Trends & Patterns of Psychotropic Medication Use among Medicaid-insured Youth

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Dedication

To my parents. I would like to thank my parents for their patience on my study.

To my family, for the time I missed, and future moments that will be cherished.

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I would like to acknowledge my advisors, Dr. Zito and Dr. Young, for their invaluable feedback and your mentorship which has been instrumental in shaping both my research and my academic development. I would like to thank the members of the dissertation committee, Dr. Scott Quinlan and Dr. Angelo Elmi for their guidance and support in the development and completion of this dissertation. I would also like to thank Drs. Robert Penfold and Emma Stapp for serving as readers of this dissertation, and Dr. Sean Cleary for his support in my first couple years in the program.

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Abstract of Dissertation

Trends & Patterns of Psychotropic Medication Use among Medicaid-insured Youth

Background: Psychotropic Medication use for mental health conditions in youth has expanded greatly since the mid-1990s. Among them, 50-75% of psychotropic medications are used for indications that lack approval by the US FDA, and are therefore prescribed off-label, i.e. failing to be evaluated in clinical trials to yield evidence that the benefits exceed the risks.

Psychotropic polypharmacy or concomitant drug treatment, especially stimulant polypharmacy with antipsychotics (ATP), antidepressants (ATD) and anticonvulsant mood stabilizers (ATC-MS), in youth has been more common due to the increasing prevalence, early identification, and comorbidities of more than one psychiatric disorder. The public health concerns regarding the use of 3 or more class stimulant polypharmacy requires additional research to understand the details of the prevalence, patterns of use, polypharmacy changes, polypharmacy duration, types of polypharmacy regimens and their association with adverse drug events. Most published pediatric studies have focused on the prevalence of 2 or more class stimulant polypharmacy in a cross-sectional, typically one year framework. Higher number of stimulant class polypharmacy, for example, 3, 4, and 5 class stimulant polypharmacy, has not been fully investigated in a long-term follow-up cohort in terms of the prevalence, duration, polypharmacy changes, types of polypharmacy (concomitant) regimens and association with incident type 2 diabetes (T2DM).

Method: The data source of the dissertation comprises the 2007-2014 Medicaid administrative claims data of 2–17-year-olds from a mid-Atlantic state which included enrollment files, outpatient and physician claims files and dispensed prescription drug files. The files in the data source were linked together via an encrypted identification number.

In study 1, the comparison of patient factors between stimulant treated and treatment date-matched non-stimulant treated patients were conducted via χ^2 test. The association between patients' factors and stimulant polypharmacy were evaluated using logistic regression models.

In study 2, the demographic characteristics and clinician-reported psychiatric diagnosis in the stimulant monotherapy group, maximum 2, 3, 4 and 5 number of psychotropic classes (NPCs) between different groups were compared using $\chi 2$ analysis. Duration of NPC changes was calculated and presented as median, and interquartile range (IQR). The association between patient factor sand various maximum NPC regimens was assessed by competing-risk analysis using Fine and Gray's proportional hazards regression model and is reflected by the sub-hazard ratio (SHR).

In Study 3, the absolute risk of incident type 2 diabetes (T2DM) per 10,000 person-months was calculated in each category of number of polypharmacy classes and cumulative duration groups. The more than 120 baseline and time-dependent risk factors for pediatric T2DM were summarized as disease risk scores using discrete time failure model. The final discrete failure time model was fitted using logistic regression model, which was adjusted for disease risk score, number of polypharmacy classes and selected

demographic factors. The adjusted hazard ratio for each demographic factor was calculated.

Results:

Study 1:

The prevalence of stimulant users (16.5%,) in the entire group of 2–17-year-olds with 3-8 years continuous enrollment was approximately 2 times higher than that reported in studies with 1 year follow-up time using annual datasets. Compared with non-stimulant users, stimulant users (N=43,700) were more frequently male, white, aged 6–11 years, more often in foster care or with Supplemental Security Income (SSI), and with 7-8 years of enrollment and had externalizing disorders reported. The duration of stimulant exposure was substantial (487 median days). After adjusting other factors, the youth who were 6-11 years old, male, white, in foster care or SSI, and had 7-8 years of continuous enrollment were more likely to receive 3-5 class stimulant polypharmacy. In these 3-5 class stimulant polypharmacy users, the most prevalent combinations were stimulants with antipsychotics (ATP), antidepressants (ATD) or anticonvulsant mood stabilizers (ATC-MS).

Study 2：

Among 30,294 *new* stimulant users (no stimulant exposure in 180 days prior to first stimulant dispensing), 75.5% (N=22,882) were on stimulant monotherapy, 16.5% (N=5,004) had maximum 2 NPC; 5.4% (N=1,634); 2.2% (N=671); and 0.3% (N=103) had maximum 3, 4 and 5 NPC regimens, respectively. The NPC change pathways are

complex: 65.3% of patients stayed with 2 NPC until the end of study; 56.2% and 57.1% patients stayed with 3 NPC or 4 and 5 NPC regimens combined, respectively. For patients with a given NPC, some decreased to a lower NPC. For example, 548 patients (24.7%) dropped from 3 NPC to 2 NPC. The patients who started concomitant use took substantial time to change to the next higher or lower NPC or to stay at the same NPC. For example, 223 days for staying in 2 NPC, and 417 median days for dropping from NPC 5 to NPC 3. Competing risk analysis was applied to investigate the association between patient factors and 2-5 NPCs (event of interest or outcome variable): age group 12-17 years, white, patients in foster care or SSI, and with 3-4 years continuous enrollment were significantly related to 2-5 NPCs. Antipsychotics (ATP), antidepressants (ATD), and anticonvulsant mood stabilizers (ATC-MS) were the most frequent psychotropic class combinations used.

Study 3：

Among 30,112 new stimulant users aged 2-17 years old, with an average 6.4 years of follow-up, 43 patients had incident T2DM diagnosis following initiation with stimulants, 30,069 patients were non-diabetic. Compared to non-diabetic patients, T2DM patients were more frequent among 6–11-year-olds, females, African Americans, 7–8-year continuous enrollees, those with disability or poverty coverage and had disease risk scores greater than 75%. The absolute risk (AR) of incident T2DM increased with the higher class and longer duration of polypharmacy regimens, especially for 3 to 5 class stimulant polypharmacy regimens with antipsychotics (ATP), antidepressants (ATD), and anticonvulsant mood stabilizers (ATC-MS). The relative risk (RR) of patients factors showed stimulant polypharmacy with ATP, ATD or ATC-MS were significantly more

likely to develop T2DM for 3 class or 4 and 5 combined class psychotropic polypharmacy [RR=2.58, 95% CI (1.05,6.82) and 5.81, 95% CI (2.29,14.75), respectively] and for longer cumulative duration (120-779 days) in 4 and 5 class combined stimulant polypharmacy [RR=3.78, 95% CI (1.16,12.40)].

Conclusions and Significance:

Psychotropic medication concomitant use (polypharmacy) in youth has increased greatly in the past 30 years and the use patterns have grown complex and we are still largely unclear about the effectiveness and safety of these polypharmacy regimens. The findings of this dissertation show stimulant polypharmacy, particularly 3-5 class polypharmacy, has a substantial prevalence, a complex flux of use patterns, long polypharmacy durations, and is significantly associated with incident T2DM. Collectively, the findings from the three studies can guide pediatric psychotropic drug prescription practice monitoring and improve the clinical practice for children and adolescents with emotional and behavioral disorders. The findings provide new information for future studies to investigate the appropriateness, effectiveness and safety of polypharmacy, in other databases, in vulnerable populations, particularly foster care insured youth, and in robust simple trial designs, which can support clinical practice and policy change in the Medicaid use population.

Table of Contents

Dedication iv

Acknowledgements v

Abstract of Dissertation vi

List of Tables xvi

List of Abbreviations xix

Chapter 1: Introduction 1

Chapter 2: Background and Specific Aims 4

2.1 U.S. Pediatric Psychiatric Disorders and their Treatment 4

2.2 Medicaid & Government Oversight 9

2.3 Psychotropic Medications 10

2.4 Pediatric Psychotropic Medication Use 11

2.5 Pediatric Polypharmacy 16

2.5.1 Metrics for Polypharmacy 19

2.5.2 Database and polypharmacy study design 21

2.5.3 Psychiatric diagnosis group 22

2.5.4 Outcomes Reported in Pediatric Psychotropic Polypharmacy Studies 23

2.6 Risks vs. Benefits of Pediatric Polypharmacy 35

2.6.1 Benefits 35

2.6.2 Risks 35

2.7 Summary 41

2.8 Specific Aims 42

Chapter 3: Study 1 43

3.1 Abstract: 44

3.2 Introduction 46

3.3 Method 47

3.3.1 Study Design 47

3.3.2 Setting 47

3.3.3 Procedure to Identify Medication Exposures 48

3.3.4 Outcome Measures 49

3.3.5 Statistical Analysis 51

3.4 Results 52

3.5 Discussion 56

3.5 Conclusion 61

3.6 Clinical Implications 61

Chapter 4: Study 2 71

4.1 Abstract 72

4.2 Introduction 74

4.3 Methods 75

4.3.1 Data Source 75

4.3.2 Study Design and Study Population 76

4.3.3 Psychotropic Medication and Concomitant Use 77

4.4 Statistical Analysis 79

4.5 Results 80

4.7 Discussion 84

4.8 Conclusions 89

4.9 Clinical Implications 89

Chapter 5: Study 3 96

5.1 Abstract 97

5.2 Introduction 99

5.3 Methods 100

5.3.1 Data source 100

5.3.2 Study Design and Study Population 100

5.3.3 Incident T2DM 101

5.3.4 Psychotropic Medication and Polypharmacy 103

5.3.5 Patient Characteristics as Risk Factors 103

5.3 Outcome Measures 104

5.4 Statistical Analysis 106

5.5 Results 107

5.6 Discussion 111

Chapter 6: Conclusions and Future Directions 122

References Cited 136

List of Figures

Chapter 2 (Background and Specific Aims)

Figure 2-1. Flow chart of the review process 18

Chapter 3 (Study 1)

Figure 3-1. Flow chart for cohort selection 62
Figure 3-2. Days of stimulant exposure (duration)* total and by age group, eligibility group and length of enrollment 63

Chapter 4 (Study 2)

Figure 4-1. Detailed Patterns of Stimulant Monotherapy and Concomitant Use According to NPCs* 94
Figure 4-2. Graphic Description of Range of Time from Stimulant to Maximum NPC* 95

Chapter 5 (Study 3)

Figure 5-1. Flow Chart for the Study Cohort of Medicaid-insured Youth (2-17 year olds) who were New Users of Stimulant, 2007-2014 116

Appendix B: Chapter 4 (Study 2) Supplemental Figures

S Figure 4-1. Patient's Journey Through NPCs 156
S Figure 4-2. Flow Chart for Cohort Selection 157
S Figure 4-3. Cox Proportional Hazards and Fine and Gray's Sub-distribution Hazard Function 159

Appendix C: Chapter 5 (Study 3) Supplemental Figures

S Figure 5-1. Operational Definition of Incident Type 2 Diabetes 167
S Figure 5-2. Absolute Risk of Incident Type 2 Diabetes per 10,000 Person-Months According to Disease Risk Score 168
S Figure 5- 3. Conceptual diagram to describe the direct and indirect causal pathway 169

List of Tables

Chapter 2 (Background and Specific Aims)

Table 2-1. Key metrics and findings from child and adolescent polypharmacy literature, 2000-2020 27

Chapter 3 (Study 1)

Table 3-1. Prevalence of stimulant use among long-term Medicaid enrollees in 2007-2014: total, by age group and eligibility category 64

Table 3-2. Demographic, administrative characteristics, and prevalence of stimulant treated and treatment date-matched comparison youth with no stimulant use among those with 3-8 years of continuous Medicaid enrollment 65

Table 3-3. Polypharmacy (60 or more days overlap) in stimulant users by age group in 2007-2014 67

Table 3-4. Polypharmacy (60 or more days overlap) in stimulant users by clinician-reported diagnostic subgroup in 2007-2014 68

Table 3-5. Logistic regression analysis for 3 or more class stimulant concomitant use (polypharmacy) vs. stimulant only and 2 class stimulant polypharmacy 69

Table 3-6. Frequency of 3 and 4 class concomitant regimens in stimulant polypharmacy by age group among stimulant users 70

Chapter 4 (Study 2)

Table 4-1. Demographic and Administrative Characteristics of Stimulant Monotherapy Users and Stimulant Concomitant Users Among Those with 1-7.5 Years of Continuous Enrollees 90

Table 4-2. Adjusted Sub-hazard Ratio for Stimulant Monotherapy to Maximum NPC Using Competing Risk Model Compared with Binary Model (Column 8 and 9) 91
Table 4-3. Top Three NPC Regimens 93

Chapter 5 (Study 3)

Table 5-1. Baseline Characteristics of Diabetic and Non-diabetic New Stimulant Users.....117
Table 5-2. Absolute and Relative Risk of Incident Type 2 Diabetes According to Exposure to Stimulant Monotherapy and Polypharmacy* 119
Table 5-3. Absolute and Relative Risk of Incident T2DM According to Cumulative Duration of Stimulant Polypharmacy including ATP or ATD or ATC-MS* 120
Table 5-4. Comparison of Current Findings with Published Studies* 121

Appendix A: Chapter 3 (Study 1) Supplemental Tables

S Table 3-1. Clinician-reported psychiatric diagnoses from ICD-9 codes.....153
S Table 3-2. Clinician-reported psychiatric diagnosis in stimulant users and treatment date-matched group with no stimulants among those with 3 or more years of continuous enrollment in Medicaid.....153
S Table 3-3. Detailed diagnostic patterns among stimulant users.....155

Appendix B: Chapter 4 (Study 2) Supplemental Tables

S Table 4-1. Psychotropic Medication Classes.....158
S Table 4-2. Clinician-reported Psychiatric Diagnoses from ICD-9 Codes.....158
S Table 4-3. N and Percent of Patients with Stimulant Monotherapy and NPC changes (N=38,902) 161

S Table 4-4. Duration for Stimulant monotherapy and NPCs According to Median and Range (days) 163
S Table 4-5. Median and Range (days) to Maximum NPC 164
S Table 4-6. Distribution of Clinician-reported Comorbid Psychiatric Diagnosis in Stimulant Monotherapy Users and NPC Users According to Maximum NPC 165
S Table 4-7. Trends of Next NPC 166

Appendix C: Chapter 5 (Study 3) Supplement Tables

S Table 5-1. Operational Definition of Incident Type 2 Diabetes 169
S Table 5-2. Operational Definition of Study Covariates in a Range of Clinical, and Other Health Care Utilization Characteristics 170
S Table 5-3. Baseline Characteristics of Incident Type 2 Diabetes Patients According to Stimulant Monotherapy and Stimulant Polypharmacy 179
S Table 5-4. Adjusted Risk Ratio of Patient Characteristics for Incident Type 2 Diabetes 180
S Table 5-5. Stimulant Polypharmacy Regimens in Diabetic and Non-diabetic Patients* 181
S Table 5-6. Distribution of Clinician-Reported Comorbid Psychiatric Diagnosis in Diabetic and Non-Diabetes Patients 183
S Table 5-7. Frequency of Psychotropic Drugs Among Diabetic and Non-diabetic Patients 184

List of Abbreviations

AA	Alpha agonist
AAP	Atypical Antipsychotic
ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
ATC-MS	Anticonvulsant-Mood Stabilizer
ATD	Antidepressant
ATP	Antipsychotic
AR	Absolute Risk
AX	Anxiolytic
BD	Behavioral Disorder
CD	Conduct Disorder
LD	Learning Disorder
NAMCS	National Ambulatory Medical Care Survey
NHAMCS	National Hospital Ambulatory Medical Care Survey
ODD	Oppositional Defiant Disorder
OR	Odds Ratio
RR	Relative Risk
SCHIP	State Children's Health Insurance Program

SSI	Supplemental Security Income
SSRI/SNRI	Selective Serotonin Reuptake Inhibitor/ Serotonin and Norepinephrine Reuptake Inhibitors
TANF	Temporary Assistance for Needy Families
T2DM	Type 2 Diabetes

Chapter 1: Introduction

Mental health disorders [1-7] and their treatment in children and adolescents have become an important public health issue in the U.S. in the past 3 decades, due to the increasing diagnostic prevalence, early identification, and impact on the child, family, and community [5, 6, 8].

Among 2-17 year old youth, 9.4% (6.1 million) are diagnosed with ADHD (attention-deficit/hyperactivity disorder) [3], 7.1% (4.4 million) are diagnosed with anxiety [4], and 3.2 % (1.9 million) are diagnosed with depression [4]. It is common that some of the disorders occur together as comorbidities. For example, 73.8% of 3–17-year-olds with depression are also diagnosed with anxiety and 32.3% of 3–17-year-olds with anxiety are also diagnosed with depression [4]. Psychotropic medication is one of the most common therapies for mental health disorders. The prevalence of psychotropic medication use in youth has increased greatly in the past 30 years: the prevalence of use of several classes of medication grew 2- to 3- fold from 1987 to 1996 [9] and again from 1997 to 2006 [10].

In addition to the increasing prevalence of comorbid psychiatric disorders, is the increased prevalence of psychotropic polypharmacy, which is the use of more than one class of psychotropic medication at the same time. Psychotropic polypharmacy is defined in administrative claims data variously as concomitant psychotropic medication regimens of more than 1 psychotropic medication class (or drug) with 30-60 days overlapping days allowing for up to 15-day gaps for prescription refill.

Psychotropic polypharmacy has grown significantly in youth in the last decade [11-45]. High prevalence of polypharmacy was observed not only for 2 or more classes, but for 3 or more and 4 or more classes as well. In one study, 41.3% of medicated Medicaid youth enrollees received 3 or more classes concomitantly and 15.9% received 4 or more classes concomitantly in 2004 [41]. The time to initiation of polypharmacy and polypharmacy duration were reported in a cross-sectional framework in several studies [32, 46, 47]. Polypharmacy is a concern because there is insufficient evidence of benefits while there is increased risk of serious adverse events, including development of type 2 diabetes. Few studies have investigated the association between psychotropic polypharmacy and type 2 diabetes in the pediatric population [48-50]. Two studies [49, 50] found that concomitant use of an atypical antipsychotic (AAP) and stimulants was not associated with incident T2DM, while one study [48] showed the significant association between concomitant use of AAP and incident T2DM [RR=5.71, 95%CI 1.35-24.07].

However, knowledge gaps still exist. Understanding the details of polypharmacy metrics in terms of the clinical implications is not clear. The prevalence and incidence of polypharmacy in terms of the precise number of concomitant medications and in relation to specific diagnostic groups have not been adequately studied. No study has investigated the time from initiation of monotherapy to maximum polypharmacy across multiple years or polypharmacy duration profiling patients' journeys in community treatment settings. To date, no study has evaluated the association between the 3 or more class stimulant polypharmacy and the risk of treatment-emergent, incident type-2 diabetes in youth. This thesis further investigated the prevalence of stimulant polypharmacy, explored the trends

and patterns of psychotropic medication use, and studied the association of stimulant polypharmacy and incident T2DM among Medicaid-insured youth.

The dataset comprises Maryland 2007-2014 Medicaid claims data, as Medicaid-insured youth are more likely to receive mental health services, particularly children with disabilities and those in the foster care system than their privately-insured counterparts [51]. The Medicaid claims data include enrollment files, pharmacy claim files, and claim files for outpatient and physician services.

Chapter 2: Background and Specific Aims

2.1 U.S. Pediatric Psychiatric Disorders and their Treatment

Mental, emotional and behavioral conditions (collectively referred to as psychiatric diagnoses) and their treatments in children and adolescents have become an important public health issue in the U.S. in the past thirty years. This is largely due to its increasing prevalence, early identification, and impact on the child, family, and community. Population-based studies have consistently reported an increasing prevalence of community-based (as opposed to research validated) psychiatric diagnoses, which are conditions assessed and treated by physicians and other prescribers in community treatment settings. Population-based measures of medical care are based on health service users per 100 persons eligible for a service. Common pediatric psychiatric conditions include attention-deficit/hyperactivity disorder (ADHD) and other behavior disorders, depression and anxiety in children and adolescents (typically, less than 18 years old) [1-7].

Classification of Psychiatric Disorders

A mental disorder (or a mental illness, psychiatric disorder) is defined as changes in thinking, feeling or behaving that cause distress or disrupt a person's functioning [52]. It can be occasional (acute) or long-lasting (chronic). Sometimes called a mental health disorder in youth, these changes, delays or disturbances often interrupt the development of age-appropriate emotions, beliefs, behaviors, or interpersonal skills [53].

The classification of psychiatric disorders (taxonomy) is a key aspect of psychiatric diagnosis and psychiatric research. There are two widely accepted systems for classifying mental disorders:

- International Classification of Diseases (ICD-9, 10) issued by the World Health Organization (WHO)
- The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) issued by the American Psychiatric Association (APA)

Pediatric mental disorders encompass a range of conditions listed below [1-7]. For studies using diagnostic information from physician service reimbursement claims, a revised categorization of clinician-reported diagnosis can be created depending on the research question.

- Anxiety disorders
- Attention-deficit/hyperactivity disorder (ADHD)
- Disruptive disorders, e.g. Conduct disorder (CD) and oppositional defiant disorder (ODD)
- Depression
- Learning disorder (LD)
- Bipolar disorder
- Intellectual disability,
- Autism spectrum disorder (ASD)
- Schizophrenia
- Adjustment disorder

- All other mental disorders

Diagnostic Prevalence

Diagnostic surveillance during 1994-2011 revealed estimates of psychiatric diagnostic prevalence increased every year with a total of 13%-20% of U.S. children receiving a psychiatric diagnosis in a given year [5]. Recent analysis of the 2016 National Survey of Children's Health data indicated that the national prevalence of at least one psychiatric disorder in U.S. youth was 16.5% (weighted estimate, 7.7 million) [6]. Studies have reported the number of youth diagnosed with ADHD or autism spectrum disorders based on clinician-reported claims data increased greatly in recent years [54, 55].

There has been an increasing trend for comorbid psychiatric diagnoses, i.e. the co-occurrence of more than one psychiatric diagnosis in a given child [8]. Among children 3-17 years old, 73.8% of children diagnosed with depression also had a diagnosis of anxiety and 36.6% of children with behavioral diagnoses have diagnosed comorbid anxiety [4]. While these multiple conditions may be valid, it is notable that a large proportion do not meet full criteria for the comorbid condition and instead meet only partial criteria [12]. This situation adds to the public health concern of whether treatment of multiple community clinician-assessed comorbid psychiatric diagnoses with multiple medications will prove to be effective and safe in community populations.

Large scale pharmacoepidemiologic studies are based on administrative claims from health insurers with data on community-based treated populations and have emerged in

the past 35 years as a valuable source of population health trends [56]. These studies have demonstrated notable differences of gender, age group, self-reported racial/ethnic identity and insurance status in terms of diagnoses and treatments. Boys, older youth (12–17-year-olds), and non-Hispanic white youth are significantly more likely to receive psychiatric diagnoses and treatment compared to girls, other age groups, and racial/ethnic counterparts [2, 4, 9]. Population trends in mental health services present new opportunities to profile real world patterns of diagnosis and treatment in community populations.

Age of Onset of Psychiatric Disorders

The onset of many mental disorders typically occurs during childhood and adolescence, both in the U.S. [57] and globally [58, 59]. In the U.S., a national survey [57] found that: 1. Concerning early onset: Approximately 5% of patients were diagnosed with a mental disorder at a very young age. Specifically, individuals with ADHD, anxiety disorders, and impulse-control disorders received their first diagnosis at age 5 or younger. 2. Young median age of onset: The median age of onset varied by disorder—for example, ADHD at age 7, anxiety disorders at age 11, impulse-control disorders at age 11. 3. Relatively narrow age range of onset: age of onset occurred in a narrow age IQR range (i.e., the age range between the 25th and 75th percentiles interquartile ranges) for most disorders. For instance, ADHD (age 7-8 years), anxiety disorders (age 6-21 years), and impulse-control disorders (age 7-15 years).

Treatment

The causes of mental disorders are multiple and often unclear. It is difficult to differentiate the behavioral and emotional changes which are common in a typical child's development with those which cause concerns. Many disorders such as ADHD and adjustment disorder occur during childhood which makes diagnosis and treatment challenging. Social determinants, e.g. parental education and economic stability can complicate a child's development, including mental health services.

Treatment options include:

- Psychotherapy (or talk therapy), such as family counseling, parent training, teaching skills and practicing skills at home or at school [60].
- Psychotropic medications either alone or in combination with psychotherapy.

A mental health professional typically develops a treatment plan for the child and family. In this proposal, we focus on psychotropic medication use, especially polypharmacy, in the pediatric population. There is no standard definition of polypharmacy. Polypharmacy is considered as concurrent use of more than one medication by a patient. Polypharmacy may indicate the patient has complex medical conditions and is considered to increase the risk of adverse medical outcomes. Most prescription drugs for mental health use in children are off-label, i.e. without sufficient evidence that benefits outweigh risks [61, 62]. Psychotherapy is not the focus of the proposal as information on these practices is

very limited in large administrative data sets such as Medicaid which will be the source for the proposed analyses.

2.2 Medicaid & Government Oversight

State Medicaid programs are public insurance programs responsible for covering healthcare services of 37 million children (less than 18 years of age) [63]. As of 2016, Medicaid covers a total of 39% of the overall U.S. child population and 77% of children who are living in poverty [64]. Medicaid and Children's Health Insurance Program (CHIP) cover 44% of approximately 11.2 million children with special health care needs in the U.S. [64]. Mental, emotional and behavioral disorders are among the most costly conditions treated in children in the U.S., with health care, special education and decreased productivity of youth less than 24 year old costing an estimated $247 billion per year [5]. Since the pharmacologic treatment cost is considered an essential part of Medicaid expenditures, Medicaid administrative claims data have proven to be a valuable source of population-based treatment patterns [65].

Compared to privately insured children, publicly-insured children are more likely to receive mental health services, particularly children with disabilities and those in the foster care system who often experience multiple placement disruptions [51].

Numerous government reports over the past decade have raised concerns about pediatric psychotropic medication use, particularly antipsychotic use for non-psychotic behavioral disorders and have called for efforts to improve the oversight of pediatric psychotropic

medication use in state Medicaid programs [66-69]. A federal agency report (Government Accountability Office) emphasized polypharmacy and the high prevalence of antipsychotics, especially among foster care youth, the most vulnerable group eligible for Medicaid coverage [68].

2.3 Psychotropic Medications

Psychotropic medication is a broad category of drugs which treat many different conditions. The term refers to drugs used to treat the symptoms of mental, emotional and behavioral conditions. The mechanisms of action of these drugs involve blocking or enhancing neurotransmitters in the brain, such as dopamine, gamma aminobutyric acid (GABA), norepinephrine, and serotonin.

There are 7 major classes of psychotropic medications used in treating youth according to Anatomical Therapeutic Chemical (ATC) Classification system [70]:

1. Antipsychotics (FDA-approved for the treatment of schizophrenia, mania and autism)
2. Anti-anxiety agents. A subcategory of anti-anxiety drugs includes hypnotics for sleep.
3. Antidepressants
4. Anticonvulsant-mood stabilizers (used in the treatment of bipolar disorder)
5. Stimulants (used in the treatment of ADHD)
6. Selected alpha-agonists (i.e., clonidine and guanfacine)
7. Lithium

The use of psychotropic medication for the treatment of psychiatric disorders in children and youth has increased in the past 30 years. Between 1995 and 2010, the prevalence of psychotropic medication use doubled as the primary management strategy for children with psychiatric disorders [71]. Use of these medications has increased dramatically since the mid-1990s according to numerous data sources [9, 71, 72].

In terms of evidence-based prescribing practices, 50%-75% of pediatric medications are used for indications or in age groups that lack approved labeling by the U.S. Food and Drug Administration (FDA) and are termed off-label prescribing. Prescribing in this way occurs despite the lack of robust clinical trial evidence that the benefits exceed the risks of medication use [73]. Notably, off-label prescribing is legal in the U.S., although the expanding use of off-label drug class combinations (polypharmacy) and their long-term safety are growing concerns. Indeed, when labeled use is extended beyond 6 months, the long-term safety in community-treated youth is largely unknown.

2.4 Pediatric Psychotropic Medication Use

Prevalence

The increased prevalence of psychotropic medication use among youth has been reported from various sources, including HMO services, Medicaid youth claims data and medical surveys [9, 10]. The prevalence of psychotropic medication youth users grew greatly for several classes of medication from 1987 to 1996 [9]. Youth psychotropic treatment prevalence during the 1990s nearly reached adult psychotropic prevalence—an

unprecedented trend in youth treatment for mental health problems. In a study using data from the National Health and Nutrition Examination Survey (NHANES), psychotropic medication use in the past month in 12-19 year old adolescents during 2005–2010 was evaluated [10]. Approximately 6.0% of adolescents reported any psychotropic medication use in this timeframe. The use of ADHD medications, principally stimulants and antidepressants predominated, followed by antipsychotics, and anxiolytics/sedatives/hypnotics. ADHD drugs were more often used by males while antidepressants were more often used by females. Non-Hispanic whites proportionally had the highest psychotropic drug use of any race/ethnic groups.

A recent large study was conducted on data obtained from commercial claims (Market Scan) and the public insurance Medicaid database to evaluate the prevalence of psychotropic medication use in youth in the U.S. in the year 2004 compared with 2014 [74]. The prevalence of overall use of (any) psychotropic drugs among 2-18-year-olds increased slightly (from 8.6% to 9.0%) in a 10-year period. The prevalence of antidepressants, antipsychotics and anticonvulsant-mood stabilizers decreased. In both time periods, stimulant/alpha-agonist, antidepressant, and anxiolytics were the most frequently utilized drug classes.

In an earlier decade, psychotropic medication overall prevalence changes from the 2-to 3-fold increases between 1987 to 1996 in Medicaid data from 2 states and prescription dispensing data from a health maintenance organization. For example, in Maryland Medicaid, stimulants increased from 14.3% to 38.4%, and antidepressants increased from

1.9% to 20.5% [9]. In another study, it was reported that a slight increase of prevalence of any psychotropic medication prescription between 2004 to 2014 in Market Scan and Medicaid database from 8.6% to 9.0% [74]. However, the patterns for privately insured youth are understudied.

Specific classes of psychotropics have received particular attention. Atypical antipsychotics (AAP) are second generation antipsychotic products that are a particular concern for the treatment of non-psychotic behavioral conditions. Prevalence of AAP use in one state Medicaid-enrolled youth population more than doubled in 10 years from 1.2% to 3.2% between 1997 to 2006 [27]. Psychotropic drugs were prescribed at higher rates to foster care, disabled youth (qualified by social security income payments) and poor youth covered by Medicaid insurance (family income below poverty (TANF) and up to 200% above poverty level (SCHIP) compared with children covered by commercial insurance [75]. More broadly, the off-label use of AAPs in children and adolescents is prevalent in the United States. In a study using the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS), more than 65% of AAP use did not have a diagnosis for an FDA-approved indication. During 2007 to 2010, the most common diagnosis associated with AAP use was ADHD, an off-label diagnosis [76]. Similar results were found in a study using 2003-2010 NAMCS and NHAMCS data; AAP prescription users were 2-fold-greater among publicly insured youth than those covered by private insurance. More than one-third of AAP prescription users were concomitantly treated with 2 or more psychotropic medication classes [12]. The relatively recent expansion of AAP prescribing for non-

psychotic behavioral problems, especially in very young children [77], has been the source of great concern related to the weak or absent evidence of effectiveness and increasing risk of harm [78].

Controversy in interpreting pediatric psychotropic medication prevalence

A majority of the research studies reviewed for this proposal reported on youth using a single drug class and have demonstrated that use of psychopharmacological agents for youth is increasing, in line with the increasing clinician-reported psychiatric diagnoses, particularly in young children in the U.S. [79-81]. However, the interpretation of study findings may be controversial with respect to conclusions of under-treatment or over-treatment when the researchers compare the prevalence of pediatric psychotropic medication patterns with the published clinician-reported psychiatric diagnostic prevalence.

In a study which used data from a commercially insured population (2008 IMS Life Link Rx National Longitudinal Prescription database), the authors evaluated the national patterns and prevalence of commonly prescribed psychotropic medication classes (stimulants, antidepressants, and antipsychotics) in 3 to 24 year olds diagnosed with ADHD [82]. The authors concluded that ADHD is undertreated because several published national community diagnostic surveys indicated a higher prevalence of ADHD diagnosis (8.6%) while the prevalence of stimulant treatment was found to be 4.6% in 6-12 year old children and 3.8% in adolescents [83]. The authors also compared antidepressant treatment prevalence (1% in 6-12 year old children, 2.8% in adolescents)

with the published national community diagnostic prevalence estimates of depression (4%) [84] and concluded that depression is undertreated as well.

The notion that each diagnosed youth should receive a corresponding medication is an assumption without evidence. The idea may spring from evolving practices related to a biological model of psychiatry as opposed to the traditional model of a biopsychosocial practice model [85]. Increasing medication use may also reflect the expansion of psychiatric comorbidities, even for partial symptom criteria [8]. Psychotherapy, an alternative to medication use tends to be less accessible or available than medication [86].

