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Long-Term Physiological Harms of Exposure to Prescribed Psychotropic Drugs in Children Aged 6 to 12: a Population-Based Retrospective Cohort Study

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Long-Term Physiological Harms of Exposure to Prescribed Psychotropic Drugs in Children Aged 6 to 12: a Population-Based Retrospective Cohort Study

A dissertation submitted in partial satisfaction
of the requirements for the degree
Doctor of Philosophy in Social Welfare

by

Alexander Recalt

2022

ABSTRACT OF THE DISSERTATION

Long-Term Physiological Harms of Exposure to Prescribed Psychotropic Drugs in Children Aged 6 to 12: a Population-Based Retrospective Cohort Study

by

Alexander Recalt
Doctor of Philosophy in Social Welfare
University of California, Los Angeles, 2022
Professor David Cohen, Chair

Background. Prescription rates of psychotropic drugs to US children, and average duration of use, rose sharply in recent decades. However, little evidence supports their safety in children, whose physiological, psychological, and social development is still occurring. Previous safety literature is meager, especially on long-term use, but points to potentially harmful short- and long-term physiological consequences that require further investigation. **Methods.** From research and reference sources, I constructed a database of 587 non-behavioral physiological outcomes described as potential adverse drug reactions (PADRs) to 104 prescribed psychotropics, affecting 29 human physiological systems. Three pediatric clinicians classified each PADR as non-serious or serious per established standards. I linked PADR information, converted to ICD-9 and ICD-10 diagnoses by three pediatric clinician coders, to the Colorado All-Payer Claims Database (APCD) from 2009 to 2018 (N = 1,066,005

members under 18 years), a comprehensive population-based source of public and private health and pharmacy claims data in that US state. I conducted a retrospective cohort study comparing children first prescribed a psychotropic drug between the ages of 6 and 12 (n_1 = 42,362) to randomly sampled psychotropic drug-unexposed children in the same age range (n_2 = 42,362). Descriptive analyses of the analytic dataset (n = 84,724; mean followup time: 7.7 years, SD = 2.1; mean duration of psychotropic treatment in the exposed: 4.0 years, SD = 2.9) characterized prescribed psychotropic use and PADRs by duration of use, human physiological system, PADR seriousness, age, gender, median household income by member ZIP code, and epilepsy or recurrent seizure diagnosis. Next, 10 mixed effects Cox proportional hazards models related PADR hazard overall (2 models) and in specific physiological systems (8 models) to psychotropic exposure, polypharmacy, and covariates over time. Cox models accounted for within-subject heterogeneity using a frailty term Z, and included a time-varying predictor for psychotropic exposure. **Results.** Exposed children experienced substantially more PADRs (n = 582,003) than unexposed children (n = 218,741), with most PADRs in each group occurring in central nervous, sensory, gastrointestinal, and cardiovascular systems. Compared to drug-unexposed APCD members with the same age, gender, income, and seizure disorder diagnosis, psychotropic exposure increased the expected hazard of PADRs of any level of seriousness by 45.0% (*HR* 1.45, 95% CI [1.39, 1.52]), and serious PADRs by 60.0% (*HR* = 1.60, 95% CI [1.51, 1.70]). Psychotropic polypharmacy occurred in most (59.2%) of the exposed, and increased the hazard of PADRs compared to children on monotherapy in every statistical model (range of *HRs*: 1.33, 95% CI [1.10, 1.64], to 7.30, 95% CI [6.29, 8.48]). Exposure interacted significantly with time in every model, suggesting a slowly decreasing expected hazard of PADRs over time in ev-

ery analysis. To my knowledge, this is the first study of prescribed psychotropic drug harm in children to combine long followup time, multiple drug classes and physiological systems, a population-based dataset, the majority of known or suspected non-behavioral PADRs, and rigorous control for time-varying exposure and within-subject heterogeneity. Its primary limitations include incomplete control of confounding by indication; moderate inter-rater reliability; and absence of control of non-psychotropic prescription drug use.

The dissertation of Alexander Recalt is approved.

Thomas R. Belin

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Jorja Jean Manos Leap

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University of California, Los Angeles

2022

I dedicate this study to my family. Without you, I wouldn't have gotten here, and I wouldn't have become who I am. Thank you.

Dedico este estudio de investigación a mi familia. Sin vosotros, la persona que soy hoy no se entendería, y no habría llegado hasta aquí. Gracias.

Jeg dedikerer denne afhandling til min familie. Uden den ville jeg ikke være nået hertil og ville ikke være blevet til den jeg er. Tak.

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My time in this field, in research more broadly – the last decade and change of my life, if I'm being honest – couldn't have happened without David Cohen. There isn't a kinder, more generous, more patient mentor on the planet who is also as utterly top-line and fearless a critical thinker and scholar. I still don't know how he does it, and I've known him a long time. He has taught me to be patient and methodical, to strive for clarity of thought and simplicity in writing, and to be courageous in questioning assumptions – others', sure, but above all my own. Without him, I wouldn't have looked at mental health through the lenses of history, culture, ethics, and power. More than anything, though, David has shown me that when the boxes are checked, all cylinders are firing, and you've been in front of your data for 8 hours and there are easily another 8 to go, this research stuff is actually a lot of fun, and it's critical to enjoy it. During my time in graduate school I always felt like I'd been let in on some secret, allowed to use the toll road for free while others plodded along in traffic: how did I luck so completely out with this man as a guide and friend? Thank you, David, for everything.

I may have David to thank for where I've gone in my thirties, but I owe my whole life to my family. Any tenacity and persistence I have are my mother's, and when I

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It's odd that after thirty-something years of never writing computer code, never thinking about writing computer code, nor thinking about people who write computer code, I now do all three regularly – and for science, to boot! Several real-life people helped me learn to do so, all of whom have been included above. But there's one last group left to thank here: all the nameless or pseudonymous people on the internet who replied to my questions, posts, Tweets, and emails about programming and statistics and scientific computing and R and PostgreSQL and LaTeX and Python and Julia and liquid-cooling a CPU and all the rest. Particular gratitude goes to the merge-god AK; LD in Bristol; Terry Therneau and Thomas Lumley, who replied; and the Stack Overflow, Cross Validated, and TeX-LaTeX communities on Stack Exchange – in particular the users akrun, whuber, EdM, Ben, TarJae, and ThomasIsCoding.

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PUBLICATIONS AND PRESENTATIONS

Recalt, A. M., Cohen, D. (2019). Withdrawal confounding in randomized controlled trials of antipsychotic, antidepressant, and stimulant drugs, 2000–2017. *Psychotherapy and psychosomatics, 88*(2), 105-113.

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CHAPTER 1

Introduction

1.1 Prescribed psychotropic drugs and adverse drug reactions: key terminology

1.1.1 Drugs

The phrase *prescribed psychotropic drugs* refers to any of more than 100 chemical compounds approved for sale by the US Food and Drug Administration (FDA) and available by prescription that change brain function, typically ingested by a user to ameliorate the symptoms of psychological distress by altering mood, behavior, and/or perception. ("Psychotropic", commonly used as a synonym of "psychoactive", refers to that alteration.) The term is often used interchangeably with "psychiatric drug" and "psychiatric medication", which may be understood by a lay or non-specialist reader as something like "medications that psychiatrists prescribe for mental health."

These compounds are commonly grouped into classes and sub-classes; such groupings figure prominently in this dissertation and thus deserve an introduction. The five major classes are *antidepressants*; *antipsychotics*; *benzodiazepines & other anxiolytics*; *mood stabilizers*; and *psychostimulants*. *Antidepressants* include popular drugs like fluoxetine (Prozac) and sertraline (Zoloft), which are prescribed to treat

many more disorders than depressive ones; they are used in everything from eating disorders to post-traumatic stress disorder (PTSD). These two specific drugs are commonly referred to by their chemical sub-class, selective serotonin reuptake inhibitors or SSRIs, so called because of their putative action on neurotransmitters in the brain and central nervous system (Aronson, 2015). The antidepressant class also includes older drugs like imipramine (Tofranil) - a tricyclic antidepressant (TCA), another antidepressant sub-class - and newer compounds like venlafaxine (a serotonin-norepinephrine reuptake inhibitor or SNRI) and bupropion (Wellbutrin, sometimes called an *atypical antidepressant*). While antidepressants are commonly given for depression, their popularity is due to other indications as well: for instance, SSRIs are also commonly prescribed to treat Generalized Anxiety Disorder (GAD), for example, and bupropion is prescribed (as well as approved by the FDA and marketed) for quitting smoking. (Smoking cessation is bupropion's only approved indication in the United Kingdom, in fact.)

Antipsychotic drugs, once mostly referred to as *neuroleptics* or *major tranquilizers*, were first discovered in the 1950s during the development of new anesthetics for surgical applications. They exploded in popularity after their extreme tranquilizing effects on psychiatric patients were noticed. Today, while their primary indication remains the treatment of psychotic disorders such as schizophrenia, these drugs are increasingly popular for depression, ADHD, and insomnia (Birnbaum et al., 2013; Anderson and Vande Griend, 2014).

Benzodiazepines are among the most popular types of drugs given to alleviate symptoms of anxiety and panic as well as to induce or improve the quality of sleep. Because of this, the name is often used interchangeably with *anxiolytic* or *anti-anxiety* drugs in colloquial use, despite the fact that a number of *non-benzodiazepine anxiolyt-*

ics are commonly prescribed for anxiety and sleep (buspar, brand name Buspirone, and zolpidem, brand name Ambien, are two examples of these).

For many decades the only drug to be described as a *mood stabilizer* was lithium, given then as now to people suffering the high and low moods of manic depression (later renamed bipolar disorder; Harris, Chandran, Chakraborty, and Healy, 2003). Today, however, the class has expanded to include a number of anticonvulsant (or antiepileptic) drugs purported to have similar effects – particularly on mania – as lithium. These agents include valproate (Depakote), lamotrigine (Lamictal), and carbamazepine (Tegretol).

Stimulants, sometimes called *psychostimulants*, are the most common drugs prescribed to children and adults with behavioral issues related to inattention, hyperactivity, and conduct (e.g. attention-deficit hyperactivity disorder or ADHD). In American children and minors, stimulants are by a large margin the most prescribed class of psychotropics altogether. More detail on the popularity of stimulant and other psychotropic prescription in children follows shortly.

A caution for the reader: at most levels of classification - be it as a general group of pharmaceuticals or in specific classes, e.g. *antidepressants* - definition and classification are mutable and shaped not only by scientific but by historical, cultural, economic, and political factors, as well. Even the definitions of *psychotropic* and *psychoactive* (often used interchangeably) are to be used with caution, as compounds not typically understood to be psychoactive may in some cases, for some people, and at certain doses have effects on mood, cognition, and perception. The extent to which the entire topic is socially constructed is fascinating but ultimately outside this project's scope. Nonetheless, the reader is advised to know that while certain

terms make up the *lingua franca* of mental health and psychiatric research, and will find using them unavoidable, their mutability and subjectivity is fundamental.

