

Poor medication adherence, the process by which patients take medications as prescribed,[91] can reduce medication effectiveness. Adherence should be encouraged at SSRI initiation and evaluated as a reason for non-response before dosing or agent changes. Antidepressant non-adherence is common among children and adolescents[21,22] and in adults with anxiety.[92-94] However, there is limited information specifically on SSRI adherence in children and adolescents with anxiety.

Medication adherence is influenced by many factors, including medication related, patient related, and provider and system related factors.[25,96] For child adherence, parents and caregivers play an important role.[25] Parents have responsibility in storing their child's psychotropic medication and monitoring medication adherence, benefits, and side effects[97] with psychotropic medication considered a more challenging treatment option when there is limited family investment or adult supervision.[97] Parent attitudes towards and involvement in a child's treatment have been associated with child psychotropic adherence[98,157] and children and parents share common barriers to adherence.

Identifying ways to assist patients in adhering to medications remains a research priority.[23-25] Determining if parent prior adherence is predictive of child SSRI adherence could target interventions in children prior to 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 immediately after initiation in a large population of commercially insured children and adolescents with anxiety and to determine if prior parental medication adherence was predictive of child SSRI adherence.

4.2. METHODS

4.2.1. Study population

We identified commercially insured children in the United States from the MarketScan Commercial Claims database. We utilized enrollment files, inpatient and outpatient services, and outpatient, dispensed prescriptions. We included children (3-17 years) newly initiating an SSRI between 2005 and 2014. Children were required to have continuous prescription coverage with no record of a dispensed SSRI prescription in the year prior to SSRI initiation (Figure 4.1) and a recent anxiety diagnosis, at least 30 days prior to, or on, the date of SSRI initiation (index anxiety diagnosis). An anxiety diagnosis was defined as an inpatient or outpatient anxiety ICD-9-CM code (293.84, 300.0x-300.3x, 309.21, 309.81, 313.23) roughly corresponding to anxiety disorders in the Diagnostic and Statistical Manual of Mental Disorders, DSM-5,[27] and we additionally included post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD), which were classified under anxiety disorders in the DSM-IV.[133] We excluded children with baseline diagnoses of bipolar disorder, personality disorder, schizophrenia, or autistic disorder, as anxiety would likely be treated secondary to these conditions. We required 6-months of insurance enrollment following SSRI initiation to evaluate 6-month adherence. Lastly, we excluded children for which we could not identify at least one parent in the datasource.

4.2.2. Parent identification

The child enrollment identification number was used to identify the primary and secondary beneficiary on the child's insurance plan. We required the primary and secondary beneficiary to have enrollment with prescription coverage in the year before his or her child initiated an SSRI (Figure 4.1). We considered the primary and/or secondary beneficiary to be a parent if he or she was at least 15 years older than the child.

4.2.3. Child SSRI adherence measures

The primary measure of child SSRI adherence was the 6-month proportion days covered (PDC). The PDC was calculated by summing the days supply for all SSRI prescriptions dispensed in the first 180 days of SSRI treatment and dividing the sum by 180 days. PDC values were truncated to 1 and, where relevant, dichotomized to "low adherence" (PDC <0.80) and "high adherence" (PDC≥0.80).

We included three secondary measures to capture additional aspects of adherence, continuation for 6-months (persistence), modified medication possession ratio (MPR), and gap in medication coverage. A child was considered to have discontinued SSRI treatment when there was no record of a dispensed prescription 30 days after the previous prescription's days supply ran out. If the child remained on treatment 180 days after initiation, the child was considered to be persistent at 6-months. The MPR provides an estimate of days with medication coverage during time on treatment. The MPR was calculated by summing all prescriptions' days supplies between the first and last SSRI prescription in the 6-month period (excluding the last prescription) and dividing by the number of days between the first and last prescription. Children without a second SSRI fill had a missing MPR. Lastly, we included a measure for a gap without medication coverage between the first and second SSRI prescription fill, among children with a second SSRI fill. We calculated days without medication coverage by subtracting the days supply of the first SSRI fill from the number of days between the first and second prescriptions fills (dispensing dates). We defined a long gap without medication as 20+ days. We evaluated all SSRIs and allowed switching between SSRI agents when calculating adherence measures.

4.2.4. Parent medication adherence measures

We examined parent adherence to 1) SSRIs, 2) statins, and 3) antihypertensives (ACEs, ARBs, thiazides) in the year before child SSRI initiation. We selected these medication classes since SSRIs are a common psychiatric medication (and the drug being studied in children) and statins and antihypertensives are commonly prescribed chronic, often preventative, medications. For parents, the 6-month PDC was calculated for each medication class and dichotomized in the same manner as child 6-month. Parents were required to have a prescription for a medication of interest at least 6 months before his or her child's SSRI initiation date to calculate a 6-month PDC prior to child SSRI initiation. When two parents per child had an available PDC measure for a medication class, their PDCs were averaged; selecting the higher parent PDC value was also considered and results were consistent (Table 4.3 footnote). For the parent summary adherence measure, PDCs were averaged across medication classes. For a sensitivity analysis, among children without a parent statin or antihypertensive PDC measure available we identified parents with a statin or antihypertensive prescription 1-3 years prior to child SSRI initiation. As statins and antihypertensives are often to be taken chronically, we considered these parents to have discontinued the medication and grouped them with low adherence.

4.2.5. Covariates, baseline predictors

In the year prior to SSRI initiation we measured the following child-related characteristics: age, sex, psychiatric co-morbidities, non-psychiatric co-morbidities, healthcare/medication utilization, region, and anxiety diagnosis details. The index anxiety diagnosis was grouped by the specific diagnosis (≥1 specific diagnosis were grouped under 'multiple') and as unspecified anxiety when no specific anxiety diagnosis was provided. The provider type of the index diagnosis was identified and categorized: psychiatry, psychologist, therapist; pediatrics; family practice; multi-specialty physician group; other specialty; unknown, multiple. Healthcare utilization included indicators for outpatient visits (problem-oriented and well/preventative, defined with CPT procedure codes), psychiatric and non-psychiatric related inpatient admissions, and ER visits. Medication included an overall count of therapeutic classes prescribed in the prior year, other psychiatric medications that can be prescribed for anxiety, ADHD

medications, and opioids. Prior psychotherapy use was identified through recorded psychotherapy CPT procedure codes.

For each child's parent(s), we created variables for whether either parent had a psychiatric diagnosis (anxiety, depression, adjustment disorder, substance abuse, or other), preventative/well outpatient visit, benzodiazepine prescription fill, or psychotherapy session in the prior year. We included an indicator for one parent being age 50 or older (above third quartile of parent age=49 years), since adherence in older adults may be higher.[101]

4.2.6. Statistical analysis

We described the mean 6-month SSRI PDC with 95% confidence intervals (CI) and estimated the proportion of children with high adherence overall and stratified by age group, index anxiety diagnosis, and recent (≤30 days) co-morbid depression diagnosis. We described child SSRI adherence stratified by parent adherence to SSRIs, statins, and antihypertensives. Parents were classified as low adherence, high adherence, or non-users for each medication class. This was repeated with the secondary measures of child adherence (6-month persistent, MPR, and gaps between fills). We estimated the crude predictive risk difference (RD) and risk ratio (RR) with 95% CIs of high child adherence by parent adherence. Results were stratified by sex of the parent with an adherence measure and child age. These factors were considered potential modifiers of the predictive association between parent adherence and child adherence as mothers may have more regular involvement in a child's anxiety treatment; in a randomized controlled trial in pediatric anxiety, 87% of caregiver baseline interviews were completed by mothers.[158] Child age was considered as parent involvement in medication use likely differs between older and younger children. We estimated the multivariable predictive RR of parent adherence with high child SSRI adherence in a full model with all child and parent level variables with a prevalence >2% using modified Poisson regression.[159] For a sensitivity analysis we examined results stratified by whether we identified 1 parent per child or 2 parents per child.

To determine if parent-level factors improved the prediction of child adherence over child-level predictors, we estimated the change in c-statistic and clinical risk reclassification. For the c-statistic

change, we used least absolute shrinkage and selection operator (LASSO) regression methods to automatically select predictors that resulted in the minimized cross-validated error (lambda).[160] This was done in three random training datasets (80% samples) with predictors with a prevalence >2% included as possible predictors. In the validation datasets we estimated the c-statistic for the models identified in the training datasets with and without considering the parent measures. We additionally evaluated the average c-statistic change when allowing for all possible 2-way interactions in the models with and without parent-level variables.

For clinical risk reclassification the predicted probabilities of high child adherence with only child-level variables were cross-classified with the predicted probabilities from the model also containing child and parent-level variables.[161] This was summarized with the net reclassification index (NRI).[162]

4.3. RESULTS

4.3.1. Study population

The final cohort included 70,979 children with anxiety initiating an SSRI (Figure 4.2). The median age of children at SSRI initiation was 14 years (IQR:11-16), 41% of children were male, and a quarter of children had a recent depression diagnosis (Table 4.1). The majority of children initiated on sertraline (39%) followed by fluoxetine (27%), escitalopram (15%), and citalopram (13%) and 88% had an initial SSRI days supply of 30 days with 6% of children initiating with a days supply <30 days.

4.3.2. Child SSRI adherence

The mean 6-month SSRI PDC was 0.72 with 42% of children classified as having low adherence and 58% high adherence (77% of whom had a PDC≥95%, Table 4.2). 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 a co-morbid depression diagnosis. 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) had the lowest. Results were largely consistent across the secondary adherence measures (Table 4.2) with a slightly improved MPR and less with a gap in medication for children with a recent depression diagnosis. Persistence at 6-months was highly correlated with binary PDC (Spearman's

correlation coefficient=0.87). Overall, 56% were persistent to SSRI treatment at 6-months with 20% (n=14,065) of children discontinuing treatment after the initial fill.

4.3.3. Prior parent medication adherence

Overall, two parents were identified in 70% of children. Half (49%) of children (n=34,470/70,979) had at least one parent PDC measure in the year before SSRI initiation. There were 20,268 children (29%) with a parent SSRI PDC (3% had two parent SSRI PDCs), 12,987 children (18%) with a parent statin PDC (1% had two parent statin PDCs), and 15,344 children (22%) with a parent antihypertensive PDC (2% had two parent antihypertensive PDCs). The mean 6-month PDC parent adherence was 0.81 for SSRIs, 0.85 for statins, and 0.88 for antihypertensives.

4.3.4. Child SSRI adherence by parent adherence

The mean SSRI PDC was lower in children with parents with low SSRI adherence than in children with parents with high adherence (mean PDC=0.70 vs. 0.77). Overall 64% of children had high adherence if their parent had high SSRI adherence vs. 53% of children of parents with low SSRI adherence, a 12% difference (95% CI:10-13%, RR=1.23, 95% CI:1.19-1.26). Findings were similar, but slightly attenuated, for parent statin and parent antihypertensive adherence (Table 4.3). When stratified by child age at SSRI initiation and sex of parent with a PDC measure, results were largely consistent (Figure 4.3).

The overall predictive relationship between child and parent adherence remained across the secondary measures of child SSRI adherence (Table 4.4 and 4.5). In the sensitivity analysis, 3% of children without a parent statin adherence measure had a parent with past (1-3 years prior) statin discontinuation; 3% also had past antihypertensive discontinuation. Adherence in children with parents who discontinued medication was similar to parents with low adherence in the prior year, with no changes in the risk differences when grouping past discontinuation with low adherence. Results were also consistent when stratifying by whether one or two parents were identified per child (RR=1.21, 1 parent vs. RR=1.19, 2 parents).

In the full prediction model, parent high adherence independently predicted high child 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 4.3). The parent summary measure, parent high SSRI, statin, or antihypertensive adherence was associated with a 16% increased likelihood of high child adherence. Children with parents with a substance use disorder diagnosis were less likely to be adherent (RR=0.86) and children with parents with a well visit were more likely to be adherent (RR=1.05) (Figure 4.4).

4.3.5. Improvement in prediction

The average increase in the c-statistic when parent-level variables were considered as potential predictors in addition to child-level variables was 0.012 (highest c-statistic=0.65). When allowing for potential interactions between variables, the average increase in the c-statistic after adding parent-level measures was 0.013 (highest c-statistic=0.66). With clinical risk reclassification, 8% with high child adherence saw improved reclassification into predicted probability strata (<40%, 40-70%, and >70%) and 6% had worsened reclassification,(Table 4.6) resulting in an overall positive, but low, NRI of 0.04.

4.4. DISCUSSION

In commercially insured children with anxiety beginning an SSRI, around forty-percent were classified as having low adherence, some a result of early discontinuation. SSRI adherence was higher in children with parents highly adherent to SSRIs, statins, or antihypertensives; overall associations remained when considering parent sex and child age. While adherence is difficult to predict at baseline, parental adherence offers 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.

4.4.1. Child SSRI adherence

In the Child/Adolescent Anxiety Multimodal Study (CAMS) children randomized to sertraline (an SSRI) had high adherence (≥90%) at 12 weeks; however, this estimate was based on pills returned during visits, taken over a shorter period of time, and adherence in trials is typically higher than a general population.[70] To our knowledge, there are limited estimates of SSRI adherence in pediatric anxiety outside the trial setting. In Medicaid enrolled children with depression, 21% were adherent over the first 6 months of antidepressant treatment[21] and in adults with anxiety and no depression, 40% were adherent to SSRIs or SNRIs at 6 months.[94] Both estimates show poorer adherence than we observed, but all demonstrate the prevalence of non-adherence.

We observed the highest adherence in children initiating an SSRI after an OCD diagnosis, with social phobia the next highest. This may be related to more specific guidelines on SSRI treatment length for children with OCD than non-OCD anxiety disorders.[31,125] The lowest adherence was in children initiating an SSRI after a PTSD diagnosis, which could be in part because there is less evidence of SSRI effectiveness in children with PTSD than there is for other pediatric anxiety disorders.[45,163] As such, poor adherence may be the result of higher non-response. 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.

If a child does not respond to SSRI treatment it is recommended another SSRI agent be tried before switching medication classes.[13] When poor adherence is the reason for SSRI non-response, poor adherence will likely remain with the new medication.[95] Therefore, given the amount of non-adherence to SSRIs, as recommended for pediatric ADHD,[164] medication adherence should be assessed in children before altering dosing or medication.

4.4.2 Parent adherence predicting child adherence

Parent adherence to SSRIs, statins, and antihypertensives at baseline was predictive of future SSRI adherence in children with anxiety. Family history of SSRI response can be a factor considered in SSRI selection for a child.[165,166] If family SSRI response is associated with child SSRI response, we may

expect to see higher child SSRI adherence in parents with higher SSRI adherence. This assumes parents with high adherence were more likely to be responders. Additionally high parent SSRI adherence may be a sign the parent has more favorable views on SSRIs, which could translate to improved child SSRI adherence. However, the parallel associations with parent statin and antihypertensive adherence and child SSRI adherence point to other, or additional, explanations for the observed association between parent and child adherence.

Larger unmeasured contextual factors such as pharmacy access, insurance medication coverage and co-payments, refill reminders, relationship with provider, or family socio-economic status[25,96,167,168] affecting both parent and child adherence may contribute, at least in part, to our observed link between parent and child adherence. Parent views or behaviors that influence their own adherence may directly influence their child's adherence, or indirectly if the child shares a parent's views or behaviors. These could include perceived value/acceptability of medications and their side effects, health literacy, or general healthy behaviors. Child views of psychotropic medications has been linked with treatment adherence.[157] This has also been shown for parent views, with higher ADHD medication adherence in children with parents reporting higher perceived psychosocial benefits of medication,[99] higher asthma medication adherence in children with parents who believe the medication was necessary and outweighed medication concerns,[169] and negative parent views on stimulant medications related to the child's willingness to discontinue medication.[100] There is limited evidence for the association between individual health literacy and adherence,[170] including in individuals with anxiety disorders.[171] However, in children with epilepsy, inadequate parent health literacy was associated with more missed medication doses.[172]

Statins and antihypertensives are often used as preventative medications and parents initiating and adhering to these medications may represent parents more likely to partake in other healthy behaviors[173,174] that could influence the parent's care and involvement in his or her child's treatment. Adherent parents may also be accustomed to taking daily medications to manage illness and making regular trips to the pharmacy. Since the association between parent and child adherence held across age groups, even though adolescents are more in control of their medication as parents are recommended to

let the child manage their own medication at this age,[157,175] shared family contextual barriers or shared parent-child behaviors likely contribute to the observed association.

4.4.3. Clinical utility of parent adherence as a predictor

Despite the lack of narrowing in on the specific mechanism that associates parent adherence with child SSRI adherence, parent adherence alone can help a provider predict a child's future SSRI adherence. The clinical utility of using parent adherence to predict child adherence is lessened by the fact that self-reported adherence is often higher than actual adherence.[176] Nevertheless, the results do highlight the important role parents have in their child's care and an important step to addressing adherence could be conversing with parents on their barriers to adherence and whether those barriers will translate to barriers for their child. In the future electronic health records may incorporate family medication utilization, which could help identify children at highest risk for poor adherence. Relatedly, future research could examine the potential benefit of synchronizing family prescription refill schedules to reduce barriers.

The no parent adherence category essentially represents missing information on the parent's medication adherence. This group combines parents who started and already discontinued the medication, were prescribed but never filled the prescription, do not need the medication, or may need but were never prescribed the treatment. Therefore, it is difficult to interpret findings comparing parents with low adherence vs. no use of the medication class. Expanding the research to include additional medication classes and medication use spanning further in the parent history, as our sensitivity analysis touched on, would reduce the number of children without parent adherence information.

More broadly, parent adherence could potentially be used for adjustment in pharmacoepidemiologic studies to proxy for contextual factors and familiar-level behaviors not captured through child-level claims.

4.4.4. Limitations

Our study has a number of strengths including using objective adherence measures for the parent and child as parents have been shown to overestimate adherence in children,[164,177] measuring parent adherence prior to the child beginning medication treatment, and comprising a large population of commercially insured children in standard care. However, some limitations should be considered. We use the term 'parent' throughout; however, the beneficiary could be a much older sibling or another individual on the insurance plan and may not be an individual the child considers a caretaker or an individual with involvement in the child's medication care. In some instances low adherence values are blended with discontinuation. The reason for SSRI discontinuation may have been appropriate; the FDA antidepressant black-box warning could have been associated with early discontinuation. We evaluated parent adherence to three medication classes with multiple indications; the association between parent adherence and child SSRI adherence may not hold across other medication classes. Additionally, parent adherence was relatively high in our population. This is partially because we did not require parents to be new users of medications and thereby include prevalent users who have demonstrated some consistent medication use. Parent adherence was the highest to antihypertensives (ACEs, ARBs, thiazides); the PDC measure could have been inflated in parents with multiple medications within the antihypertensive class. Our measures of child and parent adherence are based on dispensed prescriptions and not on taking the medication; we used a PDC at 80% to define high vs. low adherence, which may not be a clinically relevant cut-point for all cases.

Adherence measures relied on correct days supply values of dispensed prescriptions, incorrect values could have resulted in over or under-estimation of adherence; however, this would not necessarily result in misclassification of binary adherence measures. Incorrect entry of days supply values could be pharmacy specific, which would likely be shared by the child and parent. Two-percent of children were identified as a potential sibling to another child in the cohort (same insurance plan) who separately met inclusion requirements; we assume correlation with high child adherence to remain low given the infrequent occurrence of siblings and that adherence is associated with many factors. Our risk

reclassification results are sensitive to the predicted probability strata we selected. We are unaware of a validation study in MarketScan on the accuracy of enrollment identification variables in linking family members.

4.4.5. Conclusion

Low SSRI adherence in a large population of commercially insured children with anxiety was relatively common. Consequently, adherence should be prioritized and evaluated during follow-up visits. High parental adherence to chronic medications at baseline was predictive of high SSRI adherence in children with anxiety; the observed predictability could be related to specific parent, or shared child-parent, views or behaviors or contextual factors that affect adherence in both the parent and child. Parental adherence may offer a way to enhance prediction of child SSRI adherence at baseline in children with anxiety, with the hope of ultimately improving child SSRI adherence.