An additional limitation concerns methodology. Since the results were from studies using different databases (commercial insurance data vs. public insurance data), simple comparative differences in the prevalence of psychotropic drug use and psychiatric diagnosis cannot be validly concluded.

Overall, administrative claims data have proven highly reliable to assess medication use whereas clinician-reported diagnostic information is less trustworthy than research-assessed diagnosis. Nevertheless, a study linking clinician-reported diagnosis and related medication use allows the reader to observe the clinician's diagnostic rationale for prescribing, for example, a stimulant treatment for ADHD [87]. Further investigation linking clinician-reported diagnosis and medication regimen patterns, e.g. monotherapy vs. polypharmacy, for psychotropic medication use in children and adolescents is warranted.

2.5 Pediatric Polypharmacy

Psychotropic polypharmacy, which is defined as treatment with more than 1 psychotropic medication class (or drug) concomitantly, usually suggests that more medications are used than are 'clinically indicated.' It is a common and growing prescribing practice in the treatment of psychiatric disorders of children and adolescents [88]. The prevalence of pediatric polypharmacy ranges from 20% up to 48% in different age groups and subpopulations and by the design and metric used for the outcome [11-45]. The safety of polypharmacy is always a concern, for example, some studies showed polypharmacy of atypical antipsychotic with other psychotropic medication is associated with type-2 diabetes [50]. Most polypharmacy represents off-label use in children and adolescents, and lacks a robust evidence base for effectiveness and safety in short or long-term use. This means the evidence of benefits exceeding risks is unknown [89]. The research area such as prevalence of long-term high number of stimulant class polypharmacy and the associated factors (Aim 1), polypharmacy change patterns, time to polypharmacy, and types of polypharmacy regimens (Aim 2), and the association between polypharmacy of stimulants with other psychotropic medication and incident type 2 diabetes (Aim 3) has not been sufficiently studied as yet.

There are two classes of polypharmacy: within class, e.g., two antipsychotics or between class (inter-class) e.g., stimulant and alpha-agonist. The within or between classes have overlapping days supplied (estimated from administrative claims data). Usually, the overlap of the several medications is based on a rule of the length of overlap as well as gaps between prescription refills. Various rules have involved at least 30, 45, 60, or up to 90 consecutive overlapping days and allowed for 15-day gaps to refill a prescription.

Longer overlap times help to rule out switching from one drug to another. Slow switching of psychotropic drugs is often done to minimize withdrawal syndrome. Longer overlap times help to avoid unintentional polypharmacy associated with switching drugs [88].

There are several reasons for polypharmacy in managing mental disorders:

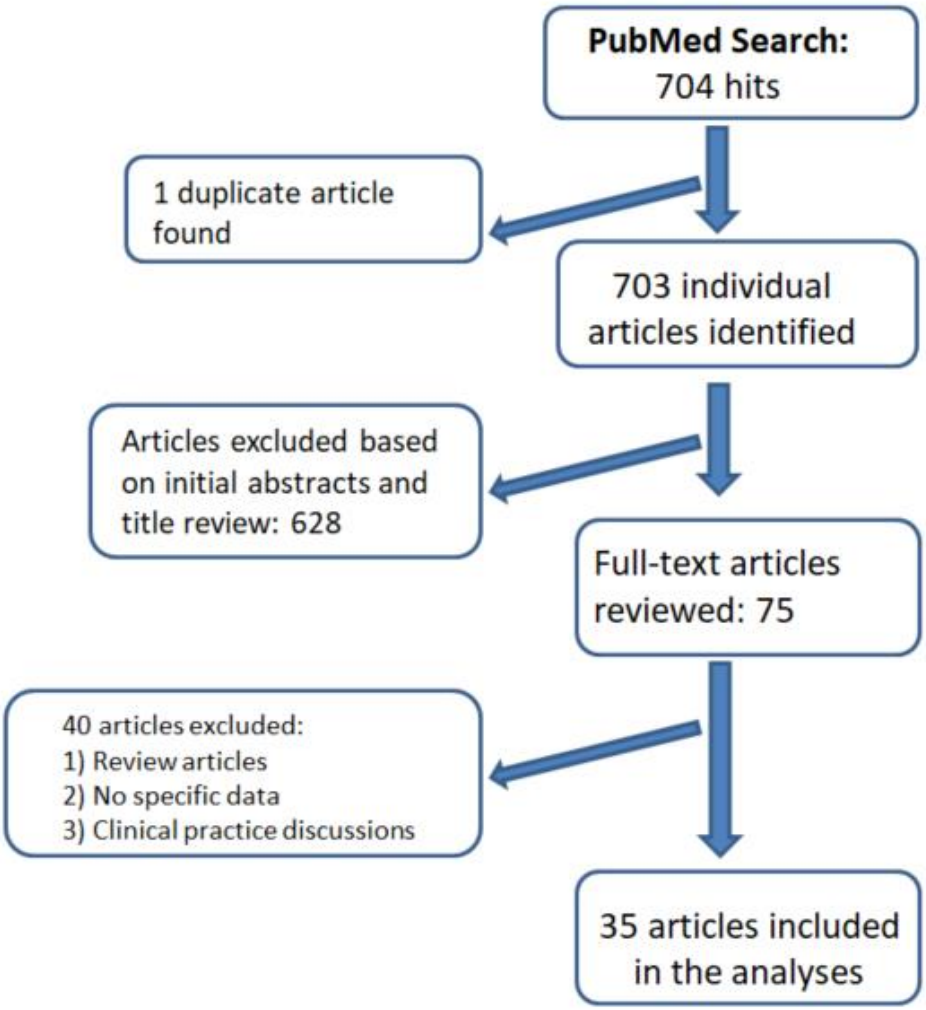
1. Limited Effectiveness of Single Treatments: Simpler treatments may not be sufficient to manage behavioral problems.

2. Emergence of New Symptoms: Patients may develop new symptoms over time, necessitating additional medications.

3. Changes in Medical Management: A new healthcare provider may adjust or modify the patient's drug regimen.

A literature search and review for the period January 1, 2000-November 3, 2020 was conducted to identify the definition, prevalence, psychiatric diagnosis group and the findings of psychotropic polypharmacy in children and adolescents (Table 2-1). A flow chart of the PubMed review process is presented in Figure 2-1. Keywords included: psychotropic, psychiatric, polypharmacy, concomitant, concurrent, pediatric, children, adolescents, youth; papers were restricted to English language and U.S. population. A total of 35 quantitative studies of U.S. youth with analysis of counts of pediatric psychotropic inter-class medication polypharmacy were identified and reviewed in detail [11-45]. These studies are population-based, mainly relying on either federal surveys of physician offices or parents or administrative drug payment claims.

Figure 2-1. Flow chart of the review process



2.5.1 Metrics for Polypharmacy

Review of the literature indicates that there are different reporting metrics for polypharmacy and some minimize the extent of the problem by reporting a summary measure, e.g. more than one concomitant drugs within or between psychotropic classes. Between class polypharmacy reported as 2 or more concomitant classes hides the extent of use among 3 or 4 or 5 or more combinations, far riskier regimens.

In some child psychiatry papers, polypharmacy and concomitant use were used interchangably [90]. However, the difference between polypharmacy and concurrent use lies in the implications in medical and pharmaceutical contexts: Polypharmacy refers to the use of multiple medications by a single patient, often to manage multiple medical conditions. It could increase the risk of drug-drug interaction and drug adverse effects. Concomitant use refers to cases with co-morbid diagnoses. It does not necessarily imply excessive medication use, as it could be appropriate. Polypharmacy generally has more negative implications than concomitant use. In a pharmacoepidemiology claims-based study, the patients accrue medications from outpatient community treatment at community pharmacies. Among 35 articles, most of the studies focus on polypharmacy based on between class psychotropic medication dispensing. In an exception, a recent analysis showed polypharmacy for within class, between class and both types [17]. Some studies investigated polypharmacy of one specific drug class with other psychotropic drug classes, for example, antipsychotic with 2 or more classes co-prescribed in a medical visit [12] or antidepressant (ATD) with ≥1 concomitant psychotropic classes with prescription fills overlapping for 60 or more days [22]. Within class studies of ≥2 antipsychotics were also common [46, 47] as the rationale for more than one antipsychotic is not backed by current

evidence but is much less common than between class polypharmacy. Several studies also conducted analysis to investigate 3 or more classes of polypharmacy [22-24, 31, 32, 43], and even 4 or more different classes of polypharmacy [41]. Learning the extent and clinical details of complex polypharmacy regimens is a public health goal of the proposed dissertation research.

Most of these studies evaluate the prescribing of psychotropic polypharmacy at a single point in time or during a specific time frame, such as at a medical visit or annually for continuously enrolled youth [43], [21]. Diagnostic criteria vary; some studies have required that the study population have at least one behavioral health diagnosis to be included [12, 36].

The overlapping period of concomitant use and the gap period allowed for prescription refills are two important aspects of polypharmacy. However, they vary in reporting the methods: In some studies, the authors studied 2 or more concomitant psychotropic medications without clearly mentioning the overlapping period [11-16, 18, 23, 27, 31, 32, 35, 36, 39, 43-45] . In some studies, the authors studied polypharmacy medication use within the same month [25, 41, 42]. In the other studies, the required overlap period varied from 7 days [26] to 15 days [43], 30 days [32, 47], 45 days [17], 60 days [19, 22] and 90 days [21, 24]. Despite the varying definitions of the overlapping period, when defining long-term polypharmacy a 60-day overlap period increases the likelihood of intentional polypharmacy and minimizes the risk of unintentional polypharmacy (switching). The gap period is used for administrative claims studies of prescription refill patterns. In some studies, the gap period between medication dispensing is up to 15 days [21], while in other studies it was not clearly defined.

2.5.2 Database and polypharmacy study design

Database

Many studies have used public insurance administrative claims data (Medicaid) for their analyses [17-26, 31, 33-43]. Several studies have used NAMCS and NHAMCS [12, 13], an annual national survey of physician office visits. An early study used the American psychiatric practice research network [30] which is no longer active, and one study used a retail pharmacy customer survey of parents receiving medication for their children [16]. Commercial insurance data (i.e., Market Scan) were used as well for psychotropic polypharmacy research [27-29, 32] but are generally less available and costly.

While the majority of studies focus on all Medicaid enrollees, several studies focused on specific Medicaid eligibility groups such as foster care [41, 42, 47]. Concern for the foster care population is based on government oversight concerns about high medication use in a population that requires extra review when the state functions *in loco parentis*. Some studies assess the outcome as a percent of medicated youth, creating a higher percent than if all enrollees had been used.

Study Design

Most of the studies used cross-sectional designs to assess mental health service use in children and adolescents and reported on annual trends of clinician-reported diagnosis, psychotropic medication use and occasionally on the adverse effects associated with these medications [16, 36].

A quasi-experimental design was used to assess the pre- to post-Coordinated Care Services (CCS) intervention impact on polypharmacy [43]. The authors utilized Maryland Medicaid data to compare psychotropic polypharmacy in youth with serious emotional and behavioral disorders in one year before CCS enrollment, one year during CCS, and one year after CCS discharge between December 2009 and May 2014. The comparison group was serious emotional and behavioral diagnosed youth who received usual outpatient mental care services in the same year. No significant difference was found for polypharmacy prevalence in the three time periods. CCS had little impact in reducing psychotropic polypharmacy prevalence in hard to manage youth (28% and 29% for pre-CCS and post-CCS periods, respectively).

2.5.3 Psychiatric diagnosis group

Among the 35 studies reviewed, several papers discussed the psychiatric diagnosis group in relation to polypharmacy [23, 47]. They used ICD-9-CM diagnostic categories to classify the primary psychiatric diagnoses: ADHD, adjustment disorders, anxiety disorders, autism spectrum disorders, disruptive behavior disorders, mood disorders, developmental disabilities, schizophrenia, and other mental disorders. Other mental disorder diagnostic tools were utilized as well, such as Diagnostic Interview Schedule for DSM-IV (DIS-IV) [42].

Other studies focused on certain psychiatric diagnosis groupings, e.g. externalizing behavior disorders [12], serious emotional and behavioral disorders [43], or autism spectrum disorder [32] in contrast to including any psychiatric diagnosis in forming the cohort. Regardless of the approach in these studies, the correlations between polypharmacy and clinical diagnostic group and the evidence base for polypharmacy regimens have not been fully investigated.

2.5.4 Outcomes Reported in Pediatric Psychotropic Polypharmacy Studies

2.5.4.1 Prevalence

Polypharmacy prevalence is the primary outcome variable in the reviewed studies (Table 2-1). The prevalence of psychotropic polypharmacy has increased in recent decades in both the adult and pediatric populations. One national survey study showed that the proportion of adult patients with a psychiatric diagnosis had prescribed polypharmacy increase from 42.6% (1996-1997) to 59.8% (2005–2006) [91]. By comparison, a lower, though increasing prevalence trend in polypharmacy use is observed in the pediatric population as well. Table 2-1 summarizes the pediatric polypharmacy prevalence in the published literature of the past decade.

In these studies, the reported prevalence varies due to the different pediatric polypharmacy definitions and duration of exposure, various datasets (Medicaid, NAMCS, commercial insurance, etc.), and selected age and diagnosis groups.

Most of the polypharmacy studies reported the prevalence of 2 or more different psychotropic medications or classes. For example, Comer et al. analyzed annual NAMCS survey data for 1996-2007 to assess the patterns of pediatric polypharmacy in office-based medical visits and showed polypharmacy treatment increased significantly in youth from 14.4% in 1996-1999 to 20.2% in 2004-2007 for youth. Among those with psychiatric diagnoses, the polypharmacy percentage increased from 22.2% to 32.3% in 10 years [13].

Another study focused on Medicaid claims data in South Carolina, showing the percentage of 2 or more concomitant medications increased from 7.9% in 1996 to 44.8% in 2005 in psychotropic medicated youth—a dramatic change in pediatric psychopharmacology to treat poor and vulnerable populations. The study showed children with major depressive disorder received greatly increased concomitant psychiatric medication in a decade, both FDA approved and off-label [36]. In a recent Medicaid study, the prevalence of 2 or more concomitant psychotropic classes (Any-class) increased from 21.2% to 27.3% from 1999 to 2009 [17].

The high prevalence of polypharmacy has not only been reported for 2 or more psychotropic polypharmacy classes, but in the 3 or more as well as 4 or more classes. In a study of Texas foster care data, 41.3% received 3 or more classes and 15.9% received 4 or more classes during 2004 [41]. Such trends were also observed in other states' Medicaid data: there was 10.2%-13.4% polypharmacy with 3 classes for 90 or more days in Kentucky Medicaid population [21]; 31.5% reported 3 or more psychotropic polypharmacy in a Midwest state Medicaid population [42], 27.3% of 3 class polypharmacy in Ohio Medicaid foster care [23], 13% of 3 class polypharmacy in New York state Medicaid data [24], 15% with 3 classes polypharmacy in a U.S. commercial health plan [32]. In one study using data from 28 state Medicaid programs, for ADHD diagnosed youth there were 3 or more concomitant psychotropic classes for 8.5%-13.4% from 1999-2006 [31].

Researchers conducted studies in certain diagnostic groups or psychiatric medications. For example, Burcu M, et al.[12] investigated the antipsychotic plus other psychotic class medications use in behavioral disorder (BD) youth in NAMCS and NHAMCS and estimated

50.7% of BD visits included a prescription for an antipsychotic and one other psychotropic class and 39.1% of BD visits included a prescription for a antipsychotic and 2 or more other psychotropic classes. The increase in the prevalence of prescribing atypical antipsychotics with other drugs may be due to their availability since late 1990s and growing off-label use.

Another study that analyzed antidepressant polypharmacy in 2014 in Maryland showed 22.1% medicated youth were prescribed antidepressant (ATD) and one other psychotropic class, 14.2% were prescribed ATD and 3 other psychotropic classes, and 5.65% were prescribed ATD and 4 other psychotropic classes [22]. Thus, reporting 3 or more would affect 20% of ATD-medicated, a more compelling safety issue than reporting 1 or 2 or more.

Pediatric polypharmacy prevalence may differ by ethnicity, gender, and Medicaid eligibility group (foster care, disability, and low family income eligibility). White, older males and children with multiple comorbid psychiatric diagnoses (e.g. attention-deficit disorders, anxiety, bipolar disorder, and depression) and those who are eligible through foster care are more likely to receive psychotropic polypharmacy treatment than their African American, younger, and female counterparts and compared to privately insured children [17, 21, 23, 41].

2.5.4.2 Time to initiate polypharmacy and duration

Besides prevalence, the time to initiate of polypharmacy and polypharmacy duration were evaluated in several studies [32, 46, 47]. Constantine RJ, et al calculated times to initiation of polypharmacy after initiation of antipsychotic monotherapy in Florida medicated youth aged 6-17 years between 2002 and 2007. The antipsychotic monotherapy was defined as youth who use a single antipsychotic and did not have polypharmacy at any prior time in the study period.

Antipsychotic polypharmacy was defined as 2 or more antipsychotic medications with 60 day overlap period and less than 15-day gaps between refills. The time to initiate antipsychotic polypharmacy was substantial: 505.8 days in children and 384.9 days in adolescents ($p < 0.001$) [46]. Mean polypharmacy duration was 170.0 days in children and 185.5 days in adolescents ($p=0.01$) [46].

In another study using Maryland Medicaid claims data from 2003 investigated the antipsychotic medication use in foster care youth, the authors found the duration of antipsychotic use in foster care youth is much longer than that in TANF insured youth (222 vs. 135 days, $p<0.001$). Antipsychotic polypharmacy for ≥180 days was mainly in foster care/adoption (24%) among Medicaid program categories [47].

Polypharmacy duration was estimated in commercial health claims data as well. Among children diagnosed with autism spectrum disorder (ASD) between 2001 and 2009, the median polypharmacy period was 346 days and the average number of polypharmacy episodes per subject was 5.63 [32].

However, these studies were conducted in a cross-sectional framework. The time to polypharmacy, polypharmacy duration, and temporal sequence of increased number of psychotropic medications have not yet been studied in a longitudinal study framework.

Table 2-1. Key metrics and findings from child and adolescent polypharmacy literature, 2000-2020

#	Authors, year	Dataset & study design	Population	Polypharmacy Definition	Psychiatric Diagnosis group	Findings
Federal and Other Population-based Surveys on Pediatric Psychotropic Polypharmacy						
1	Zhang et al. 2020 [11]	1999-2015 MEPS	0-17 years, 3 periods, 1999-2015, parent reported	≥3 classes		In 2015, nearly 300,000 youth received ≥3 classes concomitantly, a doubling in 12 years
2	Burcu M et al. 2016 [12]	2003-2010 NAMCS, NHAMCS Cross-sectional	6-19 years, N=4,603 visits w/ externalizing behavior diagnosis	Antipsychotic with 1 or ≥2 classes co-prescribed in a medical visit	Externalizing behavior disorder (BD)	One half (50.7%) of behavioral disorder visits had antipsychotic plus one other psychotropic class; 39.1% had antipsychotic plus ≥2 psychotropic classes. Antipsychotics were prescribed concomitantly with ≥2 psychotropic medication classes regardless of age group, insurance coverage (public vs. private), or even in the absence of psychiatric comorbidities.
3	Comer et al. 2010 [13]	1996-2007 NAMCS, Cross-sectional	6-17 years, N=2,603, w/ any prescribe psychotropic rx	2 or more psychotropic classes prescribed in a single pediatric visit	5 ICD-9 categories	Across 12 years, among visits with a current mental disorder diagnosis, multiclass psychotropic treatment increased from 22.2% (1996-1999) to 32.2% (2004-2007) as a proportion of medicated youth. Any multiclass prescribed psychotropic polypharmacy increased from 14.3% (1996-1999) to 20.2% (2004-2007). Increased co-prescribed classes: ADHD medications + antipsychotics; and antidepressant +antipsychotic.
4	Bhatara et al. 2004 [14]	NAMCS, 1993-4 and 1997-8	<18 years old; x-sectional, N=39,981	> 1 psychotropic medication + stimulant		As a proportion of all psychiatric visits, concomitant use grew from 2.95% to 14.69% across 5 years. Fivefold growth of stimulant with other classes. Stimulant with concomitant antidepressant was featured urging clinical trials to assess effectiveness and safety.

5	Girand et al. 2020 [15]	NAMCS 2006-2015; NHAMCS, 2006 and 2011	ADHD, 2-24 y/o,	≥2 classes	ADHD alone and with comorbiditie s	67.1% ADHD polypharmacy (stimulant + α-agonist); compared with psychotropic polypharmacy. However, atypical antipsychotics were not classified as a treatment for ADHD.
6	Hilt R J, et al. 2014 [16]	Retail pharmacy survey of parents w/ child's psychotropic dispensing, Cross-sectional	Parent survey of 3-17-year olds, N=1347, number of child's psychotropics and side effects. 7.5% response rate	2 concomitant regimen=25.9%; ≥3 regimen =13.4%	N/A	Among those reporting 2 drug psychotropic medication polypharmacy, 17% reported increased adverse effects compared to one medication (p<.001). For those reporting ≥3 concomitant drugs, 38% reported increases in average number of side effects compared to children taking one medication (p<.002). SSRIs and antipsychotic regimens had greater relative risk of side effects compared with monotherapy.
Large, Multi-state (MAX) Pediatric Psychotropic Polypharmacy Studies						
7	Soria Saucedo et al. 2018 [17]	1999-2010, in 29 states Medicaid MAX files, each 2 yr retrospective cohorts	0-17 years, N=692,485	≥2 same class, multi-class, or both types; Overlap window of ≥45 days	N/A	Any-class and multiclass psychotropic polypharmacy increased from 21.2% and 18.8% (1999–2000) to 27.3% and 24.4% (2009–2010), respectively. Polypharmacy increased over the decade for stimulants, from 0.1% to 0.6%, and for alpha agonists, from 0.1% to 0.4%. Polypharmacy varied widely across states: 6.9% to 48.8% for any-class psychotropic polypharmacy, from 0.4% to 6.4% for same-class antidepressant polypharmacy, and from 0.1% to 4.6% for antipsychotic polypharmacy.
8	Kreider et al. 2014 [18]	MAX 2004-2008, 42 states + DC= 80% U.S. Medicaid population	6-18 y/o; continuously enrolled 10/12 months	Second generation antipsychotic (SGA) with 4 classes		85% of SGA use was adding to other classes. Long-duration of SGA was observed (69-89% of medicated days). Concurrent SGA with stimulant or mood stabilizer were likely. While foster care and youth with disabilities were prominent SGA concurrent users, increased use occurred among less severe categories, e.g. income eligible and non-comorbid ADHD .

9	Chen et al.2011 [19]	2005,4 state Medicaid MAX files, Cross-sectional	6-18 years, N=282,910 with any psychotropic dispensing	≥2 psychotropics with varying overlapping time windows	N/A	One-year polypharmacy percent prevalence among medicated youth by duration of overlap: 28.8% (14 days); 27.2% (30 days); 20.9% (60 days). The authors recommend the 60-day window to more accurately identify intentional polypharmacy as opposed to switching from one drug (or class) to another.
10	Medhekar et al. 2019 [20]	2013-2015, Texas Medicaid managed care, cross-sectional	<19 years old, any ICD-9 mental, behavioral dx, N=24,147	≥2 multiclass for ≥60 days		The relationship between psychotropic polypharmacy and care coordination intensity was found to vary: Psychotropic polypharmacy was less likely in high than low density primary care teams; reverse was true for primary care and psychiatry combination teams.
11	Lohr WD et al.2018 [21]	2012-2015 Kentucky Medicaid, Cross-sectional	0-17 years, N = 237,393, continuous enrollment ≥ 90 days with at least 1 behavioral health diagnosis	≥2 interclass combinations Overlap window of ≥90 days, 15-day gap	Behavioral diagnosis in a 4- year period	39.5% of youth with a behavioral diagnosis had ≥2 psychotropic classes for ≥90 days. As many as 57.2% had 2 classes, e.g. stimulant + alpha-agonist. There were 10.2%-13.4% with 3 classes for 90 or more days. The study defined polypharmacy using the more conservative 2015 HEDIS criterion for the persistence of overlap. There is no distribution or range of days of concomitant use.
12	Zito JM et al. 2020 [22]	2014 Maryland Medicaid data, Cross-sectional	0-20 years, 14,777 youth with an antidepressant dispensing	Antidepressant with ≥1 concomitant psychotropic classes; overlap window of ≥30 or ≥60 days.	Depression; Behavioral diagnosis; other psychiatric diagnosis, no psychiatric diagnosis	In an overlapping ≥60-day time window, 22.1% AD medicated youth had 1 other concomitant psychotropic classes; 14.2% had 2 concomitant classes and 5.65% had 3 or more concomitant classes. Overall, 19.8% had total polypharmacy for 2 or more classes. Complex combinations included: antidepressant, antipsychotic, stimulant and an alpha agonist. These combinations are largely off-label.

13	Fontanella et al. 2014 [23]	2002-2008, Ohio Medicaid, annual trends, cross-sectional	26,252 (2002) thru 50,311 (2008), 0 thru 17 years, continuously enrolled	Any ≥3 psychotropic classes (within or among classes)	9 ICD-9 categories	Any psychotropic polypharmacy grew from 2002 thru 2008: Foster care (FC) from 19.8% to 27.3%; disabled (SSI) from 18% to 24.9%; low income 8.8% - 11.5% across 7 years. Similarly, when interclass is separated from same class: (FC 17% - 22.3%; SSI from 14.3%-19.5% and low come 7.3%-9.0%), the bulk of polypharmacy is among classes and increased across the years with greatest use among foster care youth.
14	Essock SM et al. 2009 [24]	New York State Medicaid data, Cross-sectional	<18 years, N= 217,216 beneficiaries who had an active psychotropic prescription on April 1, 2008	≥3 psychotropic classes, >90 days duration.	N/A	Among 25,727 youths (under age 18), 13% (N=3,270) of these youths had 3 or more concurrent psychotropic trials. Only 431 (2%) individuals under age 18 were prescribed a benzodiazepine, and 48% of these youths (N=209, 48%) had a trial length of over 90 days.
15	dosReis S et al. 2005 [25]	1999, Medicaid programs in two states, Cross-sectional	<20 years, Continuously enrolled in 1999, with ≥1 mental health services, N= 16, 969	≥2 medication classes overlapping within the same month, 1-30 days	N/A	Multiple psychotropic medication dispensings for 27.9% (state A) and 29.7% (state B) with 1-5 months duration for 43.2% and 37.5%, respectively. Stimulants with antidepressants, antipsychotics, or alpha agonists were the most common combinations.
16	Martin A et al. 2002 [26]	1999, Connecticut Medicaid, Cross-sectional	Less than 19 years, N=196,549	≥2 psychotropic classes in a 7-day overlap after the index rx	N/A	Among youths who received a psychotropic dispensing, 13.6% had ≥2 psychotropic classes. The most common combinations were an antidepressant plus an antipsychotic; a stimulant + antidepressant or stimulant + α-agonist. Early method is likely an underestimate; the authors argue for longer overlap to separate polypharmacy from switching.
Pediatric Psychotropic Polypharmacy in Privately Insured Populations						

17	Zhou et al. 2020 [27]	Truven Market Scan commercial, 2011-2014	ADHD alone or w/comorbidity, continuously enrolled & ≥1 stimulants, 6-17 y/o		ADHD	Continued increase from 2009: 6-12: 22.9-25.0%; 13-17: 25.2-28.2. Mostly off-label use with SSRIs, AAPs and guanfacine in addition to stimulants.? Suggests little variation of extent of polypharmacy by age group
18	Betts et al. 2014 [28]	Truven Market Scan commercial, 2009 Cross-sectional	ADHD alone or w/comorbidity, continuously enrolled & ≥1 stimulants, 6-17 y/o	≥30 days	ADHD	Industry-sponsored comparison of monotherapy and polypharmacy by age group. Range 1-8 drug concomitants. 6-12 y/o: ≥2 20.3%; ≥3 5.7%. 13-17 y/o: ≥2 23.4%; ≥3 6.7%. Suggests little variation of extent of polypharmacy by age group.
19	Bali et al. 2015 [29]	IMS Lifelink, 2004-2007	6-16 y/o, ADHD	Long-acting Stimulant + SGA, ≥14 days	ADHD	Only 3.9% of LAS users had a concomitant antipsychotic added. 71 day greater persistence in the off-label combination was deemed improved adherence compared with LAS alone.
20	Duffy FF et al. 2005 [30]	Amer Psychiatric Practice Research Network, Cross-sectional	2-17 years, N=392, survey of psychiatric practices	≥2 psychiatric medications in a single patient visit	DSM-IV diagnoses in 7 categories	48.8% (162/332) of medicated patients received polypharmacy, ranging from 2-6 concomitant psychotropics. Highest rates of polypharmacy were among patients with bipolar disorder (87%). Antidepressant plus stimulant or antipsychotic or anti-manic (lithium or anti-convulsant mood stabilizer) were most common combinations.
Pediatric Psychotropic Polypharmacy in Diagnosed Population						
21	Winterstein AG et al. 2017 [31]	28 state Medicaid MAX files, 19992006; Longitudinal; 1-5 yr follow up	N=16,626 w/ first ADHD dx and first psychotropic rx after 6-month lookback w/out psych dx or rx	≥3 psychotropic classes		Polypharmacy was found for 25.3% in a subsequent year. Antipsychotics increased for 7.1%-14.7%; anticonvulsants for 4.0%-7.9% and ≥3 concomitant psychotropic classes for 8.5%-13.4% from 1999-2006. But increases were restricted to 3-9-year olds at first entry into the cohort. Many with psychotropic polypharmacy had no other diagnosis than ADHD.

22	Spencer D et al. 2013 [32]	U.S. commercial health plan, Cross-sectional	<20 years old, continuous health care coverage 2001-2009	2 psychotropic classes, >30 days duration	Autism Spectrum Disorder (ASD)	Among 33,565 youth with ASD, 35% reported ≥2 classes psychotropic polypharmacy, 15% reported ≥3 classes polypharmacy. The median period of polypharmacy in this study was 346 days.
23	Logan et al. 2015 [33]	So. Carolina cohort of 8 y/o ASD children in CDC monitoring program	Identified in 2000-2008 & followed for 2 years, N=629	Six 2-class combinations, ≥30-day overlap	Autism Spectrum Disorder (ASD)	Among the 60% with a dispensed psychotropic, 41% had 2-class combinations. Unfortunately, the extent of 3 or ≥4 class-combinations was not assessed.
24	Schubart et al. 2014 [34]	Medicaid MAX, 41 states, 2000-2003, <18 years old	Autism Spectrum Disorder (ASD), continuously enrolled	≥30- or ≥60-day overlap	ASD Dx required 2 separate outpt or 1 inpt dx	26% to 30% had pairs in 6 groupings. Within and intraclass polypharmacy is unclear.
25	Mandel et al. 2008 [35]	MAX, 50 states + DC, 2001, ASD diagnosed youth	<21 years old; x-sectional, N=60,641	≥3 psychotropic medications	Autism Spectrum Disorder (ASP)	56% received at least one psychotropic. Of these, 20% had ≥3 medications. Neuroleptics (antipsychotics), antidepressants and stimulants were leading classes.
26	McIntyre and Jerrell 2009 [36]	1996-2005, in So Carolina Medicaid, Cross-sectional	0-17 years, N=1,544 continuously enrolled ≥9 months/year	≥2 psychotropic medications	Major Depressive Disorder	Psychiatric polypharmacy increased from 6.7% in 1996 to 41.6% in 2005. Dispensed psychiatric polypharmacy increased as a function of the number of additional psychiatric disorders. Growth of 2, 3 and ≥4 or more classes across the years. Multiclass regimens are largely off-label class combinations. Antidepressants within class combinations were also notable.
Pediatric Psychotropic Polypharmacy in the Foster Care Population						
27	Keast et al. 2019 [37]	2016, Oklahoma Medicaid, foster care	<21 years, N=9,325 foster care; N=639,868 other Medicaid enrollees	Multiclass concomitant psychotropic use, ≥2 for 90 days; 2-		As a proportion of medicated youth, 41.3% had 2 or more psychotropic classes. 35.0% had 2-3 classes and 6.3% had 4-5 classes.

		vs. other enrollees, cross-sectional		3; 4-5 concurrent classes		Concurrent stimulants are most common in 3 or more class regimens; antipsychotic are most common in 4 or more class regimens.
28	Colorado Drug Utilization Review, 2017 [38]	Compares 2012 with 2015 data	<18 y/o; statewide foster care psychotropic oversight program	≥3 classes, ≥60-day overlap		62.9% of foster care youth had ≥3 classes compared with 51.1% non-foster care youth suggesting that 3-drug polypharmacy is usual for more than half of Colorado Medicaid youth.
29	Brenner et al. 2014 [39]	Community Intervention trial of treatment foster care	N=240, 2-21 y/o; parent-reported at baseline; southeast state	≥2 or ≥3 medication point prevalence		Of the psychotropic medicated, 35% had 2 meds; 15.5% had 3 and 9.2% had 4 or more. 61% ≥2 classes; questionable polypharmacy adapted Essock et al. criteria and found this applied to 22% of youth.
30	Rubin et al, 2012 [40]	MAX,2002-2007, foster care population	3-18 y/o;	≥3 classes for ≥30 days per year		Polypharmacy was relatively stable from 5.2% to 5.3%.
31	Zito JM et al. 2008 [41]	2004 southwest state, Medicaid *foster care*, Cross-sectional	0 to 19 years, (N=472), random selected *medicated youth*, July 2004	Manual review of overlapping dispensings of ≥2 classes in 1 month	ICD-9 clinician-reported psychiatric diagnoses	Of foster children w/ a psychotropic dispensing, 41.3% received ≥3 different classes during July 2004; 15.9% received ≥4 different classes. The use of ≥2 within class psychotropics was noted in 22.2% of those w/ polypharmacy. Class use did not vary much by diagnostic grouping.
32	Raghavan R et al. 2008 [42]	Midwest state Medicaid, Cross-sectional	17-year olds, face to face survey, N=403	Participants self-reported past month of rx use.	DSM-IV	Of medicated youth, 31.5% reported 2 concomitant medications and 31.5% reported ≥3 psychotropics; (63%) with ≥2 psychotropics. Antipsychotics, antidepressants and mood stabilizers were most common. History of physical or sexual abuse increased likelihood of polypharmacy.