The boundaries between classes, sub-classes, and psychotropic action are often unclear. For some classes, a name is a clue about its purpose (antidepressants are prescribed to act against depression); in others, not (benzodiazepines, prescribed in many cases to alleviate anxiety or panic). The reader is also cautioned not to rely too much on names to deduce a drug's therapeutic aim or use, however: antidepressants are frequently prescribed for anxiety; antipsychotics in recent years are increasingly prescribed for depression; and mood stabilizers are, in many cases, merely a newer name for antiepileptic compounds long used in neurology whose use has migrated to psychiatry in recent decades. The reader should also be wary of attributing a given psychotropic effect to a given drug or drug class on the basis of its name: "stimulants" may appear to make person calmer or make them feel more focused, for example, an effect long described as "paradoxical". Antidepressant drugs will be identified as having "anxiolytic properties", and antipsychotics will be described as possessing antidepressant and mood-stabilizing effects.

Despite the blurred lines in terminology and classification, I will use the standard classes and names throughout this dissertation unless the situation demands otherwise, in which case I will provide the relevant context. I will refer to these pharmaceuticals as "prescribed psychotropic drugs", "prescribed psychotropics", or simply "psychotropics" (unless otherwise stated) when speaking about them as a general group. With respect to particular drugs, I will use the generic name (fluoxetine) instead of the brand name (Prozac) unless stated otherwise.

1.1.2 Adverse drug reactions, adverse events, and side effects

The language for describing the unwanted or harmful effects of drugs can be as difficult to parse as that of the drugs themselves. The definitions of a number of commonly used terms overlap and are used interchangeably. Further, different sources sometimes disagree on precise definitions.

The phrases *adverse effect* or *adverse event* (both abbreviated AE) refer to a result of any medical treatment in addition to or in extension of its desired therapeutic effect; this usually connotes an undesirable effect (Stedman, 2005). The International Conference on Harmonization (1996) stipulates in its definition that AEs do not necessarily have a causal relationship with a given treatment; AEs are simply untoward occurrences in treated patients (ICH, 1995, 1996). *Side effect* is similar term, frequently used to refer to the unintended but not necessarily undesirable effects of a drug.

Adverse drug reactions (or *effects* or *events*; ADRs and ADEs) overlap with *adverse effects* but are more precise, especially for this study's purposes. The term refers specifically to the unwanted, uncomfortable, noxious, or dangerous effects of a drug related to any dose (Smith Marsh, 2018; ICH, 1996). Drug harm is sometimes described as a form of *toxicity*, as it pertains to severe and progressive diseases and conditions that result from exposure to a toxin (a poison) or toxic amounts of a substance that doesn't cause harm at lower doses (O'Toole, 2013).

Since the focus of this project is on drug-related therapeutic harm, I will primarily use the term *adverse drug reaction* and ADR to refer to the harms of prescribed psychotropic drugs under study here. Because this study does not seek to firmly establish causal relationships between drugs and reactions (nor can this methodological

approach do so), I will also use the term *potential adverse drug reaction* or PADR to refer specifically to analytical details and study results.

1.1.3 Time

This study focuses on the use of prescribed psychotropic drugs in children beyond the immediate days and weeks after beginning use. As I discuss in the literature review, few studies have looked rigorously at what happens to child and adolescent physiology over the course of a longer period of use, and those that have defined "long-term" quite differently. Further, there appears to be no standard definition for "long-term" when referring to either the duration of drug use or the length of follow-up in a drug safety study. Consequently, I will define "long-term" as time frames beyond one year.

1.2 Epidemiology of psychotropic drug prescription in US children and adolescents

1.2.1 Widespread overall use of prescribed psychotropic drugs in minors

Psychotropic drugs are widely prescribed to children, and prescription rates have increased since the 1980s for many drug classes, primarily stimulants and antidepressants; the former remain the most prescribed psychiatric drugs for children (Olfson, Marcus, Weissman, and Jensen, 2002; Zito et al., 2003; Chai et al., 2012). There is some evidence that rates of psychotropic prescription to minors have tapered off around 2015 after hitting a peak in the mid-to-late 2000s, but overall, many more US children and adolescents are prescribed psychotropics than in previous genera-

tions, reflecting profound social, economic, and cultural changes (Olfson, King, and Schoenbaum, 2015; Lopez-Leon, Lopez-Gomez, Warner, and Ruiter-Lopez, 2018).

Figure 1.1 summarizes the key findings of 5 published studies that estimated the percentage of any psychotropic use by various age strata of US youth (age range across all studies: 0-20). (One study, Zito et al. (2003), analyzed 3 databases, and is thus included in the figure 3 times.) To make these estimates, all five studies retrospectively analyzed databases of prescription claims from public, private, or mixed sources. The sample sizes in each individual database (8 total) ranged from 6,483 to 17.8 million US minors.

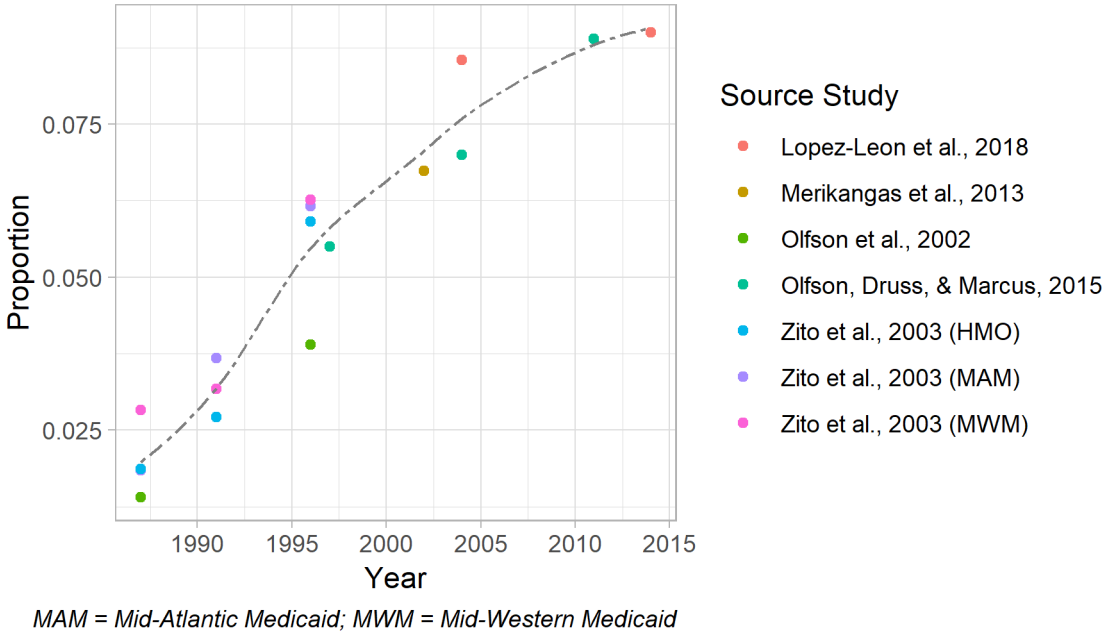


Figure 1.1. Proportion of US minors prescribed any prescribed psychotropic drug in the previous year, 1987-2015

Figure 1.2 uses the same data to display the proportion of US minors receiving

drugs of a given major psychotropic class over the course of the same period. They demonstrate that a large proportion of the increase in the prevalence of psychotropic use in children since 1987 can be accounted for by stimulants and and antidepressants. More US minors take benzodiazepines and antipsychotic drugs than they did in 1987 - some estimates show a doubling or a tripling of prevalence - but absolute increases have been relatively minor next to stimulants and antidepressants.

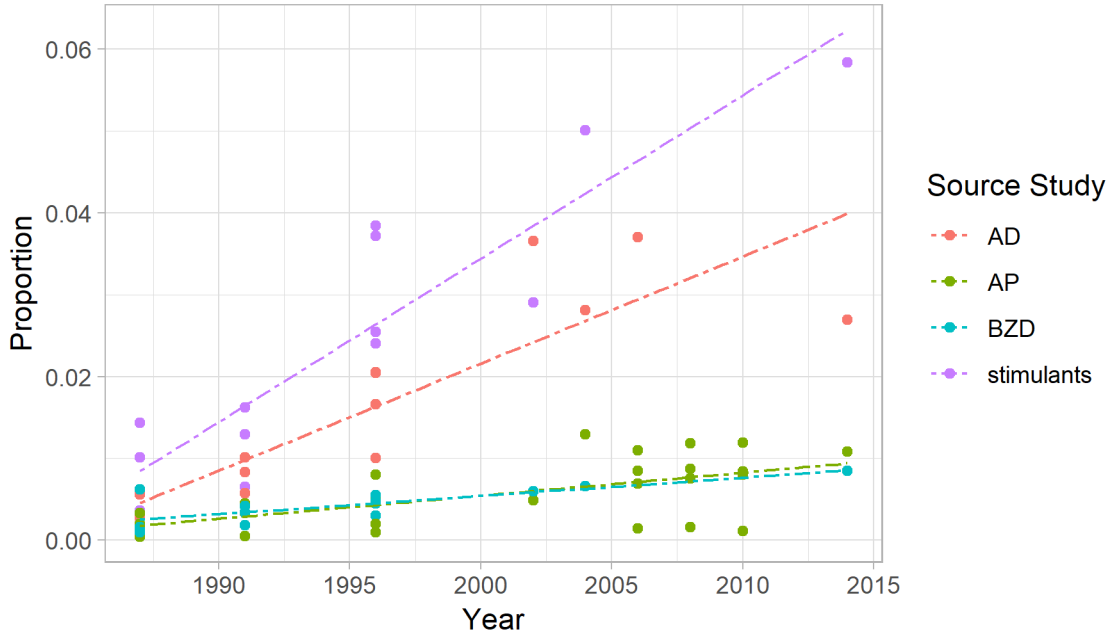


Figure 1.2. Proportion of minors prescribed psychotropic drug in the previous year (by class), 1987-2015

Some evidence exists for a slowing down in this growth of prescription rates in recent years. Lopez-Leon et al. (2018) used Truven Marketscan databases of commercially insured and Medicaid claims to estimate the annual prevalence (per 100 people) of total prescribed psychotropic drug use, psychotropic drug use by drug

class, and psychotropic drug use by individual compound among Americans aged 2 to 18 in the years 2004 (6.8 million) and 2014 (11.08 million).

Combined rates of prescription for all major psychiatric drug classes in Americans aged 3-18 nearly tripled from 1987 to 1996, from 1.4 per 100 to 3.9 per 100 (Olfson et al., 2002). Lopez-Leon et al. (2018) found that the overall percentage of minors who received any psychotropic drugs increased from 8.55 in 2004 (95% CI 8.53, 8.57) to 9.00% in 2014 (95% CI 8.98, 9.02). Stimulants and other drugs prescribed in ADHD cases increased from 5.0% to 5.83%; antidepressant use decreased from 2.81% to 2.69%; anxiolytics, hypnotic, and sedative use increased from 2.18% to 2.26%; mood stabilizer use decreased from 0.10% to 0.06%; antipsychotics decreased from 1.29% to 1.08%; drugs used to treat drug dependence remained flat at 0.02% (p-values for each drug class comparison = 0.000).

In this study, boys were more likely to have been prescribed an antipsychotic, a stimulant or other ADHD drug, or a mood stabilizer; girls were more likely to have been prescribed an anxiolytic / hypnotic, an antidepressant, or a drug to treat dependence (e.g. naltrexone). Other studies reviewed also suggest that overall growth in psychotropic prescriptions has fallen differentially on boys' shoulders, though this is further influenced by insurance and socioeconomic status. Zito et al. (2003), in their estimates of prevalence in three databases (two states' Medicaid databases and an HMO database from another state) in 1987, 1991, and 1996, found that boys' overall prevalence of psychotropic use in 1996 was approximately double girls' prevalence in the two Medicaid datasets; in the HMO dataset, however, girls' 1996 prevalence was greater than boys' by roughly ten percent (6.85% to 5.91%, respectively). Such a sex trend would make sense, given that boys have been historically more likely than girls to receive an ADHD diagnosis and, by extension, be prescribed a stimulant or

other ADHD drug (Olfson et al., 2002; Olfson et al., 2015).