Table 4.1. Characteristics of children with 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]			
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%)
Multiple specific diagnoses	1,742 (2.5%)	1,139 (2.8%)	603 (2.0%)
Social phobia	1,743 (2.5%)	1,112 (2.7%)	631 (2.1%)
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	2,325 (3.3%)	1,385 (3.4%)	940 (3.1%)
Other type	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 use, prior year[d]			
None	33,322 (46.9%)	16,928 (41.3%)	16,394 (54.7%)
1-4 claims	17,318 (24.4%)	10,693 (26.1%)	6,625 (22.1%)
5+ claims	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 depression 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 depression diagnosis	49,954 (70.4%)	28,949 (70.6%)	21,005 (70.0%)
Adjustment disorder	11,836 (16.7%)	7,352 (17.9%)	4,484 (14.9%)
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%)
Sleep disorder	3,706 (5.2%)	1,987 (4.8%)	1,719 (5.7%)
Substance use disorder	2,223 (3.1%)	895 (2.2%)	1,328 (4.4%)
Medication use in prior year			
Count of therapeutic prescription groups	3 (2-5)	3 (2-5)	3 (2-5)

0-1	26,090 (36.8%)	15,474 (37.8%)	10,616 (35.4%)
2-3	24,136 (34.0%)	14,063 (34.3%)	10,073 (33.6%)
4+	20,753 (29.2%)	11,445 (27.9%)	9,308 (31.0%)
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%)
ADHD medication	13,867 (19.5%)	7,907 (19.3%)	5,960 (19.9%)
Psychological diagnosis, evaluation[f]	40,815 (57.5%)	25,671 (62.6%)	15,144 (50.5%)
Parent-level characteristics[a]			
Male parent	59,609 (84.0%)	34,995 (85.4%)	24,614 (82.1%)
Female parent	61,002 (85.9%)	35,893 (87.6%)	25,109 (83.7%)
Parent age, median (IQR)	45 (40-49)	45 (41-49)	44 (40-49)
Parent 50+ years	20,130 (28.4%)	11,976 (29.2%)	8,154 (27.2%)
Psychiatric diagnoses			
Anxiety	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; 'recent' refers to the 30-day period before SSRI initiation

[a]Child and parent level characteristics are defined from inpatient and outpatient diagnoses and procedures and outpatient dispensed prescriptions

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

[d]Psychotherapy CPT codes based on recorded claims: 90804, 90816, 90806, 90818, 90808, 90821, 90810, 90823, 90812, 90826, 90814, 90828, 90805, 90817, 90807, 90819, 90809, 90822, 90811, 90824, 90813, 90827, 90815, 90829, 90847, 90849, 90853, 90857, 90832, 90834, 90837, 90833, 90836, 90838, 90853, 90839

[e]Psychaitric co-morbidity definitions with ICD-9-CM codes: Any psychiatric diagnosis (290-319.x); specific depression diagnosis (296.2x, 296.3x, 300.4x, 309.1x); general depression diagnosis (311.x); Adjustment disorder (309.0x, 309.22-309.29, 309.3x, 309.4x, 309.82-309.89, 309.9x,); ADHD (314.x); Disruptive behavior, conduct disorder (312.x, 313.81); Other episodic mood disorder (296.9x); Sleep disorder (307.4x, 327.x, 347.x, 780.5x); Substance use disorder (291-292.x, 303-305.x)

[f]Defined with recorded CPT codes: 90801, 90802, 90791, 90792

Table 4.2. SSRI adherence in children with anxiety: Six-month proportion days covered (PDC) and secondary adherence measures

	No. Children	6-month mean PDC (95% CI)	High adherence (PDC≥0.80)		Secondary adherence measures				
					Persistent at 6 months[b]	No. with two SSRI fills[a]	Mean MPR[a]	High MPR (≥0.80)[a]	20+ day gap between 1st and 2nd fill[a]
			No.	%	%			%	%
Overall	70,979	0.72 (0.72-0.73)	40,982	58%	56%	61,070	0.86	73%	11.2%
Age group									
3-9 years	11,192	0.76 (0.76-0.77)	7,113	64%	61%	9,785	0.88	77%	11.0%
10-13 years	19,070	0.76 (0.76-0.77)	11,986	63%	61%	16,961	0.87	74%	10.6%
14-17 years	40,717	0.70 (0.69-0.70)	21,883	54%	51%	34,324	0.86	72%	11.6%
Anxiety disorder									
Unspecified anxiety	34,220	0.71 (0.70-0.71)	18,985	55%	53%	28,958	0.86	72%	11.6%
Generalized anxiety disorder	18,094	0.74 (0.74-0.75)	10,879	60%	58%	15,900	0.87	74%	11.0%
OCD	6,251	0.79 (0.78-0.79)	4,184	67%	65%	5,623	0.89	78%	9.8%
Panic disorder	3,221	0.68 (0.67-0.69)	1,688	52%	50%	2,642	0.86	71%	12.4%
PTSD	2,808	0.65 (0.63-0.66)	1,267	45%	43%	2,325	0.84	69%	14.1%
Social phobia	1,743	0.77 (0.76-0.78)	1,112	64%	62%	1,577	0.87	75%	9.0%
Other anxiety disorder[c]	4,642	0.75 (0.74-0.76)	2,867	62%	59%	4,045	0.87	75%	10.4%
Co-morbid recent depression[d]									
Depression	17,942	0.73 (0.72-0.73)	10,355	58%	55%	15,678	0.87	75%	9.7%
No depression	53,037	0.72 (0.72-0.73)	30,627	58%	56%	45,392	0.86	73%	11.7%

OCD: obsessive-compulsive disorder; PTSD: Post-traumatic stress disorder; PDC: proportion days covered; MPR: modified medication possession ratio; CI: confidence interval

[a]Restricted to children with a second SSRI fill within 6-months, n=61,070 (86%); 4,156 of those children had a gap of more than 30 days before the 2nd fill

[b]Persistence at 6-months is highly correlated with a 6-month PDC≥0.80

[c]Children with multiple specific diagnoses included

[d]Depression diagnosis (ICD-9-CM: 296.2x, 296.3x, 300.4x, 309.1x, 311.x) in the 30 days before SSRI initiation

Table 4.3. Child SSRI adherence stratified by parent prior medication adherence (6-month PDC)[a]

	No. Children	Mean child PDC (95% CI)	Child high SSRI adherence (PDC≥0.80)				
			No.	%	Crude % Diff. (95% CI)	Crude prediction RR (95% CI)	Multivariable prediction[c] aRR (95% CI)
Parent SSRI adherence							
Low	6,585	0.70 (0.69-0.70)	3,463	53%	REF	REF	REF
High[c]	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)
No SSRI 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)
Parent statin adherence							
Low	3,323	0.70 (0.69-0.71)	1,817	55%	REF	REF	REF
High[c]	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)
No statin use	57,992	0.72 (0.72-0.72)	32,964	57%	2% (0-4)	1.04 (1.01-1.07)	1.02 (0.98-1.05)
Parent antihypertensive adherence							
Low	2,958	0.69 (0.67-0.70)	1,530	52%	REF	REF	REF
High[c]	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)
No antihypertensive 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)
Parent adherence (overall)							
Low	10,312	0.69 (0.69-0.70)	5,429	53%	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)
No adherence value	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)

PDC: proportion days covered; REF: reference; CI: confidence interval

[a]Parent low adherence: 6-month PDC<0.80, high adherence: PDC≥0.80, no use: neither parent had a prescription in that medication class in the 6 to 12 months before the child initiated an SSRI (no 6-month PDC able to be calculated)

[b]Results for alternative adherence calculation: selected higher parent PDC measure when both parents had available PDC, parent high vs. low adherence: parent SSRI adherence: RD=13% (95%CI:11-14), 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:6-11), RR=1.15 (95%CI:1.11-1.20)

[c]Full model with child and parent-level variables with >2% prevalence

Table 4.4. Child SSRI 6-month persistence stratified by prior parent medication adherence[a]

	No. Children	Children persistent at 6-months			
		No.	%	Crude % diff. (95% CI)	Crude prediction RR (95% CI)
Parent SSRI adherence					
Low	6,585	3,372	51%	REF	REF
High	13,683	8,447	62%	11% (9-12)	1.21 (1.17-1.24)
No SSRI use	50,711	27,598	54%	3% (2-5)	1.06 (1.04-1.09)
Parent statin adherence					
Low	3,323	1,759	53%	REF	REF
High	9,664	5,918	61%	8% (6-10)	1.16 (1.12-1.20)
No statin use	57,992	31,740	55%	2% (0-4)	1.03 (1.00-1.07)
Parent antihypertensive adherence					
Low	2,958	1,460	49%	REF	REF
High	12,386	7,110	57%	8% (6-10)	1.16 (1.12-1.21)
No antihypertensive use	55,635	30,847	55%	6% (4-8)	1.12 (1.08-1.17)
Parent adherence (overall)					
Low	10,312	5,266	51%	REF	REF
High	24,167	14,572	60%	9% (8-10)	1.18 (1.16-1.21)
No adherence value	36,500	19,579	54%	3% (2-4)	1.05 (1.03-1.07)

PDC: proportion days covered; REF: reference; CI: confidence interval; RR: risk ratio

[a]Parent low adherence: 6-month PDC<0.80, high adherence: PDC≥0.80, no use: neither parent had a prescription in that medication class in the 6 to 12 months before the child initiated an SSRI (no 6-month PDC able to be calculated)

Table 4.5. Secondary measures of child SSRI adherence among children with 2 SSRI fills stratified by prior parent medication adherence[a]

	No. Children with 2 SSRI fills	Mean child MPR	Child high MPR (≥0.80)				Children with 20+ day gap between 1st and 2nd fill			
			No.	%	Crude % Diff. (95% CI)	Crude prediction RR (95% CI)	No.	%	Crude % Diff. (95% CI)	Crude prediction RR (95% CI)
Parent SSRI adherence										
Low	5,612	0.83	3,750	67%	REF	REF	797	14%	REF	REF
High	12,293	0.87	9,075	74%	7% (6, 9)	1.10 (1.08-1.12)	1,314	11%	-4% (-5, -3)	0.75 (0.69-0.82)
No SSRI use	43,165	0.87	31,843	74%	7% (6, 8)	1.10 (1.08-1.13)	4,729	11%	-3% (-4, -2)	0.77 (0.72-0.83)
Parent statin adherence										
Low	2,819	0.85	1,962	70%	REF	REF	341	12%	REF	REF
High	8,581	0.88	6,565	77%	7% (5, 9)	1.10 (1.07-1.13)	831	10%	-2% (-4, -1)	0.80 (0.71-0.90)
No statin use	49,670	0.86	36,141	73%	3% (1, 5)	1.05 (1.02-1.07)	5,668	11%	-1% (-2, 1)	0.94 (0.85-1.05)
Parent antihypertensive adherence										
Low	2,487	0.84	1,688	68%	REF	REF	311	13%	REF	REF
High	10,742	0.87	7,971	74%	6% (4, 8)	1.09 (1.06-1.13)	1,136	11%	-2% (-3, -1)	0.85 (0.75-0.95)
No antihypertensive use	47,841	0.86	35,009	73%	5% (3, 7)	1.08 (1.05-1.11)	5,393	11%	-1% (-3, 0)	0.90 (0.81-1.00)
Parent adherence (overall)										
Low	8,758	0.84	5,963	68%	REF	REF	1,155	13%	REF	REF
High	21,342	0.87	16,053	75%	7% (6, 8)	1.10 (1.09-1.12)	2,192	10%	-3% (-4, -2)	0.78 (0.73-0.83)
No adherence value	30,970	0.86	22,652	73%	5% (4, 6)	1.07 (1.06-1.09)	3,493	11%	-2% (-3, -1)	0.86 (0.80-0.91)

MPR: modified medication possession ratio; REF: reference; CI: confidence interval; RR: risk ratio

[a]Parent low adherence: 6-month proportion days covered (PDC)<0.80, high adherence: PDC≥0.80, no use: neither parent had a prescription in that medication class in the 6 to 12 months before the child initiated an SSRI (no 6-month PDC able to be calculated)

Table 4.6. Clinical risk reclassification of the predicted probabilities of high child SSRI adherence

Predicted probabilities of high child SSRI adherence							
	Model with child + parent variables						
Children with high adherence	<40%		40-70%		>70%		
Model with child-level variables	No.	%, row	No.	%, row	No.	%, row	Total No.
<40%	1,380	73%	502	27%	0	0%	1,882
40-70%	845	3%	27,262	88%	2,804	9%	30,911
>70%	0	0%	1,545	19%	6,644	81%	8,189
Total No.	2,225		29,309		9,448		40,982
Children with low adherence	<40%		40-70%		>70%		
Model with child-level variables	No.	%, row	No.	%, row	No.	%, row	Total No.
<40%	2,953	84%	571	16%	0	0%	3,524
40-70%	1,414	6%	21,104	90%	1,027	4%	23,545
>70%	0	0%	703	24%	2,225	76%	2,928
Total No.	4,367		22,378		3,252		29,997

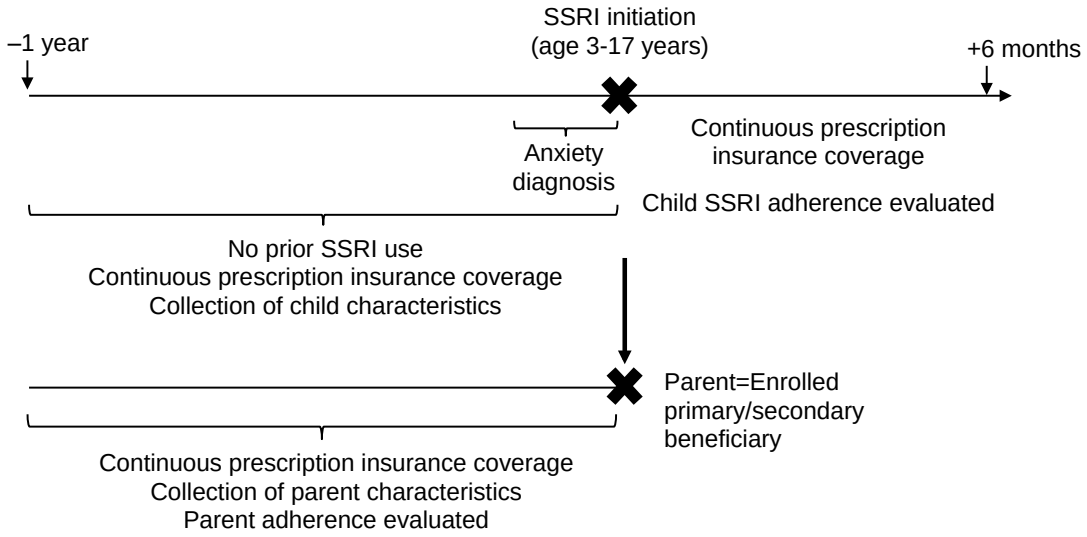


Figure 4.1. Aim 2 study schematic

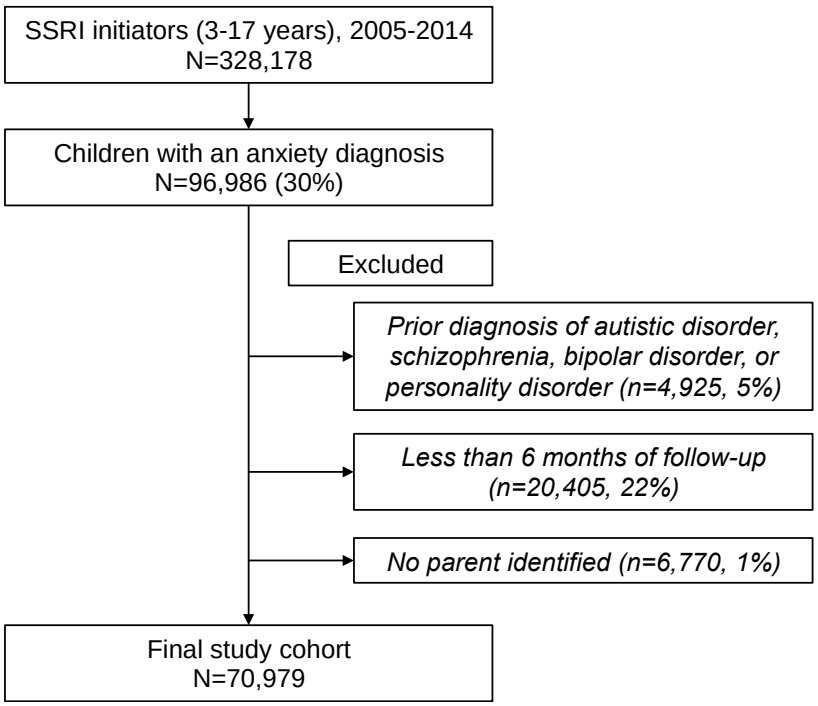


Figure 4.2. Aim 2 study cohort inclusion criteria

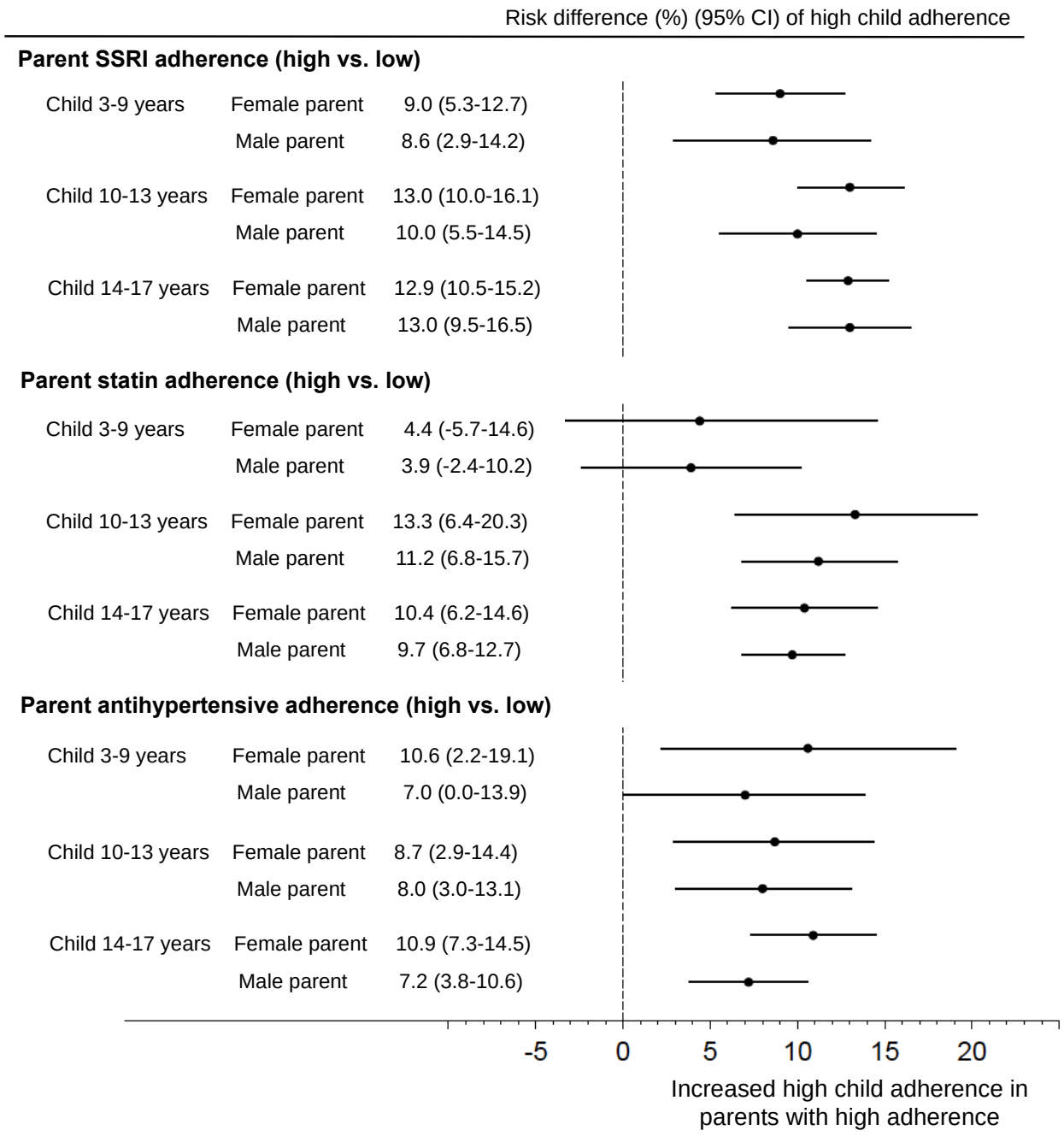
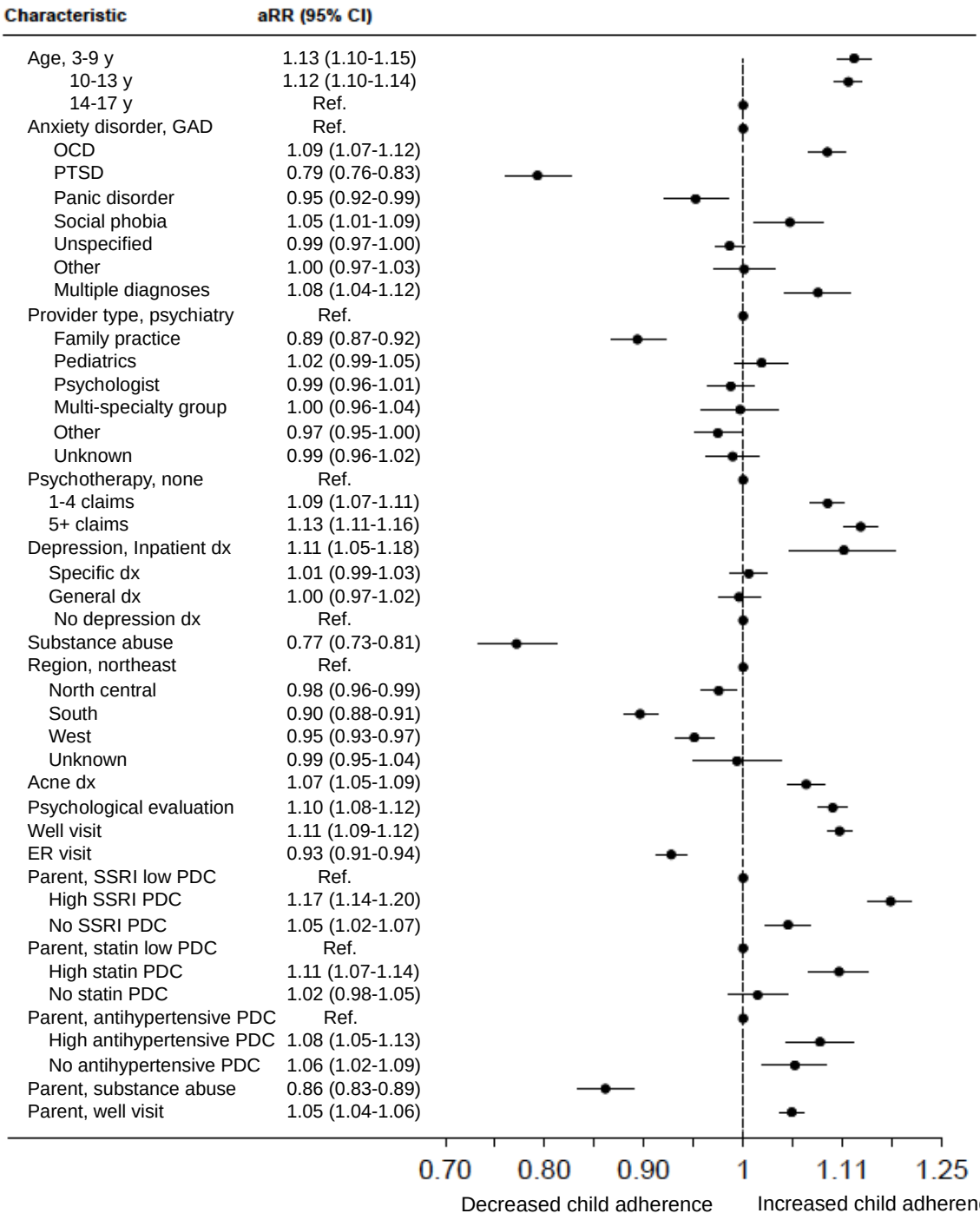