Pediatric Psychotropic Polypharmacy in Special Settings						
33	Wu B et al. 2018 [43]	2009-2014, Maryland Medicaid, A quasi-experimental design.	3-21 years, N=496, continuously enrolled for 1- year pre and post intervention	≥3 classes for 15 or more days per year	Serious emotional and behavioral disorders	Compared psychotropic polypharmacy between youths with serious emotional and behavioral disorders who were enrolled in CCS and who were in non-CCS. Polypharmacy was comparable pre-, during and post-CCS intervention: ranging from 29 to 31 to 21%, respectively.
34	vanWattum et al. 2013 [44]	Intervention study in residential treatment setting	N=131, 11-18 y/o; From admission on 4 or 5	Point prevalence in polypharmacy at admission and discharge		60% increase in discharged without medication. At 6 months post-discharge 71% doing well.
35	Lyons et al. 2013 [45]	Juvenile secure facility, I year, 2007-2008	12-22 y/o with any psychotropic within first 30 days of admission	Point prevalence of polypharmacy		Among the 10.2% receiving any psychotropic, 48.5% received concomitant: 36.8% received 2; 7.4% received 3; and 5% received 4 concomitant medications..

2.6 Risks vs. Benefits of Pediatric Polypharmacy

2.6.1 Benefits

In general, the benefits of psychiatric polypharmacy are not reliably established by robust scientific evidence. There is no interventional or observational study that specifically evaluated benefits or effectiveness of pediatric polypharmacy.

2.6.2 Risks

2.6.2.1 Risk of psychotropic medication monotherapy

The safety of psychotropic medication use in youth is especially important. In general, the medications have effects on developing brains, livers, and kidneys that may result in short or long-term toxicities which are not observed in adults. Children are more sensitive to adverse effects than adults. In a pilot double-blind randomized study of antipsychotic medications more prevalent and severe adverse effects (AE) were reported in youth than has been reported in adults [92].

There is still much unknown about the AEs of psychotropic medication in youth since widespread use has only emerged in the past twenty years. Due to the lack of sufficient long-term safety information and the weaknesses in the U.S. healthcare delivery system, physicians may be at definite disadvantage to assure safe and effective prescribing practices.

Many AEs of psychotropic medications are common and are similar across different drug classes. The top side effects include weight gain, anhedonia and emotional blurring, sleep disturbances, dry mouth and blurred version [93, 94]. Also, severe AEs such as suicide-related events have been observed [95]. For example, antidepressants were found to be associated with increased risk of suicidality, such as thoughts about suicide and attempts in an FDA meta--analyses that used data from 22 randomized placebo-controlled short-term pediatric trials [96] and another from 27 published and unpublished randomized placebo-controlled trials [97], even though no completed suicide was observed.

Causation of harm from psychopharmacologic drugs is a complex field of study. Possible causes of AEs vary: some are related to elevated medication plasma concentrations (e.g., lithium and valproate-induced tremor [98]), some are related to the mechanism of action of the medication (e.g., antipsychotics caused sleep disturbance and sedation [99]), and others are due to drug discontinuation (e.g., antipsychotic withdrawal-emergent dyskinesias based on long-term receptor blockade). Data on adverse effects derived from administrative claims are generally interpreted as associations which support further research in a controlled environment to establish causation.

2.6.2.2 Risks of psychotropic polypharmacy

Polypharmacy may lead to different pharmacodynamic and pharmacokinetic effects within the body. Due to drug regimen complexity (2 or more psychotropic drug classes concomitantly) there exist safety concerns about pediatric polypharmacy, such as the possibility of cumulative toxicity, drug-drug interactions and adverse event risks [100]. Behavioral toxicity refers to new symptoms of a mental disorder that may not be

recognized by the prescriber as emerging from the medication rather than a new *de novo* behavioral or emotional disorder [101].

Particularly for young children, information and understanding about psychotropic polypharmacy use, prescribing guidelines, efficacy, safety, and tolerability remain unclear and insufficient. Pediatric polypharmacy prescribing practice in the youth population is largely based on inappropriate generalizing from adult studies. [102].

Whether benefits outweigh the risk of harm from polypharmacy in children and adolescents is largely unknown. Several studies indicated that psychotropic polypharmacy in children and youth showed ambiguous evidence of benefit with clear evidence of safety risk [18, 89]. In a systematic review of studies using the combination of an antipsychotic and a stimulant in ADHD and disruptive behavior disorder children, polypharmacy did not show better efficacy than monotherapy [103]. Generally, studies have concluded that further research is needed to understand the effectiveness and safety of polypharmacy in community diagnosed and treated populations. There is a dearth of evidence-based strategies to guide the clinical practice of polypharmacy. In addition, reducing polypharmacy can be difficult and time-consuming. The new field of deprescribing is defined as reducing medications down to the minimum effective dosage or total discontinuation when the medication's risk outweighs the benefit [104]. Deprescribing is growing in general for elderly patients but in particular for psychiatric treatment of youth [105]. Due to insufficient research on effectiveness and safety of complex regimens of prescription drugs in the post-marketing period following approval,

current guidelines for psychiatric polypharmacy for children and adolescents are generally not detailed and recommendations are not data-driven [106, 107].

Hilt et al. investigated the side effect risks associated with one to three or more psychiatric medications concomitantly (including antipsychotics, antidepressants, α-agonists, benzodiazepines, anticonvulsant-mood stabilizers, and stimulants) in a national cohort of children and adolescents using the Child Psychopharmacological Experiences Survey (CPES) data from parents of study subjects ages 3–17 years from 30 U.S. states (7.5% response rate) [16]. Most of the study subjects reported one or more side effects. Youth with two concomitant medications or three or more concomitant medications reported 17% and 38% greater average number of side effects, respectively, than patients on monotherapy. Side effects were commonly reported in medication combinations that included a selective serotonin reuptake inhibitor (SSRI) or an antipsychotic.

2.6.2.3 Psychotropic medication induced diabetes

In recent years, the association between atypical antipsychotic use and incident type 2 diabetes mellitus in youth has been investigated in several studies. Abnormal metabolic syndrome includes weight gain and increased glucose levels which are precursors to diabetes. The plausible biological mechanism of AAP-induced diabetes is: direct effect of AAP-induced insulin resistance, or indirectly through obesity, or AAP-induced β-cell dysfunction and damage [108]. Antidepressants also have effects on glucose metabolism and induce type 2 diabetes[109].

Several epidemiology studies have shown the antipsychotic use among youth is associated with significant weight gain and increased prevalence of type 2 diabetes mellitus [110-112]. Similar results were found in Medicaid claims-derived youth cohort studies. A large retrospective cohort study of the Tennessee Medicaid program followed 6-24-year olds for incident cases of type 2 diabetes. A total of 28,858 youth who had recently initiated antipsychotic therapy (no antipsychotic use in the past year) were compared with 14,429 propensity score–matched controls who had initiated another psychotropic medication (e.g., mood stabilizer, antidepressant) [48]. There were 106 incident type 2 diabetes cases (18.9 cases per 10,000 person-years) during follow-up. Youth who were prescribed antipsychotics had a three-fold increased risk of type 2 diabetes than the control group. The increased risk was associated with cumulative dose [48]. Another retrospective cohort study using 4 state Medicaid programs found that in youth receiving AAP treatment, concomitant SSRI/SNRI had a two-fold increased risk of Type 2 diabetes which increased with duration and cumulative dose of AAP use [113].

The cardio-metabolic risk of AAP use in youth was also estimated in a prospective cohort study [94]. The patients experienced 12 weeks of treatment with aripiprazole, olanzapine, quetiapine or risperidone and were assessed the weight, BMI, fasting metabolic parameters at baseline, weeks 4, 8 and 12. Weight gain and some metabolic parameters, such as cholesterol, triglyceride/HDL ratio, glucose, insulin, and homeostasis model assessment insulin resistance (HOMA-IR) index, increased significantly in the AAP use group than the psychiatric comparison group. In another study, long term use of AAP in youth was evaluated as well [93]. In patients with an average of 2.9 years AAP treatment, overweight children were 12 times more likely to have at least one abnormal metabolic

laboratory value and 7 times more likely to have at least one metabolic syndrome criterion (e.g., high triglyceride level, high fasting glucose, high blood pressure) compared to normal BMI group.

In adults, several studies have shown antidepressant usage is associated with weight gain and increased prevalence of Type 2 diabetes [114, 115]. The effects of long-term use of psychotropic medications were evaluated as well. In one population-based, nested case-control study using Taiwan's National Health Insurance Research Database, long-term antidepressants users (> 2 years) had an increased risk of Type 2 diabetes [114]. Similar results were reported from another nested case-control study using U.K. General Practice Research Database [115].

Few studies have focused on the effect of antidepressant use on type 2 diabetes risk in the pediatric population. In one large, Medicaid-insured youth retrospective cohort study, the researchers found the use of antidepressant medications [primarily, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)] was associated with increased risk of incident type 2 diabetes. The authors also found that increased risk was associated with longer duration of use, higher cumulative dose and higher average daily dose. The average follow-up period was 22.8 months [116].

Although the effect of concomitant use of antipsychotic and antidepressant on the risk of Type 2 diabetes in youth has been studied in one pediatric study [116], to date, the effect of long-term use of concomitant stimulant with other psychotropic medication classes on the risk of Type 2 diabetes has not yet been investigated.

2.6.2.4 Conclusion

The risks of polypharmacy psychotropic medication use in children and adolescents have not been adequately studied. Even though the association between adverse events and psychotropic medications has been investigated in several studies using claims data, the causal relationship has not yet been established.

The association between psychotropic medication usage and increased risk of Type 2 diabetes has been shown in several studies. However, few studies evaluated the association of concomitant psychotropic medications and risk of Type 2 diabetes in a longitudinal model, except for two articles [113, 116]. In these studies, the long-term effect (i.e. in a time window greater than 2 years) of polypharmacy of stimulants with other psychotropic medication class on the risk of Type 2 diabetes was not investigated.

2.7 Summary

This focused review of the pediatric psychopharmacotherapy literature illustrates the interest in quantitative analysis on the medication patterns of use for the treatment of mental, emotional and behavioral disorders of youth. Population based trends illustrate the growth in use of psychotropic medications to unprecedented levels in U.S. children and adolescents. Critical knowledge gaps concern the relative absence of details of polypharmacy for the clinical implications of its measurement.

To our knowledge, there is minimal analysis in the details of prevalence of higher number of stimulant class polypharmacy and the associated factors (Aim 1), Additionally, characterizing stimulant polypharmacy according to age group would extend knowledge of pediatric drug use patterns in very young age group (Aim 1). There is no study has attempted to characterize the details of maximum number of

polypharmacy (NPC), e.g., distribution of NPC, NPC change patterns, and duration of NPC regimens, across multiple years (Aim 2). Finally, the association between ≥ 3 class polypharmacy (stimulants with ≥ 2 other psychotropic classes) and the risk of type 2 diabetes in a cohort framework has not investigated (Aim 3).

2.8 Specific Aims

There are three specific aims in this thesis:

1. To evaluate the prevalence of long-term stimulant monotherapy and stimulant polypharmacy in a large continuously enrolled Medicaid pediatric cohort, and to investigate the association between risk factors and stimulant polypharmacy, especially 3-5 class stimulant polypharmacy users.

2. To fully understand the distribution (N and Percent) of the observed maximum number of polypharmacy classes (NPC), NPC change patterns, and duration of NPC regimens in a large continuous enrolled Medicaid cohort, and to investigate the association between risk factors and the maximum NPCs (event of interest and outcome).

3. To identify the incident type-2 diabetes (T2DM) patients in continuously enrolled Medicaid stimulant users, and to show the absolute risk and relative risk of T2DM in 2-5 maximum class stimulant polypharmacy groups, and to investigate the association between risk factors and incident T2DM.

Chapter 3: Study 1

Stimulant Patterns, Alone or with Other Psychotropic Classes, in Medicaid-Insured Youth Continuously Enrolled for 3–8 Years

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3.1 Abstract:

Objective: Little U.S. pharmacoepidemiologic study is based on treatment during continuous enrollment for periods more than a year. This study aims to show pediatric patterns of stimulant use (alone or with other psychotropic classes) from Medicaid administrative claims data for stimulant patterns of 3-8-year continuous enrollees.

Methods: A retrospective cohort study was derived from Medicaid enrollment, pharmacy, and diagnosis claims data (2007-2014) in a mid-Atlantic state. Youth 2-17 years of age with 3-8 years of continuous enrollment treated with stimulants were compared with a date-matched comparison group treated without stimulants. Major outcomes include prevalence and duration of stimulant use and patterns of stimulant polypharmacy across relatively long enrollments (3-8 years).

Results: Among 264,518 unique 2–17-year-olds with 3-8 years continuous enrollment, 16.5% had stimulant prescription dispensings, doubling the annual national prevalence of 8.1%. Subgroup analysis showed the highest prevalence of stimulant use was for 6-11-year-olds (20.4%), foster care eligible youth (42.3%) and those with 7-8 years of continuous enrollment (20.1%). Externalizing psychiatric disorders were far more common in those treated with stimulants than those treated with no stimulants. The duration of stimulant exposure overall was 487 median days, half that of foster care stimulant users. Stimulant polypharmacy with 2 or more psychotropic classes concomitantly characterized 29.8% of stimulant users. Among those with 3- or 4-or more class polypharmacy, 85% and 88%, respectively, had concomitant stimulant and

antipsychotic use. The adjusted odds ratio (AOR) of 3 or more class polypharmacy significantly increased in 12–17-year-olds age group (AOR=1.8), foster care eligibility (AOR=4.5) and among those with the longest enrollment (AOR=1.7).

Conclusions and Relevance: Stimulant prevalence in Medicaid-insured youth with continuous enrollment of 3-8 years was twice as common as in annual datasets. Future research should investigate 3-5 interclass stimulant polypharmacy effectiveness in reliably diagnosed community populations.

3.2 Introduction

In published research on population-based psychotropic medication use (pharmacoepidemiology) in the community treatment of children and adolescents since the mid-1990s, stimulants are the most common and best evaluated medication class for the treatment of attention deficit/hyperactivity disorder (ADHD). Over the past 25 years, clinician-reported ADHD diagnosis and medication use in community-treated populations have shown substantial increases in the U.S. and internationally [117]. More recently, pharmacoepidemiology research has focused attention on polypharmacy (concomitant use of stimulants with other psychotropic classes), particularly antipsychotics [12, 118, 119], antidepressants [15] and alpha-agonists [120].

Polypharmacy is expanding although such combinations are often off-label, i.e. lacking sufficient data on efficacy as labeled by the FDA [73] for the ADHD indication. Off-label use is common in ADHD polypharmacy and has been explored in terms of evidence of effectiveness [121]. Collectively, polypharmacy is of increasing interest to profile treatments for childhood behavioral disorders especially where off-label usage occurs [118, 120]. These profiles generate questions for robust research on outcomes of ADHD treatment.

Rarely, pharmacoepidemiologic analysis has produced follow-up studies to estimate polypharmacy in an ADHD cohort of pre- schoolers [31] or to assess the annual persistence, that is, duration of stimulant use [122]. Regardless of data sources, studies have provided limited information from community treatment on exposures beyond 1-year enrollee data sets for stimulants alone or concomitantly with other psychotropic classes. Thus, the current study examined stimulant patterns of use in a large cohort of

Medicaid-insured youth aged 2– 17 years with 3–8 years of continuous enrollment. The study aims to investigate the prevalence of stimulant users in terms of socio-demographic and clinician-reported diagnostic groups and compared with treatment date-matched enrollees without stimulant use. In addition, the duration of stimulant whether used alone or in inter class polypharmacy regimens is assessed.

3.3 Method

3.3.1 Study Design

In this retrospective cohort study of Medicaid enrollees, the study population comprised stimulant users (at least one stimulant dispensing) 2-17 years old (y/o) at the time of dispensing and had continuous (3-8 consecutive years) Medicaid enrollment from first stimulant use (N=43,700). The Medicaid enrollment data were generated based on each patient's monthly Medicaid enrollment status. To be eligible for a full year enrollment, the patient needed to be enrolled at least 10 months per year [75].

The flowchart in Figure 3-1 illustrates the selection process. Among stimulant users, the vast majority (91.1%) had continuous enrollment of 3-8 years in Medicaid (N=43,700). A comparison group consisted of treatment date-matched youth without stimulant use and continuous 3-8 years of Medicaid enrollment (N=220,818).

3.3.2 Setting

Medicaid administrative claims data from a mid-Atlantic state included enrollment files, outpatient and physician claims files and dispensed prescription drug files. Patients' enrollment files were linked to their outpatient and physician claims file and dispensed prescription drug file via an encrypted identification number.

The enrollment files comprise enrollees' sociodemographic characteristics, monthly Medicaid enrollment status, and Medicaid eligibility category. The outpatient and physician claims files included information on clinician-reported psychiatric diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The dispensed prescription drug file included information on national drug codes, dispensing date, days of supply, and quantity of supply which were used to identify the name, and duration of dispensed prescription drugs.

This study is covered under #HP-00056963, IRB University of Maryland, Baltimore.

3.3.3 Procedure to Identify Medication Exposures

We focused on 5 psychotropic drug classes (alpha-agonists, anticonvulsant-mood stabilizers, anxiolytics, antidepressants, antipsychotics) and stimulants according to the therapeutic classification system of the American Hospital Formulary Service [123]. In order to collapse all pharmacy claims records for each individual into one person record, 6 timeline variables were created for the drug classes. These timelines consisted of 2,923 columns -- one for each day from 01/01/2007 to 12/31/2014 inclusive plus one column to mark the end of the timeline. As each pharmacy claim was processed, it was assigned a drug class, and the pharmacy fill date and days supply determined the start and end dates. These dates flagged the columns for the drug class timeline as the drug being taken on those days. Gaps of 15 days or fewer between the same drug class fills were also flagged. Once all pharmacy claims were processed for an individual, a summary timeline was created indicating the number of concomitant drug classes taken on each day. With the use of these timelines, we were able to determine the sequence of concomitant drug usage and the duration of concomitant drug usage.

3.3.4 Outcome Measures

Outcome measures for stimulant users included: 1) prevalence of stimulant use in long-term Medicaid enrollees; 2) demographic, administrative and diagnostic factor comparison of stimulant users and treatment date-matched youth with no stimulant use; 3) duration of stimulant exposure; 4) stimulant polypharmacy for stimulant + 1, 2, ≥3 classes among continuous enrollees (3-8 years); 5) Clinician-reported diagnostic patterns in relation to polypharmacy.

1) Prevalence of Stimulant Use in Long-term Medicaid Enrollees

In this study, stimulant prevalence was defined as the number of stimulant users per 100 eligible 3-8 year enrollees in calendar years 2007 through 2014. We assessed the prevalence, overall and stratified by age group, Medicaid eligibility category and length of continuous enrollment.

2) Sociodemographic, Administrative and Diagnostic Factors of Stimulant Users and Treatment Date-matched Youth without Stimulant Use

The sociodemographic, administrative, and clinical characteristics of stimulant and treatment date-matched youth with no stimulant use were compared. These characteristics included age group (2-5, 6-11, 12-17 years old), gender, race/ethnicity (White, African American, Hispanic, Native American/Asian/Pacific Islander, and Unknown), Medicaid eligibility category (foster care, youth with 200-300% of federal poverty income---SCHIP [State Children's Health Insurance Plan], youth with disability coverage---SSI [Supplemental Security Income], and youth eligible by family income at

or below the federal poverty level---TANF [Temporary Assistance for Needy Families]); length of continuous Medicaid enrollment (3-4 years, 5-6 years, 7-8 years).

For psychiatric diagnoses, we grouped clinician-reported diagnoses into five groups based on ICD-9-CM codes: 1) Externalizing disorders (ADHD, disruptive behavioral disorders (conduct disorder and oppositional defiant disorder); 2) Internalizing disorders (depression, anxiety disorders); 3) Both externalizing disorders and internalizing disorders; 4) Other psychiatric diagnoses, i.e. Neither internal nor external disorder; and 5) No psychiatric diagnosis. Up to 8 diagnosis fields were available in the data and all psychiatric diagnoses from stimulant start date were recorded (Table S3-1).

3) Stimulant Duration of Use

For each stimulant user in the study, the patient's stimulant duration of use was calculated based on the timelines described above. The mean, median, and interquartile range of stimulant duration were calculated overall and stratified by age group, eligibility category, and length of continuous enrollment.

4) Stimulant Polypharmacy

The patient's other psychotropic medication class duration of use was calculated as described for stimulants. Stimulant polypharmacy was defined conservatively as at least 60 consecutive overlapping days of stimulant use that included the concomitant use of ≥1 other psychotropic classes. We defined four mutually exclusive groups upon which we classified each patient's maximum number of drug classes taken concomitantly with stimulants: (1) Stimulant monotherapy (no other psychotropic class); (2) two drug class stimulant polypharmacy; (3) three drug class stimulant polypharmacy; (4) ≥four drug

class stimulant polypharmacy. An additional secondary analysis identified the most common medication class combinations of stimulant polypharmacy.

5) **Diagnosis and Polypharmacy**

Finally, we assessed clinician-reported diagnostic groups in relation to stimulant polypharmacy regimens. Also, the details of ADHD comorbidities were assessed.

3.3.5 Statistical Analysis

In 3-8-year enrollees, we began with descriptive analyses of the prevalence of stimulant use and compared the demographic characteristics and clinician-reported psychiatric diagnosis in the stimulant cohort to the cohort of treatment date-matched youth with no stimulant use. Characteristics between stimulant and the treatment date-matched group with no stimulants were compared using χ^2 test for categorical variables. Duration of stimulant use (overall and in stratified groups) was also calculated.

In the multivariate logistic regression, the odds of 3- or ≥4-class stimulant polypharmacy was assessed using adjusted odd ratios (AORs) and 95% confidence intervals (CI). The outcome variable was ≥3 class stimulant polypharmacy vs. stimulant monotherapy and 2 class stimulant polypharmacy. Statistically significant covariates were adjusted in the final multivariate regression model. The significance level was set at .05 and all tests were 2-sided. Data processing and analyses were performed using SAS version 9.4 (SAS Institute Inc, NC). Results were stratified by age group, eligibility category and length of enrollment.

3.4 Results

1) Stimulant Prevalence

The average cumulative prevalence of stimulant users among 2-17 y/o with 3–8-year continuous enrollment was 16.5% (Table 3-1). As a percentage of eligible 6-11-year-olds, this school age group had the highest stimulant prevalence (20.4%) followed by 2-5 y/o (15.1%) and 12-17 y/o (13.0%). The prevalence of stimulant use in foster care (42.3%) and in SSI (38.4%) were 3-4 times higher than those by family income alone [SCHIP (11.2%) and TANF (13.8%)]. Stimulant users who were enrolled in Medicaid for longer periods had higher prevalence of stimulant use: 20.1% for those with 7-8 years of enrollment—twice as high as for those with 3-4 years of continuous enrollment (Table 3-1). In a comparison by length of enrollment, the long-term (continuously enrolled in Medicaid for 3-8 years) stimulant user cohort (N = 43,700) represents 91.1% of all 2–17-year-old Medicaid stimulant users enrolled between 2007 and 2014 in this mid-Atlantic state (Figure 3-1). Among 43,700 stimulant users, amphetamine products alone were used by 29.1%, methylphenidate products alone by 33.7% and 37.2% had dispensings for both types of stimulants.

Among stimulant users, youth with externalizing psychiatric disorders alone predominated, followed by both comorbid internal and external psychiatric disorders: 85.5% in total compared with 8.4% in the comparison group with no stimulants (Table 3-2). More specifically, ADHD was the leading diagnosis (83.2%), followed by depression (31.4%), and disruptive behavioral disorder (30.3%) (Table S3-2). On average, 2.4 psychiatric diagnoses per stimulant user were found (Table S3-2). Table S3-3 provides a

more detailed profile of comorbidity patterns. Among 36,304 stimulant users who were diagnosed with ADHD, 11,816 (32.5%) had ADHD alone and 24,488 (73.5%) had ADHD and other psychiatric comorbidities. Among the 24,488 who had ADHD and other psychiatric diagnoses, 12,160 (49.7%) had disruptive, 12,075 (49.3%) had depression, and 8,368 (34.2%) had anxiety.

2) Stimulant Users Compared with Treatment Date-matched Group with No Stimulant Use

In the comparison of stimulant users (N=43,700) with those with no stimulant use (N=220,818), stimulant users were more frequently male, white, aged 6-11 years, more often in foster care or with disability insurance (SSI), and among youth with the longest enrollment time (Table 3-2).

3) Stimulant Duration

Figure 3-2 provides duration of stimulant use overall and stratified by key characteristics. Overall, the average duration of use was 718 days compared with median of 487 days and indicates the presence of long duration "outliers". The 6-11 y/o age group had the highest average duration of use with more than 2 years of stimulant exposure, followed by younger and older aged youth. Stimulant users in foster care had the longest duration of use with a mean of 908 days and median of 740 days. Stimulant users with 7-8 years of continuous Medicaid enrollment had twice the stimulant exposure as those with 3-4 years of continuous Medicaid enrollment. Collectively, the data reflect relatively long stimulant exposures (up to 2.7 years) in these 3–8-year continuous enrollees.

4) Stimulant Polypharmacy

Among stimulant users, approximately 30% had dispensings of 2 or more concomitant classes (stimulant plus ≥1 other psychotropic classes). This was distributed as follows: 18.2% had 2 class polypharmacy; 7.3% had 3 class polypharmacy; and 4.3% had ≥4 class polypharmacy (Table 3-3).

The prevalence of 2 class polypharmacy was highest in 2-5 y/o (20.0%) with slightly lower prevalence in 6-11 y/o (18.6%) and dropping further in 12-17 y/o (15.4%). By contrast, the prevalence of 3 and ≥4 drug class polypharmacy increased linearly with age: 7.9% in 2-5 y/o; 12.0% in 6-11 y/o; and 14.8% in 12-17 y/o eligible youths (Table 3).

Externalizing disorders alone were dominant (56.9%) in the stimulant only subgroup and dramatically decreased as polypharmacy increased (43.4% in 2 drug class, 22.0% in 3 drug class, and 11.7% in ≥4 drug class). In youth with both clinician-reported externalizing and internalizing disorders, polypharmacy significantly increased as a proportion of each polypharmacy class (26.4% in stimulant monotherapy, 46.6% in 2 drug class, 69.2% in 3 drug class, and 82.3% in ≥4 drug class) (Table 3-4).

Results of the logistic regression analysis are presented in terms of adjusted odds ratios in Table 3-5 stratified by age group, gender, race/ethnicity, eligibility category and length of enrollment. The odds of experiencing ≥3 class polypharmacy vs. experiencing stimulant only or 2 class polypharmacy increased with age group after adjusting for other covariates. Compared with 2-5 y/o, 12-17 y/o and 6-11 y/o enrollees, respectively, had greater odds of receiving 3 or more class polypharmacy as follows: (12-17 y/o, adjusted

odds ratio [AOR] = 1.82, 95% CI = 1.66, 2.00, $p < 0.001$; 6-11 y/o, adjusted odds ratio [AOR] = 1.55, 95% CI = 1.43, 1.67).

Males were more likely to receive ≥3 class polypharmacy than females (AOR = 1.13; 95% CI = 1.01, 1.21; $p < 0.001$); white race (AOR = 1.79; 95% CI = 1.59, 2.02; $p < 0.001$) increased the odds of receiving ≥3 class polypharmacy compared to other races. Stimulant users in foster care and SSI had 4.49-fold (95% CI = 4.11, 4.91; $p < 0.001$) and 3.88-fold (95% CI = 3.60, 4.19; $p < 0.001$), respectively, greater odds of receiving ≥3 class polypharmacy than TANF i.e., the reference group. SCHIP was not different than TANF in likelihood to receive 3 or more interclass polypharmacy. Those continuously enrolled in Medicaid for 7-8 years were more likely to receive ≥3 class psychotropic medications concomitantly than those who were enrolled for 3-4 years (AOR = 1.68; 95% CI = 1.51, 1.86; $p< 0.001$) (Table 3-5).

5) Common Concomitant Stimulant Regimens

The combination of psychotropic classes in 3 and ≥4 stimulant polypharmacy regimens were investigated: in summary, 85% of the 3-drug stimulant polypharmacy cohort and 88% of the ≥4 class stimulant polypharmacy cohort had a regimen that included a stimulant with at least one antipsychotic dispensing for 60 or more days of concomitant use (Table 3-6).

In 3-class polypharmacy, the most prevalent combination was ‘stimulant/antipsychotic/ antidepressant’. In 4-class polypharmacy, the most prevalent combination was ‘stimulant/ antipsychotic/antidepressant/alpha agonist” (Table 3-6).

3.5 Discussion

Our study design is novel and permits population-based knowledge on the length of exposure to stimulants among youth with 3-8 years of continuous enrollment. There are several main findings from this population-based analysis of continuously enrolled youth in a mid-Atlantic Medicaid program. First, across youth with 3-8 years of continuous enrollment, 16.5% of youth were unique stimulant treated youth, twice as great a prevalence as is reported by annual national estimates of stimulant use. For example, Visser et al. [124] showed a stimulant prevalence of 8.1% for youth insured by Medicaid or CHIP. This is a good fit with our insured cohort. But the full importance of the doubling of stimulant users in our cohort compared with a one-year cohort concerns the empirical support we now have for extended treatment patterns both for the 70% who received stimulant monotherapy and the 30% treated with medication classes concomitantly with stimulants. By contrast, international data for 2010 show a wide range of annual stimulant use from 0.27% to 6.7% [117]. The consistency or contrast with published studies on U.S. pediatric stimulant polypharmacy will be explored below.

Second, the substantial prevalence of stimulant medication users in our 3-8-year continuously enrolled Medicaid cohort, particularly among foster care enrollees, has been the topic of federal agency warnings for the past 20 years [125, 126]. Thus, the stimulant disparity by income level for publicly (5.8%) versus privately insured youth (2.9%) [127] presents thought-provoking questions regarding the social determinants of health. For example, ethnicity and geographic isolation of family residence are associated with barriers to ADHD treatment services as illustrated with claims data linked with geographic zip code and county data [128]. Overall, the clinical implications for

behavioral treatment with medications are important, particularly for stimulant polypharmacy where in our study 5,047 stimulant users had 3-5 stimulant interclass concomitant regimens although such combinations have not been identified in published effectiveness studies of ADHD combinations [121].

When adjusted for covariates, logistic regression analysis revealed that older age, foster care eligibility category and 7-8 years of continuous enrollment significantly increased the likelihood of ≥3 interclass polypharmacy. Notably, although the African American racial subgroup had the highest prevalence of stimulant use (Table 3-2), white youth had the greatest adjusted odds of 3 or more interclass polypharmacy, suggesting long-term persistence favors white youth.

Concomitant Use of Antipsychotics, Antidepressants and Stimulants

The frequent combination of stimulant with antipsychotic and antidepressants is corroborated by numerous annual studies in both national and Medicaid cohorts. National data showed the prevalence of antipsychotics for the treatment of behavioral disorders to be prominent and nearly twice as likely in publicly insured youth [12]. ADHD medication with antipsychotic or selective serotonin reuptake inhibitors (SSRIs) was also reported in the national annual trends' dataset of Girand et al. [15]. Similarly, medical expenditure panel survey data across 16 years to 2015 corroborate these patterns [129]. Olfson et al. [130] analyzed data from 60% of pharmacies in the nation, illustrating the prominence of stimulant and antipsychotic regimens among these largely commercially insured youth. Moreover, combinations of stimulant and antipsychotic medication were prevalent even in 3-6 year old foster care enrollees [131].

Girand et al. [15] measured more than one class concomitantly and found ADHD polypharmacy in 31.5% of ambulatory prescription drug outpatient visits among 2-24-year olds in 2015. Similarly, Lohr et al. [120] examined recent state Medicaid data among children less than 18 year of age. Interclass psychotropic polypharmacy (regardless of stimulant use) was observed in 39.5% among those with ≥90 days of continuous enrollment and a behavioral diagnosis although the maximum length of enrollment was not given. In summary, approximately 29%-39% of Medicaid-insured youth treated with stimulants are likely to be treated with complex medications increasing the potential for serious adverse events while being used in the absence of robust evidence of effectiveness [121]. Annual period prevalence of polypharmacy treated youth in privately insured youth was not far behind (25%-28%) [27]. By contrast, in a European Union study of ADHD medication polypharmacy was found to be 14.1%, i.e., half of the proportion in our Medicaid youth cohort [132].