Racial differences exist in pediatric psychotropic prescription, though there is less data on this subject for youth than in adults. In 1987, white children and teens reported approximately triple the use of any prescribed psychotropic by black and Hispanic youth (1.69% vs. 0.56% and 0.55%, respectively), but by 1996 this difference had decreased while all ethnic groups' rates increased substantially: 4.68% of white youth now reported any psychotropic use in the past year, while 2.79% of black youth and 2.16% of Hispanic youth did so (Olfson et al., 2002).

Given their central place in the overall growth in the proportion of US youth prescribed a psychotropic in the last thirty years, stimulants bear a closer look. Drugs such as methylphenidate, dextroamphetamine, and mixed amphetamine salts (Ritalin, Dexedrine, and Adderall, respectively) are commonly prescribed to children and adults diagnosed with attention-deficit hyperactivity disorder (ADHD). Methylphenidate was the most prescribed drug to adolescents (Americans aged 12-17) in 2010, and the fifth-most prescribed among children aged 2-11 in the during the same interval (Chai et al., 2012). Rates of stimulant prescription among public school children increased from 0.6 per 100 children to 2.4 per 100 from 1987 to 1996 in one pair of studies from the early 2000s (Olfson et al., 2002; Olfson, Gameroff, Marcus, and Jensen, 2003). The largest increases during that period were found among poor children.

1.2.2 Polypharmacy

Epidemiological analyses of drug prescription rates also show that psychotropic or psychiatric polypharmacy - the concurrent use of more than one prescribed psy-

chotropic drug - has increased among children and minors (Mojtabai and Olfson, 2010; Rittmannsberger, 2002; Soria Saucedo et al., 2018).[1] Soria Saucedo et al. (2018) analyzed Medicaid pharmacy data in 29 US states from 1999 to 2010 to estimate the prevalence, state-level variation, and age-level variation of same- and multi-class polypharmacy among youth between 0 and 17 years. Both any-class polypharmacy and multi-class polypharmacy increased over the course of the 10 years under study, beginning at 21.2% and 18.8% for any-class and multi-class polypharmacy, respectively, in 1999-2000, and ending at 27.3% and 24.4% in 2009-2010.

Evidence for the effectiveness of psychotropic polypharmacy is lacking, and there is both evidence and acknowledgment among researchers that in children, the practice is harmful, leading to increased rates of adverse drug reactions and events (Stahl and Grady, 2004; Preskorn et al., 2005; Silkey et al., 2005).

1.2.3 Psychotropics in adults

Psychiatric drug prescription and use is widespread among adults in the United States, and parallels the epidemiological picture of minors over the last three decades. Approximately 16.7% of American adults reported having filled 1 or more antidepressant, antipsychotic, or anxiolytic prescriptions in 2013 (Moore and Mattison, 2017). Women used psychiatric drugs at close to double the rate in men (21.1% to 11.9%, respectively). A quarter of adults over 60 years old used psychiatric drugs in

[1]Some sources go further in defining the concept, stating that for concomitant medication use to be considered polypharmacy, the drugs involved must be of the same or similar chemical class or pharmacological action and be used to treat the same condition. Using thyroid drugs to augment the effect of fluoxetine, an SSRI, would be considered polypharmacy in this instance; using thyroid drugs to treat hyperthyroidism while also using fluoxetine to treat depression would not (Kingsbury and Lotito, 2007). But in reviews of the literature conducted for this doctoral dissertation, this definition has been uncommon.

the past year. Large differences exist in use among racial/ethnic categories: 20.8% of white adults reported psychiatric drug use, while 9.7% of blacks, 8.7% of Hispanics, and 4.8% of Asian-Americans did.

Epidemiological assessments of psychiatric drug use indicate that a significant majority of those who report taking a psychiatric drug are long-term users, even though prescribing information for antidepressants, the leading drug class, includes limited information about the appropriate duration of treatment (Pratt, Brody, and Gu, 2011). Pratt and colleagues (2011) estimate that of the 11% of Americans aged 12 and over who take an antidepressant drug (approximately 32.8 million people), 61.2% have done so for more than 2 years (approximately 20 million people) and 13.6% have taken these drugs for more than a decade.

Psychiatric polypharmacy has increased in adults. In an analysis of survey data, Mojtabai and Olfson (2010) found that among office-based (i.e. outpatient) US psychiatry practices, the number of patient visits in which 2 or more medications were prescribed increased from 42.6% in 1996 to 59.8% in 2006, an effect which persisted even after controlling for patient background characteristics and diagnoses. They argued that while polypharmacy is indicated in some psychiatric settings, many combinations of more than one drug prescribed to patients are not well supported.

1.3 Well-documented iatrogenic effects in children across all psychotropic drug classes.

1.3.1 Drug harm

Drugs can be dangerous to human physiology; by nature, any substance capable of producing a therapeutic effect can also produce unwanted or adverse effects (Edwards and Aronson, 2000). In part this is because drugs are by most definitions substances other than food that have physiological effects on a living organism. Because we give (or take) a drug to intentionally interrupt or interfere with biological systems, and because those systems are both complex in themselves and in constant interaction with other physiological systems, as well as being heterogeneous between individuals, the result of such interruptions is often unpredictable and thus almost always carries some inherent risk. In addition, while many effects may be considered harmful universally (e.g. sudden death, loss of balance, or type 2 diabetes mellitus), where other effects lie on a spectrum of benefit and harm depends on an individual's judgment (e.g. loss of appetite, sleepiness, or headache). Harm induced by medical treatments, diagnostic procedures, or even clinicians' words is known as *iatrogenic* harm (O'Toole, 2013).

Further complicating drug safety assessment is the degree to which interconnected physiological systems may allow milder or shorter-term adverse drug reactions to lead to other, perhaps more severe health outcomes in the medium or long terms. Called *sequelae* in medical contexts, conditions that result and follow from a disease are common: depression and anxiety are known potential sequelae of traumatic brain injury (TBI), for example (Rao and Lyketsos, 2000; Venes, 2017). Hypertension is

common, frequently asymptomatic and chronic, and is a known potential adverse reaction of many drugs - including drugs in every major class of prescribed psychotropic. It is also a major contributor to mortality worldwide; for adults between ages 40 and 69, every 20 mm Hg increase in systolic blood pressure is associated with a doubling or more in the risk of death from stroke, ischemic heart disease, and other cardiovascular conditions (Prospective Studies Collaboration, 2002; WHO, 2013).

As a result of such complexities, these effects' potential for harm is difficult to ascertain at both the macro and micro levels. Classification systems for ADRs have often sought to assess the severity of such reactions, but doing so carries the risk of underestimating effects that may be perceived as more or less harmful by the patient than by their clinician. IBM Micromedex, one of the most comprehensive databases of drug information[2], divides drugs' adverse effects into "common" and "serious", which belies the ambiguity at issue: "common" ADRs of fluoxetine (Prozac) include tremor (experienced by 3-13% of people) and anxiety (3-15%), while "serious" reactions include depression and seizure. Why depression is serious but anxiety is not is unexplained.

Specific harms or kinds of harm need not be specific to a given drug or drug class, either, complicating the risk-benefit calculation necessary in any decision to take a drug. In a systematic review, Melo et al. (2018) examined the potential association between psychostimulants, antidepressants, and anticonvulsants (mood stabilizers) and sleep bruxism (SB; the grinding, clenching, or gnashing of teeth) in children. They found statistically significant increases in the odds of SB for duloxetine, paroxetine, and venlafaxine - all antidepressants - as well methylphenidate (Ritalin) and

[2]And one used extensively throughout this project

barbiturates. Falisi, Rastelli, Panti, Maglione, and Quezada Arcega (2014) speculated that psychotropic drugs' effects on neurochemical pathways - dopamine, in particular - are connected to evidence that SB's etiology is found in the same systems in the human brain. Drugs like methylphenidate (a CNS stimulant with energizing, invigorating effect) and barbiturates like phenobarbitol (CNS depressants with sedative effects) have very different short-term effects.

1.3.2 Organization of adverse drug reactions in relation to human physiology

A number of frameworks exist for organizing and understanding ADRs and their effects on human health. Rawlins and Thompson proposed classifying ADRs whose causality has been established (i.e., which have been proven to be caused by the drug in question) into Type A and Type B reactions: the former are dose-dependent and predictable from the known pharmacology of the drug, while the latter are dose-independent and unpredictable (J. K. Aronson and Ferner, 2003). While some still use these terms, Aronson (2003) led the charge for an updated system, arguing that many ADRs could not be conclusively assigned to a single category. The new framework sought to account for the effects of drug *dose*, the *time-course* over which ADRs occur (e.g. immediate, delayed reactions), and the *susceptibility* factors that influence the probability of occurrence (e.g. age, sex, and genetics); the system's name, DoTS, is a portmanteau of these factors.

The reporting of ADRs in human beings parallels their classification. This study relies greatly on ADR reporting systems in structuring its analytical approach, primarily because such reporting systems are organized around the effects of ADRs

on particular human physiological systems and groups of organs. These systems are fundamentally collections of agreed-upon terminology - dictionaries, essentially - that are used alongside disease classification systems such as the ICD and employed by individual nations' regulatory agencies and pharmacovigilance systems (the US Food and Drug Administration's Adverse Event Reporting System, FAERS, is an example). For many decades, the World Health Organization's Adverse Reaction Terminology (WHO-ART) was the accepted standard, and was built on four central components: terms, preferred terms, high-level groupings for preferred terms, and physiological systems and organ classes. In 2008, WHO-ART was replaced by the Medical Dictionary for Regulatory Activities (MedDRA), which was intended for use as validated terminology dictionary for all of medicine and not just ADR reporting. Its ADR classification is similar to WHO-ART's, though: a hierarchy of medical terms sitting inside of a list of System Organ Classes (n=27).

The ADRs I describe and investigate are organized into a similar list of physiological systems, modeled after MedDRA and employed in the standard reference text for ADRs, *Meyler's Side Effects of Drugs* (15th and 16th editions; Aronson, 2006).

1.3.3 Psychotropic drug harm in children and adolescents

Adverse drug reactions have been documented in children for all major psychotropic drug classes. Such reactions, while potentially harmful across the human lifespan, have special bearing on children. In a call for the development of standardized adverse event monitoring in pediatric psychopharmacology trials, Coates, Spanos, Parmar, Chandrasekhar, and Sikich (2018) write that psychiatric medications have developmentally-dependent adverse events (AEs) that differ from those observed in

adults. Amitai, Chen, Weizman, and Apter (2015) acknowledge the same in a review of the literature on SSRI-induced activation syndrome[3] in children and teens, while Bentley and Walsh (2013) caution social workers that school-age children metabolize, eliminate from their bodies, and respond to psychotropic drugs differently, in large part due to their ongoing physical and psychological development, resulting in the need for social workers to recognize that otherwise effective drugs may have side effects that specifically impact developmental processes in ways not applicable to adults.