Figure 4.3. Difference in the proportion of children with high SSRI adherence by parent high vs. low adherence: Stratified by parent sex, parent medication class, and child age[a]



PDC: proportion days covered; Ref.: reference; RR: risk ratio; dx: diagnosis

[a]Multivariable, full model with all child and parent-level variables with >2% prevalence; Variables with less than 5% change in multivariable RR (i.e. 0.952<RR <1.05) not displayed and include (multivariable RR): female (1.04), prior contact with psychiatrist (1.03), ICD-9 codes for potential anxiety-related symptoms (0.97), 3+ anxiety diagnoses before SSRI initiation (1.04), adjustment disorder diagnosis (1.00), ADHD diagnosis (0.96), development delay/learning disability diagnosis (1.03), disruptive behavior/oppositional defiant disorder diagnosis (0.96), other episodic mood disorder diagnosis (1.00), sleep disorder diagnosis (0.97), antidepressant (0.97), benzodiazepine (0.99), ADHD medication (0.98), antipsychotic (1.02), hydroxyzine (0.95), opioid (0.97), prescription medication use (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), 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), injury: fracture/sprain (0.99), injury: head injury (0.95), injury: other (0.98), 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)

Figure 4.4. Multivariable predictability of high (PDC≥0.80) child SSRI adherence with child and parent characteristics included[a]

CHAPTER 5: INCIDENCE OF MENTAL HEALTH HOSPITALIZATIONS, INPATIENT TREATED SELF-HARM, AND EMERGENCY ROOM VISITS FOLLOWING A NEW ANXIETY DIAGNOSIS IN CHILDREN AND ADOLESCENTS, UNITED STATES 2005-2014

5.1. INTRODUCTION

Anxiety disorders are one of the most common mental illnesses in children and adolescents with estimates of current worldwide prevalence from 2%[1] to 7%.[2] In the United States (US) estimates of the lifetime prevalence of pediatric anxiety range from 15-20%[3,28] with a third of individuals having an anxiety disorder by age 75.[11] Symptoms of anxiety disorders often begin during childhood,[10,11] making childhood an important age to consider the effects of anxiety. Children with anxiety disorders are at a heightened risk for subsequent anxiety disorders, depression, alcohol use, and substance abuse.[6-9,31,37]

Anxiety disorders can have a sustained impact on daily life, ranking 23rd in causes of global disability-adjusted life years (DALYs) in children[4] and individuals with anxiety disorders have demonstrated high utilization of healthcare services.[32,102-104] In 2013, anxiety disorders were 20th in conditions with the largest personal health care spending in the US for children <20 years of age, totaling 3.4 billion US dollars with 8.3% spent in inpatient settings, 3.8% on pharmaceuticals, and 82.1% in ambulatory care.[178]

Emergency room (ER) visits, mental health related hospitalizations, and self-harm events are serious events that place a significant burden on the patient, caregivers, or healthcare system.[102,106,107,179,180] In 2010 suicide was the 4th leading cause of death in children 5-14 years, 3rd in children 15-24 years.[109] While the causal effect of anxiety on suicide in children is not established, anxiety has been shown to be a risk factor for suicide related behaviors in children.[113] In 2011 the rate of inpatient hospitalizations related to mental health in children was 26/10,000 with a mean cost of $5,805 per hospitalization and mean length of stay of 7 days.[108] While relatively uncommon in the overall population, mental health related hospitalizations occurred in 7% of Medicaid enrolled children with a

mental health diagnosis.[106] ER visits are common in children, with 18% of US children having an ER visit in a year period,[109] injury being a common cause for pediatric ER visits.[111] Between 2009 to 2011, around 1.2 million ER visits for anxiety occurred with 6% of occurring in children under 18 years.[103]

Previous important work has described how many serious events are related to anxiety,[108] but there is less work longitudinally evaluating how many children with anxiety typically experience one of these events. Describing the risk of serious, impactful events in children newly diagnosed with an anxiety disorder can help inform clinicians, caregivers and patients at a time when information may be particularly sought-after. This information can contribute to the clinician's larger discussion with caregivers and patients on the importance of managing symptoms, when to seek additional care, and the impact of co-morbid psychiatric conditions. Additionally, comparing the risk of events in children with anxiety vs. similar children without anxiety can provide context to further guide expectations and focus research efforts.

Therefore, in a cohort of commercially insured children newly diagnosed with anxiety in an office setting we aimed to estimate the risk of mental health related hospitalizations, inpatient treated self-harm, and ER visits overall and by age and the presence of psychiatric co-morbidities. We also estimated the incidence of these events in a similar population of commercially insured children without diagnosed anxiety.

5.2. METHODS

5.2.1. Datasource & study population

We used Truven Health Analytics' MarketScan Commercial Claims and Encounters database. We utilized data from January 1, 2004 to December 31, 2014, including inpatient admissions and services, outpatient services, outpatient dispensed prescriptions, and health plan enrollment files.

We identified a population of children (3-17 years) newly diagnosed with an anxiety disorder from 2005-2014. We selected the first anxiety diagnosis recorded in database history (2004-2014). An anxiety diagnosis was defined as an ICD-9-CM code (293.84, 300.0x, 300.2x, 300.3x, 309.21, 309.81, 313.23) corresponding to anxiety disorders in the Diagnostic and Statistical Manual of Mental Disorders,

Fourth Edition (DSM-IV)[181] which included post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD). We required children to have at least one year of continuous insurance enrollment (with prescription benefits and mental health services coverage) prior to the first observed anxiety diagnosis; this was to increase the likelihood that we identified a new anxiety diagnosis (Figure 5.1). For example, this requirement removed children with a first anxiety diagnosis in the few months after insurance coverage began, since with the limited history we cannot determine if that diagnosis represented a new diagnosis. We excluded children with a diagnosis of bipolar disorder (296.0x, 296.4x-.8x), personality disorder (301.x), schizophrenia (295.x), and autistic disorder (299.00) as it is likely that children with these conditions have more complex history and treatment regimens with anxiety a secondary diagnosis.

We additionally excluded children with anxiety-related treatments in the year before their new anxiety diagnosis as we aimed to identify children naïve to anxiety treatment. We excluded children with a dispensed SSRI prescription or a recorded psychotherapy session (CPT code) in the year prior to the new anxiety diagnosis. We further excluded children with a benzodiazepine, buspirone, other antidepressant, hydroxyzine, or antipsychotic prescription in the prior year as these can be used to treat anxiety, and antipsychotics are used to treat some of the co-morbid conditions we excluded. We did allow other baseline prescription medications that are sometimes used to treat anxiety (ex. beta-blockers, anticonvulsants, clonidine/guanfacine) since these medications are rarely used as an initial anti-anxiety pharmacotherapy(Chapter 1) and have primary non-anxiety indications.

Finally, the cohort was restricted to children with a new anxiety diagnosis in an office setting (83%). This restriction was to focus on a more similar, clinically relevant subset of children and exclude children diagnosed with anxiety outside an office (i.e. inpatient hospitalization, ER visit, urgent care) who likely had a different trajectory leading to their diagnosis.

Incident event definitions

Children were followed beginning the day after their new office-based anxiety diagnosis for up to 2 years. We identified the first event of interest per child. A mental health related hospitalization was defined as an inpatient admission record with a psychiatric diagnosis (ICD-9-CM code=290-319) in any placement on the inpatient admission record. For a secondary definition we defined a mental health related hospitalization as an inpatient admission record with a psychiatric diagnosis in the primary diagnostic position.[182] A treated self-harm event was defined as an inpatient record with an ICD-9-CM external cause code (E-codes: E950-E958) for intentional suicide and self-inflicted injury.[183-185] For another secondary outcome we examined recorded suicide ideation (ICD-9 code=V62.84, available late 2005) to observe how often the code was used, acknowledging very low sensitivity.[186]

ER visits were defined as a claim with a category of service designated as an ER.[187] Anxiety-related ER visits were defined as ER visits with a diagnostic code for an anxiety disorder used to define anxiety in the patient population or a diagnostic code for adjustment disorder with anxiety (309.24, 309.28) or acute stress disorder (308.x). Injury-related ER visits (including poisoning) were defined broadly as ER visits with an ICD-9-CM diagnostic code 800-999,[182] excluding late effects of injuries (905-909), or E800-999, excluding late effects (E929, E959, E969, E977, E989, E999) and E849 (place of the injury).

5.2.2. Comparison cohort

A comparison cohort included children in the same database who matched with a child in the anxiety cohort on age, sex, date (defined as a recorded diagnostic code on the date a child was diagnosed with anxiety, termed "match date" for the comparison cohort), and region (Figure 5.1). From all possible matches (15 million children), the same inclusion requirements used to define the anxiety cohort were applied: 1) prior year with prescription and mental health services insurance coverage, 2) no diagnosis of anxiety prior to or on the match date, 3) no psychotherapy, SSRI, benzodiazepine, buspirone, other antidepressant, antipsychotic, or hydroxyzine use in the prior year, 4) no diagnosis of schizophrenia, personality disorder, autistic disorder, and bipolar disorder, and 5) at least one diagnosis on the match

date from an office setting. From the remaining possible matches (8 million children) we randomly selected up to 10 matches per child with anxiety. A child in the comparison cohort was only allowed to match once even if they matched to multiple children. Children in the anxiety cohort were allowed in the comparison cohort if they matched to a period before their anxiety diagnosis (3% of the comparison cohort were children from the anxiety cohort). We defined and collected covariates and incident events in the same manner for the comparison cohort as the anxiety cohort.

5.2.3. Primary patient covariates

For each child, age, sex, year of first anxiety diagnosis (or year of match date), and provider of first anxiety diagnosis (or provider of diagnoses on match date) were included. For children with anxiety we grouped children by the specific anxiety disorder diagnosis. In the year prior to a child's new anxiety diagnosis (or match date), we created indicators for psychiatric and non-psychiatric co-morbidities, inpatient and outpatient visits, ER visits, and medication use. A primary variable of interest was psychiatric co-morbidity, defined as 1) no psychiatric co-morbidity diagnosis in the prior year, 2) co-morbid depression diagnosis in the prior year (inpatient or outpatient ICD-9-CM code=296.2x, 296.3x, 300.4x, 309.1x, or 311.xx), and 3) a non-depression psychiatric co-morbidity (ICD-9-CM: 290-319, excluding anxiety and depression diagnoses). As the study cohort is restricted to treatment naïve children, a proportion of children previously treated for depression or other psychiatric co-morbidities were, by default, excluded. The primary covariates were used to describe the study population, as stratification criteria, and to compare the anxiety cohort with the comparison cohort.

5.2.4. Statistical analysis

We described the cohort of children newly diagnosed with anxiety and the comparison cohort. We used Kaplan Meier estimator to estimate the cumulative incidence and associated 95% confidence interval (CI), of each incident event. Children were censored at the occurrence of the first event, insurance disenrollment, end of data (12/31/2014), or 2 years after the anxiety diagnosis (or match date). The cumulative incidence was reported at 1 month, 6 months, and 1 year after the anxiety diagnosis (or match date) and displayed up to 2 years. We stratified results by age group and psychiatric co-morbidity. For the

comparison cohort we only present the stratification with no baseline psychiatric co-morbidities, given the low prevalence of psychiatric co-morbidities. The analysis for recorded suicide ideation was restricted to children diagnosed with anxiety (or match date) from 2006-2014 since the ICD-9 code was not available until late 2005. For a sensitivity analysis we examined the incidence in a cohort of children with a second anxiety diagnosis in the 3 months after their first diagnosis, as 1 diagnostic code may not represent a true diagnosis, i.e. claim was rule-out diagnosis, data entry error, or patient referred to specialist for assessment and not subsequently diagnosed.[188]

5.3. RESULTS

From 2005-2014 there were 198,450 children with a new anxiety diagnosis in an office setting without prior anxiety treatment. Children had a median age of 12 years (IQR: 8-15 years) and 45% were male (Table 5.1). The majority had a new anxiety diagnosis of unspecified anxiety (53%), followed by 25% diagnosed with generalized anxiety disorder then 5% with OCD and 4% with PTSD. A psychiatrist or psychologist/therapist was associated with the anxiety diagnosis in 46% of children followed by 21% diagnosed by a pediatrician. Six-percent of children had a baseline depression diagnosis, with 86% of them having a depression diagnosis at least 30 days prior to the anxiety diagnosis. The average length of follow-up insurance enrollment was 558 days (IQR: 233-1164) in the anxiety cohort and 658 days (IQR: 337-1213) in the comparison cohort.

For the comparison cohort, 10 matches were identified for >99% children in the anxiety cohort. The comparison cohort had a lower baseline prevalence of psychiatric co-morbidities, medication utilization, outpatient visits, and selected non-psychiatric co-morbidities (Table 5.1). Of the top 70% most common ICD-9 diagnoses recorded on the match date, 37% had a code related to a vaccination or routine visit/exam, 3% were psychiatric diagnoses, 8% were injury/pain related diagnoses, 32% related to general acute concerns (ex. fever, ear infection, common cold), 8% were related to conditions likely requiring repeat visits but less severe (ex. acne, skin infection, chronic rhinitis), and 11% diagnoses for potentially for more chronic, severe conditions (ex. asthma, obesity, unspecified chest pain).

5.3.1. Cumulative incidence in children with diagnosed anxiety

Table 5.2 displays the 1-month, 6-month, and 1-year cumulative incidence of each event in children with anxiety (Figure 5.2, 5.3). One-year after a new anxiety diagnosis 2.0% of children had a mental health related hospitalization. The incidence lowers slightly to 1.7% (95% CI: 1.6-1.8) when restricting to hospitalizations with a mental health diagnosis listed in the primary position. Around 6 per 10,000 (0.06%) children had an inpatient, treated self-harm event 6-months after a new anxiety diagnosis and 8 per 10,000 by 1 year. A recorded suicide ideation claim occurred in 1.0% of children in the year after an anxiety diagnosis. ER visits were common with 12% of children having an ER visit within 6-months and 20% within 1 year. Anxiety-related ER visits occurred in 1.4% of children a year after a new anxiety diagnosis.

5.3.2. Cumulative incidence in the comparison cohort

In the comparison cohort, the cumulative incidence of each outcome was lower than in children with anxiety (Table 5.2, Figures 5.2, 5.3). One-year after the match date 0.5% of children had a mental health related hospitalization. Around 1 in 10,000 children had an inpatient treated self-harm event by the end of one-year. The incidence of an ER visit was 8% at 6-months and 13% at 1-year and injury related ER visits at 4% and 7% respectively.

5.3.3. Age and psychiatric co-morbidity stratification

The cumulative incidence of each event varied by age at anxiety diagnosis and the presence of baseline psychiatric co-morbidities (Table 5.3: 1-year incidence). The incidence of mental health related hospitalizations (6-months: 5.1%, 95% CI:4.6-5.6), inpatient treated self-harm events (6-months: 0.43%, 95% CI:0.30-0.60), and anxiety-related ER visits (6-months: 2.2%, 95% CI:1.9-2.6) following a new anxiety diagnosis occurred more frequently in children 14-17 years with co-morbid depression compared to other ages and co-morbidity groups (Figure 5.4). In turn, in children 14-17 years without a psychiatric co-morbidity diagnosed at baseline, the incidence of mental health related hospitalizations at 6-months was 1.6% (95% CI:1.5-1.7), inpatient treated self-harm events 0.07% (95% CI:0.05-0.10), and anxiety-related ER visits 1.4% (95% CI:1.3-1.5).

Restricting the comparison cohort to children without any baseline psychiatric co-morbidity (N=1,805,682, 91%), the cumulative incidence of events remained lower than in children with anxiety and no psychiatric c-morbidity (Table 5.3).

5.3.4. Sensitivity analysis

In children with a second recorded anxiety diagnosis at least 90 days after the first diagnosis (n=113,437, 57%), the incidence of ER visits overall and injury related ER visits was similar in children without a follow-up anxiety diagnosis within 90 days (n=85,013). There was an increased cumulative incidence in inpatient treated self-harm events, mental health related hospitalizations, and anxiety related ER visits in children with a second, follow-up anxiety diagnosis (Table 5.4). For example, 2.4% (95% CI: 2.3-2.5) had a mental health related hospitalization 1 year after a new anxiety diagnosis in the cohort with a second anxiety diagnosis compared to 1.3% (95% CI: 1.2-1.4) in children with one anxiety diagnosis.

5.4. DISCUSSION

Serious, high healthcare utilizing events were relatively common in the months after children were newly diagnosed with anxiety in an office setting. Older children with co-morbid depression had a higher incidence of mental health related hospitalizations, anxiety-related ER visits, and inpatient treated self-harm events. However, these events still occurred in children with anxiety and no baseline psychiatric co-morbidity and at a higher incidence than in a similar population of children without anxiety. Our findings add to the literature on pediatric anxiety to inform patients, caregivers, and providers at a time when understanding the condition and future risks may be particularly useful.