Defining Long-term Use

While the term 'long-term use' lacks agreement in the literature, some estimates are based on relatively short time periods. For example, Olfson et al. [130] defined long-term use as 120-365 days [versus ≤30 days (short-term)] of continuous stimulant use in a one-year window. In our cohort of 3–8-year continuous enrollees, substantially longer exposures were observed. For example, according to eligibility group, 50% of stimulant users had more than one year duration: foster care (>2 years); disabled (SSI) (>1.6 years); SCHIP (>1.4 years) and TANF (>1.1 years). An exceptional study in terms of very long

stimulant exposures is the Rochester, Minnesota birth cohort of Barbaresi et al. [133]. Subjects with research identified ADHD (N= 379) were followed retrospectively from birth to a mean of 17.2 years yielding an average of 33.3 months of stimulant use.

However, the Rochester community represents a small region of largely white, privately insured youth. Despite the richness of the long-term follow-up, its generalizability is low. There are several pertinent stimulant studies that were designed as follow-up studies, e.g.1 year following an initial stimulant use [122] or from first diagnosis of ADHD and stimulant use to estimate risk of 3 or more classes anytime in follow-up years 1 to 5 [31]. In Winterstein et al.'s [31] Medicaid study, the finding that polypharmacy was greatest for the youngest aged children contrasts with our finding that polypharmacy increased with age, as in other studies with shorter enrollments [17, 120].

Policy Implications

Greater Medicaid continuity of enrollment in our study likely explains the greater number of youth with access to diagnosis and treatment in our study population compared with annual estimates. Numerous policy efforts, e.g. the 2009 CHIPRA legislation [134] encouraged continuity of enrollment in Medicaid and CHIP enrollees and is reflected in the 67% of youth with 7-8 years of continuous enrollment in our dataset (Table 3-2). Also, wraparound services are likely to have contributed to the state's efforts to improve care coordination [135]. Furthermore, policy analysis of Medicaid data [136] has shown that annual datasets underrepresent the extent of enrollment (32.8% had one year enrollment vs. 41% had five year enrollment), affirming that multiyear enrollment extends the opportunity for long-term stimulant use. Collectively, U.S. studies underscore

the continuing efforts by federal agencies' Medicaid monitoring programs to rein in 'overprescription', particularly in the poor and foster care populations [125, 126].

Research for Effectiveness of Concomitant Stimulant Polypharmacy

Calls for research to evaluate the appropriateness, effectiveness, and safety of psychotherapeutic polypharmacy in community-treated ADHD-diagnosed youth come from national physician office survey studies with findings similar to ours [15]. Similarly, large simple trials [137] and 'real world data' research studies are considered to be both feasible and cost-efficient [138], and may be enhanced by the development of electronic health record technology.

Strengths and Limitations

Our choice of a 60-day window strengthens the polypharmacy definition while minimizing the likelihood of counting intentional switching or short-time medication trials. Limitations include relying on claims data measured by pharmacy dispensings as consumed, although the refill patterns support, but do not guarantee, consumption of the medications. Also, diagnoses are clinician-reported and lack the validity of research assessment. Concerns about the age of the data source may be alleviated by the consistency of findings with later dataset findings, e.g., in Medicaid [120], commercially insured [139] and from national data [15, 140]. Finally, the data are derived from a single state Medicaid program, although many findings are consistent with published multi-state studies of annual enrollees.

3.5 Conclusion

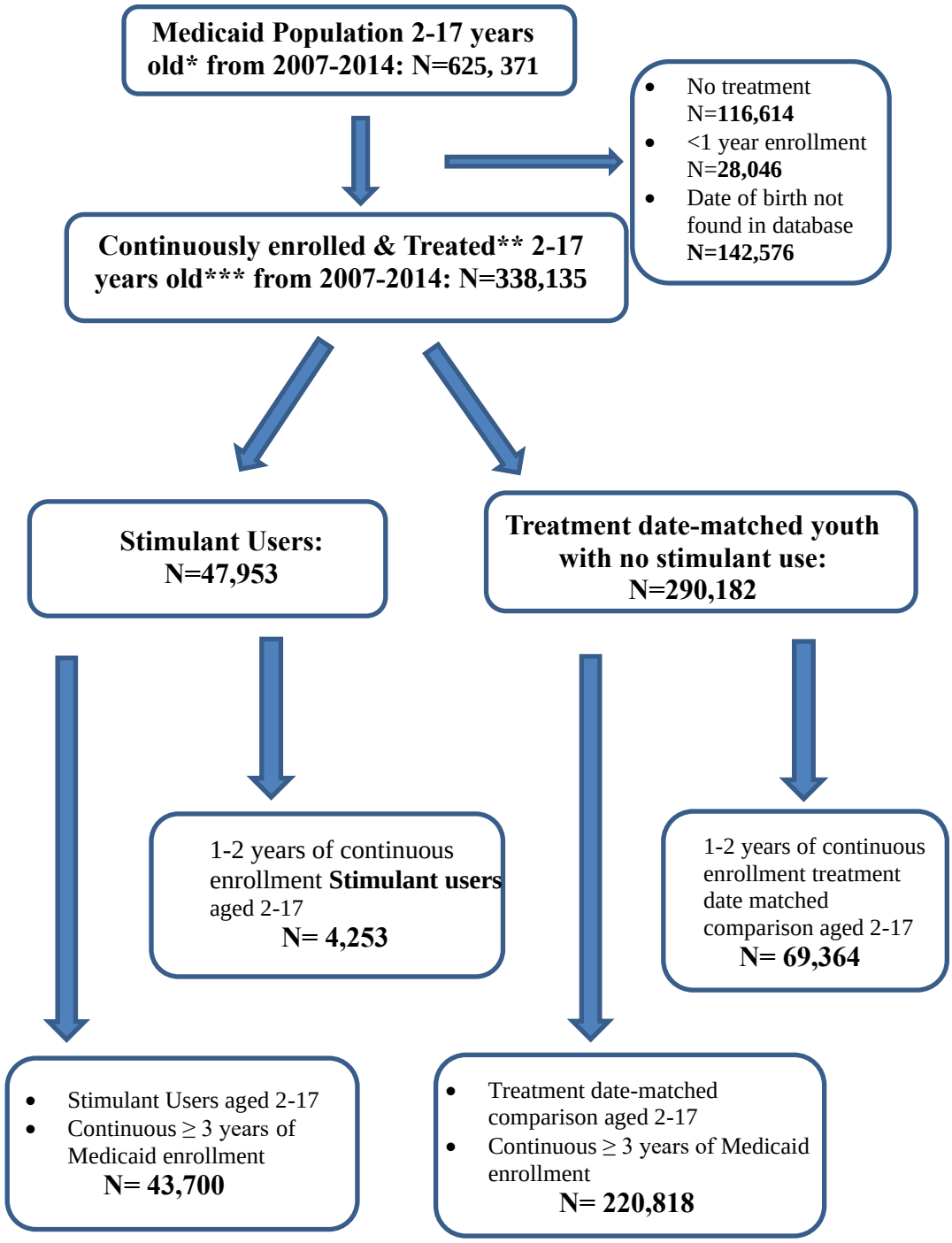
Stimulant prevalence in Medicaid-insured youth with continuous enrollment of 3-8 years was twice as common as in annual Medicaid datasets. Future research should investigate 3-5 interclass stimulant polypharmacy effectiveness in reliably diagnosed community populations.

3.6 Clinical Implications

To summarize from a clinical perspective:

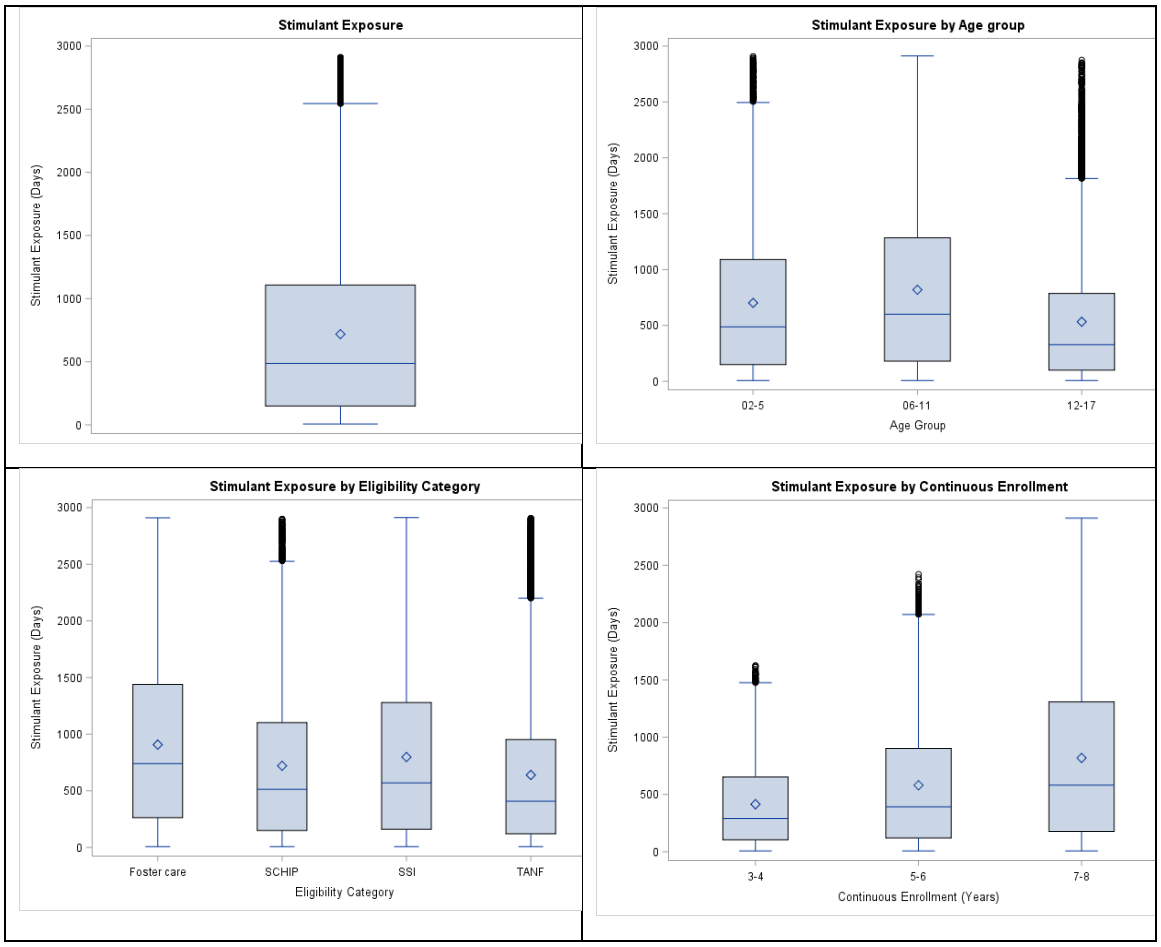
- The study findings emphasize that continuous Medicaid enrollment of 3-8 years is associated with a wider pool of stimulant-treated youth than is found in annual data.
- In addition, the duration of stimulant exposure is substantial (487 median days). Data from special subgroups, e.g., foster care and disabled youth, are higher.
- Stimulant polypharmacy for 3 or more interclass stimulant polypharmacy increased with age group while stimulant monotherapy decreased with age group.
- Particularly frequent in 3 or more interclass stimulant polypharmacy is the combination of stimulants with antipsychotics.

Figure 3-1. Flow chart for cohort selection



*Age at Medicaid enrollment
**Treatment: any medication, physician visit, or procedure
***Age at stimulant treatment

Figure 3-2. Days of stimulant exposure (duration)* total and by age group, eligibility group and length of enrollment



*The minimum stimulant exposure days is 7 days

36 stimulant users who had less than 7 days of stimulant exposure were excluded

Table 3-1. Prevalence of stimulant use among long-term Medicaid enrollees in 2007-2014: total, by age group and eligibility category

	Stimulant Users n=43,700	**Prevalence**
	n	**% (95% CI)**
Total, eligibles n=264,518	43,700	16.5 (16.4-16.7)
Age Group (years) eligibles		
2-5 = 82,696	12,455	15.1 (14.8-15.3)
6-11 = 103,026	20,976	20.4 (20.1-20.6)
12-17 = 78,796	10,269	13.0 (12.8-13.3)
Eligibility Category* eligibles		
Foster care= 11,203	4,741	42.3 (41.4-43.2)
SCHIP =76,004	8,482	11.2 (11.0-11.4)
SSI =24,300	9,324	38.4 (37.8-39.0)
TANF=153,011	21,153	13.8 (13.7-14.0)
Continuous Enrollment (years) eligibles		
3-4 = 58,410	5,689	9.7 (9.5-10.0)
5-6 = 60,082	8,696	14.5 (14.2-14.8)
7-8 = 146,026	29,315	20.1 (20.0-20.3)

* SCHIP=State Children's Health Insurance Program; SSI=Supplemental Security Income; TANF=Temporary Assistance for Needy Families

Table 3-2. Demographic, administrative characteristics, and prevalence of stimulant treated and treatment date-matched comparison youth with no stimulant use among those with 3-8 years of continuous Medicaid enrollment

	Stimulant treated N= 43,700		**Treatment date-matched comparison N= 220,818**		**P-value**
	N	%	N	%	
Age Group (years)					
2-5	12,455	28.5	70,241	31.8	<0.0001
6-11	20,976	48.0	82,050	37.2	
12-17	10,269	23.5	68,527	31.0	
Gender					<0.0001
Male	29,441	67.4	101,016	45.8	
Female	14,259	32.6	119,802	54.3	
Race/Ethnicity					<0.0001
African American	20,073	45.9	109,685	49.7	
White	18,012	41.2	52,370	23.7	
Hispanic	1,409	3.3	19,875	9.0	
Nat Am/Asian/Pac Islander	442	1.0	9,075	4.1	
Unknown	3,764	8.6	29,813	13.5	
Eligibility Category**					<0.0001
Foster care	4,741	10.9	6,462	2.9	
SCHIP	8,482	19.4	67,522	30.6	
SSI	9,324	21.3	14,976	6.8	
TANF	21,153	48.4	131,858	59.7	
Continuous Enrollment (years)					<0.0001
3-4	5,689	13.0	52,721	23.9	
5-6	8,696	19.9	51,386	23.3	
7-8	29,315	67.1	116,711	52.9	
Clinician-reported psychiatric diagnosis					<0.0001
Externalizing disorders***	21,829	50.0	12,432	5.6	
Internalizing disorders***	1,491	3.4	18,535	8.4	

Both***	15,531	35.5	6,284	2.8	
Other psychiatric diagnoses	1,143	2.6	21,140	9.6	
No Psychiatric diagnosis	3,706	8.5	162,427	73.6	

*Age is the age of first stimulant use (column 2) or age of first drug/medical service use (column 4)

** SCHIP=State Children's Health Insurance Program; SSI=Supplemental Security Income; TANF=Temporary Assistance for Needy Families

*** Externalizing disorders include ADHD, disruptive behavioral disorders; Internalizing disorders include depression, anxiety disorders; Other psychiatric diagnoses include adjustment disorder, autism spectrum disorder, learning disorder, schizophrenia, intellectual disability, tic disorder, bipolar disorder, and other mental health diagnoses

Table 3-3. Polypharmacy (60 or more days overlap) in stimulant users by age group in 2007-2014

	Stimulant users N=43,700		**Age 2-5 N=12,455**		**Age 6-11 N=20,976**		**Age 12-17 N=10,269**		**P-Value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Stimulant Only	30,696	70.2	8,976	72.1	14554	69.4	7166	69.8	Ref
2 drug class polypharmacy (Stimulant + 1 other psychotropic class)	7,957	18.2	2,486	20.0	3890	18.6	1581	15.4	<0.005
3 drug class polypharmacy (Stimulant + 2 other psychotropic classes)	3,194	7.3	650	5.2	1,584	7.5	960	9.3	<0.005
≥4 drug class polypharmacy* (Stimulant + ≥ 3 other psychotropic classes)	1,853	4.3	343	2.7	948	4.5	562	5.5	<0.005
Total	43,700		12,455		20,976		10,269		

***** 4 concomitant drug classes were observed for 1,559 youth (3.6% of stimulant users)

5 concomitant drug classes were observed for 294 youth (0.7% of stimulant users)

Table 3-4. Polypharmacy (60 or more days overlap) in stimulant users by clinician-reported diagnostic subgroup in 2007-2014

	Stimulant only N=30,696		2 drug class polypharmacy N=7,957		3 drug class polypharmacy N=3,194		≥4 drug class polypharmacy N=1,853		P-value
Diagnostic Group	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Externalizing Disorder	17,455	56.9	3,454	43.4	704	22.0	216	11.7	<0.005
Internalizing Disorder	1,120	3.6	227	2.9	92	2.9	52	2.8	<0.005
Both	8,090	26.4	3,705	46.6	2,211	69.2	1,525	82.3	<0.005
Other Psychiatric Diagnoses*	931	3.0	119	1.5	74	2.3	19	1.0	<0.005
No Psychiatric Diagnosis	3,100	10.1	452	5.7	113	3.5	41	2.2	Ref

* Externalizing disorders include ADHD, disruptive behavioral disorders; Internalizing disorders include depression, anxiety disorders; Other psychiatric diagnoses include adjustment disorder, autism spectrum disorder, learning disorder, schizophrenia, intellectual disability, tic disorder, bipolar disorder, and other mental health diagnoses

Table 3-5. Logistic regression analysis for 3 or more class stimulant concomitant use (polypharmacy) vs. stimulant only and 2 class stimulant polypharmacy

	Adjusted Odds Ratio*	95% CI	P
Age Group (years)			
6-11	1.55	1.43 - 1.67	<0.001
12-17	1.82	1.66 - 2.00	<0.001
2-5	1	Ref	
Gender			
Male	1.13	1.05 - 1.21	<0.001
Female	1	Ref	
Race/Ethnicity			
White	1.79	1.59 - 2.02	<0.001
African American	0.74	0.66 - 0.84	<0.001
Hispanic	0.79	0.62 - 0.92	0.02
Native Am/Asian/Pac Islander	1	Ref	
Eligibility Category**			
Foster care	4.49	4.11 - 4.91	<0.001
SCHIP	0.94	0.85 - 1.04	n.s.***
SSI	3.88	3.60 - 4.19	<0.001
TANF	1	Ref	
Continuous Enrollment (years)			
5-6	1.17	1.04 - 1.32	0.01
7-8	1.68	1.51 - 1.86	<0.001
3-4	1	Ref	

* Adjusted for Age, Gender, Race/Ethnicity, Eligibility Category, Continuous Enrollment

** SCHIP=State Children's Health Insurance Program; SSI=Supplemental Security Income; TANF=Temporary Assistance for Needy Families

***n.s. = nonsignificant

Table 3-6. Frequency of 3 and 4 class concomitant regimens in stimulant polypharmacy by age group among stimulant users

	Age 2-5 N=12,455		Age 6-11 N=20,976		Age 12-17 N=10,269		Total N=43,700	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
3 drug class polypharmacy								
Stimulant + ATP + ATD	172	26.5	640	40.4	460	47.9	1,272	39.8
Stimulant+ ATP + AA	333	51.2	516	32.6	134	14.0	983	30.8
Stimulant + ATP + ATC-MS	38	5.8	167	10.5	197	20.5	402	12.6
Stimulant + ATD + ATC-MS	20	3.1	92	5.8	83	8.6	195	6.1
Stimulant + AA + ATC-MS	54	8.3	90	5.7	17	1.8	161	5.0
Other 3 class polypharmacy	33	5.1	79	5.0	69	7.2	181	5.7
Total	650		1,584		960		3,194	
4 drug class polypharmacy								
Stimulant + AA + ATP + ATD	137	47.1	363	45.3	123	26.3	623	40.0
Stimulant + ATP + ATD +ATC-MS	25	8.6	156	19.5	194	41.5	375	24.1
Stimulant + AA+ ATP + ATC-MS	74	25.4	162	20.2	57	12.2	293	18.8
Stimulant + AA + ATD+ ATC- MS	37	12.7	57	7.1	18	3.9	112	7.2
Stimulant + ATP + ATD + AX	4	1.4	23	2.9	36	7.7	63	4.0
Other ≥4 drug class polypharmacy*	14	4.8	40	5.0	39	8.4	93	6.0
Total	291		801		467		1,559	

AA=Alpha agonist; ATP=Antipsychotic; ATD=Antidepressant; ATC-MS=Anticonvulsant-Mood Stabilizer, AX=Anxiolytic

***** Stimulant + ATP + AX+ ATC- MS; Stimulant + ATP + AX+ AA; Stimulant + ATD+ ATC- MS+AA; Stimulant + ATD+ ATC-MS+AX; Stimulant + ATD+ AX+ AA; Stimulant + AX + AA+ ATC- MS;

Stimulant + ATP + ATD+ AA+ ATC- MS; Stimulant + ATP + ATD+ AX+ ATC- MS; Stimulant + ATP + ATD+ AX+ AA; Stimulant + ATP + AX+ ATC- MS+ AA; Stimulant + ATD + AX+ ATC- MS+AA

Chapter 4: Study 2

Stimulants Concomitant with other Psychotropic Classes: A Competing Risk Analysis in Medicaid-Insured Youth

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4.1 Abstract

Objective: Pharmacoepidemiologic research shows increasing use of polypharmacy to manage behavioral treatment of youth. Methods to increase precision, e.g., competing risk analysis, to capture psychotropic patterns of concomitant stimulant treatment changes over time have not been explored.

Methods: A retrospective cohort study was derived from Medicaid enrollment data, prescription drug and clinician-reported diagnosis claims data from 2007-2014. Youth aged 2-17 years with 1-7.5 years of continuous enrollment who were new users of stimulants were followed. Major outcomes include detailed changes of concomitant use according to the number of psychotropic classes (NPC); competing risk assessment of patient factors according to NPC; and time factors related to changes in NPC.

Results: Among 30,294 new stimulant users, 75.5% remained on stimulant monotherapy and 24.5% had stimulant concomitant regimens. Among the latter, great flux was observed, revealing exposure to combinations changed substantially across time. As a proportion of all changes, retention of the maximum NPC was observed for 65.3% of 2 concomitant classes, 56.2% of 3 concomitant classes, 57.1% and 56.2% of 4 and 5 concomitant classes, respectively.

Median duration according to NPC showed a linear decrease in time from 223 days for 2 class, 172 days for 3 class, 141 days for 4 class and 113 days for 5 class combinations. By contrast, the path to maximum NPC regimens took median times of 491-833 days as NPC increased from 2 to 4 concomitant classes.

Competing risk analysis demonstrated significantly increased hazard ratios according to the number of concomitant classes for 12–17-year-olds, patients with foster care or disability coverage and those with 3-4 years of continuous enrollment.

Conclusions: Detailed NPC changes illustrate great flux in concomitant stimulant patterns among Medicaid-insured youth. Competing risk analysis brings more precise patient characteristics risk information to assess NPC changes compared with a binary model.

4.2 Introduction

Stimulants have been the most common psychotropic medication class for the treatment of pediatric attention deficit/hyperactivity disorder (ADHD) for more than 25 years. Clinician-reported ADHD diagnosis and stimulant usage in community-treated populations have increased substantially in the U.S. For example, Zhang et al. assessed 1999-2015 national data and found ≥2 psychiatric diagnoses grew from 57.8% to 77.7% of youth across 17 years. Also, stimulants from 1990-2010 were the most common psychotropic class among youth with polypharmacy (concomitant use) regimens (77.8% to 82.1%) [129]. Similarly, in a national survey of physician office visits across 12 years, Girand et al., found ADHD medication (essentially stimulants) virtually doubled from 4.8% to 8.4% and ADHD psychotropic polypharmacy increased from 16.8% to 20.5% [15].

In recent years, stimulant polypharmacy including antipsychotics [117, 119, 141], antidepressants [15] and alpha-agonists [120] has grown substantially, particularly among publicly-insured youth. Some papers reflect negatively on polypharmacy. However, Chen et al. noted that "Despite the paucity of evidence for and against polypharmacy, in some situations short-term polypharmacy is clearly appropriate or even necessary. For example, to cross-titrate two drugs." [19]. In this study, we use 'stimulant concomitant treatment' [with (inter-class) psychotropic classes] to describe stimulant 'polypharmacy'. Notably, physicians can appropriately prescribe concomitant regimens according to FDA guidelines [73]. However, complex regimens in vulnerable populations, e.g. foster care youth, receive monitoring oversight at both federal [126] and state [142] levels.

To address the evolution of patterns of concomitant stimulant regimens, i.e., the change from stimulant monotherapy to 2, 3, 4 or 5 as the number of psychotropic classes used (NPC), we undertook a retrospective cohort analysis among those with at least 1 and up to 7.5 years of continuous Medicaid enrollment. With rare exception [31], previous studies have been limited to a cross-sectional framework, typically annual trends, [17, 19, 22, 32, 43, 143] as opposed to a longitudinal framework. In this study, we aimed to capture the patient's longitudinal journey through concomitant stimulant use based on a detailed temporal sequence of NPC changes: patients usually start with stimulant monotherapy and if the prescriber determines that a stimulant isn't sufficiently effective, s/he may prescribe additional concomitant psychotropic class(es). The NPC may reduce over time, e.g., if symptoms diminish or complex regimens bring adverse effects.

In the case of multiple possible events, for example increasing from monotherapy to 2, 3, 4 or 5 NPC and then back to a lower NPC or monotherapy, where one event can be affected by other events, competing risk analysis can provide more detailed patient information into the likelihood of each NPC option and in relation to patient characteristics risk factors.

4.3 Methods

4.3.1 Data Source

The data source comprises the 2007-2014 Medicaid administrative claims data from a mid-Atlantic state which included enrollment files, outpatient and physician claims files

and dispensed prescription drug files. The files in the data source were linked together via an encrypted identification number.

The enrollees' sociodemographic characteristics, monthly Medicaid enrollment status and Medicaid eligibility category are included in the enrollment files. The clinician-reported psychiatric diagnoses are based on the ICD-9-CM codes located in the outpatient physician claims files. The prescription dispensing information such as national drug codes, dispensing date, days supplied, and quantity supplied are included.

This study was reviewed and approved by the Institutional Review Board of the University of Maryland, Baltimore.

4.3.2 Study Design and Study Population

We used a retrospective cohort design to reflect the NPC changes in new stimulant users with up to 7.5 years of follow-up in the database. The design allowed us to detail the patient's journey through concomitant treatment and to assess the association between patient characteristics and the probability that a stimulant user would have additional dispensings for psychotropic drug classes. A graphical depiction of patterns of NPC changes is shown in S Figure 4-1.

The Medicaid enrollment data were generated based on each patient's monthly Medicaid enrollment status. To be eligible for a full year enrollment, the patient had to be enrolled at least 10 months per year [75]. The patient's daily stimulant usage was calculated based on the stimulant dispensing dates, days supplied and allowable 15-day gaps for prescription refills. Based on daily stimulant usage in the database, we built a daily stimulant usage string up to 7.5 years for each patient in the study within their continuous

enrollment period. Following the same methodology, daily usage of the other six psychotropic classes was calculated as well. All patients were followed to the end of drug therapy or end of 2014, whichever came first.

4.3.3 Psychotropic Medication and Concomitant Use

Psychotropic medications were grouped into seven classes according to the classification system of the American Hospital Formulary Service [123]: antipsychotics; anxiolytics; antidepressants; anticonvulsant-mood stabilizers; stimulants; selected alpha-agonists and lithium (S Table 4-1).

Stimulant concomitant use was defined conservatively as at least 60 consecutive overlapping days of stimulant use that included the concomitant use of ≥1 other psychotropic classes.

We defined five mutually exclusive groups in which we classified each patient's maximum NPC taken concomitantly with stimulants: stimulant monotherapy; concomitant stimulant therapy with 2-5 NPCs.

4.3.4 Outcome Measures

1) Patient Characteristics and Diagnostic Factors of Stimulant Monotherapy and Concomitant Users

Patient characteristics included age group at initial start of stimulants (2-5 years old, 6-11 years old, 12-17 years old), gender, race/ethnicity (White, African American, Hispanic, Native American/Asian/Pacific Islander, and Unknown), Medicaid eligibility category (foster care, SCHIP [State Children's Health Insurance Plan], SSI [Supplemental Security

Income], and TANF [Temporary Assistance for Needy Families for youth eligible by family income at or below the federal poverty level] and length of continuous Medicaid enrollment (1-2 years, 3-4 years, 5-6 years, 7-8 years).

For psychiatric diagnoses, we grouped ICD-9 codes for clinician-reported diagnoses into 11 categories. (S Table 4-2).

2) Maximum NPC

S Figure 4-1 illustrates complexity of stimulant users' changes according to NPC. Among new stimulant users, some patients changed to 2 NPC over time, some changed to 3, 4, or 5 NPC, while others continued stimulant monotherapy until the end of the study. During the change, patients received additional psychotropic class(es) until maximum NPC, decreased to a lower NPC or remained at the same NPC. Among the various changes, 468 patients (1.5%) had 2 or more of the same NPC. For example, a change from 2 NPC increased to 3 NPC and then decreased to 2 NPC and increased to 3 NPC again. A sensitivity analysis showed no significant difference between the average change time of multiple changes and the first change time (Data not shown). In such cases, we kept the first change.

3) Duration of Concomitant Change

In each change, duration of concomitant use (days) was calculated based on the start date of stimulant monotherapy or NPC and start date of next level of NPC or the last date of the study period.

4) Time to Maximum NPC

Time to maximum NPC was calculated from the start date of stimulant or initial NPC and start date of maximum NPC. The median and interquartile range of time to maximum NPC were calculated.

5) Event of Interest and Hazard Ratio Using Competing Risk Analysis

Maximum 2 to 5 NPCs are the events of interest in the competing risk analysis, and stimulant monotherapy is used as the reference group. Finally, the adjusted sub-hazard ratios for patient characteristics in relation to NPC regimen changes were assessed using a competing risk model described further in 'Statistical Analysis'.

4.4 Statistical Analysis

The demographic characteristics and clinician-reported psychiatric diagnosis in the monotherapy group, maximum 2, 3, 4 and 5 NPCs were assessed (number and percent). Characteristics between different groups were compared using χ^2 test for categorical variables.

The number and percent of patients with NPC changes were calculated. Duration of NPC changes was calculated and presented as median, minimum, maximum, and interquartile range (IQR). The linear trends for patient characteristics within the maximum NPCs were tested using Cochran-Armitage trend test.

The association between patient characteristics and various maximum NPC regimens was assessed by competing-risk analysis using Fine and Gray's proportional hazards regression model (S Figure 4-3). This approach is an extension of the Cox proportional

hazard model and accounts for competing events by modeling the effect of the patient characteristics on the sub-distribution hazard.

The association between patient characteristics and NPC is reflected by the sub-hazard ratio (SHR), which is the ratio of hazards associated with the cumulative incidence function in the presence of a competing risk. We also tested the linear trends for SHR within NPCs using Cochran-Armitage trend test.

Binary survival analysis using Cox regression model was used to assess the association between patient characteristics and any NPC and evaluated hazard ratios of the characteristics. A two-sided p value < 0.05 was considered statistically significant. All analyses were done using SAS software (version 14.0).

4.5 Results

Maximum NPC

Among 2–17-year-old stimulant users with 1-7.5 years of continuous Medicaid enrollment, 30,294 were new stimulant users with clinician-reported diagnosis (S Figure 4-2). During the follow up period, 75.5% (N=22,882) continued stimulant monotherapy while the remaining 24.5% changed to NPC: 16.5% (N=5,004) had maximum 2 NPC, while 5.4% (N=1,634), 2.2% (N=671), and 0.3% (N=103) had maximum 3, 4 and 5 NPC regimens, respectively (S Figure 4-2).

Patient Characteristics in Stimulant Monotherapy and Maximum NPC

Characteristics of the study population are presented in Table 4-1 according to stimulant monotherapy or maximum NPC. Among monotherapy users, the majority (45.3%) were 6-11 years old; proportionately more were male (66.0%) and African American (46.2%). A majority of patients in the monotherapy group had family income below the poverty level, i.e. TANF (55.0%), and had 7-8 years of continuous enrollment (57.3%) (Table 4-1).

Across the maximum NPC for 2, 3, 4 and 5 NPC, the percentages for 12–17-year-olds, white youth, and patients with foster care or SSI coverage, increased linearly. Linear trends were also observed for continuous enrollment of 3-4 and 7-8 years (Table 4-1).

Concomitant Therapy Pathways

The pathways for various NPCs are described according to the initial number of concomitant psychotropic classes (Figure 4-1 a-e). The multiple pathways reveal the rationale for a competing risk analysis. Among the 30, 294 stimulant users, 708 patients were excluded because they initiated treatment with NPC. In 29,586 patients who began monotherapy, 22,882 (77.3%) patients continued with stimulants as the only psychotropic medication, 5,357 (18.1%) patients switched to 2 NPC, and less than 5% of patients escalated to 3, 4 or 5 NPC regimens (S Table 4-3).