In a study conducted to explore which psychotropic side effects have the largest impact on children's school performance, Kubiszyn, Mire, Dutt, Papathopoulos, and Burridge (2012) argued that studies of the iatrogenic effects of psychotropics are arguably more important in children and teens than in adults because their immature and still-developing central nervous systems may be more vulnerable to both the immediate and long-term effects of those drugs. The interaction of a still-developing human body and the pharmacokinetic properties of psychotropics may be partially to blame. In a review of therapeutic drug monitoring in pediatric settings, Soldin and Steele (2000) caution clinicians and lab workers that age is a major influence on drug metabolism - how drugs are broken down, used, and disposed of by the human body. In children aged six months to the beginning of puberty, the hepatic microsomal enzyme system - responsible for the majority of drug metabolism in human beings - has double the activity of an adult's, resulting in much faster drug

[3]A cluster of primarily psychiatric and behavioral symptoms that appears during SSRI treatment, often during the first few weeks after starting. The syndrome is more common in children and teens than in adults, and more common in children than in teens. Symptoms may include irritability, agitation, anxiety / panic, restlessness, hostility, aggression, akathisia, paranoia, impulsivity, or emotional lability

breakdown. Health workers caring for children on drug regimens, especially those children approaching adolescence, must monitor patients closely lest "therapeutic misadventures" occur: a drug's half-life for adults may be shorter in a child, which could justify more frequent drug administration. This could, however, increase the risk of AEs both from usage and drug withdrawal (Safer & Zito, 2006).

The idea of childhood and adolescence as *critical periods* of development - times during which the environment has its greatest impact (O'Toole, 2013) - ties together discussions of the particular susceptibility that minors may have to drug harm. In a review of the potential long-term damage that sleep disorders may have on children's brains, Jan and colleagues (Jan et al., 2010) wrote that children's neurological structures are simultaneously highly responsive to new information and more susceptible to damage than in later stages of life, and cite the devastating teratogenic (birth defect-inducing) effects of even small amounts of alcohol during pregnancy on fetal development as an example of how precarious these periods are for both individual physiological systems and the entire person.

The majority of the current knowledge of prescribed psychotropic ADRs in children and teenagers concerns effects that occur within days or weeks of beginning the use of the drug. The following subsections, organized by drug class, describe some of these. Table 1.1 summarizes known ADRs by psychotropic drug class and major human physiological system, using reactions documented in *Meyler's Side Effects of Drugs (16th Edition)* and *IBM Micromedex*, two comprehensive sources of known ADRs compiled from the empirical literature and adverse event reporting systems. For each physiological system, one known serious and non-serious ADR is given; serious ADRs are defined as reactions that are fatal, life-threatening, require inpatient hospitalization (or the prolongation of hospitalization), result in persistent

or significant disability, or that require intervention to prevent any of these (ICH, 1996). Because of the relative paucity of specifically *pediatric* psychotropic safety studies, the information presented in Table 1.1 and in the class-specific subsections that follow include ADRs documented across the human lifespan.

Table 1.1

Examples of serious and non-serious physiological adverse drug reactions by drug class & physiological system

	Cardiovascular		Non-behavioral CNS			Metabolic	Hematological	
Drug class	Serious	Non-serious	Serious	Non-serious	Serious	Non-serious	Serious	Non-serious
Stimulants	Myocardial infarction	Hypertension	Subarachnoid hemorrhage	Vocal tic		Retardation of growth (height and weight)	Hemolytic anemia	Gingival bleeding
Antidepressants	Hypertensive crisis	Hypertension	Parkinsonism	Bruxism	Weight gain	Galactorrhea	Gastrointestinal hemorrhage	Nosebleed
Antipsychotics	Heart failure	Bradycardia	Neuroleptic malignant syndrome	Sedation	Diabetes mellitus	High triglycerides	Agranulocytosis	Nosebleed
Benzodiazepines & other anxiolytics	Atrial fibrillation	Hypotension	Seizure	Dizziness	Metabolic acidosis	Increased plasma glucose		Leukopenia
Mood stabilizers	Sudden cardiac death	Sinus node dysfunction	subcortical dementia	Headache	Hyperammonemia	hyperinsulinemia	Bone marrow failure	Anemia

1.3.3.1 Psychostimulants and drugs used for ADHD

The psychostimulants comprise various drugs and drug sub-classes: amphetamine-based drugs such as mixed amphetamine salts (Adderall) and lisdexamfetamine (Vyvanse), and non-amphetamine stimulants like methylphenidate (Ritalin) and modafinil (Provigil). Non-stimulants such as atomoxetine (Strattera) are also used to ameliorate the symptoms of ADHD and related diagnoses. The majority of children treated with psychostimulants experience some adverse effects (Efron, Jarman, and Barker, 1998), and concerns remain that despite existing literature, the true degree of safety of these drugs remains unknown and their ADR profiles are not fully characterized (Graham et al., 2011; Inglis et al., 2016).

ADRs of various rates of incidence and degrees of severity for amphetamine-based drugs are largely cardiovascular, gastrointestinal, neurological, and psychiatric or behavioral in nature (Aronson, 2006; Aronson, 2015; Micromedex, 2019). A 2011 qualitative review of empirical studies that recorded ADR information in ADHD drugs (n=43 studies and 7244 children) found that headache, gastrointestinal pain, appetite decrease, insomnia, and anorexia were reported in at least 10% of children taking an amphetamine derivative (Aagaard and Hansen, 2011). Approximately 6% of minors who take an amphetamine-based drug experience anxiety or nervousness, while between 2% and 9% of adolescents experience mood swings (Micromedex, 2019). In Aagard and Hansen's review, a number of serious ADRs were identified. The majority are psychiatric or behavioral, and include suicide attempts, aggression, and anorexia.

Non-amphetamine psychostimulants have known ADR profiles that overlap to some degree with those of amphetamine-based drugs, but which differ in other ways

due to in part to their distinct drug action. Methylphenidate causes headache, GI pain, and appetite decreases as well, but adds nausea and vomiting (12% and 10%, respectively; Micromedex, 2019). Erythema multiforme, a red and bulging rash-like lesion, is also a common reaction. Methylphenidate causes a similar number of psychiatric reactions: mania, psychosis, aggression, and depression have been documented (Aagaard and Hansen, 2011; Aronson, 2015; Micromedex, 2019). In December of 2004, the FDA issued a black box warning and medication guide concerning the increased risk of suicidal ideation in children and teens who take atomoxetine (Strattera).

A range of *physiological* ADRs have been identified as well, and across all sub-classes the cardiovascular effects are among the best documented. Acute myocardial infarction, stroke, and neurological tic syndromes such as Tourette's have been documented in amphetamine-based drugs, while between 4.9% and 21.5% of children who take atomoxetine experience high blood pressure. Atomoxetine can cause severe liver injury and liver failure, while modafinil can cause a range of mild and serious dermatologic reactions (e.g. rash in the former case and toxic epidermal necrolysis in the latter; Aronson, 2015; Micromedex, 2019).

1.3.3.2 Antidepressants

A wide array[4] of ADRs have been documented for antidepressants of all sub-classes in adults and minors, with the bulk of these affecting the cardiovascular, nervous, hematologic, and gastrointestinal systems, along with the skin and sexual functioning (Csoka and Shipko, 2006; Aronson, 2006; Schweitzer, Maguire, and Ng, 2009;

[4] *Meyler's* describes it as "bewildering" (Aronson, 2015, p. 3489).

Aronson, 2015; Micromedex, 2019).

Antidepressant (AD) ADRs vary across sub-classes. Tricyclic ADs (TCAs) share structural similarities with older antipsychotic (AP) drugs, which may partially account for the fact that neurological movement disorders such as tremors and parkinsonism (often grouped together as *extrapyramidal symptoms* or EPS) have been documented across both classes (Aronson, 2015). Similar effects have been documented in newer and chemically distinct antidepressants of the selective serotonin reuptake inhibitor (SSRI) type, however; citalopram (Celexa) appears to cause tremors in 8% to 16% of users (Micromedex, 2019). This leaves open the question of whether a given set of effects are more common in a certain drug class, or are simply more or less well documented than in other classes.

While of less interest to this study, which focuses on *physiological* ADRs of psychotropics, psychiatric and behavioral reactions are prominent in the antidepressant group and warrant further mention. In October of 2004, the US Food and Drug Administration issued a black-box warning for all antidepressant drugs, having found that they were associated with increased suicidal thinking and behavior in children and adolescents (T. E. Hammad, 2004; R. A. Friedman, 2014). The results of the FDA analysis, published in JAMA Psychiatry two years later, found a doubling of risk of suicidality across all drug indications (T. A. Hammad, Laughren, and Racoosin, 2006). Children and adolescents taking paroxetine were found to experience significantly higher rates of suicidal ideation than clinical trial participants taking an inert placebo (Apter et al., 2006; FDA). Hammad and colleagues (2006) found that in 24 RCTs of ADs, consisting of 4582 pediatric subjects, the suicide attempt rate increased among drug-treated patients, and that 1% to 3% of those patients would be at risk of suicidality induced by ADs (Breggin, 2008). These findings were especially

worrisome given the fact that such trials go to great lengths to exclude participants whose histories include suicidal thinking and behavior; to the extent that RCTs, when conducted rigorously, *can* say something about causal effects, this made the case for ADs' potential danger that much stronger. The FDA warning may have contributed to the relative paucity of antidepressant safety studies in children and teens since that time, especially studies dealing with primarily physiological reactions to the drugs.

While few empirical studies exist comparing antidepressant ADRs in minors and adults, reactions may occur more frequently in young people. Safer and Zito (2006) compared the frequency of commonly-reported AEs of SSRI antidepressants in children, adolescents, and adults in an analysis of published, double-blind RCTs of SSRIs that separated findings by age group. They found that, in the case of activation-related AEs, rates were consistently higher for children (6-12 years old) than for adolescents (12-18 years old): they ranged from 8% to 17% for children in RCT active drug groups (mean: 10.7%) but ranged from 2-3% for teens in the same groups (mean placebo rates for children and teens were 3.4% and 1.0%, respectively). In comparison studies of adults, activation-related AEs were almost never mentioned.

1.3.3.3 Antipsychotics

Antipsychotic drugs, originally labeled neuroleptics, were in large part responsible for the drug revolution in psychiatry after their discovery in the 1950's. After decades of widespread use of the so-called first-generation or "typical" antipsychotics, knowledge of the high prevalence of their debilitating effects, primarily neurological, became widespread. In the 1990's, pharmaceutical companies introduced a new wave

of these drugs: second-generation or "atypical" antipsychotics. Drug manufacturers, along with clinicians and researchers, touted the new drugs' reduced rates of extrapyramidal symptoms (e.g. parkinsonism) and greater effectiveness. As a result, sales and prescription rates of atypicals quickly outpaced that of typical APs (Alexander, Gallagher, Mascola, Moloney, and Stafford, 2011). But it did not take long for further research to cast doubt on the new drugs' effectiveness and to reveal different but equally concerning rates of serious adverse events (Dolder, Lacro, Dunn, and Jeste, 2002; Gardner, Baldessarini, and Waraich, 2005). In particular, atypical antipsychotic drugs pose a much higher risk of metabolic ADRs (e.g. weight gain, diabetes), cardiovascular events, and, in the case of older adults with dementia, a somewhat higher risk of death, than their first-generation counterparts.