5.4.1. Variation by age and psychiatric co-morbidity

We observed a higher incidence of treated self-harm, mental health related hospitalizations, and ER visits in older children. This is consistent with previous findings; the rate of ER visits for anxiety or stress disorders in children increased substantially by age with the rate in children 10-14 years 6-fold higher than children 5-9 years, and even higher for children 15-17.[180] In another example, anxiety-related ER visits occurred at a rate of 0.8 per 1,000 children <15 years of age and 5.4 per 1,000 aged 15-19 years.[189] The rate of self-harm injury also increases with age (i.e. 2012-2014 rate: age 5-9 years: 4 per

100,000; age 10-14: 154 per 100,000, 15-19: 390 per 100,000).[190] To note, we measure age at a new, recorded anxiety diagnosis and we do not know the age when symptoms began.

Children with a baseline depression diagnosis prior to or on the date they received a new anxiety diagnosis had a higher risk for the events considered than children without co-morbid depression. This is consistent with other research including higher reported medical costs in individuals with anxiety and co-morbid depression compared to individuals with only anxiety.[191] Co-morbid depression is highly prevalent in those with anxiety[192] with depressive disorders most often developing secondary to pediatric anxiety.[9] Given our baseline restrictions (no prior antidepressants and psychotherapy) and that we examined children with a new anxiety diagnosis, only 6% of children in our cohort had diagnosed depression. Depression is especially associated with self-harm events[193] and monitoring suicide risk in children with anxiety and co-morbid depression is recommended.[31] While inpatient treated self-harm events were much less common in children without a co-morbid depression diagnosis at baseline, they did occur in a small number. The prevalence of depression is expected to increase over time and understanding if and when depression symptoms developed in children would further inform the results.

Further, baseline anxiety severity, which we cannot directly measure, would be another important factor to consider in addition to age and psychiatric co-morbidity. We saw a higher incidence of mental health related events in children with a follow-up anxiety diagnosis. Children with a recorded follow-up anxiety diagnosis may have higher baseline severity. Children without a follow-up anxiety diagnosis within 3 months may include children with more mild anxiety, but also children with moderate to severe anxiety that do not receive follow-up care.

5.4.2. Comparison cohort considerations

Prior studies found serious events to occur more frequently in individuals with anxiety disorders compared to individuals without anxiety. For example, adults with anxiety had higher mental-health related inpatient admissions, inpatient visits, and ER visits than controls,[104,194] including adults with anxiety and no co-morbid depression.[104] In Denmark, the incidence of death by suicide was 0.61% over 15 years in adults with PTSD compared to 0.04% in the comparison cohort.[115] Not specific to anxiety

disorders, 34% of Medicaid enrolled children (0-21 years) with a mental health diagnosis had an ER visit in 1999 compared to 20% in other enrolled children.[106]

Some of the observed differences in incidence between the anxiety and comparison cohorts could be related to baseline differences in co-morbidities, as the anxiety cohort had higher recorded co-morbidities and prior healthcare utilization. In the literature, selected comorbidities were higher in adults with anxiety than control groups[104,194] along with a higher Charlson comorbidity index prior to a stress disorder diagnosis compared to a control group.[115] Relatedly, we do not investigate a causal relationship between anxiety and the events considered; the differences in the cumulative incidences between the anxiety and comparison cohorts should not be interpreted causally. While we have the date of a new anxiety diagnosis, we do not know when anxiety first developed and cannot ensure temporality for baseline covariates. For example, somatic symptoms are common in children with anxiety and can include chest pain, abdominal pain/stomachaches, and headaches.[32,195,196] The baseline differences we see in diagnoses for migraines/chronic headaches and cardiac disorders could be diagnoses resulting from the anxiety disorder, before anxiety was recognized. The differences in baseline co-morbidities are part of the full picture when estimating how often events are experienced in a population with and without an anxiety disorder.

The comparison cohort in our study is also not meant to provide incidence estimates for the national, general population, but in a commercially insured cohort with the same baseline exclusions as the anxiety cohort (ex. naïve to certain psychiatric treatments/diagnoses). For reference, in the US the estimated annual percentage of privately insured children 6-17 years in with an ER visit was 16% in 1997, 15% in 2010, and 11% in 2012.[111] This is fairly similar to our comparison cohort (2005-2014), with 13% of children 3-17 years with an ER visit in a year.

5.4.3. Timing and follow-up of events

For treated self-harm, mental health related hospitalizations, and anxiety related ER visits we see greater separation in the cumulative incidence between the comparison and anxiety cohorts in the first months after the anxiety diagnosis. We expect more events following a new anxiety diagnosis, as children

with a new anxiety diagnosis are likely experiencing symptoms at a level that resulted in seeking advice/care from a medical provider. In contrast, many children in the comparison cohort were matched on a diagnosis associated with routine care (vaccination, well visit) and we would not expect to see an increase in events following those diagnostic codes. Future research could examine the care received leading up to and at an anxiety diagnosis but also the care received during and after each of these serious events to determine where improvements are needed. Only 13% of all aged individuals saw a mental health specialist during an anxiety-related ER visit.[103] In Canada, almost 3% of children with an ER visit for anxiety or stress-related returned within 3 days for another mental health related problem and only 30% of children had a follow-up visit 7 days after discharge.[180]

5.4.4. Treated self-harm estimates, part of the picture

The treated, inpatient self-harm events and recorded suicide ideation we observe represent a small fraction of all suicidal ideation and behavior. The results presented may be considerably underestimated and should be viewed as a lower limit of the event incidence. This is partially because our definition for self-harm required a recorded E-code, which are often incomplete in claims data,[197,198] with low sensitivity but high specificity in identifying suicide attempts.[199] The ICD-9 code for suicide ideation was found to be present in only 3% of patients with suicide ideation recorded in health record notes.[186] Suicide ideation and behavior are self-reported more frequently than our specific event definitions; in high school students, 16% reported they had seriously considered suicide and 8% reported they had attempted suicide one or more times during the prior year.[29,111] In the CAMS 12-week randomized controlled trial of children with moderate to severe anxiety 0.8% reported self-harm behavior, 2.3% suicide ideation, and no suicide attempts.[70] We saw a lower incidence of treated self-harm events than the trial population especially considering the trial excluded children with baseline depression; however, this is a component of our definition and that we identified children at a new diagnosis and included children with all severity levels. In a longitudinal study, children treated with cognitive behavioral therapy for anxiety (n=66) were followed for 7-19 years and 9% had made at least 1 suicide attempt and 27% reported experiencing

suicidal ideation.[112] These findings highlight that risk can remain over time and are important to consider past the 2 years we evaluated in our study.

5.4.5. Management of anxiety disorders

Children and adolescents often do not seek professional help for mental health problems[200] including children and adolescents with anxiety disorders, despite the impairments. Eighteen-percent of adolescents with anxiety reported receiving care for their condition, 29% of adolescents with a severe anxiety disorder, lower than care in adolescents with depression (38%) and ADHD (60%)[201] similar to other findings.[39] For some children with mild severity, education and support may help manage symptoms, but anxiety should be monitored at follow-up visits for changes.[32] Typically the course for pediatric anxiety disorders is thought to be chronic and persistent;[127] the majority of children in the Child/Adolescent Anxiety Multi-Modal Extended Long-term Study (CAMELS) experienced relapse or chronic anxiety during the 5 years of follow-up.[202] The costs of untreated anxiety disorders could potentially be reduced with appropriate care.[103] While we did not consider treatment or care received following a new anxiety diagnosis or know the baseline severity, the incidence of the evaluated events hints to the fact that many children with anxiety may need improved care.

5.4.6. Limitations

Limitations of the work should be considered. As we mention previously, treated self-harm and suicide ideation are underestimated based on our definition and results should be viewed as the lower limit of the actual incidence. We cannot be certain we are identifying the date of each child's first anxiety diagnosis. Children may have been previously diagnosed and children with a recorded ICD-9 anxiety diagnosis may not meet the clinical criteria for an anxiety disorder. Relatedly, children in the comparison cohort could have had undiagnosed anxiety. We miss any outcomes that resulted in death if the patient was not first admitted to the hospital; given the age of the study cohort (3-17 years), death does not account for substantial loss to follow-up and the competing risk of death would have a minimal influence on estimates. Differences in recorded suicide ideation between the anxiety cohort and the comparison cohort could be related to reporting opportunities; children subsequently receiving psychotherapy may

have more opportunities to report suicidal ideation. Our definition of injury related ER visits is broad and allows an injury-related ICD-9 diagnostic code to be in any diagnostic position (ex. not just the primary/secondary cause). When considering co-morbid depression, administrative codes for depression have shown reasonable concordance with medical records;[203] however, undiagnosed, unrecorded depression is missed. We additionally exclude children with previously treated depression given exclusion criteria. As stated previously, we recognize some treated self-harm behaviors were missed, but it is very likely that the outcomes identified were true events. We restricted our analysis to children diagnosed with anxiety in an office setting to provide information on a clinically relevant subset of children. While outside the scope of this study, children with an anxiety diagnosis first recorded outside an office are an important subset to describe further. Our comparison cohort was meant to provide context for the incidence of events under the same definitions and in a similar population of children, it is possible that due to inclusion requirements we selected a sicker or healthier subset than intended.

5.4.7. Conclusion

Following a new anxiety diagnosis, a significant proportion of children experience a mental health related hospitalization, inpatient treated self-harm, or an ER visit. The incidence of events in children with anxiety varied by age and by the presence of psychiatric co-morbidities and occur more often than in children without anxiety. Describing the incidence of these events adds to understanding the impact and burden of pediatric anxiety disorders. The information can possibly encourage proper management of anxiety symptoms and help focus research efforts within pediatric anxiety.

Table 5.1. Patient characteristics of children newly diagnosed with anxiety and children in the comparison cohort

	Children with new anxiety diagnosis (n=198,450)		Comparison cohort (n=1,980,082)	
	No.	%	No.	%
Matching factors				
Male	89,341	45.0%	891,444	45.0%
Age, Median (IQR)	12 (8-15)		12 (8-15)	
3-9 years	65,052	32.8%	648,983	32.8%
10-13 years	56,462	28.5%	563,197	28.4%
14-17 years	76,936	38.8%	767,902	38.8%
Year of treatment initiation				
2005-2006	15,582	7.9%	155,025	7.8%
2007-2009	37,197	18.7%	370,582	18.7%
2010-2012	78,245	39.4%	781,564	39.5%
2013-2014	67,426	34.0%	672,911	34.0%
Region of first anxiety diagnosis				
North central	53,987	27.2%	539,754	27.3%
Northeast	41,423	20.9%	413,809	20.9%
South	61,423	31.0%	614,178	31.0%
Unknown	2,313	1.2%	19,512	1.0%
West	39,304	19.8%	392,829	19.8%
Child characteristics[b]				
Initial anxiety diagnosis				
Unspecific anxiety	104,838	52.8%	-	
Generalized anxiety disorder	50,433	25.4%	-	
OCD	9,816	4.9%	-	
PTSD	8,066	4.1%	-	
Panic disorder	6,861	3.5%	-	
Separation anxiety disorder	5,674	2.9%	-	
Other, multiple[a]	12,762	6.4%	-	
Provider type, anxiety diagnosis/match date				
Psychiatry; Psychologist, therapist	91,539	46.1%	39,781	2.0%
Pediatrics	42,633	21.5%	702,458	35.5%
Family practice	20,309	10.2%	266,621	13.5%
Multi-specialty group	7,615	3.8%	101,543	5.1%
Other	26,012	13.1%	621,388	31.4%
Unknown, multiple	10,342	5.2%	248,291	12.5%
Anxiety related symptoms, prior 90 days	28,339	14.3%	140,823	7.1%
Psychiatric co-morbidities				
Any other psychiatric diagnosis	53,963	27.2%	174,400	8.8%
Depression	12,294	6.2%	16,270	0.8%
Adjustment disorder	6,619	3.3%	26,423	1.3%
ADHD	23,895	12.0%	95,854	4.8%
Developmental delay, learning disability	5,204	2.6%	16,387	0.8%
Disruptive behavior, conduct disorder	5,428	2.7%	10,136	0.5%
Other episodic mood disorder	1,653	0.8%	2,830	0.1%

Sleep disorder	5,917	3.0%	14,255	0.7%
Substance abuse	1,529	0.8%	4,931	0.2%
Suicidality				
Self-harm	124	0.1%	144	0.0%
Suicide ideation	488	0.2%	708	0.0%
Medication use in prior year				
Count, therapeutic subgroups	2 (1-3)		1 (0-3)	
0-1	92,765	46.7%	1,034,653	52.3%
2-4	82,995	41.8%	793,672	40.1%
5+	22,690	11.4%	151,757	7.7%
ADHD medication	19,895	10.0%	106,283	5.4%
Opioid	16,759	8.4%	164,418	8.3%
Non-psychiatric co-morbidities				
Acne	14,870	7.5%	145,646	7.4%
Allergic rhinitis	24,822	12.5%	195,983	9.9%
Anemia	2,414	1.2%	20,731	1.0%
Asthma	18,603	9.4%	154,189	7.8%
Cancer diagnosis	486	0.2%	4,533	0.2%
Cardiac disorder	3,188	1.6%	17,629	0.9%
Dysrhythmia	1,886	1.0%	10,267	0.5%
Diabetes	1,067	0.5%	10,345	0.5%
Epilepsy, convulsions	2,461	1.2%	15,583	0.8%
Fainting, dizziness	6,865	3.5%	33,827	1.7%
Gastro-esophageal reflux disease	5,480	2.8%	19,576	1.0%
Hearing loss/problems	3,844	1.9%	29,311	1.5%
Injury				
Fracture, sprain	25,280	12.7%	290,402	14.7%
Head injury	6,169	3.1%	54,348	2.7%
Poisoning	595	0.3%	1,839	0.1%
Other	37,935	19.1%	358,908	18.1%
Migraine, chronic headache	4,042	2.0%	22,211	1.1%
Overweight, obese	3,257	1.6%	23,463	1.2%
Spine curvature	3,551	1.8%	32,009	1.6%
Visual disturbance/loss	3,527	1.8%	22,959	1.2%
Well visit	115,380	58.1%	1,221,235	61.7%
Outpatient, problem oriented visit	3 (1-5)		2 (1-4)	
0-1	50,283	25.3%	653,417	33.0%
2-5	101,050	50.9%	1,011,636	51.1%
6+	47,117	23.7%	315,029	15.9%
Inpatient admissions				
Psychiatric diagnosis	546	0.3%	1,519	0.1%
No-psychiatric diagnosis	2,733	1.4%	24,063	1.2%
Emergency room visit				
None	160,212	80.7%	1,652,013	83.4%
1 visit	29,433	14.8%	264,833	13.4%
2+ visits	8,805	4.4%	63,236	3.2%

IQR: interquartile range; PTSD: post-traumatic stress disorder; OCD: obsessive-compulsive disorder; ADHD: attention-deficit/hyperactivity disorder

[a]Agoraphobia 0.4%; anxiety due to medical condition 0.5%; social phobia 1.8%; other, specific phobia 1.5%; other anxiety 1.1%; selective mutism 0.5%; multiple specific anxiety diagnoses 0.7%
[b]Detailed definitions of covariates in Appendix 5

Table 5.2. Cumulative incidence of serious events at 1 month, 6 months, and 1 year in children following a new anxiety diagnosis and in the comparison cohort

	1 month		6 months		1 year	
	No. events	Risk (95% CI)	No. events	Risk (95% CI)	No. events	Risk (95% CI)
Mental health related hospitalization						
Children with anxiety	642	0.33% (0.30-0.35)	2,189	1.20% (1.15-1.25)	3,248	1.95% (1.89-2.02)
Comparison cohort	1,168	0.06% (0.06-0.06)	4,827	0.26% (0.26-0.27)	8,318	0.49% (0.48-0.50)
Inpatient, treated self-harm						
Children with anxiety	31	0.02% (0.01-0.02)	101	0.06% (0.05-0.07)	131	0.08% (0.06-0.09)
Comparison cohort	20	0.00% (0.00-0.00)	126	0.01% (0.01-0.01)	230	0.01% (0.01-0.02)
Anxiety-related ER visit						
Children with anxiety	599	0.31% (0.28-0.33)	1,620	0.88% (0.84-0.93)	2,371	1.41% (1.36-1.47)
Comparison cohort	590	0.03% (0.03-0.03)	2,645	0.14% (0.14-0.15)	4,657	0.27% (0.27-0.28)
ER visits (any)						
Children with anxiety	5,198	2.7% (2.6-2.7)	21,173	11.7% (11.6-11.9)	32,518	19.8% (19.6-20.0)
Comparison cohort	34,573	1.8% (1.8-1.8)	145,612	7.9% (7.9-7.9)	233,108	13.5% (13.4-13.5)
Injury-related ER visits						
Children with anxiety	1,764	0.9% (0.9-0.9)	9,148	5.1% (5.0-5.2)	15,186	9.4% (9.3-9.5)
Comparison cohort	12,932	0.7% (0.6-0.7)	67,485	3.7% (3.7-3.7)	113,483	6.6% (6.6-6.7)
Recorded suicide ideation[a]						
Children with anxiety	312	0.17% (0.15-0.18)	1,080	0.62% (0.58-0.66)	1,626	1.02% (0.97-1.07)
Comparison cohort	435	0.02% (0.02-0.03)	2,021	0.11% (0.11-0.12)	3,597	0.22% (0.21-0.23)

[a]Children diagnosed with anxiety (or match date) in 2005 excluded from analysis

Table 5.3. One-year cumulative incidence of events after a new anxiety diagnosis in children stratified by age at anxiety diagnosis and co-morbid psychiatric conditions

	Total No.	Mental health related hospitalization		Inpatient treated self-harm		Anxiety-related ER visits		ER visits		Injury-related ER visits	
		No. events	Risk (95% CI)	No. events	Risk (95% CI)	No. events	Risk (95% CI)	No. events	Risk (95% CI)	No. events	Risk (95% CI)
Age at anxiety diagnosis											
3-9 years	65,052	229	0.4% (0.4-0.5)	*	-	233	0.4% (0.4-0.5)	8,988	17% (16-17)	4,198	8% (8-9)
10-13 years	56,432	789	1.7% (1.6-1.8)	22	0.04% (0.03-0.07)	621	1.3% (1.2-1.4)	8,388	18% (18-18)	4,348	9% (9-10)
14-17 years	76,936	2,230	3.5% (3.3-3.6)	109	0.17% (0.14-0.20)	1,571	2.3% (2.2-2.5)	15,142	24% (23-24)	6,640	11% (10-11)
Psychiatric co-morbidity[a]											
Depression	12,294	630	6.3% (5.8-6.8)	46	0.43% (0.32-0.57)	301	3.1% (2.7-3.4)	2,629	27% (26-28)	1,187	13% (12-13)
3-9 years	1,056	*	-	*	-	*	-	159	19% (16-22)	80	10% (8-12)
10-13 years	2,903	125	5.3% (4.4-6.3)	10	0.39% (0.20-0.70)	65	2.8% (2.2-3.6)	558	24% (22-26)	275	12% (11-14)
14-17 years	8,335	497	7.4% (6.8-8.0)	36	0.50% (0.36-0.69)	230	3.5% (3.0-3.9)	1,912	29% (28-31)	832	13% (12-14)
Other	41,669	757	2.2% (2.1-2.4)	20	0.06% (0.04-0.09)	449	1.3% (1.2-1.5)	6,903	21% (20-21)	3,297	10% (10-10)
3-9 years	16,691	118	0.9% (0.7-1.0)	*	-	78	0.6% (0.5-0.7)	2,441	18% (17-19)	1,101	8% (8-9)
10-13 years	12,456	186	1.9% (1.6-2.2)	*	-	123	1.2% (1.0-1.5)	1,838	18% (18-19)	966	10% (9-11)
14-17 years	12,522	453	4.4% (4.4-4.8)	19	0.18% (0.11-0.27)	258	2.5% (2.2-2.8)	2,624	26% (25-27)	1,230	12% (12-13)
None recorded	144,487	1,861	1.5% (1.5-1.6)	65	0.05% (0.04-0.07)	1,621	1.3% (1.2-1.4)	22,986	19% (19-19)	10,702	9% (9-9)
3-9 years	47,305	103	0.3% (0.2-0.3)	*	-	149	0.4% (0.3-0.4)	6,388	16% (16-16)	3,017	8% (7-8)
10-13 years	41,103	478	1.4% (1.3-1.5)	11	0.03% (0.02-0.06)	433	1.2% (1.1-1.3)	5,992	17% (17-18)	3,107	9% (9-10)
14-17 years	56,079	1,280	2.7% (2.6-2.9)	58	0.12% (0.09-0.15)	1,039	2.2% (2.0-2.3)	10,606	23% (22-23)	4,578	10% (10-10)
Reference cohort, no psychiatric co-morbidity[b]											
3-9 years	595,329	356	0.1% (0.1-0.1)	*	-	363	0.1% (0.1-0.1)	60,993	12% (12-12)	27,764	6% (6-6)
10-13 years	510,547	1,309	0.3% (0.3-0.3)	21	0.01% (0.00-0.08)	1,008	0.2% (0.2-0.2)	51,710	12% (12-12)	28,496	7% (6-7)
14-17 years	703,050	3,626	0.6% (0.6-0.6)	141	0.02% (0.02-0.03)	2,376	0.4% (0.4-0.4)	92,556	15% (14-15)	43,656	7% (7-7)