Among the NPC changes, a majority of patients stayed with NPC: 4,080 (65.3%) patients stayed with 2 NPC until the end of study; 1,245 (56.2%) patients stayed with 3 NPC; 425 (57.1%) and 58 (56.2%) patients had 4 and 5 NPC regimens, respectively (S Table 4-3).

For patients with a higher NPC, some decreased to a lower NPC, for example, 33 (32.0%) dropped from 5 NPC to 4 NPC, 202 (27.1%) patients dropped from 4 NPC to 3

NPC, and 548 (24.7%) patients dropped from 3 NPC to 2 NPC regimens. S Table 3 details these patterns.

Time to Next NPC

The median, minimum and maximum (days) for the stimulant and NPC changes are presented in S Table 4-4. For patients who started on stimulant monotherapy, the median time was 471 days, time to go to 2 NPC was 448 median days, to 3 or 4 NPC was 334 median days and 365 median days, respectively, and to 5 NPC regimens was median 259 days.

As the number of psychotropic classes increased, the duration of staying in the same NPC decreased. Thus, the median time of exposure according to the NPC showed a linear decrease in time from 223 days for 2 NPC, 172 days for 3 NPC, 141 days for 4 NPC and 113 days for 5 NPC.

For patients with a higher NPC, it took more than one year to decrease to a lower NPC. For example, 417 median days were used to drop from NPC 5 to NPC 3, and 437 days to drop from NPC 4 to NPC 2.

Time to Maximum NPC

The median, minimum, maximum and IQR (days) for time to maximum NPC are presented in Figure 4-2 and S Table 4-5. Among initial monotherapy users, it took 491 and 577 median days to reach maximum 2 or 3 NPCs, respectively, and 833 median days to maximum 4 NPC, and 789 median days to maximum 5 NPC respectively. The median time to maximum NPC increased in patients with higher NPC (491 days and 577 days for maximum 2 or 3 NPC, and 833 and 789 days for maximum 4 or 5 NPC, respectively).

However, there was no significant difference in the maximum time to 3, 4 or 5 NPC (2,591 days, 2,548 days, and 2,555 days), respectively.

Clinician-reported Psychiatric Diagnosis in Stimulant Monotherapy and Concomitant Users

The frequency of psychiatric comorbid diagnoses according to NPC is presented in S Table 4-6. Large increases in clinician-reported comorbid psychiatric diagnoses are associated with concomitant regimens. For example, manifold increases in bipolar disorder (941% increase), schizophrenia (739% increase), and autism (457% increase) were observed in maximum 5 NPC compared with stimulant only.

Competing Risk Analysis for Stimulant Monotherapy to Maximum NPC

Table 4-2 shows the adjusted sub-hazard ratio for patient characteristics in a competing risk model and in a binary model (column 8 and 9). In the competing risk model, compared with stimulant monotherapy, there was a linear relationship between several patient characteristics and 2, 3, and ≥4 NPC: age group 12-17 (HR=0.71, $p<0.001$), white race (HR=1.34, $p<0.001$), patients in foster care (HR=1.50, $p<0.001$) and SSI (hazard ratio=1.02, $p<0.05$), and with 3-4 years continuous enrollment (HR=1.09, $p<0.05$).

The results from binary analysis showed several risk factors are correlated with any NPC (2, 3, 4 and 5 NPC): white (HR=1.46, $p<0.001$), patients with foster care (HR=2.03, $p<0.001$), SSI (HR=1.43, $p<0.001$), 3-4 years of continuous enrollment (HR=1.18, $p<0.001$). Nevertheless, the impact of these factors was substantially increased in the competing risk model.

Common Concomitant Stimulant Regimens

The various combinations of psychotropic classes in 2, 3, 4 and 5 maximum NPC were investigated. In summary, 85% of the maximum 3 NPC, 88% of maximum 4 NPC, and 90% of maximum 5 NPC had a regimen that included a stimulant with at least one antipsychotic dispensing for 60 or more days of concomitant use (Table 4-3).

In maximum 3 NPC, the most prevalent combination was 'stimulant, antipsychotic and antidepressant'. In maximum 4 NPC, the most prevalent combination was 'stimulant, antipsychotic, antidepressant and alpha agonist"; in maximum 5 NPC, the most prevalent combination was 'stimulant, antipsychotic, antidepressant, alpha agonist and anticonvulsant-mood stabilizer" (Table 4-3).

4.7 Discussion

To our knowledge, this is the first study using a competing risk methodology for pediatric psychotropic stimulant concomitant treatment illustrating changes in the NPCs across lengthy enrollment periods in a real-world population; the findings show patient characteristic risk factors had a significantly greater impact with a higher NPC. We are unaware of any study that investigated the change from monotherapy to concomitant use in terms of change from 2 classes to 3, 4 or 5 classes. Details of the changes in the number of psychotropic classes (NPCs) in this study is novel and illustrates the dynamic nature of regimens of stimulants concomitant with other psychotropic classes.

The major findings of this study include:

1. Among new stimulant users, 24.5% had 2-5 NPC regimens within 1-7.5 years of follow-up with a median of 2.2 years for patients to reach a maximum of 5 NPCs.

2. During the follow-up, the majority (49.6%) increased to a higher NPC while 36.3% stayed at maximum NPC and 14.1% decreased their NPC.
3. Patients who started concomitant use took substantial time to change to the next higher or lower NPC or to stay at the same NPC. Concomitant therapy was used for relatively long periods and the treating physician has adjusted the regimen for various reasons. Perhaps if it was not effective or adverse drug events were not tolerated or acute symptoms have resolved.
4. The competing risk model showed that NPC changes brought more risk factor information compared with a binary model. For example, foster care patients were more likely to have ≥4 NPC using competing risk rather than using a binary model which is limited to any NPC (HR 5.66 vs. 2.03 respectively).
5. NPC patterns in this large cohort emphasize the complexity of psychotropic class treatment patterns for youth: the majority (49.6%) of NPC changes involved an increased NPC, while one third (36.3%) stayed at their maximum NPC and 14.1% had a decreased NPC (S Table 4-7).

Overall, the findings provide details on the patterns of polypharmacy over time and will generate hypotheses for future research studies on effectiveness, safety and tolerability of complex polypharmacy regimens.

Comparison with Published Polypharmacy (Concomitant Use) Studies

Published studies of the past 15 years have featured inter-class polypharmacy (concomitant use). Polypharmacy has been variously defined as 2 or more concomitant psychotropic classes of medications with an overlapping prescription window of varying duration including 15 days [43], 30 days [32, 47], 45 days [17], and 60 days [19, 22].We

chose a conservative window of 60 days or more to minimize the chance of intentional switching of drugs. We also conducted a sensitivity analysis for 30-day overlapping windows for concomitant use and observed similar findings (Data not shown).

In terms of prevalence, in this study, we found 75.5% patients had stimulant monotherapy and 24.5% patients had stimulant concomitant use. This result aligns with Girand et al.'s finding that ⩾2 ADHD drugs + other psychotropic classes increased from 26.0% to 40.7% across 10 years using NAMCS 2006-2015 data [15]; Chen et al.'s finding that 20.9% of youth with ≥2 polypharmacy occurred among 6-18 year olds in 2005 Medicaid data from 4 states [19]. Zhou et al. found that ≥1 psychotropic concomitant medication occurred 22.9-25.0% of children and 25.2-28.2% of adolescences using US privately insured data [27]. Zhang et al., assessed national MEPS data and found that ≥3 class concomitant therapy doubled in 12 years [140].

Distinct from published studies which use a broad definition of polypharmacy (2 or 3 NPCs) [129], this study focused on specific NPC changes from 2 to 5 classes and evaluated the changes with greater precision. In this study, we described detailed information for providing each NPC change using community treatment data. It demonstrates the complexity of each regimen change: the patients' polypharmacy journey is in a dynamic pattern. Few patients stayed in the higher NPC suggesting several possibilities: symptoms may have resolved, patients may have experienced adverse drug events or a lack of improvement.

Patient Characteristics' Risk Factors Associated with NPC

Psychiatric polypharmacy has been shown to be associated with male, older, white, and foster care youth, from the traditional binary model analysis: Chiang et al., found ≥3 psychotropic classes was significantly associated with youth who were in foster care (OR=3.31); among 10 to 14 year olds (OR= 1.94) and 15 to 17 year olds (OR=2.41); and among white (OR=2.0) [144]. In another study, compared with 2-3 class polypharmacy, 4-5 class polypharmacy was significantly more likely to occur in males (OR = 1.66) and patients in foster care (OR = 1.66) [37].

In this study, the competing risk analysis suggested patients who are 12–17-year-olds, male, white, with 3-4 years of enrollment, and enrolled in foster care or SSI had higher risk of developing concomitant use in higher NPC than those in the binary model. For example, hazard of foster care was 3.12 and 5.66 times more likely to have 3 and ≥4 NPC and was 2.03 more likely for any NPCs.

Future Research

Numerous authors emphasize off-label use suggesting the possibility of insufficient effectiveness and safety data in community-treated populations. An extensive literature review of concomitant regimens in pediatric psychopharmacology showed 2 NPC regimens (specifically stimulant and alpha agonist) have supportive evidence of effectiveness. Thus, combinations of ≥3 classes should receive targeted interventions to assess benefit-risk [121]. With respect to safety, complex concomitant therapy increases the likelihood of adverse effects for combinations of 3, 4 or 5 NPCs [89]. Similarly, in a questionnaire survey conducted with parents who filled a prescription for their children, the authors found that adverse events of psychotropic medications were more common and severe with increasing number of medications use [16]. Other studies underscore

Baker et al.'s call for the study of effectiveness and safety of 3 or more class concomitant use [121]. For example, in a 2015 international consensus of pediatric psychopharmacology investigators, research on effectiveness and safety of commonly used off-label regimens was a leading priority [145]. Future robust studies should assess the benefits and risks of complex NPC and establish the safety of the considerably long exposures seen in our study of Medicaid-insured youth. Large simple trials are suggested as a design for these studies [137, 146]. The availability of electronic health records at major academic institutions points the way to conduct robust research that would not break the bank [147] but would generalize to usual treatment patterns in community-treated populations.

Limitations

Several limitations which may bias the results should be noted. First, we focused on a single state Medicaid dataset. The results may not generalize to other state Medicaid populations. Second, there is likely to be information bias on the medication exposure and clinician-reported psychiatric diagnosis. The diagnoses are based on clinician-reported claims data and lack the reliability of research assessed diagnoses. Third, the psychotropic medication dispensing in Medicaid may not mean the patient actually consumed the drug, although the frequently long exposures to medication in this dataset may reduce the likelihood that medications were not consumed. Fourth, a small group of patients had more than one series of variable changes or had different 2 NPC combination. For example, 340 (1.12 %) of patients had more than one 2 NPC regimen, e.g., stimulant and antipsychotic, 102 patients had more than one 3 NPC, and 46 and 5 had 4 NPC, and 5 NPC regimens, respectively (Data not shown). To reduce the impact of

multiple repeat changes from individual patients, we selected only the first transition change. Fifth, the reasons for changing/stopping polypharmacy are unclear and Medicaid claims data do not provide such information. Finally, information on provider type was not available for this study. Thus, the impact of provider type on the diagnosis and prescribing patterns could not be evaluated.

4.8 Conclusions

Detailed changes illustrate great flux in NPC patterns among Medicaid-insured youth. Competing risk analysis brings greater patient characteristics' risk information to assess NPC changes compared with a binary model.

4.9 Clinical Implications

The findings of this study provide detailed information regarding patient risk factors' affect on NPC. For example, the greater impact of foster care was on higher NPCs. In addition, the study estimated the substantial duration of NPCs including the time to maximum NPC. This new information sheds light on the impact of NPC changes. The results suggest close clinical monitoring for higher NPC regimens. Real world clinical practices in community treatment involving 3 or more concomitant classes may carry risks of unnecessary and lengthy exposures to complex, typically off-label psychopharmacological regimens [89, 121, 148]. These detailed patterns of NPC add new knowledge for close monitoring of pediatric stimulant psychotropic concomitant use, including NPC changes, time to next or maximum NPC, and on regimen complexity.

Table 4-1. Demographic and Administrative Characteristics of Stimulant Monotherapy Users and Stimulant Concomitant Users Among Those with 1-7.5 Years of Continuous Enrollees

	Stimulant only N=22,882		**Max 2 NPC N=5,004**		**Max 3 NPC N=1,634**		**Max 4 NPC N=671**		**Max 5 NPC N=103**	
	N	%	N	%	N	%	N	%	N	%
Age Group (years)*										
2-5	8,160	35.7	2,197	43.9	524	32.1	206	30.7	32	31.1
6-11	10,356	45.3	2,124	42.4	705	43.1	288	42.9	45	43.7
12-17	4,366	19.1	683	13.6	405	24.8	177	26.4	26	25.2
Gender										
Male	15,106	66.0	3,362	67.2	1,047	64.1	447	66.6	70	68.0
Female	7,776	34.0	1,642	32.8	587	35.9	224	33.4	33	32.0
Race/Ethnicity										
African American	10,569	46.2	1,970	39.4	629	38.5	245	36.5	34	33.0
White	8,733	38.2	2,414	48.2	844	51.7	364	54.2	60	58.3
Hispanic/ Nat Am/Asian/Pac Islander/Unknown	3,580	15.6	620	12.4	161	9.9	62	9.2	9	8.7
Eligibility Category**										
Foster care	1,550	6.8	623	12.5	318	19.5	162	24.1	17	16.5
SCHIP	5,194	22.7	901	18.0	209	12.8	64	9.5	10	9.7
SSI	3,553	15.5	999	20.0	507	31.0	279	41.6	51	49.5
TANF	12,585	55.0	2,481	49.6	600	36.7	166	24.7	25	24.3
Continuous Enrollment (years)										
1-2	2,529	11.1	452	9.0	108	6.6	35	5.2	6	5.8
3-4	3,124	13.7	642	12.8	219	13.4	94	14.0	17	16.5
5-6	4,121	18.0	884	17.7	322	19.7	130	19.4	19	18.4
7-8	13,108	57.3	3,026	60.5	985	60.3	412	61.4	61	59.2

*Age is the age of first stimulant use (column 2) or age of first drug/medical service use (column 4) ** SCHIP=State Children's Health Insurance Program; SSI=Supplemental Security Income; TANF=Temporary Assistance for Needy Families

Table 4-2. Adjusted Sub-hazard Ratio for Stimulant Monotherapy to Maximum NPC Using Competing Risk Model Compared with Binary Model (Column 8 and 9)

	Stim-> Max 2 NPC		Stim-> Max 3 NPC		Stim-> Max 4 and 5 NPC		Stim -> Any NPC in binary model	
	Hazard Ratio	**95% CI***	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**
Age Group (years)								
12-17	0.71	0.70-0.79	1.92	1.67-2.21	2.25	1.84-2.75	1.03	0.96-1.11
6-11	0.74	0.65-0.78	1.09	0.97-1.22	1.16	0.98-1.37	0.83	0.79-0.88
2-5	1		1		1		1	
Gender								
Male	0.91	0.86-0.97	0.86	0.77-0.95	0.95	0.82-1.11	0.90	0.86-0.95
Female	1		1		1		1	
Race/ Ethnicity								
African American	0.86	0.79-0.95	0.87	0.73-1.04	0.75	0.57-0.97	0.84	0.78-0.91
White	1.34	1.23-1.47	1.73	1.46-2.05	1.92	1.49-2.47	1.46	1.36-1.58
Hispanic/ Nat Am/Asian/Pac Islander/Unknown	1		1		1		1	
Eligibility Category**								
Foster care	1.50	1.37-1.63	3.12	2.72-3.59	5.66	4.60-6.96	2.03	1.90-2.18
SCHIP	0.87	0.81-0.94	0.86	0.77-0.95	0.93	0.71-1.22	0.87	0.82-0.93
SSI	1.02	0.95-1.10	2.16	1.92-2.45	4.42	3.68-5.30	1.43	1.35-1.52
TANF	1		1		1		1	
Continuous Enrollment (years)								

7-8	0.77	0.69-0.85	1.09	0.89-1.33	1.09	0.78-1.51	0.86	0.79-0.94
5-6	1.0	0.88-1.11	1.28	1.02-1.59	1.37	0.96-1.94	1.07	0.97-1.18
3-4	1.09	0.97-1.23	1.35	1.07-1.71	1.71	1.19-2.46	1.18	1.07-1.31
1-2	1		1		1		1	

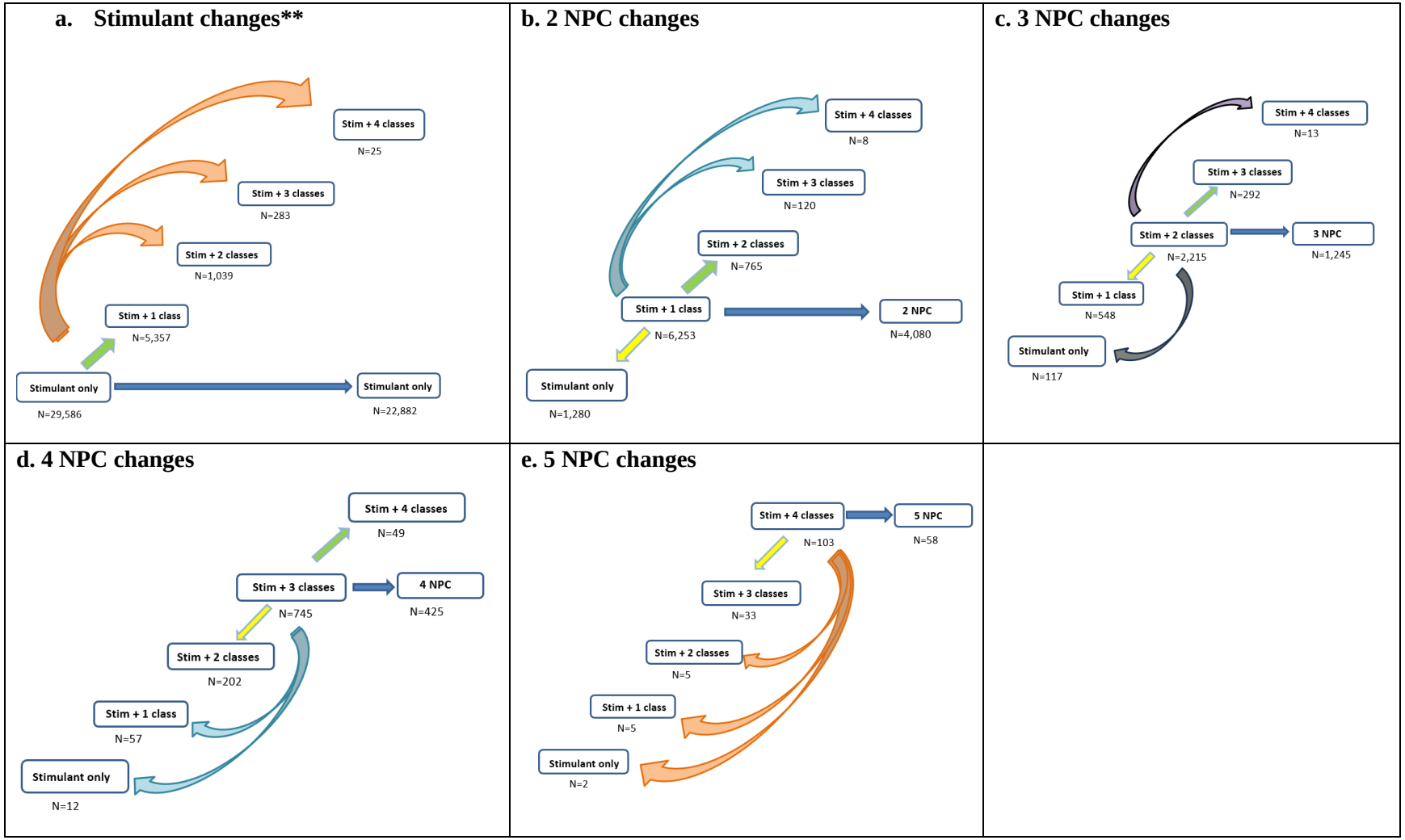
*Confidence Interval

Table 4-3. Top Three NPC Regimens

	N	%
2 NPC		
Stimulant + AA	2,565	51.3
Stimulant + ATD	1,526	30.5
Stimulant + ATP	986	19.7
3 NPC		
Stimulant + ATP + ATD	630	38.6
Stimulant+ ATP + AA	545	33.4
Stimulant + ATP + ATC-MS	202	12.4
4 NPC		
Stimulant + AA + ATP + ATD	287	42.8
Stimulant + AA+ ATP + ATC-MS	147	21.9
Stimulant + ATP + ATD +ATC-MS	139	20.7
5 NPC		
Stimulant + ATP + ATD + ATC-MS + AA	77	74.8
Stimulant + ATP + ATD + ATC-MS + AX	11	10.7
Stimulant + ATP + ATD + AA + AX	7	6.8

AA=Alpha agonist; ATP=Antipsychotic; ATD=Antidepressant; ATC-MS=Anticonvulsant-Mood Stabilizer, AX=Anxiolytic

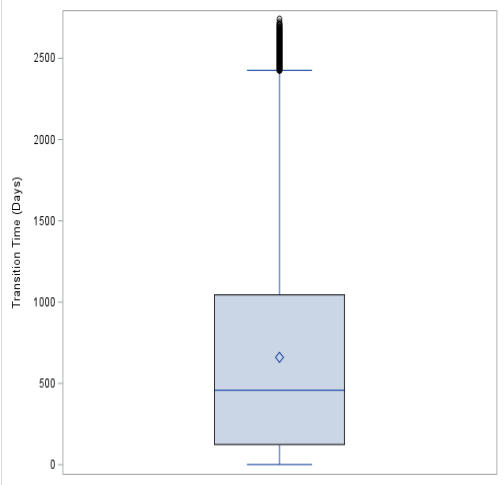
Figure 4-1. Detailed Patterns of Stimulant Monotherapy and Concomitant Use According to NPCs*



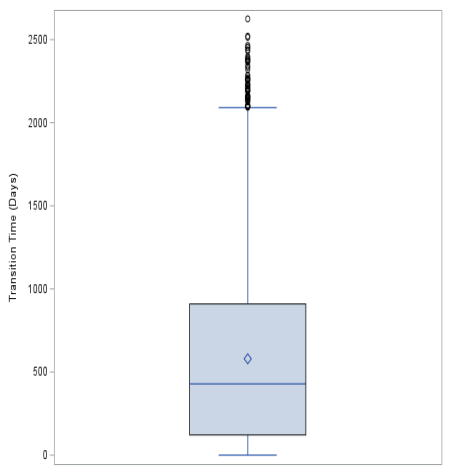
*It is based on each patient began follow up **Stimulant only transition does not include 708 patients who started the treatment with 2 or 3 or 4 or 5 NPCs.

Figure 4-2. Graphic Description of Range of Time from Stimulant to Maximum NPC*

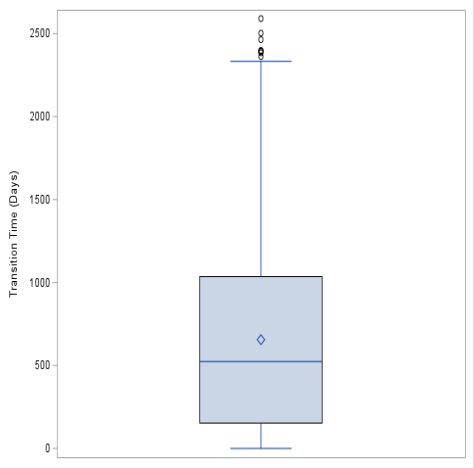
a.Time of Stimulant only



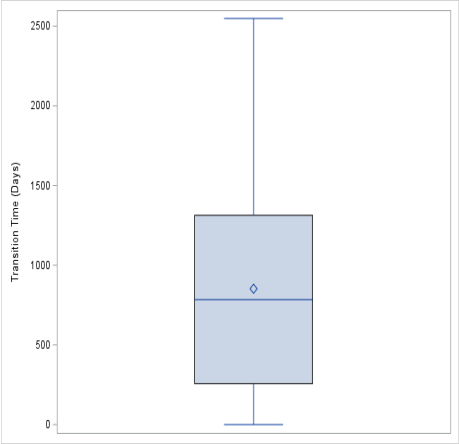
b.Time from Stimulant to Max 2 NPC



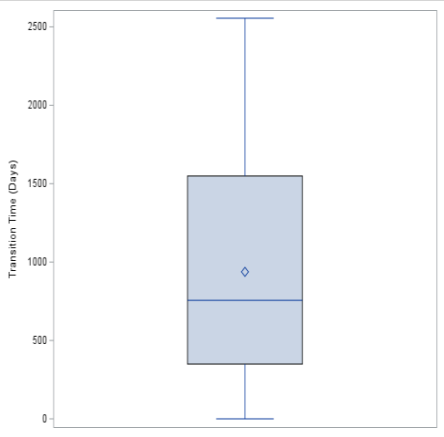
c.Time from Stimulant to Max 3 NPC



d.Time of Stimulant to Max 4 NPC



e.Time of Stimulant to Max 5 NPC



* The horizonal line in the box denotes the median value (50th percentile), the diamond represents the mean value, and the blue box contains the 25th to 75th percentiles of data. The whiskers mark the 5th and 95th percentiles, and values beyond these upper and lower bounds are considered outliers.

Chapter 5: Study 3

Association of Stimulant Psychotropic Class Polypharmacy with Incident Type 2 Diabetes among Medicaid-insured Youth

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5.1 Abstract

Objective: Stimulant polypharmacy with one other psychotropic drug class in children and adolescents has shown an inconsistent impact on the risk of type 2 diabetes mellitus (T2DM). Stimulant polypharmacy with 3-5 classes is common but the risk of T2DM is unknown.

Methods: A retrospective cohort study was conducted using Medicaid claims data from 2007-2014. Youth aged 2-17 years with 1-7.5 years of continuous enrollment who were new stimulant users with clinician-reported psychiatric diagnosis were followed. The major outcome, incident T2DM, was assessed using discrete-time failure models, after adjustment for disease risk score which was categorized using more than 120 baseline and time-dependent covariates.

Results: The study cohort had an average 6.4 years of follow-up. Among 30,112 new stimulant users, subsequently 43 were diabetes patients, 30,069 were non-diabetes patients. Compared to non-diabetic youth, T2DM patients were more frequent among 6–11-year-olds, females, African Americans, 7–8-year continuous enrollees and those with disability or poverty coverage. The absolute risk of incident T2DM in youth had an eight-fold increase from 3 to 5 class stimulant polypharmacy regimens which included antipsychotics (ATP), antidepressants (ATD) or anticonvulsant-mood stabilizers (ATC-MS) (0.5, 1.13, 4.20 per 10,000 person-months, respectively). Compared with stimulant monotherapy, stimulant polypharmacy with ATP, ATD or ATC-MS were significantly more likely to develop T2DM (adjusted relative risk [ARR], 2.58, (95% CI 1.05- 6.82); 5.81, (2.29-14.75); 18.91, (6.07-58.90) for 3, 4 and 5 class psychotropic polypharmacy, respectively). Similarly, there was a significantly greater risk of T2DM for those with

120-779 days of cumulative duration, in 4 and 5 class combined stimulant polypharmacy including ATP, ATD, or ATC-MS [ARR, 3.78, (1.16-12.40)].

Conclusions: In a large Medicaid-insured, long-enrolled youth cohort, the use of stimulant polypharmacy, particularly concomitant use with ATP, ATD and/or ATC-MS and with long duration of these combinations was associated with an increased risk of T2DM.

5.2 Introduction

Stimulants for the psychiatric treatment of children and adolescents are mainly prescribed to treat attention-deficit hyperactivity disorder (ADHD) and other disruptive behavior disorders [149]. Stimulants raise the extracellular concentration of dopamine and norepinephrine and are involved in the reinforcement of rewarding behaviors [150].Polypharmacy in the youth population is on the rise with as many as 300,000 youth receiving 3 or more classes concomitantly [90]; these regimens frequently reflect stimulant polypharmacy.

Stimulants are commonly used with atypical antipsychotics with or without second-generation antidepressants [12, 18]. Even though antipsychotics [48, 49, 113] and second-generation antidepressants [116] have been shown to be associated with increased risk of T2DM, concomitant use with stimulants showed inconsistent results. For example, subgroup analyses showed concomitant use of stimulants and antipsychotics was not significantly associated with incident risk of T2DM when compared with antipsychotic monotherapy in 5-20 year olds [113] and among 10-20 year olds [49]. However, another study of concomitant use of antipsychotics and stimulants showed a significant association with incident T2DM risk in 6 to 24 year olds [48].

To our knowledge, no study has fully investigated the association between 3 to 5 psychotropic class stimulant polypharmacy and T2DM among long continuously enrolled youth. We analyze a longitudinal cohort of youth who are new stimulant users to assess the association between 3 to 5 class stimulant polypharmacy and incident risk of T2DM.

5.3 Methods

5.3.1 Data source

We used 2007-2014 Medicaid administrative claims data from a mid-Atlantic state for the analysis, which included enrollment files, outpatient and physician claims files and dispensed prescription drug files. The files in the data source were linked together via an encrypted identification number.

The enrollees' sociodemographic characteristics, monthly Medicaid enrollment status and Medicaid eligibility category are included in the enrollment files. The clinician-reported psychiatric diagnoses are based on the ICD-9-CM codes which were extracted from outpatient physician claims files. The drug dispensing information such as national drug codes, dispensing date, days supplied, and quantity of supply were located in the dispensed prescription drug file.

This study was reviewed and approved by the Institutional Review Board of the University of Maryland, Baltimore.

5.3.2 Study Design and Study Population

This is a retrospective cohort study. The cohort is comprised of new users of stimulant [stimulant monotherapy compared with stimulant concomitant with other psychotropic medication class(es)]. A new-user design is applied by restricting the study cohort to those who initiated stimulant treatment, defined as not having stimulant dispensing in the prior 180 days. Furthermore, the study population of 2–17-year-olds were enrolled in Medicaid between 2007 and 2014 for continuous (1-7.5 years) enrollment and with a psychiatric diagnosis (N=30,112). The stimulant initiation date serves as the index date

for cohort entry. If the patient stopped using a stimulant, s/he was censored. The Medicaid enrollment data were generated based on each patient's monthly Medicaid enrollment status. To be eligible for a full year enrollment, the patient had to be enrolled at least 10 months per year [75].

The flowchart in Figure 1 illustrates the inclusion and exclusion criteria that were applied to define the study cohort. Excluded were 13,378 stimulant users who had stimulant exposure in past 180 days (non-new users), 4,281 patients without a psychiatric diagnosis, 178 patients who had prior T2DM diagnosis or antidiabetic medications exposure in the 365 days prior to first stimulant use. There are 30,112 new stimulant users in the final study population: 43 developed diabetes and 30,069 formed a comparison group.

5.3.3 Incident T2DM

In this study, the dependent variable is the incident diagnosis of T2DM, which is quantitatively expressed as the number of new cases of T2DM per 10,000 person-months of follow-up. Incident T2DM is ascertained adapting a computerized database algorithm that was previously validated in a cohort of Medicaid-insured youth and had a positive predictive value of 83.9% [48] and later applied by Burcu and colleagues [113, 116].

New cases of diabetes (type 1 or 2) were identified using diabetes-related medical care encounters: 1) inpatient and outpatient diabetes diagnosis (ICD-9-Clinical Modification codes); 2) diabetes-related dispensings (insulin, insulin adjuncts or oral hypoglycemic agents). The ICD-9-CM diabetes codes 250.4-250.8 reflect the chronic complications of diabetes and were not used to capture new cases of diabetes. Supplemental table 5-1

provides a summary of incident diabetes case definitions. Because the fourth and fifth digits of the ICD-9-CM codes are not always reported, it was not possible to sub-classify diabetes according to type using diagnostic codes alone. The cases were considered type 1 diabetes if insulin was the sole treatment within 120 days of the diabetes diagnosis date. In this study we had no type 1 diabetes patients.

As demonstrated in S Figure 5-1, an inpatient with a primary diagnosis of diabetes, by itself, met the case definition of diabetes. Otherwise, a combination of at least 2 out of 3 different diabetes-related medical care encounters within a period of 120 days met the case definition of diabetes (i.e., an outpatient visit with a primary diagnosis of diabetes, an inpatient secondary diagnosis of diabetes, or a dispensing of a diabetes medication). A single outpatient T2DM diagnosis or oral hypoglycemic agent dispensing may indicate another disease than diabetes. For example, the use of oral hypoglycemic agents in the absence of a diagnosis of diabetes might indicate treatment of polycystic ovarian syndrome [151], or prophylactic treatment to attenuate weight gain associated with antipsychotics in youth [152, 153]. We excluded 4 patients who received oral hypoglycemic treatment alone with a diagnosis of polycystic ovarian syndrome and without a diabetes diagnosis.

For youth who met the case definition of diabetes, the first diagnosis date for diabetes is assigned as the date of the initial diabetes-related medical care encounter. Youth were followed from first stimulant use to incident T2DM. For those without such events (non-diabetic population), the study cohort was followed until the end of continuous enrollment, or the end of study (December 31, 2014), whichever came first.