With the increase in AP prescription in pediatric populations in the late 1990s and early 2000s, as well as the small evidence base for using the drugs in children, several investigators sought to assess their adverse event profiles (Cheng-Shannon, McGough, Pataki, and McCracken, 2004). Cheng-Shannon and colleagues (2004) reviewed 176 reports of antipsychotic use in pediatric settings for evidence of efficacy and safety, primarily focusing on the so-called second-generation antipsychotics (SGAs). The authors summarized the frequency of adverse events in children; the most common AEs were fatigue and sedation; cardiovascular events like orthostatic hypotension and tachycardia; increased appetite and resulting weight gain; and extrapyramidal symptoms (383). They also found the common view that SGAs have less potential for long-term side effects to be incorrect, and that the drugs appear to be associated with many of the same adverse effects in children as older neuroleptic drugs (387). Moreover, SGAs appeared to be associated with metabolic effects not seen at all in older antipsychotics.

In the last two decades, antipsychotic-induced metabolic effects may be the most thoroughly-studied form of iatrogenic harm for this drug class and population. The introduction of the so-called atypical antipsychotics (e.g. risperidone, clozapine, olanzapine, aripiprazole) in the late 1990's and early 2000's came with a raft of claims of superiority over older neuroleptics with respect to side effects and adverse events; after widespread realization of the high risks of drug-induced movement disorders (e.g. parkinsonism, tardive dyskinesia) with those older drugs, manufacturers and clinicians were eager for pharmacological treatments that did not lead to such effects and, by extension, to the lower-than-desired rates of adherence for those drugs. Since that time, however, a peculiar irony has arisen in the drug safety literature, as evidence indicates that the newer formulations of these drugs carry with them a higher risk of metabolic and cardiovascular side effects than drugs such as chlorpromazine, discovered in 1950 (Correll et al., 2006). Two 2008 studies found that children in South Carolina Medicaid (n=4140) treated with 1 of 7 antipsychotic drugs had higher odds of being obese (Odds ratio = 2.13), having Type 2 diabetes (OR = 3.23), cardiovascular conditions (OR = 2.70), and hypotension (OR = 1.64; Jerrell and McIntyre, 2008; McIntyre and Jerrell, 2008). Antipsychotic polypharmacy was association with significantly higher odds of obesity and weight gain (OR = 2.28) and dyslipidemia (elevated cholesterol or other lipids; OR = 5.26). Roy and colleagues (Roy et al., 2010), compared the metabolic effects of SGA use between Canadian youths (n= 58; mean age 13.1) and adults (n=27; mean age 38.3) and found that while both groups incurred significant increased in body weight at 3 months (10.1% and 12.1%) and 6 months (11.8% and 13.1%), youths did not incur significant changes in blood lipids, while the adults did.

Overall, the claims made on behalf of "atypical" or "second-generation" APs (and

against "typical" or older APs), however, have not withstood empirical scrutiny; at best, a choice for an atypical drug over a "typical" one is a choice between a risk of one group of side effects (e.g. movement disorders) and another (e.g. metabolic and cardiovascular effects). As a class, antipsychotics seem to pose a higher risk of ADRs in children than in adults, and a full account of these drugs' safety is still lacking (Amor, 2012).

1.3.3.4 Benzodiazepines and other anxiolytics

Much of the literature on benzodiazepine-related ADRs in children is not about psychiatric effects. Database searches of terms related to benzodiazepines (BZDs), children, and synonyms of "adverse drug reactions" revealed a number of studies of BZDs in children during the course of anesthesia, a medical specialty in which these compounds have a long history, but little in the way of mental health-related research. The drugs are praised for their short-term anxiolytic, hypnotic, and anticonvulsant effects, but less specific use - particularly in healthy individuals experiencing the stresses of life - can be inappropriate and dangerous (Ashton, 2005; Aronson, 2006; Aronson, 2015). A large proportion of known side effects of benzodiazepines such as alprazolam (Xanax) are neurological and psychiatric; cognitive impairment, dependence, and withdrawal symptoms and syndromes are examples (Yaster, Kost-Byerly, Berde, and Billet, 1996; Ashton, 2005). There is particular concern about the disinhibiting effects of benzodiazepines, which may enable reckless or impulsive behavior such as self-harm and suicide (Kandemir, Yumru, Kul, and Kandemir, 2008). Common neurological ADRs include confusion, dysarthria (unclear speech), lack of coordination, and memory impairment occur in between 10% to 40%, and

often together (Micromedex, 2019). Other physiological reactions include decreased or increased appetite, weight gain, constipation, and reduced libido are also common, ranging in incidence from 8% to 33%.

1.3.3.5 Mood stabilizers

Like other major classes of prescribed psychotropic drug, the name "mood stabilizers" is as much a linguistic convenience as it is an accurate description of the effect of a group of chemical compounds on psychiatric diagnoses characterized by intense changes in mood, like bipolar disorder. It comprises several anticonvulsant or antiepileptic drugs, as well as the chemical element lithium. Some antipsychotic drugs are described as having similar effects and are thus occasionally described and prescribed as mood stabilizers, but in this analysis I will exclude them from this category.

Lithium's safety profile varies across physiological systems, with mild and severe endocrine, gastrointestinal, urinary/renal, and neurological ADRs. Unlike most other prescribed psychotropics, which have relatively few documented renal ADRs, lithium's potential effects on the kidneys are varied in number and severity (Gitlin, 1999). Nephrotoxicity due to lithium use is common and in most cases benign, but some users develop chronic renal diseases such as tubulointerstitial nephropathy, which causes kidney function to gradually deteriorate over time; the risk of serious kidney damage increases with duration of use (Hansen et al., 1979; Markowitz et al., 2000).

Anti-seizure drugs such as valproate (Depakote) and lamotrigine (Lamictal) have a different safety profile than lithium's, with a greater number of known mild and

serious ADRs overall. "Mild" reactions are fairly common, with up to half of users experiencing nausea, a quarter experiencing abdominal pain or diarrhea, and approximately one tenth experiencing loss of appetite and indigestion (Micromedex, 2019). Sensory systems such as vision are commonly affected as well, with blurred vision, diplopia (double vision), and amblyopia ("lazy eye") occuring in approximately 15% of users of valproate. Serious ADRs in one physiological system can lead to similarly serious effects on other systems; endocrine reactions such as hyperammonemia - an excess of ammonia in the blood - can cause a potentially fatal form of encephalopathy, or generalized brain dysfunction (Segura-Bruna, Rodriguez-Campello, Puente, and Roquer, 2006; Micromedex, 2019).

1.4 Limited evidence to recommend use of many prescribed psychotropics in minors

Despite increasing rates and duration of prescription in the last three decades, evidence of effectiveness for short- or long-term psychiatric drug treatment in young children is limited. The precise mechanisms of action of many, if not most, prescribed psychotropics remain unclear to researchers, complicating the picture (Inglis et al., 2016). Researchers have identified a gap between what is known about treatment for pediatric mental health diagnoses and the treatment practices of the community (Egger, 2010; Olfson, Crystal, Huang, and Gerhard, 2010; Bachmann, Lempp, Glaeske, and Hoffmann, 2014).

Cheng-Shannon et al. (2014) found that there was limited evidence to support most of the use of APs in children. Witek, Rojas, Alonso, Minami, and Silva (2005) reviewed benzodiazepine use in children and found that it is not clear what compels

physicians to prescribe them to children in increasing numbers given the limited evidence base for doing so. They found few well-powered and methodologically rigorous clinical trials of BZDs in minors, and concluded that there was no compelling evidence for using BZDs as first-line treatment for any anxiety symptoms in children (p. 294).

Newman et al. (2004) stated that of 15 controlled trials of antidepressant treatment in depressed children then in the possession of the FDA, only 3 showed efficacy. He remarked that it is easy to see why so many clinicians cite their clinical experience as a reason to trust the efficacy of ADs in children, as many did as the controversy over AD-induced suicidality came to a head in the mid-2000's: at the time, they had no way of knowing that more than 85% of the benefit they observed in children would also have occurred with placebo (1597).

In their epidemiological profile of the prevalence of ADHD diagnoses and treatment types among US children, Visser and colleagues (Visser et al., 2014) argued that while the effectiveness of medication on ADHD symptoms had probably contributed to increased prevalence of psychopharmacological interventions for the condition in the years 2003 to 2011, no one fully understands the long-term impact of taking ADHD medication over time (9). Some commentators lament the general dearth of truly long-term (>5 years) controlled studies of efficacy and safety of prescribed psychotropics (Chouinard et al., 2017).

If relatively few studies have looked at the long-term safety of various prescribed psychotropic drugs and drug classes, few epidemiologic studies have investigated the long-term effects of such drugs on children's broader (read: non-behavioral) health. Overall, there is an insufficient amount of knowledge and data about the safety profile

of each major class of prescribed psychotropic drugs as they are used in children.

1.4.1 Lack of effectiveness *and* safety evidence

There is a similar dearth of evidence for the *safety* of prescribed psychotropics in children, especially over the long term (Jensen et al., 1999). For example, while much is known about the side-effects of antidepressant drugs, the implications and complications of changes in physiological functioning are unclear (Aronson, 2006, p. 3492; Aronson, 2015). In general, the regulatory requirements for bringing a drug to the market require assessments of drug safety, but these do not take place for courses of time that are comparable to the real-world use of many drugs. Such safety assessments are based on randomized controlled trials, much like measurements of their efficacy. However, relying on such trials for evaluations of long-term drug safety in children carries a number of risks, and is inadequate given the known potential harms of psychotropic drugs.

1.4.1.1 RCTs in drug development and FDA regulatory framework

The US Food and Drug Administration (FDA) requires that manufacturers of drugs conduct *preclinical* and *clinical* trials of drugs to demonstrate effectiveness and safety before permitting a drug to be sold to the public (Friedman, Furberg, & DeMets, 2010). These trials are nominally conducted in successive phases; each phase builds on the previous phase by, for example, increasing the sample size of a study or moving from very small, "sub-therapeutic doses" to the dose intended to be sold to the public. Trials in the preclinical phase can be *in vitro* - conducted solely at the chemical level - or *in vivo* - conducted on animals. The purpose of preclinical

research is largely safety-related, oriented to discovering toxic or fatal doses for any human trials that may follow and determining if a new compound has serious safety issues (e.g. lethality).

Early *clinical* trials typically lack a therapeutic goal (e.g. effectiveness) and focus instead on factors such as tolerability and pharmacokinetic effects (e.g. how long a drug remains in the body). In later trials, primarily in Phase III, larger numbers of human beings participate - between a few hundred to a few thousand. These trials are what regulatory approval and subsequent statements about efficacy are often based on (in the early life of a drug, at least), since they involve the largest sample sizes seen in the pre-approval drug development cycle, employ a control group, and randomize subjects to treatment groups. Crucially, these human participants meet criteria for the particular mental disorder (usually specified by *DSM* criteria) that the drug maker is seeking approval for. These aspects form the essential parts of the classic RCT, and are what is used to justify its position as the "gold standard" of empirical evidence in empirical research. Regulatory approval approval for the treatment of the condition in the age group of Phase III trials may be obtained for a drug after phase III trials.