*Not displayed due to low event count

[a]Baseline psychiatric diagnoses given on the date of anxiety diagnosis or in the prior year

[b]N=1,808,926 (removed 175,568 with baseline depression or other psychiatric diagnosis)

Table 5.4. Sensitivity analysis: Cumulative incidence in the anxiety cohort restricted to children with a second anxiety diagnosis[a]

	1 month		6 months		1 year	
	No. events	Risk (95% CI)	No. events	Risk (95% CI)	No. events	Risk (95% CI)
Children with a second anxiety diagnosis (n=113,437)[a]						
Mental health related hospitalization	516	0.46% (0.42-0.50)	1,663	1.56% (1.49-1.63)	2,379	2.42% (2.32 - 2.51)
Inpatient, treated self-harm	25	0.02% (0.01-0.03)	80	0.08% (0.06-0.09)	99	0.10% (0.08-0.12)
Anxiety-related ER visits	594	0.53% (0.48-0.57)	1,439	1.33% (1.27 -1.40)	1,910	1.90% (1.81-1.98)
ER visit, any	3,211	2.8% (2.8-2.9)	12,622	12.0% (11.8-12.2)	19,233	19.8% (19.6-20.1)
Injury-related ER visits	1,076	1.0% (0.9-1.0)	5,457	5.2% (5.1-5.4)	9,018	9.5% (9.3-9.7)
Children without a second anxiety diagnosis (n=85,013)[a]						
Mental health related hospitalization	126	0.15% (0.13-0.18)	526	0.71% (0.65-0.77)	869	1.31% (1.22-1.40)
Inpatient, treated self-harm	*	-	21	0.03% (0.02-0.04)	32	0.05% (0.03-0.07)
Anxiety-related ER visits	*	-	181	0.26% (0.23-0.30)	461	0.74 % (0.68-0.82)
ER visit, any	1,987	2.4% (2.3-2.5)	8,551	11.4% (11.2-11.7)	13,285	19.7% (19.4-20.0)
Injury-related ER visits	688	0.8% (0.8-0.9)	3,691	5.0% (4.8-5.1)	6,168	9.3% (9.1-9.5)

*Not displayed due to low event count

[a]Second anxiety diagnosis recorded within 90 days of the first diagnosis

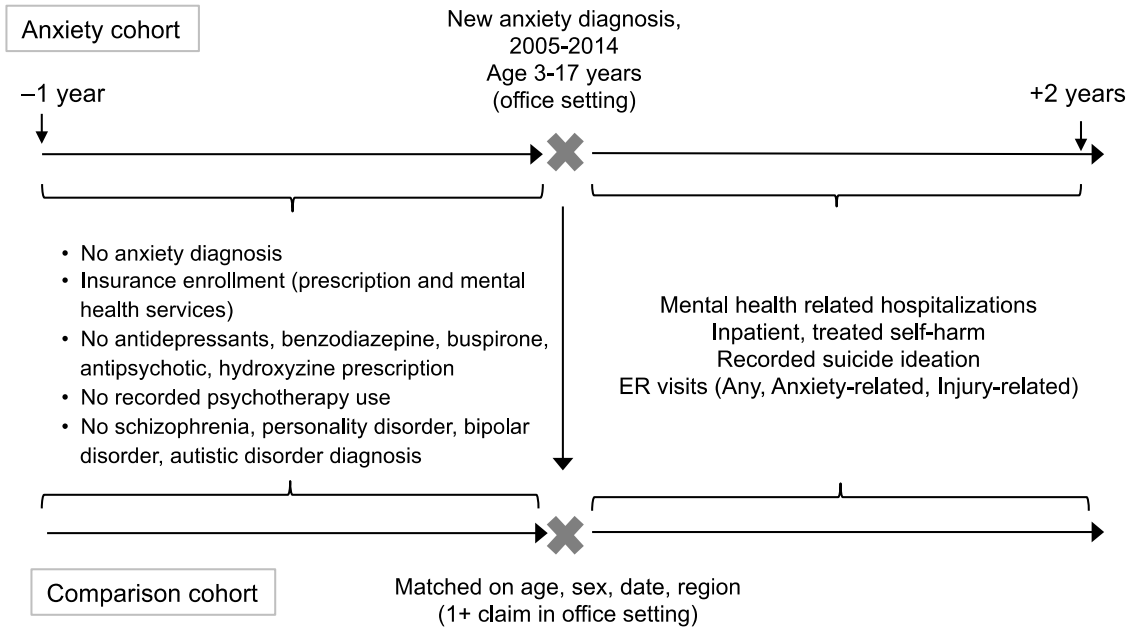


Figure 5.1. Study design with inclusion criteria for the anxiety cohort and comparison cohort

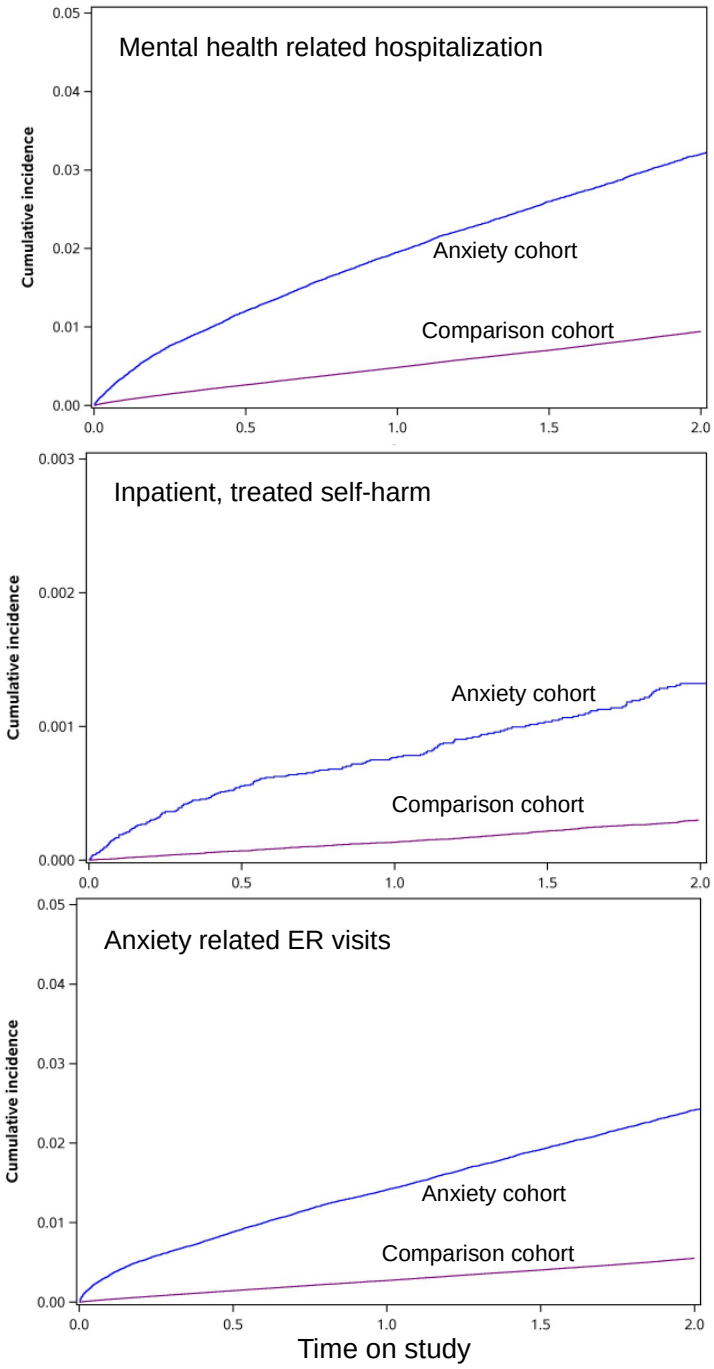


Figure 5.2. Cumulative incidence of mental health related hospitalizations, inpatient treated self-harm, and anxiety related ER visits following a new anxiety diagnosis in children and in a comparison cohort

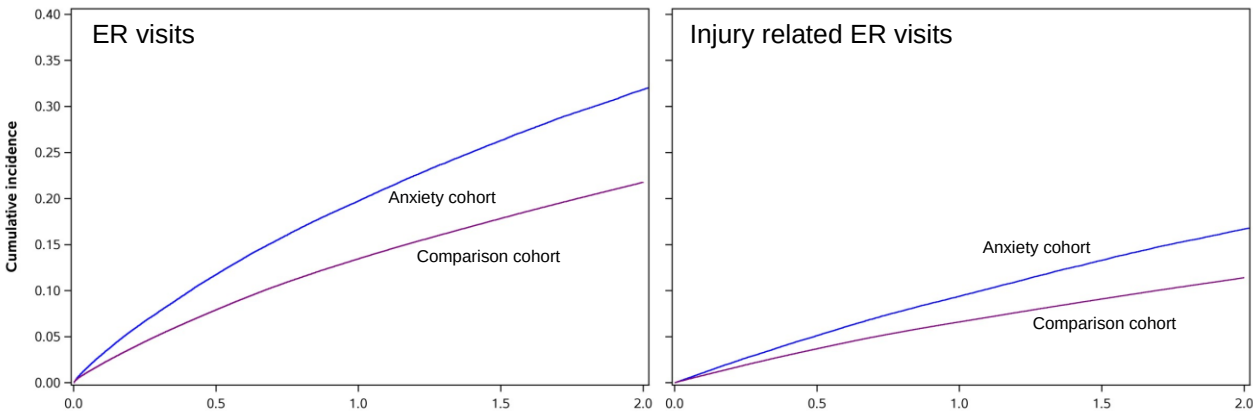
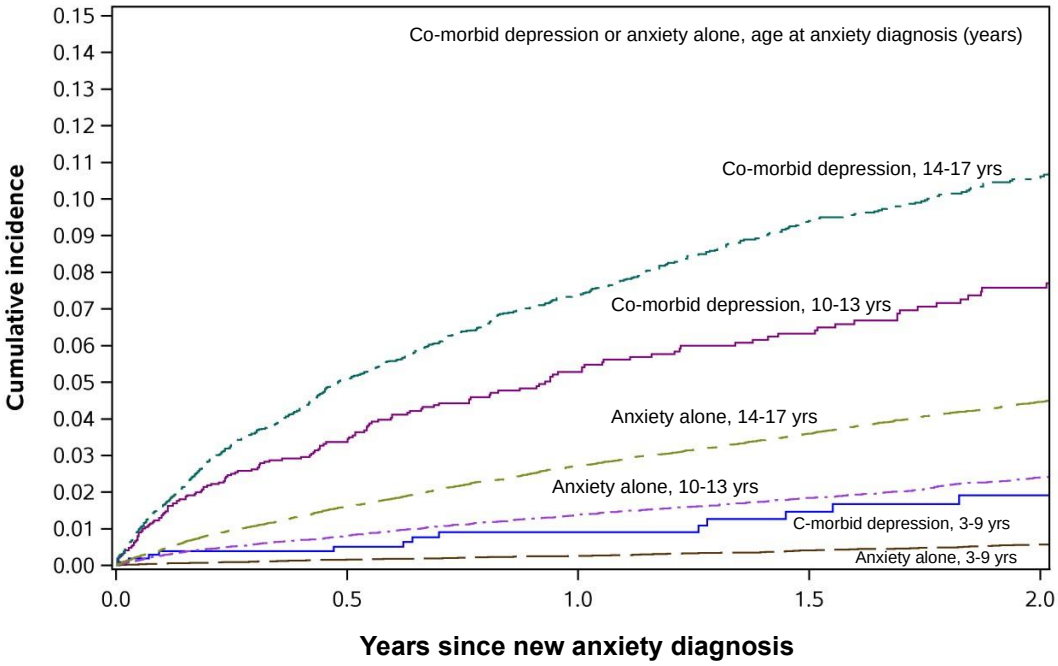
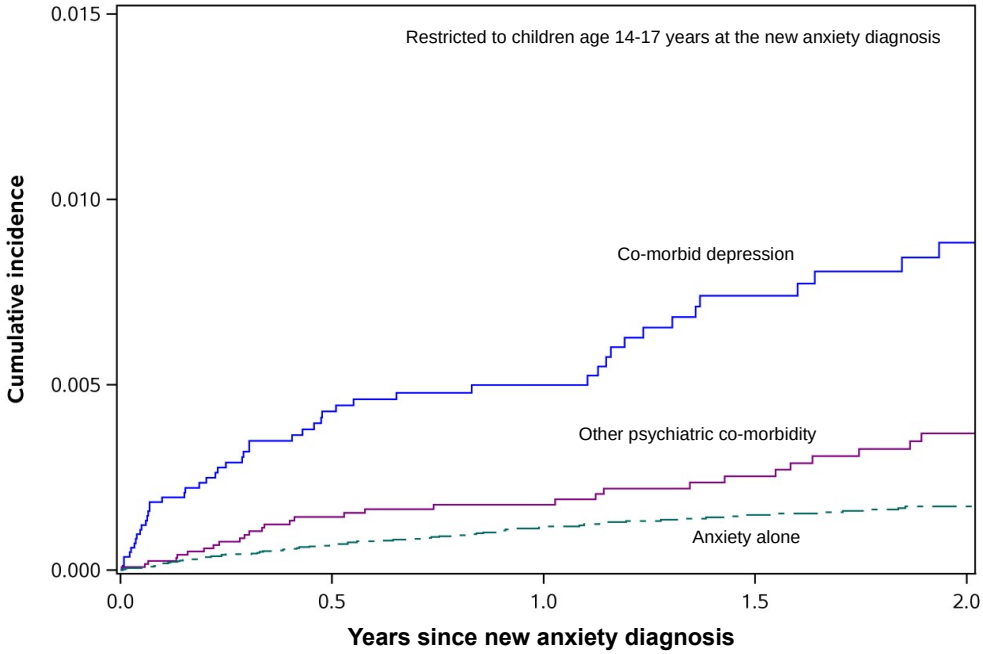


Figure 5.3. Cumulative incidence of ER visits and injury related ER visits following a new anxiety diagnosis in children and in a comparison cohort

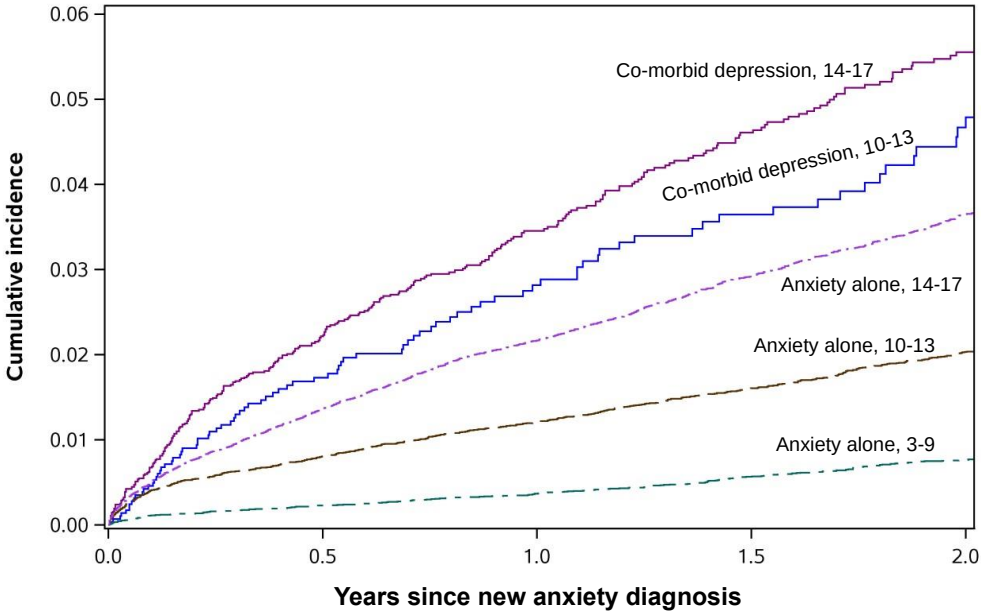
a) Mental health related hospitalizations (Not shown: results for children with a non-depression psychiatric co-morbidity)



b) Inpatient, treated self-harm (restricted to children 14-17 years at anxiety diagnosis given low event count in younger children)



c) Anxiety related ER visits (Not shown: results for children with a non-depression psychiatric co-morbidity), children aged 3-9 with co-morbid depression excluded due to low event count



d) Injury related ER visits and overall ER visits (Not shown: results for children with a non-depression psychiatric co-morbidity)

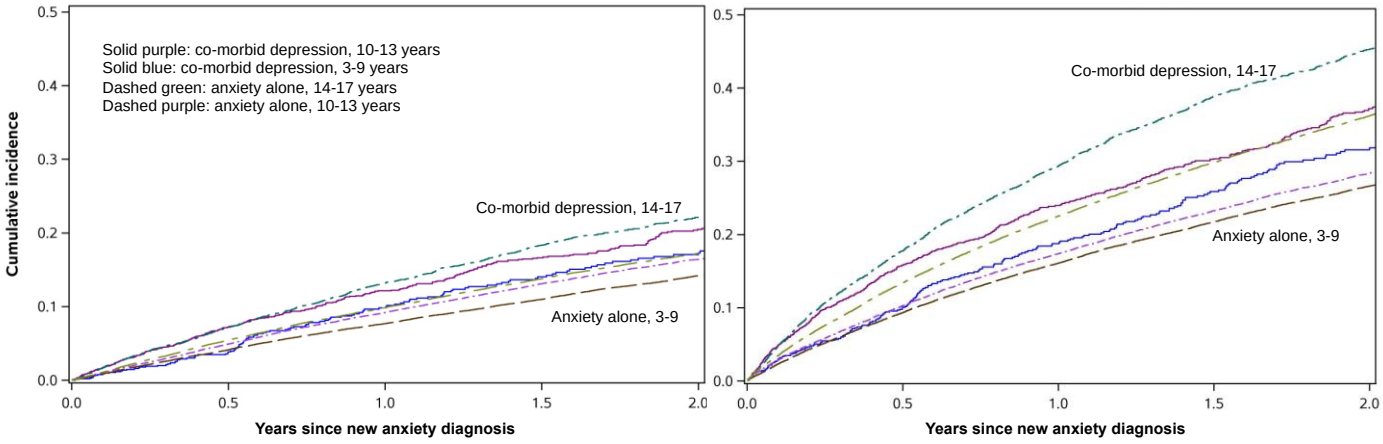


Figure 5.4. Cumulative incidence of a) mental health related hospitalizations, b) treated inpatient self-harm, c) anxiety-related ER visits, and d) injury-related ER visits and overall ER visits following a new anxiety diagnosis by age at anxiety diagnosis and psychiatric comorbidity (diagnosed at baseline)

CHAPTER 6: OVERALL DISCUSSION

6.1. SUMMARY OF FINDINGS

The aims of this dissertation were to 1) describe the anti-anxiety medication prescribed to children with anxiety beginning pharmacotherapy and psychotherapy claims surrounding medication initiation, 2) estimate SSRI adherence in children with anxiety and determine if parent adherence can be used to predict child adherence, and 3) estimate the incidence of mental health related hospitalizations, treated self-harm events, and ER visits following a new anxiety diagnosis. The aims were addressed in a commercial claims database covering privately insured children in the US. We included children aged 3-17 years with an anxiety diagnosis (defined with ICD-9 codes); the specific study cohort varied for each aim.