5.3.4 Psychotropic Medication and Polypharmacy

Psychotropic medications are grouped into 7 classes: stimulants, selected alpha-agonists, antidepressants, antipsychotics, anxiolytic/hypnotics, anticonvulsant-mood stabilizers, and lithium (S Table 5-2).

In this study, polypharmacy is defined as concomitant use of stimulants with any other psychotropic class(es) for at least 60 consecutive days (allowing for 15-day gaps in getting prescriptions refilled and helping to rule out switching). Based on each patient's maximum number of drug classes taken concomitantly with stimulants, we defined five mutually exclusive groups: stimulant monotherapy and 2 to 5 class stimulant polypharmacy.

The length of psychotropic medication use was calculated using time-dependent duration of exposure measures during the follow-up period. The patient's daily stimulant usage was calculated based on the stimulant dispensing dates, days supplied and allowable 15-day gaps for prescription refills. Based on daily stimulant usage in the database, we built a daily stimulant usage string up to 7.5 years for each patient in the study within their continuous enrollment period. Following the same methodology, daily usage of the other six psychotropic classes was calculated as well. All patients were followed to the end of drug therapy or end of 2014, whichever came first.

5.3.5 Patient Characteristics as Risk Factors

Multiple studies including systematic reviews and meta-analyses have indicated numerous risk factors for T2DM, which include clinical and other health care utilization factors [154-159]. In this study, we included more than 120 baseline and time-dependent

covariates, which include psychiatric disorders, metabolic disorder diagnoses, cardiovascular diseases, reproductive, obstetric and gynecologic conditions and related medical services, medications, etc. S Table 5-2 lists subgroups of risk factors which have been used in prior published studies assessing T2DM risk with psychotropic class use in youth [48, 113, 116]. The disease risk score method to control for these factors is discussed in the statistical methods section. We also included the other confounders such as eligibility category, age, and gender in the final model. Stimulant polypharmacy acts on T2DM through the mediator of increased blood glucose level, and the patient's BMI, and diet are considered potential confounders. Additionally, genetic factors which may directly increase the risk of T2DM, could introduce selection bias (S Figure 5-3). However, as the patients' BMI, diet, and genetic information were not available in the database, they were not included in the model.

5.3Outcome Measures

1) Sociodemographic and Diagnostic Factors of Stimulant Monotherapy and Polypharmacy Users

Patient characteristics were grouped into categories: age at initial start of stimulants (2-5 years old, 6-11 years old, 12-17 years old), gender, race/ethnicity (White, African American, Hispanic, Native American/Asian/Pacific Islander and Unknown), Medicaid eligibility category (foster care, SCHIP [State Children's Health Insurance Plan], SSI [Supplemental Security Income] for disability, and TANF [Temporary Assistance for Needy Families] for low income youth eligible by family income at or below the federal

poverty level and length of continuous Medicaid enrollment (1-2 years, 3-4 years, 5-6 years, 7-8 years). Clinician-reported psychiatric diagnoses were grouped into 11 categories via ICD-9 codes for diagnoses (S Table 5-2).

2) Absolute Risk of Incident Diabetes According to the Number of Polypharmacy Classes and Cumulative Duration

The absolute risk of incident diabetes cases was calculated based on the number of incident diabetes and the person-time to incident T2DM. The absolute risks of incident T2DM in duration subgroups were calculated.

3) Relative Risk of Incident Diabetes According to the number of Polypharmacy Classes Cumulative Duration and Disease Risk Score

The relative risk was calculated using discrete time failure models.

4) Stimulant Monotherapy and Polypharmacy Regimens and Psychiatric Diagnoses in T2DM Patients

The stimulant monotherapy and polypharmacy regimens for diabetic patients are presented in number and percentage. The clinician-reported psychiatric diagnoses for diabetic and non-diabetic patients are presented in number and percentage and compared using Chi-square analysis.

5.4 Statistical Analysis

We first examined the demographic, administrative and clinician-reported clinical diagnosis characteristics of the study cohort. We conducted Chi-square analysis to evaluate covariate differences among diabetic and non-diabetic patients and tested the linear trends for absolute risks changes using Cochran-Armitage trend analysis. A two-sided p value < 0.05 was considered statistically significant. All analyses were done using SAS software (version 14.0).

The absolute risk per 10,000 person-months was calculated by dividing the number of T2DM cases that developed subsequent to new stimulant use by the number of person-months of observation. Absolute risk was calculated in each category of number of polypharmacy classes and cumulative duration groups. For relative risk, we applied a discrete time failure model in a longitudinal framework to estimate the effect of polypharmacy on the risk of incident T2DM with person months as the unit of analysis. Discrete time analysis has been previously used [49, 160, 161] and produced estimates approximately identical to those from Cox proportional hazard regression models while providing computational efficiency as well as practical advantages, especially when there are several time-varying exposure groups in the presence of time-dependent exposures [162, 163]. In discrete time analyses, to adjust for confounding, we utilized the disease risk score methodology using the Miettinen full-cohort approach [164-166].

The disease risk score was constructed by fitting a logistic regression model with the study outcome, the exposure of interest and the covariates for the entire study population: it is computed as the fitted value from that regression model for each study subject. Then the subjects were grouped according to the quartiles of disease risk score (< 25%, 25-

50%, 51-75%, >75%). Rather than adjusting for all the study covariates, the final discrete failure time model was fitted using another logistic regression, which was adjusted for disease risk score, number of polypharmacy classes and selected demographic factors.

5.5 Results

Characteristics of the Study Cohort

The study cohort comprised 30,112 youth 2 to 17 years old with new stimulant use from 2007 through 2014 (Table 5-1). The study population had an average follow-up time of 6.4 years. There were 43 patients who developed T2DM subsequent to initiation with a stimulant. There were 30,069 non-diabetes patients for comparison.

Among the diabetic patients, there were more 6–11-year-olds (51.2%), females (55.8%), African Americans (60.5%), youth eligible for SSI (34.9%) or TANF (39.5%), and continuously enrolled for 7-8 years (74.4%). Most patients had both externalizing and internalizing disorders (69.8%) and externalizing disorders only (27.9%). There are fewer diabetic patients with stimulant only therapy (34.9%) than those with 2 to 5 polypharmacy treatment (65.1%). Most patients had more than 25% disease risk scores (86.0%). The large majority of patients had long continuous enrollments, i.e., 5 or more years (95.3%) (Table 5-1).

In addition, there were notable differences in the characteristics among stimulant monotherapy and stimulant polypharmacy users among diabetic patients. Compared with stimulant monotherapy, stimulant polypharmacy was more frequent among 12-17 year

olds (50.0%), males (60.7%), African Americans (64.3%), those with internalizing disorders (89.3%) and had disease risk scores greater than 75% (53.6%) (S Table 5-3).

In the non-diabetic population, patients were younger, more often male, white, enrolled in TANF, and slightly fewer lengthy enrollments. While polypharmacy predominated in the diabetic patient group (65.1%), stimulant monotherapy predominated in the non-diabetic patient group (75.6%). Compared with the diabetic group, the non-diabetic patients had lower disease risk score (<25%) (Table 5-1).

Absolute Risk of Incident T2DM According to Stimulant Monotherapy and Stimulant Polypharmacy

There were 15 incident cases of type 2 diabetes during 1,095,724 person-months follow-up (absolute risk [AR], 0.14 per 10, 000 person-months) among the stimulant monotherapy group. Among 2 to 5 class stimulant polypharmacy with antipsychotics, antidepressants, and anticonvulsant-mood stabilizers, there is a significant linear trend for increased absolute risk with increasing class. Consequently, AR grew from 0.50 per 10,000 person-months for 3 class regimen users to 1.13 in 4 drug regimen users to 4.20 per 10,000 person-months among 5 class regimen users. (Table 5-2).

Absolute Risk of Incident T2DM According to Cumulative Duration

Duration of polypharmacy regimens that includes antipsychotics, antidepressants, and anticonvulsant-mood stabilizers showed 1.84-fold to 3.75-fold increase of absolute risk with longer polypharmacy duration. Cumulative duration for 4 and 5 class polypharmacy were combined due to the small numbers of diabetes patients in 5 class polypharmacy. Table 5-3 illustrates the absolute risk (AR) of diabetes in long and short polypharmacy

durations. In the 3 class polypharmacy group, AR was 0.80 per 10,000 person-months in the longer duration group (120-1055 days). The combined 4 and 5 class polypharmacy group, AR was 3.91 per 10,000 person-months in the longer duration group (120-779 days).

Absolute Risk of Incident T2DM According to Disease Risk Score

The graph of S Figure 5-2 illustrates that the T2DM incidence increased with increasing disease risk scores. The incidence of T2DM was 0.08 per 10,000 person-months in those with <25% disease risk score. The incidence increased with the disease risk scores from 0.08 to 0.27 and 0.45 per 10,000 person-months in 25-50%, and 51-75% score groups. The incidence increased to 1.05 per 10,000 person-months in those with greater than 75% disease score risk (S Figure 5-2).

Relative Risk of Incident T2DM According to Stimulant Monotherapy and Stimulant Polypharmacy

Relative risk analysis revealed that compared with stimulant monotherapy users, 2 class stimulant polypharmacy users were non-significantly associated with a 1.45-fold (95% CI 0.65-3.39) increased risk of T2DM. The 3 stimulant polypharmacy class with antipsychotics antidepressants, and anticonvulsant-mood stabilizers use was significantly associated with a 2.58-fold (95% CI 1.05-6.82) increased risk of T2DM. The risks of 4 class polypharmacy and 5 class polypharmacy with antipsychotics antidepressants, and anticonvulsant-mood stabilizers were significantly associated with T2DM (RR=5.81, 95% CI 2.29-14.75; RR=18.91, 95% CI 6.07-58.90), respectively (Table 5-2).

Relative Risk of Incident T2DM According to Cumulative Duration

Similar to the absolute risk findings, the relative risk assessment of the impact of duration on diabetes, there was a significant effect of longer cumulative duration in the combined 4 and 5 class polypharmacy group. The patients with cumulative duration of 120-779 days were more likely to have incident T2DM (RR 3.78, 95% CI 1.16-12.40) (Table 5-3).

Relative Risk of Incident T2DM According to Disease Risk Score

Greater disease risk score is significantly associated with higher risk of T2DM: patients with >75% disease risk score was more likely to have incident T2DM (RR 7.74, 95% CI 2.73-21.89) followed by 51-75% disease risk score group (RR 3.72, 95% CI 1.25-11.01) (S Table 5-4). Youth in the 12-17 older age group and with greater than 50% disease risk score were significantly more likely to develop diabetes (S Table 5-4).

Distribution of Stimulant Polypharmacy Regimens and Psychiatric Diagnoses

Atypical antipsychotics, second-generation antidepressants, and anticonvulsant-mood stabilizers are the most frequent concomitant psychotropic medications in 3 to 5 class stimulant polypharmacy in T2DM patients (S Table 5-5).

With respect to clinician-reported diagnosis, more than half the diabetic patients had clinician-reported diagnosis of disruptive disorders (53.5%) and depression (67.4%). These exceeded the pattern of diagnosis in non-diabetic patients. ADHD was present in nearly all diabetic patients (95.4%) and non-diabetic patients (90.1%) (S Table 5-6).

5.6 Discussion

To our knowledge, this is the first paper using the disease risk score methodology and discrete failure time model for pediatric stimulant polypharmacy among patients with long continuous enrollment to show that a higher number of psychotropic class stimulant polypharmacy is associated with a higher risk of incident T2DM. The outcome is most pronounced among 4 and 5 class stimulant polypharmacy users in a real-world population across 7.5 years.

The major findings of this study:

1. In a study cohort followed for 6.4 years on average, the relative risk of incident T2DM was significantly associated with 3 to 5 class stimulant polypharmacy (Table 5-2), cumulative duration of 120-779 days (Table 5-3), and greater than 50% disease risk score (S Table 5-4).
2. The absolute risk of incident T2DM showed an 8-fold significant linear increase from 3 to 5 class polypharmacy regimens that included antipsychotics, antidepressants, and/or anticonvulsant-mood stabilizers (Table 5-2) and increased with longer cumulative duration (Table 5-3).
3. Compared to non-diabetic patients, diabetic patients were more frequently 6–11-years old, female, African American, with SSI or TANF coverage, and with 5 or more years of continuous enrollment.
4. In diabetic patients, stimulant polypharmacy was more prevalent (65.1%) than stimulant monotherapy (34.9%). Compared to non-diabetic patients, diabetic patients received more complex polypharmacy regimens. Atypical antipsychotics, second-generation antidepressants, and anticonvulsant-mood

stabilizers were nearly twice as common (35.8%) as in non-diabetic patients (19.8%) (S Table 5-7).

The findings provide details on the risk of incident of T2DM in different pediatric treatment subgroups and generate hypotheses for future research studies on the impact of stimulant polypharmacy on T2DM.

Strengths of the Methodology

We used a previously validated algorithm to identify incident T2DM in this cohort of youth [164-166]. In the algorithm, there is a wide range of risk factors related to the development of T2DM including medication (type, duration), underlying disease, and heath care access. To better estimate the T2DM risk, these factors were collected and adjusted in the model. Instead of adding these risk factors to the model, we utilized the disease risk score methodology from the Miettinen full-cohort approach [113, 166]. Similar to the propensity score, the disease risk score helps build a parsimonious model and improves the performance of the model, especially when there is a large number of risk factors. It has advantages over the propensity score in the presence of multiple time-dependent exposure groups [164].

Comparison of Current Findings with Published Studies

There are 3 published studies that investigated the association between 2 class concomitant psychotropic medications and diabetes in the pediatric Medicaid-enrolled population. The studies vary in age of the cohort, follow-up time, and outcome (Table 5-4). By contrast, the 2-17 year old population in our study covered children who started stimulants at a very young age, while earlier studies featured: 5-20 year olds [113], 6-24

year olds [48], and 10-18 year olds [49] (Table 5-4). In our study, we had 4 diabetic patients in the 2–5-year-old age group: 1 patient had stimulant monotherapy and 3 patients had 2 class stimulant polypharmacy (stimulant + antidepressant in 2 patients and stimulant + alpha agonist in 1 patient). These patients had high T2DM disease risk score (≥75%) and a median of 83 months from the start of treatment to T2DM (Data not shown).

Compared with the follow-up time in prior studies [4 years [48], 24.8 months [113], and 17.2 months [49]], the long follow-up time in our study is a strength: the majority of patients had an average of 6.4 years of follow-up (median follow-up 7.5 years). Bobo and colleagues showed in 4+ years of follow-up that concomitant stimulant and atypical antipsychotic was significantly associated with increased T2DM risk in 6-24 year olds [48]. In the published studies with ≤ 2 years of follow-up, the combination was not significant for stimulant plus atypical antipsychotic in 5-20 year olds [113] and in 10-18 year olds [49]. Our study results follow those of Bobo [48] in showing that the statistical significance of medication use with diabetes risk in children and adolescents largely depends on long follow-up of stimulant polypharmacy use with antipsychotics, antidepressants, and anticonvulsant-mood stabilizers.

The findings of our study show stimulant polypharmacy is associated with increased T2DM risk, which may be explained by the long duration of stimulant monotherapy and polypharmacy and younger aged stimulant users. The greater duration of exposure is particularly important for the study of relatively rare events with serious adverse effects, such as pediatric incident T2DM.

Future Research Directions

In the current study, all the foster care enrollees had stimulant polypharmacy and all developed diabetes. In view of continuing national concern for polypharmacy among foster care youth, this is a research priority [167]. Research in large simple trials [137] are feasible and cost-efficient [138] and are facilitated by the growing availability of electronic health records.

Future research on 3 or more class polypharmacy is critical because these combinations are typically off-label [121]. In a 2015 international consensus of pediatric psychopharmacology investigators, research on effectiveness and safety of commonly used off-label regimens is a leading priority [145].

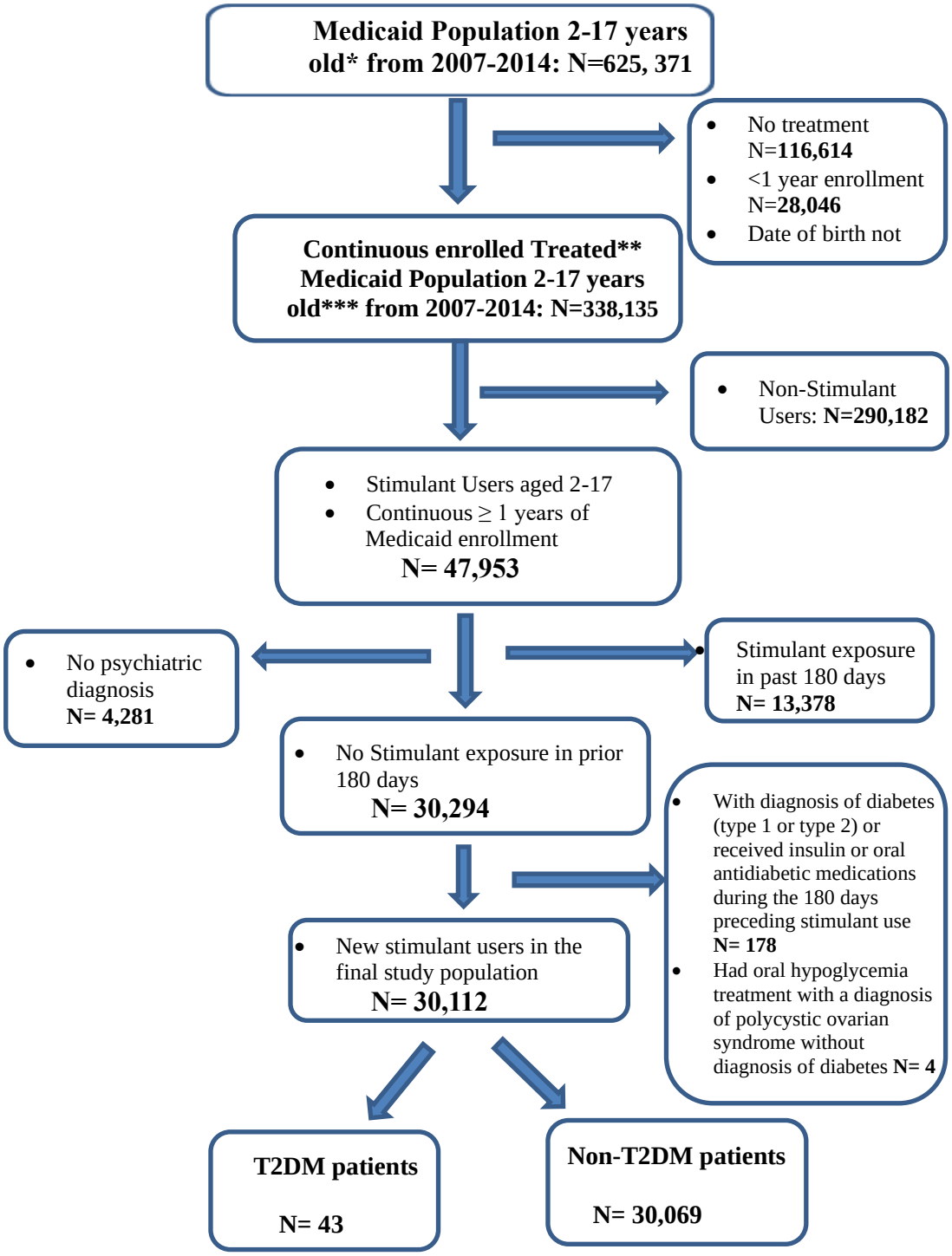
Limitations

Several limitations should be noted. First, causality cannot be inferred from observational studies; thus, the study findings should be interpreted with caution. Large simple effectiveness trials could advance the science of stimulant polypharmacy by providing more rigorous study designs. Second, we focus on a single state Medicaid dataset and the number of incident diabetes cases is limited. In terms of strengths, we follow a validated method to identify the case definition of diabetes [48]. Patients had to have at least 2 out of 3 diabetes-related medical care encounters within 120 days of the stimulant initiation date. Third, diabetes cases could have been misclassified if diagnosis information was missing. Fourth, the exposure variable (psychotropic medication dispensings) may not be accurate because patients may not actually have consumed the medication. However, the long exposures diminish the likelihood of non-adherence.

5.7 Conclusions

In a large cohort of Medicaid-insured youth with long continuous enrollment, the use of stimulant polypharmacy was associated with significantly increased risk of diabetes. The increased relative risk of diabetes and longer cumulative concomitant duration were statistically significant for 3 to 5 class stimulant polypharmacy regimens with atypical antipsychotics, second-generation antidepressants, and/or with anticonvulsant mood-stabilizers. In the face of the continuing growth of stimulant polypharmacy in the US, this study supports further investigation of effectiveness and safety of stimulant polypharmacy regimens, particularly in large community-treated youth populations especially vulnerable populations e.g., foster care.

Figure 5-1. Flow Chart for the Study Cohort of Medicaid-insured Youth (2-17 year olds) who were New Users of Stimulant, 2007-2014



*Age at Medicaid enrollment
**Treatment: any medication, physician visit, or procedure
***Age at stimulant treatment

Table 5-1. Baseline Characteristics of Diabetic and Non-diabetic New Stimulant Users

	Diabetic (T2DM) Patients N=43		Non-Diabetic (T2DM) Patients N= 30,069		P-value
	N	%	N	%	
Age Group (years)*					
2-5	4	9.3	11,035	36.7	<0.001
6-11	22	51.2	13,411	44.6	
12-17	17	39.5	5,623	18.7	
Gender					
Male	19	44.2	19,906	66.2	<0.001
Female	24	55.8	10,163	33.8	
Race/Ethnicity					
African American	26	60.5	13,351	44.4	<0.001
White	12	27.9	12,328	41.0	
Hispanic/ Nat Am/Asian/Pac Islander/Unknown	5	11.6	4,390	14.6	
Eligibility Category**					
Foster care	8	18.6	2,646	8.8	<0.001
SCHIP	3	7.0	6,314	21.0	
SSI	15	34.9	5,353	17.8	
TANF	17	39.5	15,756	52.4	
Continuous Enrollment (years)					
1-2	0	0	3,097	10.3	<0.001
3-4	2	4.7	4,059	13.5	
5-6	9	20.9	5,443	18.1	
7-8	32	74.4	17,470	58.1	
Clinician-reported psychiatric diagnosis					
Externalizing disorders only***	12	27.9	17,771	59.1	<0.001
Internalizing disorders only***	0	0	1,293	4.3	
Both***	30	69.8	10,133	33.7	
Other psychiatric diagnoses	1	2.3	872	2.9	
No. Polypharmacy Classes					
Stimulant only	15	34.9	22,732	75.6	<0.001
2 class polypharmacy	10	23.3	4,961	16.5	
3 class polypharmacy	7	16.3	1,624	5.4	
4 class polypharmacy	7	16.3	662	2.2	
5 class polypharmacy	4	9.2	90	0.3	
T2DM Disease Risk Score					
< 25%	6	14.0	15,305	50.9	<0.001
25-50%	8	18.6	5,954	19.8	

51-75%	12	27.9	5,412	18.0	
>75%	17	39.5	3,398	11.3	

*Age is the age of first stimulant use

** SCHIP=State Children's Health Insurance Program; SSI=Supplemental Security Income; TANF=Temporary Assistance for Needy Families

*** Externalizing disorders include ADHD, disruptive behavioral disorders; Internalizing disorders include depression, anxiety disorders; Other psychiatric diagnoses include adjustment disorder, au-tism spectrum disorder, learning disorder, schizophrenia, intellectual disability, tic disorder, bipolar disorder, and other mental health diagnoses

Table 5-2. Absolute and Relative Risk of Incident Type 2 Diabetes According to Exposure to Stimulant Monotherapy and Polypharmacy*

Exposure Status	Person-Months	DM Case No.	Absolute Risk per 10,000 Person-Months	Relative Risk (95% CI)**
Stimulant monotherapy	1,095,724	15	0.14	1 [Reference]
2 class polypharmacy	476,702	10	0.21	1.45 (0.62- 3.39)
• Poly 2 with (ATP or ATD or ATC-MS)	243,674	7	0.29	1.70（0.65-4.50）
• Poly 2 without (ATP or ATD or ATC-MS)	233,028	3	0.13	1.06 (0.30-3.67)
3 class polypharmacy	153,228	7	0.46	2.34 (0.90- 6.19)
• Poly 3 with (ATP or ATD or ATC-MS)	140,924	7	0.50	2.58 (1.05-6.82)
• Poly 3 without (ATP or ATD or ATC-MS)	12, 576	0	-	-
4 class polypharmacy	63,236	7	1.11	5.71 (2.25 – 14.46)
• Poly 4 with (ATP or ATD or ATC-MS)	62,101	7	1.13	5.81 (2.29-14.75)
• Poly 4 without (ATP or ATD or ATC-MS)	1,135	0	-	-
5 class polypharmacy	9,805	4	4.08	18.61 (6.0 – 57.77)
• Poly 5 with (ATP or ATD or ATC-MS)	9,513	4	4.20	18.91(6.07-58.90)
• Poly 5 without (ATP or ATD or ATC-MS)	292	0	-	-

*AA=Alpha agonist; ATP=Antipsychotic; ATD=Antidepressant; ATC-MS=Anticonvulsant-Mood Stabilizer, AX=Anxiolytic
**Adjusted for disease risk score, time of follow-up, age, gender, and eligibility.

Table 5-3. Absolute and Relative Risk of Incident T2DM According to Cumulative Duration of Stimulant Polypharmacy including ATP or ATD or ATC-MS*

2 class stimulant polypharmacy with ATP or ATD or ATC-MS				
Exposure Status	**Person-Months**	**Number of Case**	**Absolute Risk per 10,000 Person-months**	**Relative Risk****
Cumulative duration (days)				
60-119	200,112	5	0.25	1 [Reference]
120-1,414	43,562	2	0.46	1.84 (0.36- 9.47)
Total	243,674	7		
3 class stimulant polypharmacy with ATP or ATD or ATC-MS				
Exposure Status	**Person-Months**	**Number of Case**	**Absolute Risk per 10,000 Person-months**	**Relative Risk***
Cumulative duration (days)				
60-119	103,236	4	0.39	1 [Reference]
120-1,055	37,688	3	0.80	2.05 (0.46- 9.18)
Total	140,924	7		
4 and 5 class stimulant polypharmacy with ATP or ATD or ATC-MS				
Exposure Status	**Person-Months**	**Number of Case**	**Absolute Risk per 10,000 Person-months**	**Relative Risk***
Cumulative duration (days)				
60-119	58,817	6	1.04	1 [Reference]
120-779	12,797	5	3.91	3.78 (1.16- 12.40)
Total	71,614	11		

*ATP=Antipsychotic; ATD=Antidepressant; ATC-MS=Anticonvulsant-Mood Stabilizer,

**Adjusted for disease risk score, time of follow-up, age, gender, and eligibility.

Table 5-4. Comparison of Current Findings with Published Studies*

	Population	Average Follow-up time	Findings
Current study	2–17-year-olds, Medicaid Mid-Atlantic state	6.4 years	3 class poly with (ATP/ATD/ATC-MS) RR* 2.58 4 class poly with (ATP/ATD/ATC-MS) RR 5.81 5 class poly with (ATP/ATD/ATC-MS) RR 18.91
Burcu, 2017	5–20-year-olds, Medicaid Analytic eXtract (4 states)	24.8 months	In concomitant users of atypical antipsychotics and stimulants, there was no significant association: neither duration nor cumulative dose of stimulants was associated with an increased risk of T2DM
Bobo, 2013	6–24-year-olds, Tennessee Medicaid	4 years	Atypical antipsychotics + Stimulants RR*=5.71 (95%CI 1.35-24.07)
Rubin, 2015	10–18-year-olds, more than 19 million across US Medicaid population	20 months	Atypical antipsychotics + Stimulants RR*= 0.84 (0.64-1.11),

* ATP=Antipsychotic; ATD=Antidepressant; ATC-MS=Anticonvulsant-Mood Stabilizer
** RR=Relative Risk

Chapter 6: Conclusions and Future Directions

Psychotropic polypharmacy (also called concomitant drug treatment), especially stimulant polypharmacy, in children and adolescents is more common due to the increasing prevalence, early identification, and comorbidities of more than one psychiatric disorder, e.g., ADHD and depression. Most published pediatric inter-class studies have focused on the prevalence of 2 or more class stimulant polypharmacy [particularly with antipsychotics (ATP), antidepressants (ATD) and anticonvulsant mood stabilizers (ATC-MS)] in a cross-sectional, typically one year framework. In terms of outcomes, the association between type 2 diabetes (T2DM) and 2 class stimulant polypharmacy is most common. Higher number of stimulant class polypharmacy, for example, 3, 4, and 5 class stimulant polypharmacy have not been fully investigated in a long-term follow-up cohort in terms of the prevalence, duration of polypharmacy, polypharmacy changes, types of polypharmacy (concomitant) regimens and association with incident T2DM. This dissertation aimed to address these gaps by investigating Medicaid-insured youth with continuous enrollment of 1–8 or 3-8 years to build a comprehensive assessment and understanding of stimulant polypharmacy especially 3, 4, and 5 class polypharmacy patterns of use, pathways of polypharmacy over time, and impact of polypharmacy on the incidence of type 2 diabetes (T2DM).

Summary of Paper 1

To better understand stimulant patterns of use in youth with long-term health insurance enrollment, we started analysis in a large cohort of Medicaid-insured youth aged 2–17 years with

3–8 years of continuous enrollment (N=264,518). The data source comprises the 2007-2014 Medicaid administrative claims data from a mid-Atlantic state. The prevalence of stimulant users (16.5%,) in the entire group of 2–17-year-olds with 3-8 years continuous enrollment was approximately 2 times higher than that reported in studies with 1 year follow-up time in annual datasets. Compared with non-stimulant users (N=220,818), stimulant users (N=43,700) were statistically more frequently male, white, aged 6–11 years, more often in foster care or with Supplemental Security Income (SSI) (youth with disability) coverage, with 7-8 years of enrollment, and had externalizing disorders reported.

The duration of stimulant exposure was substantial (487 median days). Stimulant users who were 6-11 years old, in foster care and with 7-8 years of Medicaid enrollment had longer duration of stimulant exposure than other comparison groups. For example, the 6- to 11-year old age group had average of more than 2 years of stimulant exposure, stimulant users in foster care had the longest duration of use with a mean of 908 days and a median of 740 days, while the 7-8 year Medicaid enrollees had up to 2.7 years of stimulant exposure.

The data also showed 70% received stimulant monotherapy, while 30% were treated with stimulant polypharmacy: 18.2% had 2 class polypharmacy, 7.3% had 3 class polypharmacy, and 4.3% had 4 and 5 class polypharmacy combined. The study also showed the prevalence of 3, 4 and 5 class stimulant polypharmacy increased linearly with age of the youth. The majority of 3-5 class stimulant polypharmacy users had both externalizing and internalizing disorders (46.6% in 2 drug class, 69.2% in the 3 drug class, and 82.3% in 4 and 5 drug class).

After adjusting for other risk factors, the youth who were 6-11 years old, male, white, in foster care or SSI, and had 7-8 years of continuous enrollment were more likely to receive 3-5 class stimulant polypharmacy. In 3-5 class stimulant polypharmacy users, the most prevalent combination was stimulant with antipsychotics (ATP), antidepressants (ATD), and anticonvulsant mood stabilizers (ATC-MS).

Limitations included relying on claims data measured by pharmacy dispensings which may not have been consumed; clinician-reported diagnoses lacking the validity of research assessment, and database derived from a single-state Medicaid program. The study has several strengths:

- Among 264,518 unique 2- to 17-year olds with 3–8 years of continuous enrollment, 16.5% had stimulant prescription dispensings, doubling the annual national prevalence of 8.1%.
- Applying a 60-day window for overlapping administration to define polypharmacy minimized the likelihood of counting intentional switching of classes or short-time medication trials as if they were intentional polypharmacy.
- Extensive Medicaid continuity of enrollment (3-8 years) to reflect the "real world" situation of long-term stimulant use and avoid underrepresenting the extent of enrollment via annual datasets. Medicaid claims data provide medication use profiles in "real world" vulnerable families, which constitutes the low-income population, as well as foster care and youth with disabilities.
- The selection of children and adolescents with long Medicaid continuous enrollment helps to create pharmacologic profiles over long exposure periods. The Medicaid

enrollment information was generated based on each patient's monthly Medicaid enrollment status. As in previous studies, the patient needed to be enrolled at least 10 months/year to be eligible for a full-year enrollment [75].

In conclusion, this study provided more comprehensive information for long-term stimulant monotherapy and 2-5 class stimulant polypharmacy users. This identifies subpopulations in need of further research, given that many 3-5 drug combinations are off label, that is, lacking in effectiveness information and robust safety of long-term use.

Summary of Paper 2

To fully understand the "real world" polypharmacy regimen evolution (changes from stimulant monotherapy to 2-5 class stimulant polypharmacy), we conducted a retrospective cohort analysis among those with 1-7.5 years of continuous Medicaid enrollment among 2-17-year-old stimulant users. The database was derived from the same 2007-2014 Medicaid administrative claims data. We investigated detailed changes of polypharmacy according to number of psychotropic classes (NPC), the duration of NPC, and patients' characteristic factors related to NPC changes. The individual patient follow-up was relatively long with a median of 2.2 years to reach a maximum of 5 NPCs.