Phase IV trials may be used to evaluate a drug's safety after a regulatory body has approved it for sale to the public, and several thousand subjects are recommended to be involved (L. M. Friedman, Furberg, DeMets, Reboussin, Granger, et al., 2010; Zhang et al., 2016; FDA, 2017). These trials are "where the rubber meets the road" for a new drug: the first time the drug is tested in the real world (Suvarna, 2010).

1.4.1.2 Methodological and politico-economic problems with empirical studies for evaluating drug safety

Despite its efforts to evaluate the effectiveness and safety of newly-approved drugs, the current regulatory environment suffers from two problems that may lead to potentially harmful drug reactions being overlooked until well after approval and wide use.

The first is methodological, and concerns the inadequacy of empirical studies as currently conducted to give an complete account of drug safety. This critique applies equally to randomized controlled trials (RCT) in pre-approval phases for assessing drug safety, as well as to post-approval studies with both randomized and observational designs.

Pre-approval RCTs are largely characterized by insufficient sample sizes and short duration (Inglis et al., 2016; Meador and Loring, 2016; Chen et al., 2014). While safety is a consideration in phase III clinical trials for regulatory approval, these RCTs are primarily focused on effectiveness. A new drug's final regulatory approval is likely to lack assessment for long-term safety, and to be based on nearer-term outcomes even for compounds like those seen in psychiatry, which are taken for frequently chronic conditions (L. M. Friedman et al., 2010). Such trials are infrequently powered to be able to detect drug effects with rarer incidences than 1 to 6 per 1000, consisting as they do of between 500 and 3000 people in many cases (Strom and Kimmel, 2006; Suvarna, 2010).

Randomized clinical trials suffer from other problems, as well. Design variations on the RCT, especially those featuring intentional discontinuations of drugs, may draw invalid conclusions about both safety and effectiveness (Greenhouse, Stangl,

Kupfer, and Prien, 1991; Hazell, 2018; Cohen and Recalt, 2019; Recalt and Cohen, 2019). Other methodological problems threaten safety assessment: patients dropping out of studies due to ADRs mean that the actual number of reactions, both serious and not serious, may be much higher than reported. Other studies only report ADRs if their incidence rose above a certain threshold (2%-5%), omitting rare and potentially serious events (Aagaard and Hansen, 2011). This is closely related to the issue of statistical power to detect a true effect: if a prescribed psychotropic drug becomes a high-selling, "blockbuster" medication, as has frequently occurred in the past three decades, ADRs that are extremely rare even in a large RCT may afflict thousands or tens of thousands of real-world users, leading to increased morbidity and costs. Others critique this very critique, arguing that the idea that small RCTs can miss rare or delayed drug reactions (a now-common "mantra") is misplaced, as what are often alleged to be "rare events" are in fact not rare at all. In Healy's (2021) view, the practice of medicine – healing human beings, in other words – necessarily involves the consideration of dozens of variables and wide heterogeneity of responses to treatment across individual people. To conduct an RCT, by contrast, is to pay attention to just one of dozens or hundreds of possible things that take place when a drug enters the body. Healy cites early SSRI antidepressant trial data showing that sexual side effects occurred in less than 5% of people using these drugs, while more recent investigations suggest that these reactions occur in the vast majority of users, often within hours of first using them. This occurred, Healy writes, because investigators focused on the mood effects of these drugs to the exclusion of others. Likening this to a kind of hypnosis, Healy argues that the RCT does not fortify good clinical care; it weakens it.

The nature of ADRs, and drug harm in general, makes many empirical studies

inadequate. Aronson (2006) argues that no matter how rigorous, these trials are poor at providing evidence about harms because benefits are usually single, while harms often occur together, making them more difficult to isolate and study. Because of this, the probability of any single form of harm is usually smaller than the probability of benefit and as a result easily undetected in an RCT. In real-world settings, though, the occurrence in one patient of a handful of individually mild ADRs may affect the cost-benefit analysis of taking the drug: a headache, by itself, may be an acceptable bother for an otherwise beneficial medication, but a trio of headache with mild but frequent nausea and upset stomach may lead to a patient ceasing treatment.

As a result, an accurate cost-benefit analysis may only be possible when the collective real-world experience of researchers, clinicians, and above all patients accrues to a certain level, which may take many years. Suvarna (2010), writing about clinical trials and drug development, argues that the notion - popular among the public and clinicians alike - that drugs are so thoroughly studied and vetted that everything is known about them by the time they are released to the public is incorrect. It is only after hundreds of thousands of patients have been exposed through commercial sales of a drug that its safety profile comes into sharp focus. Until then, the generalizability of comparatively small RCTs to make valid inferences about drug safety, both before and after drug approval, is limited.

The second problem is regulatory, and is about the way in which the political and economic structure of drug development, regulation, and research in the United States today is dominated by pharmaceutical firms, with agencies like the FDA comparatively weakened and stretched thin. Financial relationships between industry, researchers, and academic institutions is pervasive, and industry's share of overall investment in biomedical research has increased while the federal government's share

has decreased (Bekelman, Li, and Gross, 2003). Analyses of such entanglements shows suggests that they have profound consequences for how biomedical research is conducted and how new drug products impact those who take them. Among these are that industry-sponsored research tends to draw conclusions that are favorable to industry products and minimize conclusions that cast doubt on product safety (Bekelman et al., 2003; Lexchin, Bero, Djulbegovic, and Clark, 2003; Vandenbroucke, 2008); that the vast majority of RCTs that conduct "head-to-head" comparisons of different drugs are industry-sponsored and employ methodological variations more likely to result in a favorable result for the sponsoring firm's product (Lathyris, Patsopoulos, Salanti, and Ioannidis, 2010; Flacco et al., 2015); that industry-sponsored research is less likely to be published if findings are not favorable to industry products (Lexchin et al., 2003); that the inclusion of unpublished industry trials in analyses of drug effectiveness may show that a drug previously considered effective actually was not (Whittington et al., 2004); and that the resulting institutional corruption of the regulatory and healthcare systems have resulted in a largely hidden epidemic of drug-induced adverse events (Light, Lexchin, and Darrow, 2013).

1.4.2 Meager evidence for psychotropic use in the context of off-label prescription

The meager case for much psychotropic drug use in pediatric context is further hampered in the context of increasing rates of off-label prescription, which rests on less extensive and rigorous empirical evidentiary grounds. The off-label prescription of drugs - the use of a drug to treat a condition for which it has not been approved by the FDA - is a double-edged sword: on the one hand, it allows physicians wide

latitude to prescribe treatments they believe will help patients, an especially useful ability in the case of rare or neglected diseases. On the other hand, off-label prescription has been associated with increased risk of adverse drug events in pediatric populations (Horen, Montastruc, and Lapeyre-Mestre, 2002; Mason, Pirmohamed, and Nunn, 2012; Bellis, Kirkham, Nunn, and Pirmohamed, 2014).

A 2011 review of off-label antipsychotic prescription using US prescription data found that AP use for indications without FDA approval increased from 4.4 million visits in 1995 to 9 million in 2008 for all age groups, at a cost of $6.0 billion. (Alexander et al., 2011).

In 2012, Czaja and Valuck sought to assess the extent to which off-label prescription of ADs occurs for US children, as well as assess the level of evidence supporting such off-label use. Using IMS Health medical and pharmacy claims, they created drug-diagnosis pairs for 290,816 minors and young adults aged 5 to 24 and evaluated whether the drug had been prescribed for an FDA-approved indication or what instead given off-label. For each drug prescription their analyses assessed as off-label, they evaluated that combination's level of evidence using proprietary Thomson-Reuters DRUGDEX efficacy ratings. They found that over 70% of first prescriptions of antidepressants were considered off-label, and of these, 80% of prescriptions in 9-12 year-olds and 90% in 5-8 year-olds had, at best, inconclusive evidence to support them.

1.4.3 Debate in the medical community

Debate continues in the medical community and the general public about the use of prescribed psychotropic drugs in children. Whether children should be taking

these drugs in the first place is itself a deeply felt issue among parents, doctors, and therapists (Dubicka and Goodyer, 2005; Herxheimer and Mintzes, 2004). Hazell (2018) asked whether it is clinically defensible to treat children long-term (for more than six months) with second-generation antipsychotics (SGAs), and reviewed the empirical evidence for their use in a number of indications in pediatric psychiatry. He argues that long-term treatment with a therapeutic agent is justified if there is either sustained benefit with minimal adverse effects or if the hazards of treatment are outweighed by the hazards of untreated illness and no safer effective alternative exists (658). In the case of SGAs, the hazards to human physiology, especially over the long term, are high enough that the use of these drugs cannot rest on the first criterion; a favorable risk/benefit profile must instead be the test of defensibility of SGAs. He concluded that longer-term SGA use in children with schizophrenia and bipolar disorders pass this defensibility test, while their use in irritable or aggressive autistic children may or may not be justified. SGA use in children diagnosed with oppositional defiant disorder or conduct disorder is not justified, and their use in children with anorexia nervosa and tic disorder lacks sufficient evidence (658). But Hazell also concludes that much of the empirical evidence for these conclusions has a moderate to high risk of bias, and that it is rare for high-quality research to demonstrate favorable risk/benefit ratios for SGAs in children, compared to low-quality research (658). He suggests that the main question for clinicians and researchers to answer should not be how to limit the risks of long-term SGA treatment (i.e. adverse events), but whether such treatment is necessary at all.

1.4.4 Concerns about long-term effects and limited empirical research

The medical reference and research literatures document some of the potential long-term sequelae of drugs. The use of benzodiazepines (e.g. alprazolam / Xanax), antidepressants, and antipsychotics in the elderly is known to increase the risk of falls and traffic accidents due to their sedative effects (Barbone et al., 1998; Hartikainen, Lönnroos, and Louhivuori, 2007; Smink, Egberts, Lusthof, Uges, and De Gier, 2010; van Strien, Koek, van Marum, and Emmelot-Vonk, 2013). Hypotension caused by tricyclic antidepressants (TCAs) may also lead to falls (Aronson, 2006, p. 3492). Hyposalivation from antidepressant use can lead to dental disease (Remick, 1988). Long-term adverse cognitive impacts are suspected in children who take antiepileptic drugs (Meador and Loring, 2016). Certain antiepileptic drugs, used in psychiatric contexts as "mood stabilizers", have been shown to be associated with long-term cardiovascular sequelae (e.g. atherosclerosis; Cheng, Prasad, and Rieder, 2010).

At the same time, admissions of the meager state of this knowledge, paired with urgent calls for investigation into the long-term effects of prescribed psychotropics, have continually appeared in the research literature and in other sources, leaving the overall impression that long-term safety profiles of most prescribed psychotropic drugs are *at best incomplete and in some cases non-existent* (Cassano and Fava, 2004; Cheng et al., 2010; Graham et al., 2011; Almandil and Wong, 2011; Amor, 2012; Margari et al., 2013). In their 2004 review of the efficacy and safety of AP use in children, Cheng-Shannon et al. (2004) cite the absence of long-term safety studies as a greater concern than their apparent lack of efficacy pediatric settings; as a result, virtually all AP use in pediatric settings is "off-label" (387). Czaja and Valuck (2012) identified at best "inconclusive" evidence for over 80% of off-label

antidepressant prescription for young children in the United States between 1997 and 2009. Meador and Loring (2016), in a review of the developmental effects of antiepileptic drugs (used as mood stabilizers in mental health contexts), cite the potential for such drugs to adversely affect long-term brain maturation.