In our first aim we found that the majority of children (70%) initiated anti-anxiety treatment with an SSRI. This included a small, but significant, proportion (7%) of children initiating with an SSRI and another anti-anxiety medication. The most common non-SSRI medications used at medication initiation included benzodiazepines (8%) followed by non-SSRI antidepressants (7%). The use of benzodiazepines as an initial anti-anxiety medication declined in older children from 2004 to 2014. Anxiety disorder, age, provider type, and co-morbid psychiatric diagnoses were some of the factors associated with the initial anti-anxiety medication class. Benzodiazepines and hydroxyzine were used primarily for short-term use, with few children refilling the initial prescription, whereas over half of SSRI initiators continued SSRI treatment for 6 months. A third of children were psychotherapy users before anti-anxiety medication initiation and most remained users after initiation. Among children who did not have psychotherapy claims before medication initiation, only 30% became psychotherapy users after initiation, with little change across time.

In our second aim we examined SSRI adherence in children with anxiety. In children with anxiety initiating an SSRI (n=70,979), 58% were classified as having high adherence (PDC≥0.80). Adherence was higher in younger children and in children with an anxiety diagnosis of OCD or social phobia and children with panic disorder and PTSD had the lowest adherence. Parent high adherence to SSRIs, statins, and antihypertensives independently predicted high child SSRI adherence compared to parent low adherence. Findings were consistent across child age groups and when considering parent gender. Parent adherence measures and other parent-level variables offered a small improvement in the ability to discriminate high vs. low child SSRI adherence at baseline when added to standard child-level variables available in claims data.

In our third aim we identified 198,450 children with a new anxiety diagnosis in an office-based setting who were naïve to anti-anxiety treatment prior to their new diagnosis. One-year after a new anxiety diagnosis 2.0% of children had a mental health related hospitalization, 0.06% an inpatient, treated self-harm event, 1.4% an anxiety-related ER visits, and 20% any ER visit. There was a higher incidence in older children with baseline co-morbid depression. In the comparison cohort of a similar population of commercially insured children without an anxiety diagnosis, the cumulative incidence of each outcome was lower than in children with anxiety.

6.2. PUBLIC HEALTH IMPLICATIONS

This dissertation addressed current research gaps in pediatric anxiety. We were able to determine that SSRIs were the most commonly used first-line anti-anxiety pharmacotherapy for pediatric anxiety. The formal guideline from the American Academy of Child and Adolescent Psychiatry for anxiety disorders (excluding PTSD and OCD) was published in 2007.[31] Since 2007 additional medications have been suggested as possible anxiety treatments; however, SSRIs typically remain the recommended first-line medication.[62,127,128] Aim 1 results revealed that a third of children initiated on a non-SSRI medication that has limited or no evidence of effectiveness for pediatric anxiety. Many of these medications have not been included in randomized controlled trials for pediatric anxiety; subsequently there is no trial evidence for or against these medications in pediatric anxiety. In many situations a non-SSRI first-line

pharmacotherapy may be entirely appropriate and we did find that psychiatric co-morbidities were associated with the initial mediation received.

The decreased use of benzodiazepines as an initial pharmacotherapy in older children is a sign that practices may have improved in pediatric anxiety, whereas in adults, benzodiazepine use was on the rise during that time period.[204] Because of dependency concerns, benzodiazepines are usually recommended for only short-term treatment.[12] We did find evidence that when benzodiazepines are prescribed to children they are typically used for short-term treatment. Initiation with two anti-anxiety medications was relatively uncommon (7%), but there are concerns surrounding psychotropic poly-pharmacy. This finding may be particularly concerning since poly-pharmacy typically increases during treatment and we saw treatment naïve children beginning pharmacotherapy with two anti-anxiety medications.

Finally, aim 1 findings showed that psychotherapy utilization (based on psychotherapy claims) could be substantially improved surrounding anti-anxiety medication initiation in pediatric anxiety. Psychotherapy should be considered as a part of the treatment plan when possible. Other forms of traditional psychotherapy such as computer/internet-delivered, community/school based, and brief behavioral therapy,[46,150] suggest that there may be flexibility in the form therapy is provided. This could allow more children to be treated with psychotherapy mono-therapy or combination therapy in the future. By describing the initial anti-anxiety pharmacotherapy prescribed in children with anxiety and psychotherapy utilization, aim 1 can inform efforts to better tailor medication and psychotherapy use in pediatric anxiety.

Aim 2 focused on SSRI adherence, which was the medication most commonly used at anti-anxiety medication initiation. Adherence to SSRIs had not been well characterized in children with anxiety. We found that adherence can be improved and that it does vary between specific anxiety disorders. Given adherence estimates, adherence should be considered before altering medication dosing or switching to another anti-anxiety medication.

In aim 2 we also identified parent adherence as a predictor of child SSRI adherence. Given the role parents play in child adherence, it was important to understand whether parent medication adherence could be used as an indicator of future child adherence. The specific mechanism behind parent adherence being associated with child adherence likely differs between parent and child pairs, but is a clinically relevant indicator that could be integrated into everyday practice to improve the prediction of child adherence at baseline. A conversation between providers and parents on the parent's barriers to adherence and if these will translate into barriers for his or her child's adherence may be the first step to integrating parent information into clinical practice. Determining if parent adherence is predictive of child adherence outside SSRIs for anxiety and if parent adherence can be used to predict other healthy behaviors in children should be highlighted in future research.

Aim 3 filled a gap in the literature on the impact and burden of pediatric anxiety disorders after a new diagnosis. Results can help inform patients, parents, and providers when a child is diagnosed, a time when this information is especially useful. Following a new anxiety diagnosis, a significant proportion of children experience a mental health related hospitalization, inpatient treated self-harm, or anxiety-related ER visit. While we do not consider treatment type or management of symptoms after a new anxiety diagnosis, the incidence of these serious events demonstrate that some children and adolescents need improved care. The typical course of pediatric anxiety disorders is thought to be chronic and persistent[127] and the costs of untreated anxiety disorders could be lessened with appropriate mental health care.[103] Better understanding the disorder will hopefully improve the care for children with anxiety disorders, especially children at highest risk for one of these serious events.

6.3. FUTURE RESEARCH

6.3.1. Medicaid and other populations

Our research centered on commercially insured children in the US; however results for each aim may differ in a Medicaid population or in countries outside the US. Prior work, not related to pediatric anxiety, has shown inferior management and treatment utilization in individuals enrolled in Medicaid compared to privately insured individuals,[116,205,206] including a higher use of antipsychotics that are

associated with more side effects.[152] It is possible that the initial anti-anxiety medication prescribed and psychotherapy claims surrounding medication initiation that we evaluated in aim 1 would differ in children covered by Medicaid.

Additionally, in Canada, adherence to antidepressants was higher in those with private insurance compared to public insurance.[207] There may be differences in child SSRI adherence in those covered by Medicaid and it is unknown if the predictability of parent adherence with child adherence would remain across populations. In reference to aim 3, serious events may also differ in non-privately insured children, for example, higher ER visits have been reported for children on Medicaid.[109] It may be particularly useful to describe the management of symptoms in other populations to help interpret any differences in serious event incidence between the populations.

6.3.2. Validation studies

There is a need for validation studies for psychiatric diagnostic codes used in children in administrative data, including the validity of ICD codes for anxiety disorders. There is the possibility that recorded anxiety diagnoses are not true diagnoses i.e. claim entered as rule-out diagnosis, data entry error, patient was referred to specialist for further assessment). In a prior study of Veterans Health Administration patients with diabetes who participated in the MENtal health-Diabetes (MEND) study, algorithms identifying anxiety disorders had a positive predictive value of 0.84 and negative predictive value of 0.66.[188] However, that is a very different population than the current research and in a different datasource. Validations studies of psychiatric diagnoses are further complicated by the fact that a 'gold standard' would involve diagnostic evaluation or evidence of an evaluation and not a just a recorded diagnosis in a medical record. With the switch to ICD-10 diagnostic codes, validating the use of these codes will be particularly important to assist in future pediatric anxiety research.

Describing psychotherapy in administrative claims data is primarily limited by the uncertainty on how often psychotherapy use is captured. In 1997, 37% of patients with anxiety were found to have self-paid for psychotherapy[154] and between 2005-2006, 72% of psychiatrists accepted private non-capitated insurance which decreased to 55% in 2009-2010.[155] However, it is unknown how often psychotherapy use

is missing from claims data. An additional consideration for psychotherapy validation is the need to have self-report use or access to information from psychiatrists and psychologists.

6.3.3. Future research related to aim 1

Additional areas of research stemming from aim 1 findings include further evaluation of follow-up treatments. Our study focused on the initial anti-anxiety medication and we hinted at subsequent medication changes in examining the proportion of non-SSRI initiators that later fill an SSRI prescription. However, treatment switches and additions are important to evaluate in closer detail. This will likely vary over the life-course and become complicated by the development of psychiatric co-morbidities. Further research is needed to determine the extent to which provider availability and costs influence the decision on whether a child receives psychotherapy as part of their treatment. Given the amount of children diagnosed with anxiety by non-mental health specialists and the low use of psychotherapy after medication initiation in children diagnosed by non-mental health providers, attention focused outside mental health specialists may be essential to improve care for pediatric anxiety.

6.3.4. Future research related to aim 2

In aim 2 we found that parent adherence was predictive of child adherence. However, as mentioned in the discussion, self-reported adherence is often overestimated, limiting the clinical utility of parent self-reported adherence to inform on the likelihood of high child adherence. More research is needed to identify the best and most feasible way parent information could be applied in everyday practice to best inform future child adherence. Using this information to improve child adherence will be related to the specific mechanism that links both parent and child adherence (ex. pharmacy access vs. needing a daily reminder).

We only evaluated the association of parent adherence to three medication classes. The predictability of parent adherence with child adherence may not hold for different parent medications, particularly medications in which adherence may not be representative of a healthy behavior (i.e. being adherent to opioids or benzodiazepines). Additionally, it would be of interest to determine if parent adherence is associated with other child behaviors. This could include whether a child receives

vaccinations according to schedule or whether children are more likely to take part in healthy behaviors when they have adherence parents. When the healthy user bias is a potential reason for unmeasured confounding in pediatric pharmacoepidemiologic studies, it is possible parent adherence (or other parent healthy behaviors) may serve as a proxy to aid with adjustment.

Adherence is likely only one aspect of treatment that is influenced by parents. Caregivers have a large say in the treatment type initiated (medication vs. psychotherapy), in managing care during follow-up (psychotherapy visits, lifestyle changes), and in when to seek care and guidance; all of these are areas of interest to explore further.

6.3.5. Future research related to aim 3

Aim 3 examined the incidence of selected serious events (mental health related hospitalizations, inpatient treated self-harm, ER visits) after a new anxiety diagnosis. We are currently conducting research to examine whether the incidence of each event varies based on the initial treatment received following a new anxiety diagnosis. However, there is significant unmeasured confounding by anxiety severity between the initial treatment received and subsequent events. Therefore, datasources with clinical details on anxiety severity will likely be necessary to answer the question of whether initial treatment type is associated with a reduction in adverse events.

Children with a new anxiety diagnosis outside an office setting were excluded from aim 3. However, this group should be described in further detail given that these children likely had undiagnosed or unrecognized anxiety until their symptoms (or symptoms of a co-morbidity) resulted in a new diagnosis in an inpatient, ER, or urgent care setting. Describing these patients could help develop interventions to get children into care earlier.

6.3.6. First recognition of pediatric anxiety

Future areas of research for pediatric anxiety in general should focus on understanding how children first enter the healthcare system. There is a low recognition of anxiety disorders, possibly related to the fact that symptoms are often internalized in children and they may be reluctant to share thoughts or behaviors.[208] During the course of the dissertation, questions were formed around which children get an

anxiety diagnosis and how do they first enter the healthcare system to receive that diagnosis. Some children may have been referred directly to a mental health provider for evaluation while a general practitioner may diagnose and treat other children. In the database used for the current research, we cannot identify additional details surrounding how the child first got into care, for example, did the child express their symptoms to their parents, were the parents observing the behavior, or did the school refer the child. Understanding how children first enter into healthcare for anxiety could help improve efforts to get more children into proper care and perhaps reduce visits for somatic symptoms with anxiety going unrecognized.

6.4. CONCLUSIONS

Given the high prevalence of anxiety disorders in children and adolescents, the impact on daily life, and the high costs associated with anxiety,[4,178] this dissertation research focused on pediatric anxiety to help understand current treatments practices and the burden of anxiety to improve care in the future. Many children with mental disorders, including anxiety disorders, never receive the specialty mental health care they need.[39,201,209] There are ongoing efforts to increase the availability of mental health treatments in children[210] including the integration of mental health services into primary care.[211] This research identifies areas of treatment that can be improved so that in the future, as more children enter care, children have the best chance to reduce the lasting, negative symptoms of anxiety.

In conclusion, through the dissertation aims we found that the majority of children with anxiety who start anti-anxiety medication do so with an SSRI, with about half remaining on treatment at 6-months and a significant proportion with low adherence. Parent adherence can be used as a baseline indicator to help predict child SSRI adherence and aid in the evaluation of distinguishing between non-responders vs. non-adherers. Lastly, evaluating the occurrence of serious, high-burden events following a new anxiety diagnosis increases awareness for patients, providers, and caregivers and supports the need for appropriate management of anxiety symptoms in children.

APPENDIX 1. EVIDENCE OF PHARMACOTHERAPIES USED TO TREAT ANXIETY

SNRIs: SNRIs included are venlafaxine (Effexor XR), duloxetine (Cymbalta), desvenlafaxine (Pristiq), levomilnacipran (fetzima; approved July 2013), and milnacipran (savella). Two RCTs found venlafaxine to be effective in treating anxiety in children, both were published after the 2007 AACAP guidelines.[212,213] One trial was in 285 children (8-17 years) with social anxiety disorder[212] the other trial in 323 children (6-17 years) with GAD.[213] SNRIs are often seen as an appropriate alternative to SSRIs or recommended if an initial SSRI is ineffective.[62,63,214,215] All SNRIs were included in the proposal.

Tricyclic antidepressants (TCAs): TCAs included are amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine, and amoxapine (dibenzoxazepinederivative TCA). Clomipramine is FDA approved for OCD in adults and children (10+ years) and doxepin (Sinequan) is approved for conditions related to anxiety in adults; other TCAs are not approved for any anxiety related conditions. Imipramine has shown effectiveness over placebo for treating GAD in adults in an RCT.[216] Canadian practice guidelines recommend TCAs as a second-line antidepressant treatment for adults with certain anxiety disorders.[62] For panic disorder in adults, the APA cites TCAs as having similar efficacy as SSRIs, SNRIs, and benzodiazepines;[139] however, given the side effects associated with TCAs and the potential lethality in overdose, TCA use is limited for anxiety.[61,63,139] The AACAP guidelines for pediatric anxiety state that TCAs have been used less since SSRIs were introduced as there is the need for close cardiac monitoring and greater medical risk of overdose and that controlled trials of TCAs for pediatric anxiety disorders show conflicting results.[5] All TCAs were included as potential medications for anxiety in children despite the limited evidence in children.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs included are isocarboxazid, phenelzine, selegiline transdermal, and tranylcypromine; none of these medications are FDA approved for treating anxiety disorders in children and adults. The NIMH lists MAOIs as a potential treatment for anxiety. The APA guidelines for panic disorder in adults state that adverse effects are a major concern for MAOIs and that MAOIs should be reserved for patients who did not respond to several other treatments,[139] as also mentioned in recommendations from the British Association for Psychopharmacology.[15] MAOIs have not been well studied in children;[217] however, as MAOIs can be used for anxiety, they were included as potential anxiety treatments.[59,65]

Other antidepressants:

- **Mirtazapine, trazodone, nefazodone**: Mirtazapine, trazodone, and nefazodone are antidepressants FDA approved for depression but, as with other antidepressants, are sometimes used to treat anxiety. There is some limited evidence from small trials of mirtazapine and nefazodone as a treatment for PTSD in adults.[15,218] There is also limited evidence for trazodone and nefazodone for adults with panic disorder,[139] and trazodone for GAD.[61] However, they are not recommended as first line treatments because of tolerability issues, liver toxicity, or common side effects.[139,218]
- **Atomoxetine**: In an RCT of atomoxetine, which is FDA approved for treating ADHD in children, atomoxetine was associated with greater symptom improvement in children with ADHD and anxiety compared to placebo.[219]
- **Bupropion**: (ex. Wellbutrin) Bupropion is an antidepressant approved for adults in the treatment of major depressive disorder (MDD) and is also indicated for the prevention of seasonal affective

disorder.[220,221] A meta-analysis found no difference in anxiolytic efficacy of Bupropion compared with SSRIs when treating patients with MDD[222] and preliminary evidence (n=24) showed bupropion has similar efficacy to an SSRI in treating GAD in adults.[223] Nevertheless, bupropion is used in the treatment of anxiety.[59,65] This treatment is frequently used for smoking cessation; however, given the young age of our population and inclusion requirements, we do not expect observed bupropion to be used for smoking cessation.

Buspirone (Buspar): Buspirone is an anti-anxiety medication that is not related pharmacologically to other typical anti-anxiety medications and is indicated in adults for anxiety disorders and the short-term relief of anxiety symptoms.[224] The 2007 AACAP guidelines for the treatment of anxiety disorders, suggest buspirone may be an alternative to SSRIs in the treatment of GAD in children.[5] However, two unpublished 6-week RCTs in children with GAD showed no significant difference between buspirone and placebo.[14]

Benzodiazepines: Benzodiazepines are commonly used for the treatment of anxiety; however, prescribing benzodiazepines for long-term use is not recommended because of the risk associated with dependency.[66-68] Additionally there is insufficient data on efficacy to warrant benzodiazepine use for anxiety in children, despite the benefits seen in adult trials.[5,12] The AACAP guidelines state that benzodiazepines are used in the short-term as adjunct to SSRI treatment when seeking to achieve reduction in severe anxiety symptoms.[5] There are many benzodiazepines and benzodiazepine derivatives available; those included as potential treatments for anxiety were: Alprazolam (Xanax), chlordiazepoxide (Librium), clobazam (Onfi, used for seizure control), clonazepam (Klonopin; BZD derivative, antiepileptic), clorazepate (Tranxene), diazepam (Valium), lorazepam (Ativan), oxazepam (Serax). Halazepam and prazepam have been discontinued in the US but were still included to capture use prior to the discontinuation. The hyponitcs and sedative benzodiazepine medications (estazolam, flurazepam, triazolam, temazepam, midazolam, quazepam) were not included. A few benzodiazepine agents are highlighted below.

- **Clonazepam**: Clonazepam is indicated for the treatment of panic disorder, with or without agoraphobia in adults and for certain seizure disorders.[225] There is not evidence of effectiveness in treating pediatric anxiety. In a double-blind crossover trial of 15 children (7-13 years) with anxiety (majority with SAD), there was no statistical benefit of clonazepam over placebo with more side effects reported during the clonazepam phase included drowsiness and disinhibition.[226]
- **Alprazolam**: Alprazolam is indicated for anxiety disorder, short-term relief of anxiety symptoms, and panic disorder with or without agoraphobia in adults.[227] In a RCT of 30 children (mean 13 years) with overanxious or avoidant disorders there was no statistical difference between alprazolam and placebo.[228]

Beta-blockers: Beta-blockers are an additional medication to treat anxiety.[59] Beta-blockers can be prescribed for performance related social anxiety, which are taken on an as-needed basis rather than regularly.[60] An open-label trial of betaxolol in patients with anxiety noted immediate improvements.[229] However, evidence is lacking on the use of beta-blockers for anxiety in children, with some small, open label evidence for children with PTSD.[230] All agents in the drug class were included: acebutolol, atenolol, atenolol/chlorthalidone, bendroflumethiazide/nadolol, betaxolol, bisoprolol fumarate, carteolol,

carvedilol, esmolol, metoprolol succinate, metoprolol tartrate, propranolol, timolol maleate, nadolol, nebivolol, penbutolol sulfate, pindolol, and sotalol.