Among 30,294 *new* stimulant users (no stimulant exposure in past 180 days), the large majority remained on stimulant monotherapy (75.5%) throughout the follow-up time, and remainder had maximum 2-5 NPC regimens (24.5%): 16.5% (N=5,004) had maximum 2 NPC, 5.4%

(N=1,634), 2.2% (N=671), and 0.3% (N=103) had maximum 3, 4 and 5 NPC regimens, respectively. Compared with stimulant monotherapy users, the percentage for 12–17-year-olds, white, those with foster care or SSI coverage, and patients with continuous enrollment of 3-4 or 7-8 years increased linearly in 2-5 class regimens.

The NPC change pathways are complex. A majority of patients who had NPC changes stayed at an NPC: 65.3% patients stayed at 2 NPC until the end of study; 56.2% - 57.1% patients stayed at 3 NPC, 4 and 5 NPC regimens, respectively. For patients with a given NPC, some decreased to a lower NPC, for example, 548 patients (24.7%) dropped from 3 NPC to 2 NPC, and 202 patients (27.1%) dropped from 4 NPC to 3 NPC.

In terms of the median time to go to the next level of NPC or to maximum NPC, the median time to go to 2 NPC was 448 median days, to 3 or 4 or 5 NPC was 334 median days, 365 median days, and 259 median days, respectively. As the number of psychotropic classes increased, the duration of staying in the same NPC decreased: 223 days for 2 NPC, 172 days for 3 NPC, 141 days for 4 NPC, and 113 days for 5 NPC. For patients with a higher NPC, it took more than one year to decrease to a lower NPC. For example, 417 median days were used to drop from NPC 5 to NPC 3, and 437 days to drop from NPC 4 to NPC 2.

As the maximum 2 to 5 NPCs are the events of interest (outcome variables) in this study and they are not binary, a competing risk analysis was applied to investigate the association between patient characteristic factors and 2-5 NPCs: age group 12-17 years, white, patients in foster care

or SSI, and with 3-4 years continuous enrollment were significantly related to 2-5 NPCs. The study also presented the most common concomitant stimulant regimens in 2-5 NPCs. Antipsychotics (ATP), antidepressants (ATD), and anticonvulsant mood stabilizers (ATC-MS) were the most frequent psychotropic class combinations used in stimulant polypharmacy in this large cohort (N=30,294).

Limitations included relying on a single state Medicaid dataset, information bias on medication exposure and clinician-reported diagnoses lack of research quality assessment. The study has several strengths:

- The study focused on the maximum NPCs and evaluated the NPC changes with greater precision describing detailed information for each regimen transition than in binary analyses. The complex polypharmacy changes and long duration suggest the regimen changes may occur for a variety of reasons. For example, complex NPC combination was not effective, adverse drug events were not tolerated, or acute symptoms had resolved.
- Applying a competing risk methodology for pediatric psychotropic polypharmacy with Number of Psychotropic Classes (NPCs) as the mutually exclusive outcome events. The competing risk method provided more information than binary survival analysis. For example, foster care patients were more likely to have $\geqslant$4 NPCs using competing risk rather than using a binary model which is limited to a simple choice (Yes/No) (Hazard Ratio 5.66 vs. 2.03 respectively).
- The study chose a conservative polypharmacy definition (window of 60 or more overlapping days) to minimize the chance of misinterpreting switching drug classes as intentional polypharmacy.

To our knowledge, this is the first study to set maximum number of polypharmacy classes (NPC) as the event of interest (outcome) and apply competing risk methods to investigate polypharmacy changes. This study presented the detailed and complex changes of NPC and highlighted great flux in NPC patterns among Medicaid-insured youth as well as the long duration of NPC regimen. Competing risk analysis brings greater patient characteristics' information to assess NPC changes compared with a binary model.

Summary of Paper 3

One of the potential side effects of concomitant use of stimulant and other psychotropic classes is type 2 diabetes mellitus (T2DM). The impact of 2 class stimulant polypharmacy on the risk of T2DM in children and adolescents has been studied [48, 113, 168]. However, the impact of stimulant polypharmacy with ≥2 psychotropic classes on the risk of T2DM is uncertain.
Using the same Medicaid claims data as study 1 and 2, we conducted a retrospective cohort study to evaluate the association between stimulant polypharmacy and incident T2DM. The more than 120 baseline and time-dependent risk factors for pediatric T2DM were summarized as a disease risk score using discrete time failure model [161]; incident T2DM was defined by a combination of at least 2 out of 3 different diabetes-related medical care encounters within a period of 120 days following methods used in validated studies [48, 113].

Among 30,112 new stimulant users aged 2-17 years old, with an average 6.4 years of follow-up, 43 patients had T2DM diagnosis, 30,069 patients were non-diabetic. Compared to non-diabetic patients, T2DM patients were more frequent among 6–11-year-olds, females, African

Americans, 7–8-year continuous enrollees and those with disability or poverty coverage. Within diabetic patients, comparing stimulant polypharmacy with stimulant monotherapy patients, stimulant polypharmacy was more frequent among 12–17-year-olds, males, African Americans, those with internalizing disorders and had disease risk scores greater than 75% than stimulant monotherapy.

The absolute risk (AR) of incident T2DM increased with the higher number of classes in 3 to 5 class stimulant regimens with ATP, ATD, or ATC-MS (0.50 per 10,000 person-months for 3 class polypharmacy, 1.13 per 10,000 person-months in 4 class polypharmacy, and 4.20 per 10,000 person-months in 5 class polypharmacy). Longer duration of polypharmacy regimens had higher absolute risk of T2DM. ARs for 3, 4 and 5 class polypharmacy were 0.80 per 10,000 person-months and 3.91 per 10,000 person-months in the longer duration group. The AR of T2DM increased with the disease risk scores from 0.08 to 0.27 and 0.45 and 1.05 per 10,000 person-months in 25-50%, 51-75% and ≥75% disease score groups.

The relative risk (RR) of patient factors showed stimulant polypharmacy with ATP, ATD or ATC-MS were significantly more likely to develop T2DM for 3, or 4 and 5 combined class psychotropic polypharmacy (RR=2.58 and 5.81, respectively). The longer cumulative duration (120-779 days) was significantly associated with greater risk of T2DM in 4 and 5 combined class stimulant polypharmacy (RR=3.78). Greater disease risk score is significantly associated with higher risk of T2DM: patients with >75% disease risk score and with 51-75% disease risk score were more likely to have incident T2DM (RR =7.74 and 3.72, respectively).

Limitations included data are derived from a single state Medicaid dataset, causality cannot be inferred from observational studies, the diabetes case could be misclassified. It was crucial to provide details of the association between ≥3 stimulant polypharmacy with ATP, ATD, or ATC-MS with the incident T2DM with the following strengths:

- The study population is patients who are 2-17 years old, which covered those who started stimulants at a very young age. The results showed 4 diabetic patients in 2–5-year-old age group, a serious clinical and ethical concern. Clinical concern is based on putting youth at risk of chronic disease without assurances that benefits outweigh risks. This is the consequence of off-label prescription usage. Ethical concern is based on poor evaluative data on the effectiveness and safety of these complex regimens, despite their legal use by prescribing doctors.
- This study has a long follow-up time (6.4 years on average, median 7.5 years). Long follow-up time is believed to be sufficient for T2DM development. The significant findings of this study are consistent with one prior study that had 4+ years of follow-up time [48] and had a statistically significant association between concomitant antipsychotic and stimulant and T2DM in 6-24 year olds.
- Applying disease risk score methodology and discrete failure time model to adjust a wide range of risk factors related to T2DM development and utilizing a comprehensive and valid definition for T2DM [48, 49, 113].

To our knowledge, this is the first paper using the disease risk score methodology and discrete failure time model for ≥3 class pediatric stimulant polypharmacy among patients with long continuous enrollment to show that the use of stimulant polypharmacy was associated with

significantly increased risk of diabetes. The increased relative risk of diabetes was statistically significant for 3 to 5 class stimulant polypharmacy with ATP, ATD, and/or ATC-MS and longer cumulative concomitant duration.

Limitations and Future Research Directions

The limitations of this research include numerous issues. For example, in study 1, we only analyzed one state Medicaid data, and the data is from 2007-2014: 11 years ago. In study 2, we lacked detailed information on why patients moved to a higher or lower number of polypharmacy classes. Possible reasons include intolerable adverse drug effects, the emergence of new symptoms, or a change in primary care physician prescriber. In study 3, the indirect causal pathway suggested that BMI and diet were potential confounders. Also, genetic factors which may directly increase the risk of T2DM, could introduce selection bias. Information on the patients' BMI, diet, and genetic information were not available in the database.

We could examine the prevalence in a recent national cohort of both Medicaid and commercially insured youth. We could investigate the primary reasons behind changes in NPC if such data become available, to determine whether treating physicians recognize and address these changes. We also could incorporate BMI, diet, and genetic information when available to control for these confounders and explore the role of genetic factors in T2DM risk.

≥3 class polypharmacy

In study 1, we found that 7.3% had 3 class polypharmacy (N=3,194); and 4.3% had ≥ 4 class polypharmacy (N=1,853). The percent of ≥3 class polypharmacy increased with age. In study 2, we demonstrated that age group 12-17, white, patients in foster care and SSI, and enrolled for 7-

8 years were more likely to experience ≥ 3 class polypharmacy. The majority of patients with ≥3 class polypharmacy remained in their current polypharmacy and the duration ranged from 113 days to 172 days. In study 3, 41.3% of T2DM patients had ≥ 3 class polypharmacy. The 4 and 5 class polypharmacy regimens including an antipsychotic, antidepressant or anticonvulsant-mood stabilizer showed significant associations with incident T2DM. Additionally, a longer duration of polypharmacy exposure was significantly associated with incident T2DM. These findings indicate that ≥ 3 class polypharmacy is not uncommon in the Medicaid pediatric population of stimulant users and showed an association with an increased risk of T2DM.

Pediatric psychotropic polypharmacy, especially ≥3 class polypharmacy, is considered off-label use [121], despite common use, namely in, about 11.6% in this cohort. The off-label use may suggest possible insufficient effectiveness and/or adverse events of these regimens in community-treated populations. The Baker et al. literature review of pediatric psychotropic polypharmacy showed 2 class polypharmacy (specifically, stimulant and alpha agonist use) have supportive evidence of effectiveness. However, benefit-risk of ≥3 class polypharmacy has not been fully evaluated. Numerous studies showed complex polypharmacy treatment increases the likelihood of adverse drug effects [16, 89, 129] emphasizing the priority for research on appropriateness, effectiveness and safety of commonly used off-label ≥3 class polypharmacy regimens [121, 145].

Long-term use of psychotropic polypharmacy in children and adolescents may cause different type of adverse events, such as cardio-metabolic risk [94, 169], endocrine disturbances [170], neurological complications [171], and behavior changes [102]. In this study, our focus was on the risk of type 2 diabetes mellitus in association with ≥3 class stimulant polypharmacy, which is

new to the literature. Future research could investigate other adverse drug events of pediatric psychotropic polypharmacy, such as cardiovascular events.

Foster Care

In Study 1, we showed the prevalence of stimulant use with foster care covered youth had the highest prevalence (42.3%). Stimulant users in foster care had the longest duration of use with a mean of 908 days and median of 740 days compared with the other eligibility groups. Stimulant users in foster care were more likely to receive ≥3 class polypharmacy than the other eligibility groups (OR=4.49, 95% CI = 4.11, 4.91). In Study 2, we found that across the maximum of 2-5 number of psychotropic classes (NPC), the prevalence for patients with foster care coverage increased linearly (12.5%, 19.5%, 24.1%, and 16.5%, respectively) and the hazard ratio for patients with foster care coverage also increased linearly for maximum 2, 3, and combined 4 and 5 classes [HR=1.50, 95% CI (1.37, 1.63), 3.12, 95% CI (2.72, 3.59), 5.66, 95% CI (4.60, 6.96)], respectively. In Study 3, 18.6% of T2DM patients (N=8) had foster care coverage, while 8.8% of non-T2DM patients were from foster care. Eight foster care patients who developed T2DM had stimulant polypharmacy regimens. These data show that the youth with foster care coverage had a higher prevalence of stimulant use and longer duration of stimulant exposure, and were more likely to receive a higher NPC. The foster care patients were more likely to develop T2DM (HR=1.15, 95% CI = 0.44, 3.06). The findings were not significant due to the small number of T2DM patients. In future research, a similar analysis in a larger dataset would be critical. The findings imply further research in polypharmacy might be conducted in foster care covered patients, as it is a research priority and the topic of federal agency warnings for the past 20 years [125, 126].

Several U.S studies emphasized the continuing efforts by federal agencies' Medicaid monitoring programs to rein in ''overprescription,'' particularly in the poor and foster care populations [126, 167]. In these dissertation studies, we showed prevalence and duration of stimulant polypharmacy exposure is higher in foster care youth than other eligible groups. Patients who were enrolled in foster care are more likely to experience higher class (more complex, less evidence-based treatment polypharmacy). Among diabetic patients, all patients who were foster care enrollees had stimulant polypharmacy. In view of the continuing national concern about polypharmacy among foster care youth, future research should target the psychotropic polypharmacy in vulnerable populations, such as foster care, as a research priority.

Large simple trials

This dissertation used a single state Medicaid database. Future robust studies may apply large simple trials as a design across the US pediatric population [137, 172]. Distinct from observational studies, large simple trials are pragmatic randomized clinical trials that focus on clearly defined clinical outcomes of important to patients and clinicians and enroll participants who represent typical patients receiving treatment from community prescribers. The availability of electronic health records at major academic institutions points the way to conduct robust simple trials that are feasible and cost-efficient [138, 147] and the results can be generalized to usual treatment patterns in community-treated populations including privately insured youth as well as the Medicaid population.

Conclusion

This dissertation aimed to identify the prevalence, patterns of use, stimulant polypharmacy changes, duration, and the association of incident T2DM with stimulant polypharmacy, especially ≥ 3 class stimulant polypharmacy. The findings provide new information for future studies to pursue the investigation of the appropriateness, effectiveness and safety of stimulant polypharmacy, in other databases, in vulnerable populations, and in robust trial designs.

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Appendix A: Chapter 3 (Study 1) Supplement

S Table 3-1. Clinician-reported psychiatric diagnoses from ICD-9 codes

	ICD-9-CM* diagnosis codes
ADHD	314.xx
Disruptive disorder	312.0-312.4, 312.81, 312.82, 312.89, 312.9, 313.81
Learning disorder	307.0, 307.9, 315.0-315.2, 315.31, 315.32, 315.39, 315.9
Adjustment disorder	308.0-308.2, 308.4, 308.9, 309.0-309.4, 309.82, 309.83, 309.89, 309.9
Anxiety disorder	293.84, 300.0, 300.2, 300.3, 308.3, 309.21, 309.81, 313.0, 313.2, 313.89
Depression	293.83, 296.2, 296.3, 296.9, 298.0, 300.4, 311
Autism spectrum	299.0
Schizophrenia	295, 297, 298
Bipolar disorder	296.0, 296.1, 296.4-296.7, 296.80, 296.89, 301.13
Intellectual disability	299, 317-319
Other mental disorders	V40, V66.3, V67.3, 290-319 (except codes listed above)

*ICD-9-CM: International Classification of Disease, Ninth Revision, Clinical Modification

S Table 3-2. Clinician-reported psychiatric diagnosis in stimulant users and treatment date-matched group with no stimulants among those with 3 or more years of continuous enrollment in Medicaid

	Stimulant Users N= 43,700		**Treatment date-matched comparison N= 220,818**	
ADHD	36,304	83.2	10,706	4.9
Depression	13,692	31.4	17,748	8.1
Disruptive Behavioral Disorder	13,216	30.3	11,522	5.2
Anxiety Disorder	9,275	21.3	14,703	6.7
Bipolar Disorder	5,929	13.6	3,488	1.6
Learning Disorder	5,711	13.1	8,730	4.0
Adjustment Disorder	4,178	9.6	7,108	3.2
Autism Spectrum Disorder	2,388	5.5	2,764	1.3
Schizophrenia	1,776	4.1	1,797	0.8
Intellectual Disability	1,293	3.0	2,138	1.0
Tic disorder	869	2.0	968	0.4
*Other MH Disorder	10,477	24.0	23,163	10.5

Diagnoses exceed 100% because more than one diagnosis may apply to a child.

*Other Mental Health diagnosis not listed above

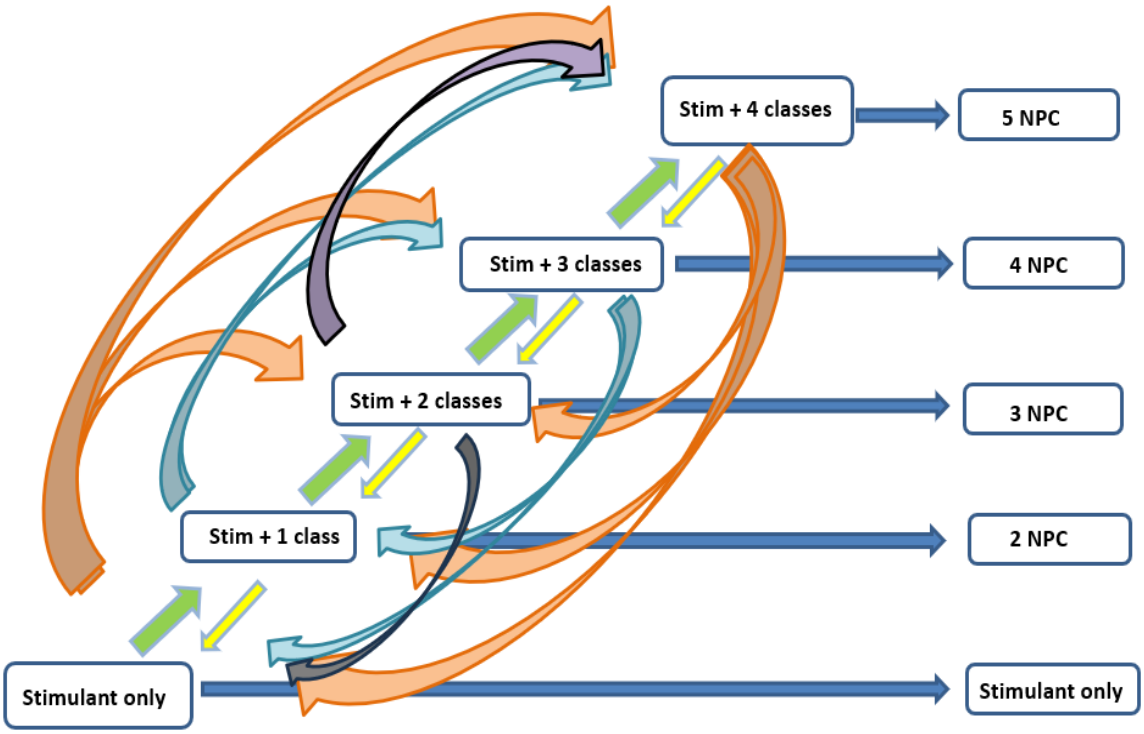
S Table 3-3. Detailed diagnostic patterns among stimulant users

	ADHD Only	ADHD	Depression	Disruptive	Anxiety	Bipolar	Learning	Adjustment	Autism	Schizo[b]	Intell[c]	Tic	Other[d]	Total
ADHD	11,816	24,488	12,075	12,160	8,368	5,323	5,310	3,810	2,130	1,582	1,175	824	9,002	98,063
Depression	359	12,075	13,333	6,769	5,945	4,807	2,334	2,509	1,039	1,483	679	335	6,120	57,787
Disruptive Dis[a]	341	12,160	6,769	12,875	4,430	3,391	3,169	2,346	1,396	1,097	844	389	4,392	53,599
Anxiety	158	8,368	5,945	4,430	9,117	2,948	2,016	2,013	1,013	971	533	322	3,770	41,604
Bipolar	58	5,323	4,807	3,391	2,948	5,871	1,157	1,103	536	1,087	416	156	3,403	30,256
Learning Dis	113	5,310	2,334	3,169	2,016	1,157	5,598	1,051	1,130	479	676	225	1,534	24,792
Adjustment Dis	48	3,810	2,509	2,346	2,013	1,103	1,051	4,130	361	379	236	104	1,620	19,710
Autism	70	2,130	1,039	1,396	1,013	536	1,130	361	2,318	207	484	138	589	11,411
Schizo[b]	13	1,582	1,483	1,097	971	1,087	479	379	207	1,763	237	48	1,083	10,429
Intell Dis[c]	23	1,175	679	844	533	416	676	236	484	237	1,270	52	502	7,127
Tic Dis	16	824	335	389	322	156	225	104	138	48	52	853	199	3,661
Other[d]	640	9,002	6,120	4,392	3,770	3,403	1,534	1,620	589	1,083	502	199	10,036	42,890

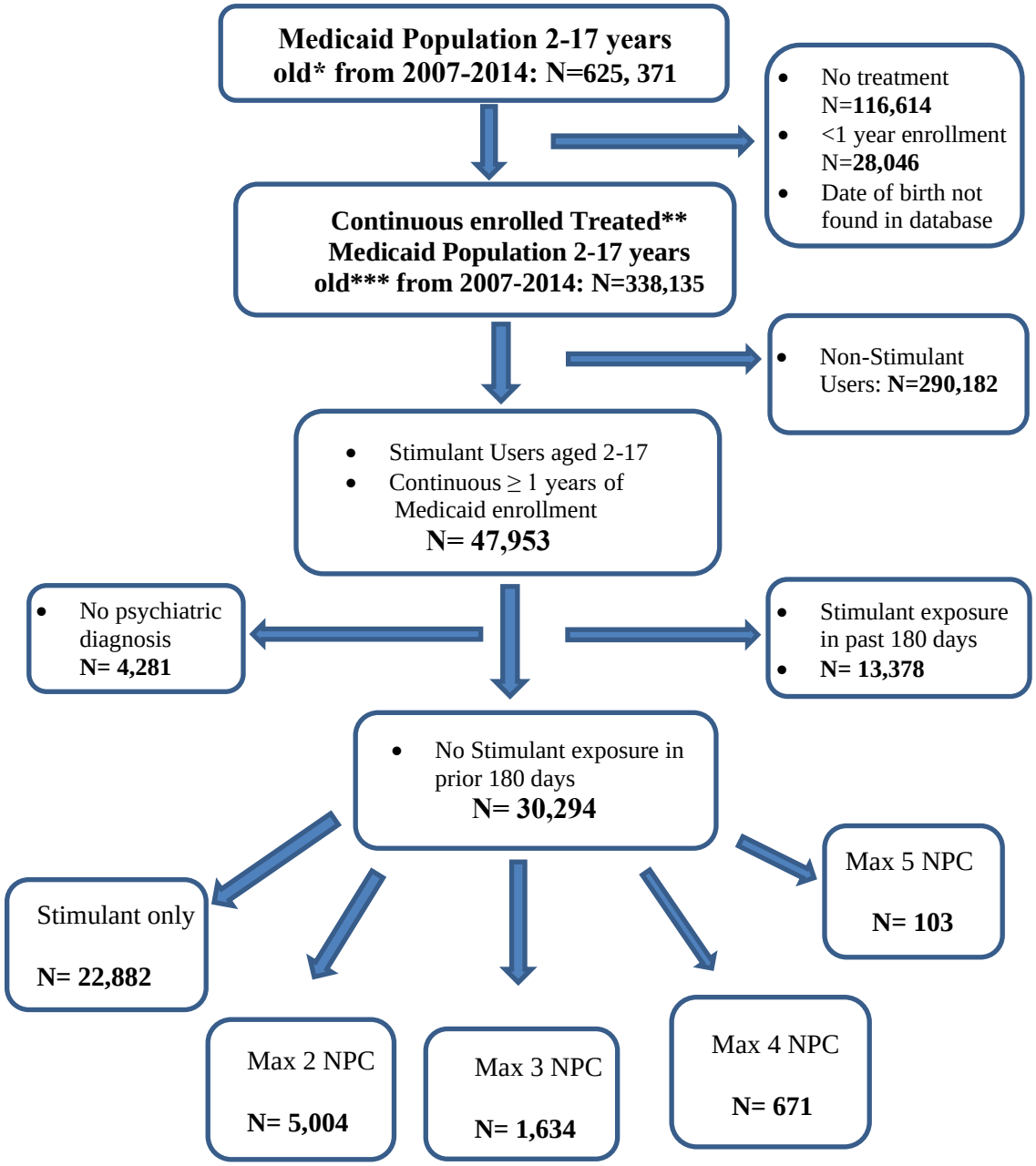
[a]Disorder; [b]Schizophrenia; [c]Intellectual Disability; [d]Other = Mental Health diagnosis not listed above among 290.xx--319.xx

Appendix B: Chapter 4 (Study 2) Supplement

S Figure 4-1. Patient's Journey Through NPCs



S Figure 4-2. Flow Chart for Cohort Selection



*Age at Medicaid enrollment
**Treatment: any medication, physician visit, or procedure
***Age at stimulant treatment

S Table 4-1. Psychotropic Medication Classes

Psychotropic Class	Generic Name
Antipsychotics	aripiprazole, olanzapine clozapine, paliperidone, quetiapine, risperidone, ziprasidone, chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, thioridazine, thiothixene
Anxiolytic/hypnotics	buspirone, chloral hydrate, clonazepam, diazepam, eszopiclone, lorazepam, midazolam, ramelteon, zaleplon, zolpidem
Antidepressants	amitriptyline, amitriptyline/chlordiazepoxide, amoxapine, bupropion, citalopram hydrobromide, clomipramine, desipramine, desvenlafaxine succinate, doxepin, duloxetine, escitalopram oxalate, fluoxetine, fluvoxamine maleate, imipramine, mirtazapine, nefazodone, nortriptyline, paroxétine, paroxetine mesylate, protriptyline hcl, sertraline, trazodone, venlafaxine
Anticonvulsant-mood stabilizers	carbamazepine, divalproex, lamotrigine, oxcarbazepine, valproate, valproic acid
Stimulants	methylphenidate, dexmethylphenidate, amphetamine, salts, dextroamphetamine, lisdexamfetamine
Selected alpha agonists	clonidine, guanfacine
Lithium	lithium

S Table 4-2. Clinician-reported Psychiatric Diagnoses from ICD-9 Codes

	ICD-9-CM* diagnosis codes
ADHD	314.xx
Disruptive disorder	312.0-312.4, 312.81, 312.82, 312.89, 312.9, 313.81
Learning disorder	307.0, 307.9, 315.0-315.2, 315.31, 315.32, 315.39, 315.9
Adjustment disorder	308.0-308.2, 308.4, 308.9, 309.0-309.4, 309.82, 309.83, 309.89, 309.9
Anxiety disorder	293.84, 300.0, 300.2, 300.3, 308.3, 309.21, 309.81, 313.0, 313.2, 313.89
Depression	293.83, 296.2, 296.3, 296.9, 298.0, 300.4, 311
Autism spectrum	299.xx
Schizophrenia	295, 297, 298
Bipolar disorder	296.0, 296.1, 296.4-296.7, 296.80, 296.89, 301.13
Intellectual disability	299, 317-319

Other mental disorders	V40, V66.3, V67.3, 290-319 (except codes listed above)

*ICD-9-CM: International Classification of Disease, Ninth Revision, Clinical Modification

S Figure 4-3. Cox Proportional Hazards and Fine and Gray's Sub-distribution Hazard Function

The traditional Cox proportional hazards regression model:

$$\log(\lambda(t)) = \log(\lambda_0(t)) + \mathbf{X}\beta$$

$$\lambda(t) = \lambda_0(t)\exp(\mathbf{X}\beta)$$

Where $\lambda_0(t)$ is the baseline hazard function, X is the set of risk factors/covariates, and β is the associated regression parameters.

The Fine and Gray's sub-distribution hazard function model:

$$\bar{\lambda}_j(t|x) = \bar{\lambda}_{0j}(t)e^{x'\beta_j}$$

Where $\bar{\lambda}_{0j}(t)$ is a baseline sub-hazard, X' is the set of risk factors/covariates, and β_j is the associated regression parameters. $e^{x'\beta_j}$ is a relative risk for events of type j. It denotes the instantaneous risk of failure from the jth event in subjects who have not yet experienced an event of type j. There is a distinct sub-distribution hazard function for each of the distinct types of events.

In both models, we adjusted for patient characteristics that have been previously shown to be associated with polypharmacy.

Example:

Using traditional Cox regression model,

a 12–17-year-old male white stimulant user who was enrolled in foster care with 5-6 year of continuous enrollment had a hazard rate (short term risk) which is 2.03 times higher to develop any NPC when compared with a 12–17-year-old male white stimulant users who was enrolled in TANF with 5-6 year of continuous enrollment. The calculation is:

Exp [(log1.03-log 1.03) + (log0.90- log 0.90) + (log 1.46- log 1.46) + (log 2.03- log 1) + (log1.07-log1.07)] = exp(log 2.03)= 2.03

Using the Fine and Gray's sub-distribution hazard function model,

a 12–17-year-old male white stimulant user who was enrolled in foster care with 5-6 year of continuous enrollment had a hazard rate (short term risk) which is 5.66 times higher to develop max 4 or 5 NPC when compared with a 12–17-year-old male white stimulant users who was enrolled in TANF with 5-6 year of continuous enrollment. The calculation is

Exp [(log 2.25-log 2.25) + (log 0.95-log 0.95) + (log 1.92-log 1.92) + (log 5.66-log 1) + (log 1.37-log 1.37)] = exp (log 5.66) = 5.66

S Table 4-3. N and Percent of Patients with Stimulant Monotherapy and NPC changes (N=38,902)

Next Regimen / Start Regimen	Stimulant only		2 NPC		3 NPC		4 NPC		5 NPC		Total
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**
Stimulant monotherapy*	**22,882**	**77.3**	5,357	18.1	1,039	3.5	283	1.0	25	0.1	29,586
2 NPC	1,280	20.5	**4,080**	**65.3**	765	12.3	120	2.0	8	0.1	6,253
3 NPC	117	5.3	548	24.7	**1,245**	**56.2**	292	13.2	13	0.6	2,215
4 NPC	12	1.6	57	7.7	202	27.1	**425**	**57.1**	49	6.9	745
5 NPC	2	2.0	5	4.9	5	4.9	33	32.0	**58**	**56.2**	103

*Stimulant only transition does not include 708 (2.3%) patients who started the treatment with 2 or 3 or 4 or 5 classes (530 patients started with 2 NPC, 131 patients started with 3 NPC, 43 patients started with 4 NPC, 4 patients started with 5 NPC).

Example:

A patient may have several changes. Therefore, in this study, there are more changes (N=38,920) than number of patients (N=30,294).

Below are detailed changes for the patients who had maximum 2 NPC and have 3 changes:

- Patients who started with stimulant monotherapy, increased to 2 NPC and remained 2 NPC until the end of study.
- Patient who started with 2 drugs NPC and remained 2 NPC until the end of study.
- Patients who started with stimulant monotherapy, increased to 2 NPC and decreased to stimulant monotherapy until the end of study.

Max poly 2	
changes*	**No. of Patients who had changes**
1->2 & 2->2	4,080
1->2->1	924
Total	5,004

*1 stands for stimulant monotherapy; 2 stands for 2 NPC

S Table 4-4. Duration for Stimulant monotherapy and NPCs According to Median and Range (days)

Next Regimen / Start Regimen	Stimulant only			2 NPC			3 NPC			4 NPC			5 NPC		
	Median	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**
Stimulant only*	**471**	1	2,740	448	1	2,625	334	1	2,503	365	1	2,548	259	21	1,903
2 NPC	420	60	2,300	**223**	60	2,576	437	65	2,233	733	79	2,034	422	235	1,875
3 NPC	477	63	1,874	387	60	2,081	**172**	60	2,661	431	63	2,309	440	93	1,382
4 NPC	350	128	955	437	83	2,316	310	60	1,585	**141**	60	2,194	288	62	1,701
5 NPC	605	577	632	495	174	1,584	417	211	784	219	60	1,453	**113**	60	876

Emboldened cell counts show the linear decreasing duration of stimulant monotherapy and NPC.