1.5 Accounting for prescription rates in light of limited evidence.

A number of reasons have been put forth for why millions of Americans now take drugs for disorders that were considered extremely rare as little as three decades ago, but they can be broadly divided into conventional and critical views.

The conventional view is one of revolutionary progress in our scientific understanding of the brain since the middle of the 20th century, aided in large part by the serendipitous discovery and sophisticated further development of psychiatric medication as well as valid and reliable diagnostic categories for mental disorders (Lieberman and Ogas, 2015). Psychiatric disorders account for a large proportion of overall morbidity and health-related disability in human beings, being associated with poor overall physical health and poor long-term outcomes (e.g. life expectancy; Mathers and Loncar, 2006; Gøtzsche, Young, and Crace, 2015). The medications prescribed to treat them are impressively effective, superior to placebo, prevent recurrence of disorder, and safe (Nutt, Goodwin, Bhugra, Fazel, and Lawrie, 2014. The influence of the pharmaceutical industry on psychiatric research should not necessarily be of concern, either, and concerns about such influence implicitly stem from extreme points of view. Scientific research in mental health should be judged on the basis of the rigor of a given study, not on the affiliations of investigators, corporate or

otherwise (Tohen, 2007). On the conventional view, the rise in prescription rates of psychiatric medication reflects our improved ability to detect and treat mental disorders, which until now have been under-reported and under-treated.

I call this point of view "conventional" because those who hold it are not merely a plurality or a majority in mental health research and practice, but are those who hold the most power over research agendas, funding, policy, and practice. For historical reasons related both to the discovery of antipsychotic drugs in the mid-twentieth century and changes in leadership within the mental health professions, primarily psychiatry, the predominant scientific and clinical approaches of past fifty years in mental health can be characterized by the assumption that mental illness and disorder are physiological illnesses like any other. Before this paradigm shift, clinicians thought of their patients in terms of the way they were with other people, and sought to construct complex accounts of patients' lives. Here, the boundary between health and illness was not clear-cut. With the rise of biological orthodoxy, clinicians learned to memorize patterns, to think in terms of discrete disease entities, and see their patients in terms of illness (Luhrmann and Uhlmann, 2001). 'Conventional', then, refers to a now mainstream view on both the nature of the sorts of suffering that the mental health professions aim to alleviate, as well as the most effective ways to do so.

After decades at the intellectual and fiscal helms of mental health, some who hold the conventional view have begun to see cause for alarm in soaring rates of psychotropic prescription in children. Rapoport (2013), who in another 2013 paper cited in this dissertation argued that concerns about rates of drug prescription in children were overblown, lauded the historically vibrant field of pediatric psychopharmacology, in particular the stimulant and antidepressant drug classes, for

bringing much-needed help to "treatment-refractory" patients and inspiring generations of researchers. At the same time, though, she conceded the precarious state of the field at the beginning of the 21st century, in which an over-acceptance of drug treatment in children, as well as the unleashing of market forces and managed care upon the US healthcare system, led to a "reductionist biology" that suffuses the mental health professions (121). Like other commentators, she acknowledged a growing awareness of the long-term adverse effects of medications and the inadequacy of long-term drug surveillance efforts to effectively shed light on them.

These doubts are increasingly public and are being aired in forums with wide reach. Pennap et al. (2018) recently summarized the state of psychotropic use in children in *JAMA Pediatrics*:

> The increase in the prevalence of treated psychiatric diagnoses and the use of psychotropic medications in pediatric populations in the United States has generated public health concerns, particularly regarding the expanded use of antipsychotics for the behavioral management of children. *Most pediatric psychotropic medication use (67%) is not approved by the US Food and Drug Administration and is therefore prescribed off-label, whereby the evidence for the benefits is not available to balance the risk of potential harm.* The differential use of psychotropic medications among poor, near-poor, and foster care children, who are more likely than privately insured youth to receive psychotropic medications, raises social and ethical concerns. *Although there is evidence to support the efficacy of stimulants in the management of attention-deficit/hyperactivity disorder (ADHD) and antipsychotics for aggression in autism spectrum disorders*

(ASD), concerns continue unabated about off-label use and the short- and long-term neurobiological effects of early exposure to complex combinations of medications in community populations. [Emphasis added.]

That the entire case for the use of psychotropic medications in children can be summed up like this in one of the world's leading pediatric journals is surprising at best and damning at worst. For those who have critiqued the assumptions of conventional views, it is also something of a vindication because it points directly to their own arguments. This critical view holds that modern mental health research and practice rests on dangerously uncertain scientific ground, having overstated the case for both the diagnosis and treatment of mental disorders. The boom in psychotropic prescriptions in children and adults in the US and much of the developed world is not the result of the drugs being validly shown to be effective, nor is it because of discoveries in the underlying causes of mental disorders or advances in diagnosis (Davies, 2017). Instead, prescription growth rests on uncritically accepted claims about prescribed psychotropic drugs driven by the confluence of cultural, economic, and ideological forces (Kirk, Gomory, and Cohen, 2013). Among these is the influence of pharmaceutical companies, who for a number of decades have operated in an increasingly permissive regulatory environment that allows them a great deal of direct influence over prescribers and consumers (Donohue and Berndt, 2004; Donohue, Berndt, Rosenthal, Epstein, and Frank, 2004; Moncrieff, 2007). Beholden primarily to shareholders, who demand that firms maximize profits, pharmaceutical companies have learned that large markets can become accessible to their psychiatric products by joining in efforts to convince potential customers and anyone with influence over them (e.g. prescribers) that emotional and behavioral problems are caused by biochemical abnormalities - "chemical imbalances" being one of the most

common phrasings to enter the zeitgeist, but far from the only one (Timimi, 2008).

In the critical view, this has particularly pernicious effects in the treatment of such problems in children. Kids are surrounded by more potential sources of influence and authority than adults - not just clinicians, friends, or peers, as might be the case with people over 18, but by teachers and parents, too. Timimi (2008; 2017) argues that child psychiatry is especially vulnerable to industry influence: without objective diagnostic testing for any pediatric mental disorder, the boundary between normality and mental illness can be more easily manipulated; diagnosis and assessment in pediatric mental health are additionally dependent on the reports of various adults in caring or influential relationships with children, increasing the avenues for influence over decision-making in a child's healthcare.

To be sure, proponents of the critical view do not lay blame solely at the feet of "big pharma"; wide acknowledgment exists that it is clinicians, parents, and ultimately the public itself who demand pharmacological solutions to issues of psychological distress and thus interplay closely with corporate behavior, especially in the US. But pharmaceutical company influence ties many sources of demand together and, if successful with a given drug, can feed further demand back into the loop.

Clinicians, parents, and potential users are not alone; researchers are also important targets of industry influence (Moncrieff, 2007). Indeed, that "evidence-based" claims of the effectiveness of psychiatric medication rest on shoddy science is the other pillar of the critical view of the boom in psychotropic prescriptions for US adults and children (Kirk et al., 2013; Davies, 2017). Proponents of the critical view reassess those claims and make a broad counter-claim: the drugs are not only not meaningfully different from placebo in clinical measures, but they hold potential risks

that other treatments (and no treatment) don't have. Overall, the critical view holds that prescribed psychotropic drugs probably cause more harm than good (Gøtzsche, 2015; Gøtzsche et al., 2015).

1.6 Social welfare impact and justification

Psychotropic drugs potentially affect all human physiological systems. Even when they have the effect desired by a user or their caregivers, they have the potential to affect aspects of individual and social functioning beyond the strictly medical. Conceiving of human health and functioning within a biopsychosocial framework means acknowledging that when thinking about disease and dysfunction, causality is highly complex, with multiple causes and influences feeding into and out of a given event (Borrell-Carrió, Suchman, and Epstein, 2004). Prescribed psychotropics do not exist by themselves, acting only on their users' central nervous systems, but directly and indirectly affect the rest of human physiology and psychological and social functioning.

1.6.1 Social impact of drugs on children and adolescents

Choudhury, McKinney, and Kirmayer (2015) explored how prescribed psychotropic drugs function as vehicles for socialization in the lives of adolescents who take them (n=14), transforming the ways in which they understand, experience, and manage their selves. They found that using psychiatric medications enrolls teens into discourses of choice, responsibility, and risk management - all realms of adulthood - while at the same time denying them the ability to freely choose, to take responsibility, and to manage their own risk, because after all, they are "still children". This

paradox is compounded by another one: teens show adult "responsibility" and "autonomy" precisely by complying with adult demands to conform with a therapeutic regime, all of which make selfhood even more difficult to parse at an age where doing so is already a tall order.

Indeed, questions of selfhood are at the core of the literature on the social welfare impact of prescribed psychotropic drugs on young people. In a memoir of her childhood and adolescent use of antidepressant drugs, Sharpe (2012) writes that the usual justifications for psychotropic medication use among adults - that antidepressants restore a "true self" distorted and hidden by depressive illness - are not available to young people, who have not yet found (or made) those true selves. For her, taking a medication that might frustrate that search was a dizzying and scary prospect that led to a different sort of angst: are one's thoughts and feelings while on Zoloft really one's own, or are they the drug talking?

In a society like ours, in which tremendous pressures are exerted on young people to live up to their "full potential" in a number of domains (academic, social, athletic, religious), psychiatric medications also function not as pharmacological treatments for mental illness, but as a tool for easing some of this burden. Sharpe cites Davis (2009), who identifies the ideal human beings society asks children and teens to be as "the achieving self": someone who is proactive, aggressive, and impressive, while also being easy-going, non-defensive, flexible, resilient, and resourceful (256).

1.6.2 Social workers' role in psychopharmacology & drug safety

Tomes argued (2008) that the field of mental health - currently constituted by psychiatry, psychology, social work, and nursing - is among the most interdisciplinary.

In the first place, the nature of the problems that mental health professionals aim to help treat and overcome is highly heterogeneous, being comprised of psychological, social, and biological factors, each of which lends itself to an array of approaches in assessment, treatment, and empirical investigation (657). As a result, the notion of a mental health "team", operating in a specific treatment environment (e.g. an outpatient clinic) and of which social workers form a part, has been present since the growth of the mental health field at the beginning of the 20th century.

As the largest single group of mental health professionals in the US, social workers are intimately involved with drug effects despite their being unable to prescribe the drugs. Hughes and Cohen (2010) reviewed the practice of safety monitoring in FDA-monitored clinical trials of psychotropic drugs and concluded that the safety information available to mental health professionals about these drugs, based as it is largely on information gleaned from these trials, prohibits clinicians from building a realistic portrait of potential and expected drug harms. Because of the profession's major involvement with medicated clients, they urge social workers to move beyond medication management tasks in their work[5] and engage substantively with drug safety by using ADR checklists with clients and sharing results with them, their families, and the treatment teams in which social workers frequently operate. By doing so, social workers can leverage their large numbers in allowing comprehensive accounts of clients' experiences with psychotropic drugs to become part of the official account - "what is known" - about psychotropic benefits and harms.

[5]Tasks which often emphasize compliance with a medication regimen.

1.6.3 Economic impact of prescribed psychotropic drug use

As overall rates of psychotropic prescription rose in the 1990s and 2000s, the socioeconomic profile of the children who receive them has shifted. Early adopters of stimulant treatment in children, for example, tended to be wealthier and whiter (CITE); today, more poor and middle-class children, as well as minorities, take a prescribed psychotropic drug than ever before. This has potentially strong implications for drug safety, as more privileged children belong to families who are better able to deal with adverse events because of greater resources.