Atypical antipsychotics: Atypical antipsychotics have been suggested for possible treatments for anxiety or augmentations to treatments for anxiety; however, the long-term use of antipsychotics is associated with significant side effects.[41,63] Nationally, the prescribing of antipsychotics for the treatment of anxiety disorders has risen (source: National Ambulatory Medical Care Survey).[80] Given the potential side effects and limited RCT evidence, atypical antipsychotics are often recommended as only the second or third-line therapy or adjunctive therapy in adults, as in the Canadian clinical practice guidelines for the management of anxiety and PTSD.[62] The World Federation of Biological Psychiatry guidelines for the pharmacological treatment of anxiety disorders suggest that treatment with atypical antipsychotics be reserved to specialist settings.[63] Given the lack of evidence, guidelines do not recommend atypical antipsychotics for treating anxiety disorders in children; [62] [31] however, the AACAP guidelines for treating children with PTSD cite that novel antipsychotics may be helpful for youth with PTSD.[45] The APA guidelines for adults with PTSD also suggest second-generation antipsychotic medications may be helpful in treatment PTSD.[218,231] Rather than including all atypical antipsychotics, only those with evidence (even if minimal) or those mentioned in reviews on anxiety treatment were included:

- **Aripiprazole** (Abilify): The approved indications for Aripiprazole include schizophrenia, manic and mixed episodes associated with bipolar I, adjunctive treatment of MDD, and tourette's disorder, some of which are approved for pediatric use.[232] Results from two small, open label trials that augmented treatment with aripiprazole in patients with GAD demonstrated promising results.[61] A review of aripiprazole stated that the use of aripiprazole in anxiety should be explored given the existing data, the neurobiology of anxiety, and the pharmacology of aripiprazole.[41]
- **Ziprasidone** (Geodon): The approved indications for ziprasidone include schizophrenia, manic or mixed episodes associated with bipolar I disorder, and adjunct to lithium or valproate in bipolar I disorder for adults.[233] A small, open label trial of ziprasidone in patients with treatment resistant GAD was successful in the reduction of symptoms.[234] Canadian clinical practice guidelines, cite some evidence of the use of ziprasidone for monotherapy in the treatment of GAD in adults.[62]
- **Quetiapine** (Seroquel): The approved indications for quetiapine in the US include schizophrenia, bipolar I disorder, depressive episodes associated with bipolar disorder, and MDD adjunctive therapy with antidepressants.[235] Quetiapine is licensed for GAD in other countries. RCTs, including a large (n=873) 8-week trial, found quetiapine to be effective in treating GAD in adults compared to placebo but not SSRI antidepressants,[236] a finding demonstrated in other studies as detailed in a National Institute for Health and Care Excellence off-label review of quetiapine for GAD.[237] A RCT of adults with GAD stabilized to quetiapine XR (n=432) and subsequently randomized to continue quetiapine XR or placebo found quetiapine XR to reduce the risk of anxiety symptom recurrence.[238]
- **Olanzapine** (Zyprexa) and olanzapine/fluoxetine (Symbyax): Approved indications for olanzapine in the US include schizophrenia and bipolar disorder in those 13+ years and the combination olanzapine/fluoxetine for bipolar disorder and treatment resistant depression.[239] Adjunct olanzapine to fluoxetine treatment in adults (n=46) with GAD resulted in improved treatment response compared to fluoxetine alone.[240] Olanzapine is one of the recommended options for acute treatment of social anxiety disorder by the British Association for Psychopharmacology.[15]
- **Risperidone** (Risperdal): Indications for risperidone include schizophrenia, bipolar disorder, and irritability associated with autistic disorder.[241] There is some evidence that risperidone may improve

PTSD symptoms, including two open label trials (one in 3 preschool aged children) and case reports.[230] Another small (n=18) open label trial of risperidone in young males with PTSD, showed improvement in symptom remission.[242] An RCT of risperidone as adjunctive therapy for GAD in adults showed improvement over placebo while another showed no significant difference.[243,244]

- **Lurasidone** (Latuda): Lurasidone was approved in 2010 and is indicated for schizophrenia (13+ years) and bipolar disorder (adults). Since lurasidone was approved in late 2010 we expect to see low use in our study population. Along with other atypical antipsychotics, it is recommended in adults as a second or third line therapy.[62]

Antihistamines: The antihistamine hydroxyzine, which was launched in 1956, has been used as an anxiety treatment.[15,134,245,246] In the US hydroxyzine (Vistaril, Atarax) is indicated for the "symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested" in children and adults.[247] The 2005 evidence based guidelines from the British Association for Psychopharmacology, include hydroxyzine in their list of pharmacotherapies for acute treatment of GAD based on two RCTs in adults with GAD.[15,248,249] A 2010 Cochrane review on the use of hydroxyzine for GAD in adults concluded that, while hydroxyzine was more effective than placebo, there was a lack of evidence to recommend hydroxyzine as the first line treatment for GAD and, given the low quality of evidence, they could not conclude on the efficacy of hydroxyzine compared with active comparators.[250] The World Federation of Biological Psychiatry guidelines for the pharmacological treatment of anxiety disorders published in 2012, recommended that hydroxyzine only be considered when other medications have been unsuccessful.[63] A primary deterrent of hydroxyzine use is sleepiness/drowsiness.[61,250]

Anticonvulsants: There is evidence that anticonvulsants are an effective treatment for anxiety disorders in adults.[251,252] The AACAP guidelines for anxiety disorders do not mention anticonvulsants as a treatment for anxiety disorders. However, the AACAP guidelines for PTSD says anticonvulsants may show promise in treating PTSD symptoms.[45] Because of the potential side effects, along with the lack of research, anticonvulsants are not a recommended treatment option for pediatric anxiety.[128] Anticonvulsants, while not recommended for first-line therapy, are suggested to be useful for augmentation in partial responders or among persons who cannot tolerate SSRIs.[252] The anticonvulsants included as potential treatments for anxiety are listed below with some brief details:

- **Carbamazepine** (Tegretol): Carbamazepine is indicated for epilepsy and trigeminal neuralgia.[253] A small (n=28) open label study[254] provided limited evidence that carbamazepine may be useful for children with PTSD.[255] The Canadian clinical practice guidelines recommend carbamazepine for a potential third-line treatment for PTSD in adults.[62]
- **Gabapentin** (Neurontin): In the US gabapentin is approved for postherpetic neuralgia in adults and adjunctive therapy in the treatment of partial onset seizures in patients (3+ years) with epilepsy. Off-label use of gabapentin is high, including for the management of anxiety;[256] the drug was even associated with illegal marketing, including for psychiatric conditions, resulting in a settlement.[257] There is limited evidence that gabapentin may improve anxiety disorder symptoms.[258]
- **Pregabalin** (Lyrica): In the US approved indications for pregabalin include adjunctive therapy for adult patients with partial onset seizures and fibromyalgia.[259] In the European Union and other countries, however, pregabalin is approved to treat GAD in adults. In controlled trials (4-8 weeks), 52% of pregabalin treated patients had 50%+ improvement from baseline based on HAM-A total

score compared to 38% in patients treated with placebo.[260] There is also evidence of pregabalin for treating social phobia.[252]

- **Tiagabine** (Gabitril): Tiagabine is indicated for adjunctive therapy in the treatment of partial seizures for adults and children (12+ years). Open label trials have shown tiagabine to reduce symptoms for social phobia, PTSD, GAD, and panic disorder; however, a larger RCT (n=272) showed no statistically significant difference in the reduction of symptoms compared to placebo.[252] The APA guidelines for PTSD do mention tiagabine as a newer medication that has been tested but requires larger RCTs.[231]
- **Valproate/Valproic Acid** (Depakote): In the US approved indicators for valproic acid include manic episodes associated with bipolar disorder and migraines.[261] Some limited evidence exists for the use of valproic acid in certain anxiety disorders in adults; however, the evidence is mostly from small (n=10-21) open-label studies.[252,258,262] APA guidelines for panic disorder suggest more controlled studies are needed before it can be recommended.[139]
- **Lamotrigine** (Lamictal): In the US lamotrigine is approved for epilepsy and bipolar disorder.[263] There is limited evidence that lamotrigine is an effective treatment for anxiety. A small RCT (n=15) found that patients with PTSD responded better to lamotrigine than placebo.[264]
- **Topiramate** (Topamax): In the US topiramate is indicated for epilepsy (2+ years) and migraines (12+ years).[265] In open label trials, adults with PTSD or social phobia showed improvement with topiramate.[252] In a RCT (n=38) of adults with PTSD, topiramate showed improvements over placebo.[266]
- **Levetiracetam** (Keppra): In the US levetiracetam is approved for treating seizures in people with epilepsy. An open label trial with levetiracetam in social phobia showed symptom improvement, as did a case report in patients with GAD. A later RCT did not find levetiracetam to be effective, but in another study levetiracetam was effective as augmentation in treatment-resistant PTSD.[251,252]

Anticonvulsants not included: Felbarnate, Vigabatrin, Zonisamide, Oxcarbazepine, Phenytoin.

Other medications: The additional medications listed below have been highlighted as potential treatments for pediatric anxiety.

- **Riluzole**: Riluzole is a medication indicated for patients with amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). Two open label studies in adults showed reduction in anxiety symptoms with riluzole [61,64] and it was included in a recent review on novel approaches to treat pediatric anxiety, yet an RCT in children with OCD found no significant difference compared to placebo.[267]
- **D-cycloserine**: D-cycloserine (DCS) is approved for the treatment of pediatric tuberculosis. Studies have found that DCS used to augment exposure therapy was superior to therapy alone in adults with social phobia, panic disorder, specific phobia (heights), and OCD.[128,268] A preliminary trial in children with OCD did not show any effect; however, a larger trial is underway.[128,267] DCS may be beneficial for cases when CBT was not successful or there is a need for fast treatment effects.[128]
- **Memantine** (Namenda): Memantine is used in the treatment of Alzheimer's disease, but has also been used in the treatment of anxiety disorders. The majority of research has focused on OCD, although memantine has not been formally studied in children with OCD; a small open label in adults with GAD showed promising results.[64,128] Canadian guidelines for anxiety in adults recommended memantine for a second or third line treatment for some disorders, and did not recommend it for the treatment of GAD.[62]

- **Prazosin, guanfacine, and clonidine** (alpha blockers): These medications are listed in the Anxiety Disorders Association of America list of medications prescribed for anxiety in adults, specifically for PTSD.[65] There are case reports of prazosin for youth with PTSD, but no open-label trials or RCTs.[230] A review of treatments for children with anxiety suggests that anti-adrenergics such as guanfacine and clonidine may have promise in treating pediatric anxiety.[14]

Treatments not included: Ondansetron is a serotonin antagonists that was mentioned in a few review articles for anxiety treatments in adults[61,64] based on RCT (n=54) results. However, follow-up studies have not been conducted and as it is not included in treatment guidelines it was not included. Historically barbiturates (i.e. phenobarbital, butabarbital) were used to treat anxiety, until the late 1960s when they were replaced with benzodiazepines.[245] As barbiturates were not included in any treatment recommendations, they were not included; also not included are paraldehyde and meprobamate.

Over the counter medications: There are over-the-counter, natural therapies that have been suggested to be helpful in treating anxiety. These include valerian, melatonin, kava, tryptophan/hydroxytryptophan, and St. John's Wort. This study only included prescription medications.

APPENDIX 2. ESTIMATES OF PSYCHOTHERAPY USE IN CHILDREN

The table below contains information on psychotherapy utilization. As the literature is limited on psychotherapy use in children with anxiety, the table includes available estimates in children and adults with anxiety and with other mental illnesses.

Relevant literature on psychotherapy use in children and adults with anxiety and other mental illnesses				
Datasource	Reference; Year	Age	Psychotherapy definition	Psychotherapy use finding
Medical Expenditure Panel, MEPS	Olfson, 2010[54] 1998 (n=22,953, n=220 w/anxiety); 2007 (n=29,370, n=557 w/anxiety)	All ages	Respondents asked: what type of care was provided during each outpatient visit… categories included mental health counseling or psychotherapy	By treated mental health condition, 2007: • Anxiety: Psychotherapy and medication 35% (42% in 1998), psychotherapy only 9% (20% in 1998), medication only 56% (38% in 1998) • Depression: 43% psychotherapy +medication, 6% psychotherapy only, medication only 51%
	Olfson, 2015[40] 2003-2005 (n=19,450), 2010-2012 (n=18,865)	6-17 years	Psychotherapy use=1 or more psychotherapy visit	Psychotherapy use by mental health impairment, 2003-2005 and 2010-2012 • More severe = 22.5%, 26.1% • Less severe/none= 2.7%, 3.6%
National Ambulatory Medical Care Surveys	Olfson, 2014[55] 4 surveys: 1995-2010 (n=446,542)	0-13, 14-20, 21+	Four indicators of mental health care: clinical mental disorder diagnosis, psychotropic medication prescription, psychotherapy provision, and psychiatric care	Population rates: Number of visits with psychotherapy per 100 youth (0-20 years): • 4.2 (2003-2006) • 3.2 (2007-2010)
	Jameson, 2010[269] 2006 (n=11,658 visits to primary care providers)	N/A	Receipt of referral for psychotherapy	Psychotherapy referral rates in primary care patients Patients with anxiety: • 22% rural vs. 19% nonrural Patients with depression: • 8% rural vs. 14% nonrural
	Harman, 2002[270] 5 surveys: 1985-1998 (n=3,052 visits w/anxiety diagnosis)	18+	Response to the question: 'Was psychotherapy provided or ordered during the visit'	Visits with an anxiety disorder diagnosis given: • In 1985 48% of visits psychotherapy offered alone or with medication, to 30% of visits in 1997-1998 • 1997-98: visits to a psychiatrist, 28% psychotherapy only, 39% psychotherapy and medication, and 30% medication only vs. primary care physician (2%, 3%, 55% respectively)
	Olfson, 2012[271]	0-13, 14-20,	Determined whether psychotherapy was	Among children and adolescents with a visit including antipsychotic

	1993-2009 (n= 484,889 visits)	21+	provided by the physician at the visit	treatment: • Psychotherapy provided during 31% of visits
	Mojtabai, 2008[272] 1996-2005 (n=14,108 visits to psychiatrist)	All ages	Determined whether psychotherapy was provided by the psychiatrics at the visit; limited to psychotherapy visits to those longer than 30 minutes	Visits to psychiatrist with psychiatric diagnosis • Percentage of visits involving psychotherapy: 44.4% in 1996-1997, 28.9% in 2004-2005 • 76% of psychiatric visits were by patients who had 6+ previous visits to the same psychiatrist (2005) • With GAD diagnosis: 24.8% of visits involved psychotherapy in 2004-2005, 25.2% panic disorder, 34.1% PTSD, and 29.3% social phobia
National Health Interview Survey – Child	Child health data[273] 2011/12 (n=1,795)	2-17 years	During the past 12 months, has child seen or talked to a mental health professional such as a psychiatrist, psychologist, psychiatric nurse, or clinical social worker about child's health?	• All children (nationwide): 7.9% with a mental health visit in last year
Parent/child survey	Chavira, 2004[39] Pediatric patients, university clinic (n=714; n=190 telephone interview)	8-17 years	Parents were asked yes–no questions about treatment received for anxiety, depression, and behavioral problems during the child's lifetime.	• 35% (n=66) received at least three sessions of counseling for various reasons at some point • Treatment for anxiety received: 9% medication, 28% counseling, 31% medication or counseling • Treatment for depression ever received: 20% medication, 40% counseling, 40% medication or counseling
Psychiatrist survey	Wilk, 2006[274] 1999 (n=587 psychiatrists, 3 patients each)	18+ years	Psychotherapy = if the psychiatrist indicated that he or she or another provider had provided psychotherapy in the past 30 days	• 66% of patients received some form of psychotherapy from the physician or another provider in the past 30 days (all diagnoses)
Marketscan *unclear if studies were restricted to persons with mental health services coverage	Harpaz-Rotem, 2012[20] 2005	18+ years	Psychotherapy CPT codes; Receipt of any (1) outpatient individual therapy	• Anxiety: 30% received any psychotherapy • Depression: 62% received any psychotherapy
	Olfson, 2010[124] 1999-2007	2-5 years	CPT codes for psychotherapy	• 1.2-1.3% of children received psychotherapy • 0.3%-0.2% of children on antidepressant • 41% of those treated with antipsychotics had psychotherapy
	Wu, 2012[117] 2005-2007	18-64 years	Used psychotherapy 6-months prior to antidepressant start	• Initiators of an antidepressant with MDD: 29% prior psychotherapy
	Kniesnera,	18-65	Any psychotherapy	Adults with a depression diagnosis:

	2005[275] 1990-1994	years	during the year following diagnosis	• 35% no treatment • 10% medication only • 35% Psychotherapy only • 20% combination Average # of visits: 8
IMS	Olfson, 2015[276] 2006-2010	1-24 years	Any psychotherapy; outpatient CPT codes	Psychotherapy use among people with antipsychotic prescription (all diagnoses, 2009) • 13.5% (1-6 years), 20.4% (7-12 years), 24.8% (13-18 years)
Medicaid	Stein, 2013[56] 2006-2010	6-17 years	CPT codes for psychotherapy	Minimally adequate psychotherapy (4+ visits in 12 weeks) in depressed youth starting treatment 6-11 years: 66% 12-17 years: 63%
	Finnerty, 2016[146] 2008	0-20 years	Outpatient psychosocial service: 1+ CPT code for psychosocial services	Outpatient psychosocial service prior to a new start of an antipsychotic (prior 90 days, any diagnosis) • 0-5 years: 39% • 6-12 years: 50% • 12-17 years: 52% • Patients with anxiety diagnosis = 36% (excludes other MH diagnoses)

APPENDIX 3. ANXIETY DEFINITIONS: ICD-9-CM CODES

Appendix 3 Table. Anxiety disorders: ICD-9-CM codes for cohort inclusion

DSM-5 Anxiety Disorders	ICD-9-CM
Unspecified anxiety disorder	300.00
Panic disorder (without agoraphobia)	300.01
Panic disorder with agoraphobia	300.21
Generalized anxiety disorder	300.02
Other specified anxiety disorder	300.09
Specific phobia (ICD-10, specific phobias)	300.29
Unspecified phobia	300.20
Agoraphobia (without panic attacks)	300.22
Agoraphobia with panic attacks	300.21
Social anxiety disorder (social phobia)	300.23
Separation anxiety disorder	309.21
Selective mutism	313.23
Anxiety disorder due to a general medical condition	293.84
Obsessive-compulsive disorder (OCD) *	300.3x
Post-traumatic stress disorder (PTSD) **	309.81

*Under 'Obsessive-Compulsive and Related Disorders'
**Under 'Trauma- and Stressor-Related Disorders'
ICD-9-CM: International Classification of Diseases, Ninth Revision; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition

APPENDIX 4. PSYCHOTHERAPY CPT CODES

Appendix 4 Table. CPT codes for psychotherapy visits with 2013 changes

Individual psychotherapy		2013 code changes*	
20 - 30 min.	90804, 90816	30 min. (16 - 37)	90832
45 - 50 min.	90806, 90818	45 min. (38 - 52)	90834
75 - 80 min.	90808, 90821	60 min. (53+)	90837
Interactive individual psychotherapy			
20 - 30 min.	90810, 90823	30 min. (16 - 37)	90832 + 90785
45 - 50 min.	90812, 90826	45 min. (38 - 52)	90834 + 90785
75 - 80 min.	90814, 90828	60 min. (53+)	90837 + 90785
Individual with evaluation management			
20 - 30 min.	90805, 90817	30 min. (16 - 37)	E/M code + 90833
45 - 50 min.	90807, 90819	45 min. (38 - 52)	E/M code + 90836
75 - 80 min.	90809, 90822	60 min. (53+)	E/M code + 90838
Interactive individual with evaluation management			
20 - 30 min.	90811, 90824	30 min. (16 - 37)	E/M code + 90833 + 90785
45 - 50 min.	90813 90827	45 min. (38 - 52)	E/M code + 90836 + 90785
75 - 80 min.	90815, 90829	60 min. (53+)	E/M code + 90838 + 90785
Family	90847, 90849		(no changes)
Group	90853, 90857		90853 (+90785)

*E/M codes selected based on services provided, not on time;
Psychiatric diagnostic evaluation: Pre-2013 (90801, 90802), 2013 changes (90791, 90792)

APPENDIX 5. DETAILED COVARIATE DEFINITIONS

Below are the detailed covariate definitions that are used throughout the dissertation aims. Current prevalence estimates included are from the 2011/2012 National Survey of Children's Health.