S Table 4-5. Median and Range (days) to Maximum NPC

	Stimulant only			Max Poly 2			Max Poly 3			Max Poly 4			Max Poly 5		
	Median	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**
Stimulant only	471	1	2,740	491	1	2,625	577	1	2,591	833	1	2,548	789	21	2,555

S Table 4-6. Distribution of Clinician-reported Comorbid Psychiatric Diagnosis in Stimulant Monotherapy Users and NPC Users According to Maximum NPC

	Stimulant only N=22,882		**Max 2 NPC N=5,004**		**Max 3 NPC N=1,634**		**Max 4 NPC N=671**		**Max 5 NPC N=103**		**% Increase from Stimulant only to 5 NPC***
	N	%	N	%	N	%	N	%	N	%	
ADHD	20,343	88.90	4,598	91.89	1,476	90.33	613	91.36	95	92.23	4
Disruptive disorder	6,425	28.08	1,899	37.95	864	52.88	420	62.59	68	66.02	135
Depression	5,283	23.09	1,898	37.93	1,103	67.50	550	81.97	93	90.29	291
Anxiety disorder	3,855	16.85	1,353	27.04	679	41.55	363	54.10	65	63.11	275
Bipolar disorder	1,514	6.62	609	12.17	642	39.29	375	55.89	71	68.93	941
Schizophrenia	557	2.43	161	3.22	173	10.59	123	18.33	21	20.39	739
Intellectual disability	408	1.78	134	2.68	59	3.61	57	8.49	9	8.74	391
Autism spectrum	998	4.36	338	6.75	200	12.24	108	16.10	25	24.27	457
Adjustment disorder	2,048	8.95	574	11.47	269	16.46	124	18.48	21	20.39	128
Learning disorder	3,164	13.83	773	15.45	316	19.34	173	25.78	31	30.10	118
Tic disorder	436	1.91	131	2.62	48	2.94	25	3.73	5	4.85	154
**Other MH disorders	4,458	19.48	1,071	21.40	600	36.72	278	41.43	44	42.72	119

Diagnoses exceed 100% because more than one diagnosis may apply to a child.

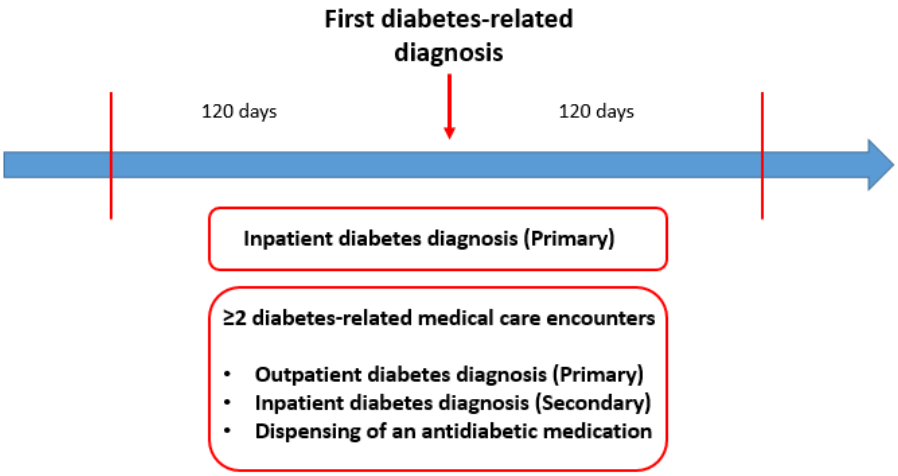
*% increase was calculated by subtracting the Max 1 percent from the Max 5 percent, taking the difference, and dividing it by the Max 1 percent. Then the number multiplied 100 to convert to percentage. **Other Mental Health diagnosis not listed above

S Table 4-7. Trends of Next NPC

	N	%
Stay at max NPC at the end	5,808	36.3
Any increase of NPC	7,951	49.6
Any decrease of NPC	2,261	14.1

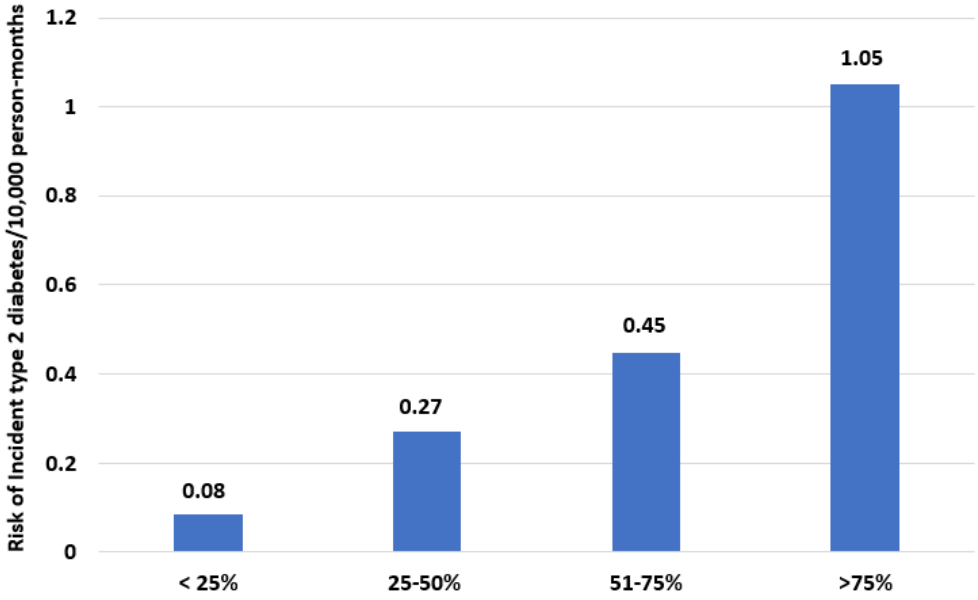
Appendix C: Chapter 5 (Study 3) Supplement

S Figure 5-1. Operational Definition of Incident Type 2 Diabetes



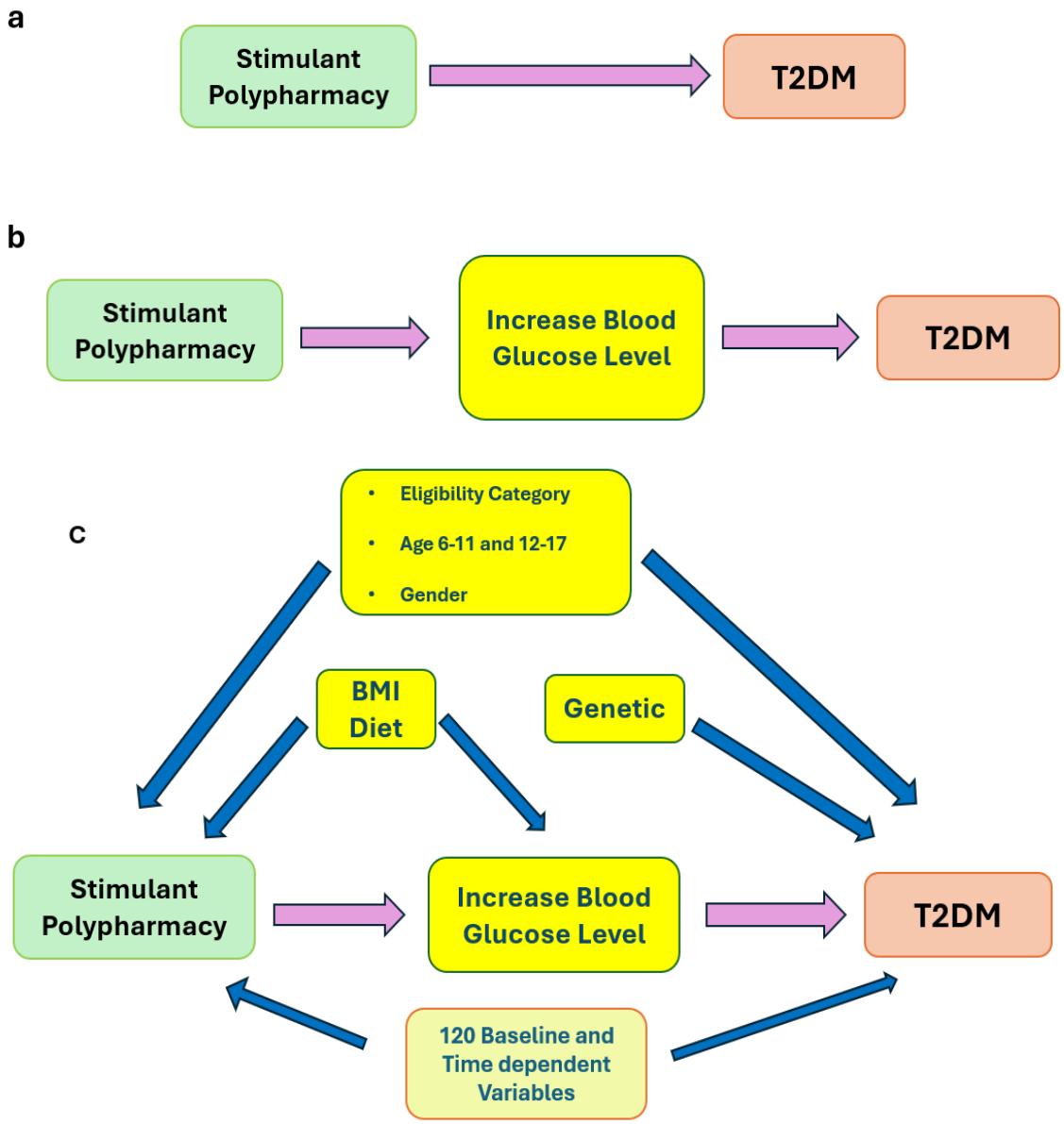
Diabetes	N	%
Inpatient diabetes diagnosis	22	51.2
≥2 diabetes-related medical care encounters	21	48.8

S Figure 5-2. Absolute Risk of Incident Type 2 Diabetes per 10,000 Person-Months According to Disease Risk Score



Note: The disease risk score was estimated in a time-dependent manner for each person in each month of follow-up. We grouped the person-months into discrete groups, expressed as percentile ranks of the estimated disease risk score distribution. To check for the validity of the disease risk score estimation, we assessed the incidence of type 2 diabetes in these groups (from the lowest to the highest risk group). The figure shows that the risk of incident type 2 diabetes increased with increasing quartile disease risk score.

S Figure 5- 3. Conceptual diagram to describe the direct and indirect causal pathway



a. Stimulant polypharmacy (the exposure) causes T2DM (the outcome).
b. Stimulant polypharmacy acts on T2DM through the mediator of increased blood glucose level.
c. The variables Both externalizing and internalizing disorders, long continuous enrollment, age 6-11 and 12-17, BMI and Diet, and other 120 baseline variables increased both exposure and outcome, and therefore are confounders. Genetic factors increased risk of T2DM and could cause selection bias.

S Table 5-1. Operational Definition of Incident Type 2 Diabetes

ICD-9-CM	250, 250.0, 250.1, 250.2, 250.3, 250.9
Diabetes related prescriptions	insulin, insulin adjuncts, or oral hypoglycemic agents

S Table 5- 2. Operational Definition of Study Covariates in a Range of Clinical, and Other Health Care Utilization Characteristics

a. Psychotropic medication groups

Covariate	**Generic name**
Antipsychotics	aripiprazole, olanzapine clozapine, paliperidone, quetiapine, risperidone, ziprasidone, chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, thioridazine, thiothixene
Anxiolytic/hypnotics	buspirone, chloral hydrate, clonazepam, diazepam, eszopiclone, lorazepam, midazolam, ramelteon, zaleplon, zolpidem
Antidepressants	amitriptyline, amitriptyline/chlordiazepoxide, amoxapine, bupropion, citalopram hydrobromide, clomipramine, desipramine, desvenlafaxine succinate, doxepin, duloxetine, escitalopram oxalate, fluoxetine, fluvoxamine maleate, imipramine, mirtazapine, nefazodone, nortriptyline, paroxétine, paroxetine mesylate, protriptyline hcl, sertraline, trazodone, venlafaxine
Anticonvulsant-mood stabilizers	carbamazepine, divalproex, lamotrigine, oxcarbazepine, valproate, valproic acid
Stimulants	methylphenidate, dexmethylphenidate, amphetamine salts, dextroamphetamine, lisdexamfetamine
Selected alpha agonists	clonidine, guanfacine
Lithium	lithium

b. Clinician-reported psychiatric diagnoses from ICD-9 codes

	ICD-9-CM* diagnosis codes
ADHD	314.xx
Disruptive disorder	312.0-312.4, 312.81, 312.82, 312.89, 312.9, 313.81
Learning disorder	307.0, 307.9, 315.0-315.2, 315.31, 315.32, 315.39, 315.9

Adjustment disorder	308.0-308.2, 308.4, 308.9, 309.0-309.4, 309.82, 309.83, 309.89, 309.9
Anxiety disorder	293.84, 300.0, 300.2, 300.3, 308.3, 309.21, 309.81, 313.0, 313.2, 313.89
Depression	293.83, 296.2, 296.3, 296.9, 298.0, 300.4, 311
Autism spectrum	299.xx
Schizophrenia	295, 297, 298
Bipolar disorder	296.0, 296.1, 296.4-296.7, 296.80, 296.89, 301.13
Intellectual disability	299, 317-319
Other mental disorders	V40, V66.3, V67.3, 290-319 (except codes listed above)

*ICD-9-CM: International Classification of Disease, Ninth Revision, Clinical Modification

c. Covariates for metabolic conditions and related medical services

Covariate	**ICD-9-CMa diagnosis codes**
Overweight/obese	278.0, 783.1, V77.8, V85.3, V85.4, V85.53, V85.54
Acanthosis nigricans	701.2
Weight management	V65.3
Hyperlipidemia	272.0-272.2, 272.4
Hypothyroidism	243, 244
Hypothyroid screening	V77.0
Hyperthyroidism	242
Other thyroid gland disorder	240, 241, 245, 246
Nutritional deficiency	260-269
Insulin resistance/metabolic syndrome	251.1, 277.7
Other endocrine disorder	240, 241, 245, 246, 253, 255, 258, 259.0, 259.1
Symptoms related to high blood glucose	783.5, 788.42, 790.2
Other metabolic disorder	270, 271, 272.3, 272.5-272.9, 275.0-275.3, 277.2-277.6, 277.8, 277.9
Metabolic screening test	

Lipid test	
Glucose test	V77.1

aICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

d. Covariates for cardiovascular conditions and related medical services

Covariate	**ICD-9-CMa diagnosis codes**
Hypertension (diagnosed)	401-405
Congenital anomalies of heart and circulatory system	745-747
Acute myocardial infarction	410
Ischemic heart disease	411-414, 429.7
Cardiac valve disease (mitral)	394, 396, 424.0
Other cardiac valve disease	395, 397, 424.1-424.3
Conduction disorder	426
Arrhythmia	427
Cardiomyopathy	425
Heart failure	428
Occlusion of cerebral arteries	430-434, 436
Transient cerebral ischemia	435
Other cerebrovascular disease	437, 438
Peripheral vascular disease	440.2, 440.3, 443, 444.2, 444.8, 445.0, 785.4
Renal insufficiency	582-588
Other cardiovascular disease	390-459 (except codes listed above)
Cardiovascular symptoms	780.2, 785.0, 785.1, 785.2, 785.3, 785.50, 785.51, 785.9, 786.5

aICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

e. Covariates for cardiovascular medications

Covariate Generic name	Covariate Generic name
Angiotensin-converting-enzyme (ACE) inhibitor	benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Angiotensin II Receptor Blocker (ARB)	candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Beta blocker	acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, sotalol, timolol
Antilipemic agent	atorvastatin, cholestyramine, colesevelam, colestipol, ezetimibe, fenofibrate, fenofibrate, fenofibric acid, fluvastatin, gemfibrozil, lovastatin, niacin, niacin (inositol niacinate), omega-3 fatty acids, pravastatin, rosuvastatin, simvastatin
Cardiotonic agent	digoxin, milrinone
Calcium channel blocker	amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil
Antithrombotic agents	alteplase, anagrelide, cilostazol, clopidogrel, dalteparin, enoxaparin, eptifibatide, fondaparinux, heparin, ticlopidine, tinzaparin, warfarin
Other cardiovascular disease medications	adenosine, aliskiren, ambrisentan, amiodarone, amyl nitrite, bosentan, diazoxide, dipyridamole, disopyramide, dofetilide, doxazosin, eplerenone, epoprostenol, flecainide, hydralazine, iloprost, isosorbide, isoxsuprine, lidocaine, mecamylamine, mexiletine, minoxidil, nesiritide, nitroglycerin, papaverine, prazosin, procainamide, propafenone, quinidine, ranolazine, reserpine, spironolactone, terazosin, treprostinil

f. Covariates for reproductive, obstetric and gynecologic conditions and related medical Services

Covariate	ICD-9-CMa diagnosis codes	ICD-9-CMa procedure codes
Pregnancy screening	V72.4	
Sterilization	V25.2, V26.51	66.21, 66.22, 66.29, 66.31, 66.32, 66.39
Contraceptive management	V25.0, V25.1, V25.4, V25.5, V25.8, V25.9	
Absence of menstruation	626.0	
Scanty or infrequent menstruation	626.1	
Excessive or frequent menstruation	626.2	
Irregular menstrual Cycle	626.4	
Other disorders of menstruation/abnormal bleeding	626.3, 626.8, 626.9	
Cervical cancer screening	V76.2, V72.32	
Cervical dysplasia	622.1	
Ovarian cysts	620.0, 620.2	

aICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

g. Covariates for contraceptive medications and devices

Covariate	Generic name
Oral contraceptive	desogestrel, drospirenone, ethinyl estradiol, estradiol, ethynodiol d-ethinyl estradiol, ethynodiol diacetate, levonorgestrel, mestranol, norethindrone, norgestimate
Other contraceptive	diaphragm (arc-spring), diaphragm (coil spring), estradiol, norethindrone, ethinyl estradiol, etonogestrel, intra-uterine device (iud), levonorgestrel, nonoxynol 9, norelgestromin, octoxynol 9

Medroxyprogesterone	medroxyprogesterone

h. Covariates for respiratory /allergy conditions and related medical services

Covariate	ICD-9-CMa diagnosis codes
Asthma	493
Bronchitis	490, 491
Other respiratory disease and allied conditions	492, 494-496
Smoking (diagnosed)	305.1, 649.0, 989.84, V15.82
Sleep apnea	327.2, 780.51, 780.53, 780.57
Anaphylactic reaction/allergy	995.0, 995.27, 995.29, 995.3, 995.6
Asphyxia, shortness of breath, wheezing	786.05, 786.07, 799.0
Other respiratory symptoms	786.00-786.04, 786.06, 786.09, 786.1-786.4, 786.8, 786.9

[a]ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

i. Covariates for respiratory/ allergy medications

Covariate	Generic name
Antihistamine	acrivastine, azatadine, brompheniramine, carbinoxamine, cetirizine, chlorphenir, chlorpheniramine, clemastine, cyproheptadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, fexofenadine, levocetirizine, loratadine, pheniramine, phenindamine, phenyltoloxamine, pyrilamine, phenyltoloxamine, triprolidine
Hydroxyzine	hydroxyzine
Inhaled corticosteroid	**beclomethasone, budesonide, ciclesonide, flunisolide,** fluticasone, mometasone, triamcinolone
Other corticosteroid	hydrocortisone, methylprednisolone, prednisolone, prednisone

Bronchodilator	albuterol, arformoterol, formoterol, levalbuterol, metaproterenol, pirbuterol, salmeterol, terbutaline
Other asthma medications	ipratropium, tiotropium, omalizumab, cromolyn, montelukast, nedocromil, zafirlukast, zileuton

j. Covariates for other conditions and related medical services

Covariate	**ICD-9-CMa diagnosis codes**	**ICD-9-CMa procedure codes**
Intentional injury	E950-E959, E980- E989	
Maltreatment (abuse, neglect, assault)	994.2, 994.3, 995.5, V15.4, V61.21, V71.5, V71.81, E904.0- E904.2, E960.1, E961- E968	
Psychotherapy		
Crohn's disease	555.0-555.2, 555.9	
Ulcerative colitis	556.0-556.6, 556.8, 556.9	
Other upper GI disorders	530-538, 578	45.11-45.14, 45.16
Chronic liver Disease	571, 572.8	
Other liver disorders	570, 572.0-572.4, 573	
Congenital anomalies of digestive system	750.3, 751	
Epilepsy/seizures	345, 780.32, 780.33, 780.39	
Rheumatologic Disorders	710, 712, 714, 716, 719.2, 719.3, 720-722, 723.0, 723.2, 723.3, 723.6-723.9, 725-729	
Other musculoskeletal disorders/symptoms	710-739 (except codes listed above)	
Gallbladder/biliary tract disorder	574-576	
Nephrotic syndrome	581	

Urinary tract infection	599.0	
Hepatitis B or C	070.2, 070.3, 070.41, 070.44, 070.51, 070.54, 070.7	
Tuberculosis	010-018	
Other infections	001-009, 020-066, 070.0, 070.1, 070.42, 070.43, 070.49, 070.52, 070.53, 070.59, 070.6, 070.9, 080-139, 480-488, 507, 510, 513	
Malaise/fatigue	780.7	
Hypersomnia	327.1, 780.54	
Other organic sleep disorders	327.0, 327.3, 327.4, 327.5, 327.8, 780.50, 780.52, 780.55, 780.56, 780.58, 780.59	

[a]ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

h. Covariates for other medications

Covariate	**Covariate Generic name**
Other anticonvulsant medications	ethosuximide, ethotoin, fosphenytoin, felbamate, lacosamide, levetiracetam, mephobarbital, methsuximide, phenytoin, pregabalin, primidone, rufinamide, tiagabine, vigabatrin, zonisamide
Opiate analgesic medications	codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene, tapentadol, tramadol
Migraine medications	almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
Muscle relaxant medications	baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine,
Antibiotics	amikacin, amoxicillin, amoxicillin/potassium clavulanate, ampicillin, ampicillin/sulbactam sodium, azithromycin, aztreonam, bacitracin, carbenicillin, cefaclor, cefadroxil, cefazolin, cefdinir, cefditoren, cefepime, cefixime, cefotaxime, cefotetan, cefoxitin, cefpodoxime, cefprozil, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cephalexin, cephradine, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, colistin, daptomycin, demeclocycline, dicloxacillin, dirithromycin,

	doripenem, doxycycline, ertapenem, erythromycin, gatifloxacin, gentamicin, grepafloxacin, imipenem, kanamycin, levofloxacin, lincomycin, linezolid, loracarbef, meropenem, metronidazole, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, norfloxacin, ofloxacin, oxacillin, penicillin, piperacillin, polymyxin b, quinupristin/dalfopristin, rifaximin, spectinomycin, sulfadiazine, sulfamethoxazole, sulfanilamide, sulfasalazine, sulfathiazole/sulfacetamide/sulfabenzamide, sulfisoxazole, telithromycin, tetracycline, ticarcillin /potassium clavulanate, tigecycline, tobramycin, trimethoprim, vancomycin
Antimycobacterial agents	aminosalicylic acid, capreomycin, clofazimine, cycloserine, dapsone, ethambutol, ethionamide, isoniazid, pyrazinamide, rifabutin, rifampin

i. Covariates for medical care utilization (Intensity/No. of visits)

Covariate	**ICD-9-CMa diagnosis codes**	**ICD-9-CMa Procedure codes**
Psychiatric outpatient visit	290-319, V40, V66.3, V67.3	
Psychiatric ED visit		
Psychiatric hospitalization		
Injury-related outpatient visit	800-999, E800-E999	79.0, 79.1, 79.2, 79.3, 78.1
Injury-related ED Visit		
Injury-related hospitalization		
Other outpatient visit	All outpatient visits except psychiatric or injury-related outpatient visits	
Other ED visits	All ED visits except psychiatric or injury-related ED visits	
Other hospitalization	All hospitalizations except psychiatric or injury-related hospitalizations	

aICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

S Table 5-3. Baseline Characteristics of Incident Type 2 Diabetes Patients According to Stimulant Monotherapy and Stimulant Polypharmacy

	Stimulant Monotherapy N=15		**Stimulant Polypharmacy N= 28**		**P-value**
	N	%	N	%	
Age Group (years)*					
2-5	1	6.7	3	10.7	<0.001
6-11	11	73.3	11	39.3	
12-17	3	20.0	14	50.0	
Gender					
Male	7	46.7	17	60.7	<0.001
Female	8	53.3	11	39.3	
Race/Ethnicity					
African American	8	53.3	18	64.3	<0.001
White	5	33.3	7	25.0	
Hispanic/ Nat Am/Asian/Pac Islander/Unknown	2	13.3	3	10.7	
Eligibility Category**					
Foster care	0	-	8	28.6	<0.001
SCHIP	2	13.3	1	3.6	
SSI	6	40.0	9	32.1	
TANF	7	46.7	10	35.7	
Continuous Enrollment (years)					
1-2	0	-	0	-	<0.001
3-4	1	6.7	1	3.6	
5-6	3	20.0	6	21.4	
7-8	11	73.3	21	75.0	
Clinician-Reported Psychiatric Diagnosis					

Externalizing disorders only***	9	60.0	3	10.7	<0.001
Internalizing disorders only***	5	33.3	25	89.3	
Both***	1	6.7	0	-	
Other psychiatric diagnoses	1	2.3	872	2.9	
T2DM Disease Risk Score					
< 25%	5	33.3	1	3.6	<0.001
25-50%	4	26.7	4	14.3	
51-75%	4	26.7	8	28.6	
>75%	2	13.3	15	53.6	

*Age is the age of first stimulant use

** SCHIP=State Children's Health Insurance Program; SSI=Supplemental Security Income; TANF=Temporary Assistance for Needy Families

*** Externalizing disorders include ADHD, disruptive behavioral disorders; Internalizing disorders include depression, anxiety disorders; Other psychiatric diagnoses include adjustment disorder, au-tism spectrum disorder, learning disorder, schizophrenia, intellectual disability, tic disorder, bipolar disorder, and other mental health diagnoses

S Table 5-4. Adjusted Risk Ratio of Patient Characteristics for Incident Type 2 Diabetes

	Risk Ratio	**95% CI**
Age Group (years)*		
12-17	6.34	1.79 – 22.44
6-11	4.35	1.28 – 14.77
2-5	1	
Gender		
Male	0.67	0.34 – 1.32
Female	1	
Eligibility Category**		
Foster care	1.15	0.44 – 3.06

SCHIP	0.72	0.20 – 2.57
SSI	1.19	0.53 – 2.68
TANF	1	
T2DM Disease Risk Score		
>75%	7.74	2.73 – 21.89
51-75%	3.72	1.25 – 11.01
25-50%	1.85	0.53 – 6.44
< 25%	1	

*Age is the age of first stimulant use

** SCHIP=State Children's Health Insurance Program; SSI=Supplemental Security Income; TANF=Temporary Assistance for Needy Families

S Table 5- 5. Stimulant Polypharmacy Regimens in Diabetic and Non-diabetic Patients*

	Diabetic Patients with Stimulant Polypharmacy N=28		**Non-Diabetic Patients with Stimulant Polypharmacy N=7,337**	
	N	**%**	**N**	**%**
2 drug class polypharmacy				
Stimulant + ATD	5	50.0	1,521	27.5
Stimulant + AA	3	30.0	2,562	48.1
Stimulant + ATP	2	20.0	984	19.2
Stimulant + ATC-MS	0	-	201	3.9
Stimulant + AX	0	-	65	1.2
3 drug class polypharmacy				
Stimulant + ATP + ATC-MS	5	71.4	198	11.5
Stimulant+ ATP + AA	1	14.3	545	31.4
Stimulant + ATD + ATC-MS	1	14.3	135	8.1
Stimulant + ATP + AX	0	-	28	1.7

Stimulant + ATP + ATD	0	-	629	36.4
Stimulant + ATD + ATC-MS	0	-	135	8.1
Stimulant + ATD + AX	0	-	42	2.5
Stimulant + AX + ATC-MS	0	-	7	0.4
4 drug class polypharmacy				
Stimulant + ATP + ATD +ATC-MS	3	43.0	137	19.3
Stimulant + ATP + AA + ATC-MS	2	28.5	147	20.7
Stimulant + ATP + ATD + AX	2	28.5	35	4.9
Stimulant + ATP + ATD + AA	0	-	287	40.4
Stimulant + ATP + ATC-MS + AX	0	-	7	1.0
Stimulant + ATP + AA + AX	0	-	11	1.5
Stimulant + ATD + ATC-MS + AA	0	-	67	9.4
Stimulant + ATD + ATC-MS + AX	0	-	11	1.5
Stimulant + ATD + AA + AX	0	-	6	0.8
Stimulant + ATC-MS + AA + AX	0	-	3	0.4
5 drug class polypharmacy				
Stimulant + ATP + ATD + ATC-MS + AA	4	100	76	76.8
Stimulant + ATP + ATD + ATC-MS + AX	0	-	10	10.1
Stimulant + ATP + ATD + AA + AX	0	-	7	7.1
Stimulant + ATP + ATC-MS + AA + AX	0	-	3	3.0
Stimulant + ATD + ATC-MS + AA + AX	0	-	3	3.0

*AA=Alpha agonist; ATP=Antipsychotic; ATD=Antidepressant; ATC-MS=Anticonvulsant-Mood Stabilizer, AX=Anxiolytic

S Table 5-6. Distribution of Clinician-Reported Comorbid Psychiatric Diagnosis in Diabetic and Non-Diabetes Patients

	T2DM N=43		**Non-T2DM patients N=30,069**		**P-value**
	N	%	N	%	
ADHD	41	95.35	27,084	90.07	0.25
Disruptive disorder	23	53.49	9,659	32.12	0.003
Depression	29	67.44	8,905	29.62	<0.0001
Anxiety disorder	21	48.84	6,302	20.96	<0.0001
Bipolar disorder	19	44.19	3,197	10.63	<0.0001
Schizophrenia	11	25.58	1,027	3.42	<0.0001
Intellectual disability	4	9.30	665	2.21	<0.001
Autism spectrum	3	6.98	1,669	5.55	0.68
Adjustment disorder	8	18.60	3,030	10.08	0.06
Learning disorder	8	18.60	4,453	14.81	0.48
Tic disorder	0	0.00	645	2.15	-
*Other MH disorders	22	51.16	6,435	21.40	<0.0001

*Other MH disorders not listed above such as dissociative, stress related, or unspecified mental disorder

S Table 5- 7. Frequency of Psychotropic Drugs Among Diabetic and Non-diabetic Patients

	Diabetic patients N= 43	Percent	Non-Diabetic patients N= 30,069	Percent
Stimulant				
Dextroamphetamine Sulf-Saccharate/Amphetamine Sulf-Aspartate	17	33.3	7,627	26.5
Methylphenidate	7	13.7	6,867	23.9
Dexmethylphenidate HCL	10	19.6	5,974	20.8
Lisdexamfetamine Dimesylate	6	11.8	5,312	18.5
Dextroamphetamine Sulfate	1	2.0	232	0.8
Total	51		29,230	
Antipsychotic				
Atypical				
Aripiprazole	16	69.6	2,987	45.2
Risperidone	3	13.0	2,541	38.4
Quetiapine Fumarate	3	13.0	786	11.9
Olanzapine	0	-	186	2.8
Ziprasidone HCL	0	-	59	0.9
Paliperidone	1	4.3	38	0.6
Clozapine	0	-	6	0.1
Olanzapine/Fluoxetine HCL	0	-	6	0.1
Risperidone Microspheres	0	-	1	0.0
Total	23		6,611	
First Generation				
Haloperidol	2	100	77	45.0
Chlorpromazine HCL	0	-	59	34.5
Fluphenazine HCL	0	-	1	0.6
Haloperidol Lactate	0	-	14	8.2

Loxapine Succinate	0	-	1	0.6
Perphenazine	0	-	15	8.8
Pimozide	0	-	3	1.8
Molindone HCL	0	-	1	0.6
Total	2		171	
Antidepressant				
Second Generation				
Fluoxetine HCL	7	38.9	1,666	31.6
Sertraline HCL	4	22.2	1,354	25.7
Escitalopram Oxalate	3	16.7	1,053	20.0
Citalopram Hydrobromide	4	22.2	1,019	19.3
Paroxetine HCL	0	-	73	1.4
Duloxetine HCL	0	-	50	0.9
Venlafaxine HCL	0	-	26	0.5
Desvenlafaxine Succinate	0	-	3	0.1
Fluvoxamine Maleate	0	-	24	0.5
Total	18		5,268	
First Generation				
Bupropion HCL	7	77.8	1,258	47.9
Trazodone HCL	1	11.1	446	17.0
Mirtazapine	0	-	412	15.7
Amitriptyline HCL	0	-	275	10.5
Imipramine HCL	0	-	149	5.7
Doxepin HCL	0	-	33	1.3
Nortriptyline HCL	1	11.1	29	1.1
Clomipramine HCL	0	-	20	0.8
Desipramine HCL	0	-	5	0.2
Total	9		2,627	
Alpha Agonist				

Clonidine	16	76.2	5,053	59.4
Guanfacine HCL	5	23.8	3,383	40.1
Total	21		8,436	
Anticonvulsant Mood Stabilizer				
Divalproex Sodium	9	50	1503	51.2
Oxcarbazepine	3	16.7	621	21.1
Lamotrigine	3	16.7	599	20.4
Carbamazepine	3	16.6	179	6.1
Valproic Acid	0	-	35	1.2
Total	18		2,937	
Anxiolytic				
Benzodiazepine				
Diazepam	3	27.3	500	30.8
Clonazepam	5	45.5	447	27.5
Buspirone HCL	2	18.2	389	23.9
Lorazepam	1	9.1	280	17.2
Midazolam HCL	0	-	9	0.6
Total	11		1,625	
Non-Benzodiazepine				
Zolpidem Tartrate	2	100	188	57.5
Ramelteon	0	-	55	16.8
Chloral Hydrate	0	-	40	12.2
Eszopiclone	0	-	35	10.7
Zaleplon	0	-	9	2.8
Total	2		327	
Other				
Atomoxetine HCL	10	100	2750	100
Grand Total	165		59,982	