Psychiatric co-morbidities		
Variable	ICD-9-CM codes	Details/notes
Any non-anxiety psychiatric disorder	290.x – 319.x (with anxiety exclusions)	Excludes anxiety diagnostic codes as all patients have an anxiety diagnosis
Common psychiatric co-morbidities		
Adjustment disorder	309.0x, 309.22-309.29, 309.3x, 309.4x, 309.82-309.89, 309.9x,	Adjustment disorder with depressed mood (309.0); Adjustment reaction with predominant disturbance of other emotions (309.2, except 309.21); Adjustment disorder with disturbance of conduct convert (309.3); Adjustment disorder with mixed disturbance of emotions and conduct (309.4); Adjustment reaction with physical symptoms (309.82), Adjustment reaction with withdrawal (309.83), Other specified adjustment reactions (309.89), Unspecified adjustment reaction (309.9) Separate indicators for adjustment disorder with and without depression
Attention deficit disorder (ADD/ADHD)	314.x (specific code 314.0x also evaluated)	314 Hyperkinetic syndrome of childhood (314.x); Specific variable; Attention deficit disorder without mention of hyperactivity (314.00), Attention deficit disorder with hyperactivity (314.01)
Depression	296.2x, 296.3x, 300.4x, 309.1x, 311.x	Major depressive disorder (296.2x, 296.3x), Dysthymic disorder (300.4x), Depressive disorder, not elsewhere classified (311.x), Adjustment reaction: Prolonged depressive reaction (309.1) Estimate of current prevalence in children=2.2%
Other episodic mood disorder	296.9x	296.9x Other and unspecified episodic mood disorder
Disruptive behavior disorders	312.x, 313.81	Disturbance of conduct not elsewhere classified: Undersocialized conduct disorder aggressive type (312.0) and unaggressive type (312.1), Socialized conduct disorder (312.2), Disorders of impulse control not elsewhere classified (312.3), Mixed disturbance of conduct and emotions (312.4), disturbances of conduct not elsewhere classified (312.8), Unspecified disturbance of conduct (312.9); Oppositional defiant disorder (313.81) Estimate of current prevalence in children=3.2%
Other psychiatric co-morbidities		
Autism spectrum disorder; Pervasive developmental disorders	299.x	Childhood disintegrative disorder (299.1), Other specified pervasive developmental disorders (299.8), Unspecified pervasive developmental disorders (299.9) Autistic disorder (299.0) in exclusion criteria Estimate of current prevalence (Autism, Asperger's, PDD, other autism spectrum disorder) in children=1.8%

Bipolar disorder	296.0x, 296.4x - 296.8x, 301.13	Bipolar i disorder, single manic episode (296.0), Bipolar i disorder, most recent episode (or current) manic (296.4), Bipolar i disorder, most recent episode (or current) depressed (296.5), Bipolar i disorder, most recent episode (or current) mixed (296.6), Bipolar I disorder, most recent episode (or current) unspecified (296.7), Other and unspecified bipolar disorders (296.8), Cyclothymic disorder (301.13)
Developmental delay, learning disability	315.x, 784.61, V40.0	Developmental reading disorder (315.0); Mathematics disorder (315.1); Other specific developmental learning difficulties (315.2); Developmental speech or language disorder (315.3); Developmental coordination disorder (315.4); Mixed development disorder (315.5); Other specified delays in development (315.8); Unspecified delay in development (315.9); Alexia, dyslexia (784.61); Mental and behavioral problems with learning (V40.0) Estimate of current prevalence in children=3.6% (learning disabilities in children=8.0%)
Eating disorders	307.1, 307.5	Anorexia nervosa (307.1), Other and unspecified disorders of eating (307.5)
Enuresis, encopresis	307.6, 307.7, 788.36	Enuresis (307.6), encopresis (307.7), nocturnal enuresis (788.36)
Intellectual disabilities	317-319; 758.0x, 759.83	Mild intellectual disability (317), Other specified intellectual disabilities (318), Unspecified intellectual disabilities (319); Down's syndrome (758.0), Fragile X Syndrome (759.83) Estimate of current prevalence in children=1.1%
Personality disorder	301.x	
Schizophrenia	295.x	
Sleep disorders	307.4x, 327.x, 347.x, 780.5x	Specific disorders of sleep of nonorganic origin (307.4); Organic sleep disorders (327); Cataplexy and narcolepsy (347); Sleep disturbances (780.5)
Substance use disorder	291-292.x, 303-305.x	Alcohol-induced mental disorders (291), Drug-induced mental disorders (292), Alcohol dependence syndrome (303), Drug dependence (304), Nondependent abuse of drugs (305)
Tics	307.2x	Tic disorder unspecified (307.20), Transient tic disorder (307.21), Chronic motor or vocal tic disorder (307.22), Tourette's disorder (307.23) Estimate of current prevalence (Tourette's) in children=0.2%
Neurasthenia	300.5x	(removed from DSM)
Gender identify disorder	302.6x, 302.85	Gender identity disorder in children (302.6x); Gender identity disorder in adolescents or adults (302.85)
Somatoform disorders	300.8x	

Non-psychiatric co-morbidities		
Variable	ICD-9-CM codes	Details/notes
Acne	706.0x, 706.1x	Acne varioliformis (706.0), Other acne (706.1)
Allergic rhinitis	477.x	-
Anemia	280.x - 285.x	Iron deficiency anemias (280); Other deficiency anemias (281); Hereditary hemolytic anemias (282); Acquired hemolytic anemias (283); Aplastic anemia and other bone marrow failure syndromes (284); Other and unspecified anemias (285)
Asthma	493.x	- Estimate of current prevalence in children=8.8%
Cancer, malignant	140.x – 209.x	-
Cardiac disorders (Elizhauser, 1998)	See note	Congestive heart failure: 398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.x Cardiac arrhythmias: 426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V45.0, V53.3 Vascular disease: 093.2x, 394.0x-397.1x, 424.0x-424.91, 746.3-746.6, V42.2, V43.3 Pulmonary circulation disorders: 416.x, 417.9x
Cerebral palsy	343.x	- Estimate of current prevalence in children=0.2%
Diabetes (type I and type II)	249.x, 250.x	Diabetes mellitus, type 1 and type 2 (250); Secondary diabetes mellitus (249) Estimate of current prevalence in children=0.3%
Epilepsy, recurrent seizers; convulsions	345.x, 780.3x	Epilepsy and recurrent seizures (345); Convulsions (780.3)
Fainting, dizziness	780.2x, 780.4x	Syncope and collapse (780.2x), Dizziness and giddiness (780.4x)
Gastroesophageal reflux disease	530.81	Esophageal reflux (530.81)
Hearing loss/problem	388.12, 388.2x, 388.4x, 389.x, 744.0x, V41.2	Noise-induced hearing loss (388.12); Sudden hearing loss, unspecified (388.2); Other abnormal auditory perception (388.4); Hearing loss (389.); Congenital anomalies of ear causing impairment of hearing (744.0); Problems with hearing (V41.2) Estimate of current prevalence in children=1.2%
Hypertension	401.x – 405.x	Hypertensive disease: Essential hypertension (401), Hypertensive heart disease (402), Hypertensive chronic kidney disease (403), Hypertensive heart and chronic kidney disease (404), Secondary hypertension (405)
Hypothyroidism	243.x, 244.x	Congenital hypothyroidism (243), Acquired hypothyroidism (244)
Injury (800-999)		
Burn	940.x-949.x	-
Fracture, dislocation, sprain (excluding skull)	805.x – 848.x	Fracture Of Spine And Trunk (805-809), Fracture Of Upper Limb (810-819), Fracture Of Lower Limb (820-829), Dislocation (830-839), Sprains And Strains Of Joints And Adjacent Muscles (840-848)
Head/brain injury, concussion	800.x – 804.x, 850.x – 854.x, 959.01, 873.0x, 873.1x	Fracture Of Skull (800-804); Intracranial Injury, Excluding Skull Fracture (850-854): Concussion (850), Cerebral laceration and contusion (851), Subarachnoid subdural and extradural hemorrhage following injury (852), Other and unspecified intracranial hemorrhage following injury (853), Intracranial injury of other and unspecified nature (854); Head injury, unspecified (959.01); Open wound of scalp (873.0, 873.1) Estimate of current prevalence in children=0.3%

Poisoning from drug, biologic	960.x-979.x	Poisoning by drugs, medicinals and biological substances (960-979)
Other injury	860.x-872.x, 873.2x-904.x, 910.x-939.x, 950.x-959.x, 980.x-999.x	Internal injury of chest, abdomen, and pelvis (860-869); Open wound of head, neck, and trunk (870-872, 873.2-879); Open wound of upper limb (880-887); Open wound of lower limb (890-897); Injury to blood vessels (900-904); superficial injury (910-919); Contusion with intact skin surface (920-924); crushing injury (925-929); Effects of foreign body entering through orifice (930-939); Injury to nerves and spinal cord (950-957); Certain traumatic complications and unspecified injuries (958-959); Toxic effects of substances chiefly non-medicinal as to source (980-989); Other and unspecified effects of external causes (990-995); Complications of surgical and medical care, not elsewhere classified (996-999)
Migraine, Chronic headache	346.x, 339.02, 339.04, 339.12, 339.22	Migraine (346); Chronic cluster headache (339.02); Chronic paroxysmal hemicrania (339.04); Chronic tension type headache (339.12); Chronic post-traumatic headache (339.22)
Multiple sclerosis	340.x	-
Muscular dystrophy	359.x	Muscular dystrophies and other myopathies (359)
Overweight, Obesity	278.0x	Obesity, unspecified (278.00), Morbid obesity convert (278.01), Overweight convert (278.02), Obesity hypoventilation syndrome (278.03)
Physiological development	783.22, 783.4x	Lack of expected normal physiological development in childhood: Lack of normal physiological development, unspecified (783.40), Failure to thrive (783.41), Delayed milestones (783.42), Short stature (783.43); Underweight (783.22)
Rheumatoid arthritis, inflammatory	714.x	Rheumatoid arthritis and other inflammatory polyarthropathies (714)
Speech problems, disturbances	307.0, 438.1x, 478.3x, 784.3x, 784.4x, 784.5x, V40.1, V41.4, V57.3	Stuttering, adult onset (307.0); Speech and language deficits, late effects of cerebrovascular disease (438.1); Paralysis of Vocal Cords (478.3); Aphasia (784.3); Voice disturbance (784.4); Other speech disturbance (784.5); Mental and behavioral problems with communication including speech (V40.1); Problems with voice production (V41.4); Care involving speech-language therapy (V57.3) Developmental speech/language disorder under 'Development delay' Estimate of current prevalence (speech disorders) in children=4.8%
Spine curvature (scoliosis, kyphosis)	737.x	Adolescent postural kyphosis (737.0), Kyphosis, acquired (737.1), Lordosis, acquired (737.2), Kyphoscoliosis and scoliosis (737.3), Curvature of spine associated with other conditions (737.4), Other curvatures of spine (737.8), Unspecified curvature of spine (737.9)
Urinary incontinence	788.3x (no 788.36)	Excluding nocturnal enuresis (788.36)
Visual disturbance/loss	366.53, 368.x, 369.x, 379.53, 438.7x, 743.42, V41.0	After-cataract, obscuring vision (366.53), Visual disturbances (368); Blindness and low vision (369); Visual deprivation nystagmus (379.53); Late effects of cerebrovascular disease, disturbances of vision (438.7); Corneal opacities, interfering with vision, congenital (743.42); Problems with sight (V41.0) Estimate of current prevalence in children=1.3%

Anxiety related measures		
Unspecified anxiety diagnosis	300.00	• Diagnosis of unspecified/not otherwise specified
Inpatient anxiety diagnosis	-	• Anxiety diagnosis in an inpatient setting, considered more severe
Physiological symptoms related to psychological factors	306.x, 307.8x	• Physiological malfunction airing from mental factors (306.x); Pain disorders related to psychological factors (307.8) • Note: Codes do not specify the related mental disorder
Additional markers for anxiety related diagnoses	308.x, 313.0x, 313.21, 313.22	• Acute reaction to stress (308.x); Overanxious disorder specific to childhood and adolescence (313.0x); Shyness disorder of childhood (313.21); Introverted disorder of childhood (313.22)
Anxiety-related symptoms 3 months prior to index date	780.7x, 783.21, 784.0x, 785.1x, 786.01, 786.50, 787.01, 787.02, 789.0x,	• Abdominal pain (789.0); Chest pain, unspecified (786.50); Headache (784.0); Hyperventilation (786.01); Malaise and fatigue (780.7); Nausea with vomiting (787.01); Nausea alone (787.02); Palpitations (785.1); Weight loss (783.21)
Place of service	Associated with the anxiety diagnosis; grouped based on available MarketScan classification	• Office (#11) • (All others grouped into non-office category)

Depression severity measures		
Specific depression diagnosis	Above definition without 311.x	• Exclude 311.x (not otherwise specified) from depression definition
Inpatient depression diagnosis	-	• Depression diagnosis given in an inpatient setting (considered more severe)
Number of depression diagnoses	-	• Count of depression diagnoses during the baseline period
Recent depression diagnosis	-	• Based on whether the most recent depression diagnosis was within 30 days of indexdate or not
Suicidality measures		
Self-harm related behaviors	E950 – E959	• Inpatient and outpatient codes • Late effects (E959.x) included for baseline covariate • Aim 2 outcome definition more specific, in aim 2 text
Suicide ideation	V62.84	• Inpatient and outpatient codes • Code new in late 2005, not included in all analyses
Injury with an undetermined intent	E980 – E989	• Inpatient and outpatient codes • Codes represent injury events that may have been accidental or purposeful • Late effects (E989.x) included for baseline covariate

Healthcare utilization measures	
Variable	Details
Outpatient, problem oriented visits	• Count of outpatient visits (allowing for 1 visit a day) • CPT codes: 99201, 99202, 99203, 99204, 99205, 99211, 99212, 99213, 99214, 99215 Estimates in children (prior year) office visits to healthcare professional: 0/1 visit=30%, 2-3 visits=38%, 4+ visits=32%
Outpatient, well/preventative visit	• CPT codes: 99381, 99382, 99383, 99384, 99385, 99391, 99392, 99393, 99394, 99395, 99461 • V-codes: V20.2, V20.3, V70.0, V70.3, V70.5, V70.6, V70.8, V70.9
Inpatient psychiatric hospitalization	• Inpatient hospitalization with a psychiatric diagnostic code (290.x-319.x) as the primary diagnosis (psychiatric diagnosis in the primary/first-listed diagnosis) or secondary diagnoses
Inpatient non-psychiatric hospitalizations	• Inpatient hospitalization without an ICD-9 code of 290-319 as the primary or secondary diagnosis Estimate in children (prior year) hospitalized overnight: 2.3%
ER visits	• Count of ER visits, unique events required to have at least 1 day between date of ER services • Defined with variable SVCSCAT=Service Sub-Category Code (code indicating a detailed category of service, inpatient/outpatient), and for 2004 defined with the place of service of ER - hospital (STDPLAC=23) • Indicator added for ER visits related to anxiety and injury, defined in text under aim 3 Estimates in children (prior year) ER visits: 1=12%, 2+=6%
Psychological evaluation	• CPT codes: 90801, 90802, 90791, 90792
Screened for mental disorder, developmental handicap	• V70.1x, V70.2x, V71.0x, V79.x • General psychiatric examination requested by the authority (V70.1); General psychiatric examination other and unspecified (V70.2); Observation for suspected mental condition (V71.0); Screening for depression (V79.0); Screening for alcoholism (V79.1); Screening for mental retardation (V79.2); Screening for developmental handicaps in early childhood (V79.3); Screening for other specified mental disorders and developmental handicaps (V79.8); Screening for unspecified mental disorder and developmental handicap (V79.9)

Medication variables	
Non-SSRI anti-anxiety medications	• Medication list in table under aim 1
Count of prescriptions medications	• Count of distinct medication classes defined based on MarketScan groupings of therapeutic classes (THERCLS) **Estimate in children: regularly taken prescription medication for at 3+ months=13%
Opioid	• Buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, opium, oxycodone, oxymorphone, pentazocine, propoxyphene, tapentadol, tramadol
ADHD medication (stimulants)	• Generic names (pre-specific exclusions): Amphetamine-dextroamphetamine, amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, atomoxetine, clonidine, guanfacine, modafinil, pemoline Estimates in children: currently have ADD/ADHD and take medication for this condition: 5.4%
Asthma medications	• Albuterol, aminophylline, arformoterol, beclomethasone, budesonide, budesonide-formoterol, ciclesonide, cromolyn, dyphylline, dyphylline-guaiFENesin, flunisolide, fluticasone, fluticasone-salmeterol, formoterol, formoterol-mometasone, guaiFENesin-theophylline, levalbuterol, mometasone, montelukast, omalizumab, pirbuterol, salmeterol, theophylline, zafirlukast, zileuton
Antipsychotics	• (Separate from selected atypical antipsychotics listed under aim 1) • Generic names (pre-specific exclusions): quetiapine, aripiprazole, ziprasidone, olanzapine, risperidone, lurasidone, asenapine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, molindone, paliperidone, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, trifluoperazine, acepromazine, droperidol, lithium, mesoridazine, promazine, trifluprom azine

Additional child covariates		
Variable	Details or ICD-9 codes	Primary categories or ICD-9 details
Provider type	Associated with the anxiety diagnosis; grouped based on available MarketScan classifications (STDPROV variable)	• Psychiatry (#365), Child psychiatry (#458) • Psychologist (#860) • Family practice (#240) • Pediatrician (#400) • Therapists (Supportive) (#853)
Exposure to psychiatrist	Diagnosis from a psychiatrist prior to the anxiety diagnosis (STDPROV variable)	• 365=Psychiatry, 485=Pediatric psychiatry
Region, division	Geographical state of primary beneficiary's residence	• Grouped by region (4) or division (8)
Family difficulties marker	V61.0x, V61.20, V61.23-V61.29, V61.4x, V61.8x, V61.9x	Family disruption (V61.0); Counseling for parent-child problem unspecified (V61.20): parent-biological child (V61.23), parent-adopted child (V61.24), parent-foster child (V61.25); Other parent-child problems (V61.29); Health problems within family (V61.4): Alcoholism (V61.41), Substance abuse (V61.42), Other health problems (V61.49); Other specified family circumstances (V61.8); Unspecified family circumstance (V61.9)
Marker for child trauma, neglect	V15.4x, V61.21, V71.81, 995.5x, 995.80-995.85, E967.x	Personal history of psychological trauma presenting hazards to health (V15.4); Counseling for victim of child abuse (V61.21); Observation for suspected abuse and neglect (V71.81); Child maltreatment syndrome (995.5); Adult maltreatment/abuse (995.80-5); Perpetrator of child and adult abuse (E967)
Housing, economic concerns	V60.0x-V60.2x, V60.8x-V60.9x	Lack of housing (V60.0); Inadequate housing (V60.1), Inadequate material resources (V60.2); Other specified housing or economic circumstances (V60.8); Unspecified housing or economic circumstance (V60.9)
Problems related to lifestyle	V69.x	Lack of physical exercise (V69.0); Inappropriate diet and eating habits (V69.1); High-risk sexual behavior (V69.2); Gambling and betting (V69.3); Lack of adequate sleep (V69.4); Behavioral insomnia of childhood (V69.5); Other (V69.8); Unspecified (V69.9)

Parent variables		
Variable	Details	Primary categories
Psychiatric diagnoses	Covariates defined with same ICD-9 or CPT codes used to define child-level covariates	• Anxiety • Depression • Adjustment disorder • Substance abuse • Other psychiatric diagnosis (ICD-9: 290-319)
Self-harm event		-
Well-visit		-
Psychotherapy		-
Medication use	Indicators for each medication with SSRIs and benzodiazepines defined same as for children; adherence measures calculated for SSRIs, statins, antihypertensives	• Benzodiazepine • SSRI • Statin: Atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin • Antihypertensive: Ace inhibitors and calcium channel blockers, aliskiren and hydrochlorothiazide, angiotensin ii antagonists and diuretics, azilsartan medoxomil, benazepril, bendroflumethiazide, bisoprolol and thiazides, candesartan, captopril, chlorothiazide, deserpidine and diuretics, enalapril, eprosartan, fosinopril, hydrochlorothiazide, hydroflumethiazide, irbesartan, lisinopril, losartan, methyclothiazide, methyldopa and diuretics, metoprolol and thiazides, moexipril, nadolol and thiazides, olmesartan medoxomil, perindopril, polythiazide, propranolol and thiazides, quinapril, ramipril, rauwolfia alkaloids, reserpine, telmisartan, timolol and thiazides, trandolapril, trichlormethiazide, valsartan

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