Even when drugs are not found to be associated with adverse physiological or mental outcomes, they are capable of exacerbating problems caused by poverty. [ACE study $\rightarrow$ adverse experiences]

1.6.4 Social welfare impact and justification: summary

The use of prescribed psychotropic drugs in children is a deeply felt issue for many members of the public, and as such is another reason - in addition to the scientific argument made above - for why we need more empirical evidence about psychotropic drug safety.

Because of this, social workers in both research and clinical practice have a strong stake in documenting the possible adverse consequences of prescribed psychotropic drug use. From a social welfare perspective, the central justification for this study is its alignment with the fundamental goals of the profession, namely the reduction of harm and the increase of well-being in the people social workers serve, especially among the poor and disadvantaged. In the case of psychotropic drugs, reducing potential harm cannot fully take place until such harms have been systematically

and rigorously understood. In light of the inadequacies of the current regulatory and economic environment to fully understand the prevalence and longer-term effects of psychotropic ADRs, there is an urgent need for studies like this one to begin to do so.

It is thus essential that researchers treat the issue with the gravity it deserves and develop a deeper understanding of psychiatric drug safety in children.

CHAPTER 2

Review of the long-term adverse drug reaction literature

2.1 Long-term physiological health effects of prescribed psychotropics in children

2.1.1 Search strategy & overview of results

To assess the state of the published empirical research literature on the long-term physiological effects of prescribed psychotropics in children, I searched PsycINFO, Embase, PubMed, the Cochrane Library, Google Scholar, and bibliographical sources for studies that investigated the topic, either empirically (e.g. a controlled trial) or using secondary data.

Table 2.1 summarizes the categories of keyword included in searches in each database. Eligibility criteria were: the study of at least one of 96 prescribed psychotropic drugs, regardless of indication; study outcomes must include at least one physiological outcome (i.e. no studies of solely psychiatric ADRs); durations of drug use in participants described by investigators as "long-term"; human participants. Searches were for the entire literature across all available years in each database, and all languages as well (in cases where studies not written in English had English

abstracts). Individual search strings were modified according to each database's particular syntax. In general, searches were limited to article titles and abstracts.

Table 2.1

Literature search keywords

Keyword Type	Examples	Keywords used (n)
Names of drugs	zaleplon, alprazolam, buspirone	111
Names of drug categories	antipsychotic, antidepressant, psychiatric medication	15
Synonyms of 'child' and 'pediatric'	pediatric, child, prepubertal, early life, kid	13
Names of physiological systems	urinary, hematologic, cardiovascular, musculoskeletal	47
Synonyms of 'long-term' and 'long-term safety'	adverse event, side effect, adverse drug reaction, ADR, drug safety	10
Exclusion terms	mouse, mice, rat, animal model, scale, addict	5

Searching Google Scholar remains unpredictable for thorough literature searches despite progress in recent years. On one hand, Google's search algorithms can yield studies not found in other databases using far less specific search terms. On the other hand, the opacity of the underlying search process, along with a lack of features commonly found in other databases (e.g. MeSH terms), mean that a given Google Scholar search commonly yields either hundreds of thousands of hits (with a few relevant articles interspersed throughout) or less than one hundred hits with no relevant articles. Successive attempts to refine search strings in Google Scholar yielded a final search with 112 articles, with many of these either duplicates from

other databases already search or, much more commonly, not relevant.

Table 2.2

Frequency of search results by source

Source	Results	Unique relevant results
PsycINFO	41	20
Embase	89	29
PubMed	69	13
Cochrane Library	38	1
Google Scholar	112	1
Bibliographic sources	4	4
Total	353	68

Table 2.2 summarizes the results of searches in various sources, both before and after the removal of irrelevant and duplicate entries, while Table 2.3 categorizes those results by drug class and major physiological system. In all, 68 relevant articles were found. The majority of articles concerned psychostimulants and other drugs for ADHD; antipsychotics; and mood stabilizers / anti-epileptic drugs. Only one article studied antidepressants by themselves (Harel, Biro, and Tedford, 1995), and one article featured drugs prescribed to relieve anxiety or assist with sleep (Boafo et al., 2019).

2.1.1.1 Pharmacoepidemiological studies

Of the 68 results, 8 (11.7%) were similar in both content and design to the study conducted here: studies employing large secondary databases, often of entire populations, to retrospectively compare the risk of physiological adverse reactions in minors using psychotropic drugs for a long period of time with otherwise similar minors who

have not used such drugs. Because of these similarities, I consider these 8 results to be "direct hits", able to inform both the subject matter and design of this study while also pointing to where gaps may lie in those respects. Noteworthy, too, is that while the earliest of all 68 studies was published in 1977, the earliest of these direct hits 8 were published in 2008. This points, first, to the increasing availability of robust and comprehensive secondary data sources for investigating drug safety, which makes doing such studies more feasible. Second, it suggests an increasing response by researchers to the concern over the safety of psychotropics in children - after many decades of calls for such research to be done. Finally, it tracks chronologically with two other important trends: the increase in psychotropic prescription to children and adolescents in the US described in the introduction, and the increasing urgency by various stakeholders to expand the scope of drug safety research and developed countries turn ever more to prescription drugs, especially ones used for many years to treat chronic conditions, psychiatric or otherwise.

A brief summary of these studies follows.

In two studies, Jerrell and McIntyre (2008; McIntyre and Jerrell, 2008) used a large claims database to describe the odds of a broad range of ADRs in children and teens enrolled in Medicaid and prescribed at least one of 6 antipsychotic drugs. They also sought to identify any risk factors associated with these outcomes, including duration of treatment, in which "long-term" treatment was defined as greater than six months. The authors cited a particular need for head-to-head comparisons of the safety of various drugs to assess *relative* side effect profiles over the long term. Of a total population of 573,000 children and teens between 1996 and 2005, authors built a cohort of minors aged 0-17 who were prescribed an antipsychotic for the first time (n=4140). From the same population, a control cohort of randomly selected chil-

dren of the same age range but with no prescriptions for any prescribed psychotropic was created (n=4500). The investigators sought to assess the risk of developing any of several health conditions, coded as ICD diagnoses in their dataset. Because the incidence of many of these ADRs was very low, some drug reactions were grouped by physiological system (e.g. *neurological*), others into multi-system categories (e.g. *somatic, skin, musculoskeletal*, and *respiratory* conditions were collapsed into one), while others were left by themselves (e.g. *Type II diabetes mellitus*). Basic incidence and prevalence were calculated for each outcome. The odds of each ADR or ADR group were computed using multiple logistic regressions for each outcome, with exposure to each drug, as well as potential confounders like age, sex, and ethnicity, acting as covariates in each model. Each regression model was run with and without a covariate indicating whether or not a patient had long-term treatment with a given drug.

Compared with controls, the incidence and prevalence of obesity and weight gain, Type II diabetes, cardiovascular conditions, neurological and sensory conditions, and digestive / urogenital conditions were "notably" higher in children treated with antipsychotics. Neurological and sensory reactions were significantly more likely in those receiving long-term treatment compared with those taking the drugs for five months or less (OR = 1.21, 95% CI = 1.03, 1.42), an effect that was even more pronounced for younger children compared with adolescents (Jerrell and McIntyre, 2008). The odds of developing multiple adverse reactions were higher for females and for those taking multiple drugs; this latter association held in cases of concomitant (simultaneous) drug treatment as well as in the sequential use of different drugs. (Antipsychotic polypharmacy was present in 42% of the exposed cohort, and is known to be common in epidemiological studies.)

The drug-treated cohort was more likely to be diagnosed with obesity (OR = 2.13; 95% CI = 1.85, 2.50), type II diabetes (OR = 3.23, 95% CI = 4.34, 2.43), cardiovascular disorders (OR = 2.70, 95% CI = 2.27, 3.22), and hypotension (OR = 1.64, 95% CI = 1.28, 2.08), but the control cohort was more likely to have been diagnosed with dyslipidemia and hypertension (McIntyre and Jerrell, 2008).

Dalsgaard and colleagues (2011; 2014) conducted a nationwide, register-based cohort study of Danish children and teens to determine whether stimulant use, compared with non-use, was associated with cardiovascular disease in the Danish population of children born between 1990 and 1999 (n=714,258); whether such an association was present in a sub-sample of children and teens diagnosed with ADHD (n=8300); and to what extent time-on-drug and drug dose affected such associations.[1] Exposures to stimulant drugs were defined as the purchase of a drug containing amphetamine, dexamphetamine, or methylphenidate from the age of 5 onward, and lifetime histories of drug utilization were tracked for each child based on dates of prescription. Because exposure included a range of different drugs, the authors used defined daily dose (DDD) equivalents of 30mg of methylphenidate to standardize exposure. Outcomes of cardiovascular disease were defined as the child having inpatient, outpatient, or emergency room hospital contact that resulted in an ICD diagnosis corresponding to any of 11 diagnostic groups for various cardiovascular outcomes (e.g. all ICD diagnoses corresponding to "Hypertensive Disease"). Subjects were followed until the date of a cardiovascular outcome, or were censored at either death or the end of observation (12/31/2018). On average, each subject contributed 9.5 years of observation. Cox proportional hazards regression models were

[1]The 2011 paper by Dalsgaard and colleagues is a preliminary version, published as a conference abstract, of the 2014 paper.

used to model the hazard ratio (HR) of cardiovascular disease on stimulant exposure, dosage, and other covariates. Those covariates included sociodemographic variables (e.g. sex, region), cardiovascular risk factors (e.g. congenital heart disease), and other potential confounders (e.g. maternal smoking during pregnancy).

In the total population, there was an increased risk of cardiovascular disease compared with stimulant non-users (adjusted HR = 1.83; 95% CI = 1.10, 3.04). Among those diagnosed with ADHD, there was also an increased risk (adjusted HR = 2.34; 95% CI = 1.15, 4.75); diseases included arrhythmias (23%), cerebrovascular disease (9%), hypertension (8%), and ischemic heart disease (8%). A dose-response relationship was also detected: subjects ever treated with high doses of stimulants were 2.2 times more likely to have be diagnosed with a cardiovascular disease than subjects only ever treated with lower doses. Curiously, this relationship was reversed when the authors looked at stimulant dose at the time of the cardiovascular event: significantly more subjects diagnosed with ADHD and experiencing cardiovascular outcomes had reduced their dose in the previous year than those without any outcomes (57% vs 30%, respectively; χ^2=9.35, df=2, p=0.0022), and in the general population, significantly more subjects with cardiovascular outcomes had either discontinued drug treatment or reduced their dose than stimulant users without outcomes (43% vs 24%, respectively; χ^2=5.64, df=2, p=0.017). Citing potential biological mechanisms, the authors speculated that stopping drug treatment may shorten cardiac repolarization time (QT interval) or reduce heart rate variability (variation in time between heart beats; HRV), both of which have been associated with adverse cardiovascular events.

Patel (2017) sought to assess the long-term effects of pharmacotherapy on body mass index (BMI) in children and adolescents ($\leq$18) treated for bipolar disorder with atypical antipsychotics, mood stabilizers, and antidepressants (n=2,299) by compar-

ing them with bipolar diagnosed but drug-untreated youths of the same age range (n=4,544). Using an electronic medical record database (EMR), they identified minors with a new bipolar disorder diagnosis between 1995 and 2010 and followed them through time. Children were exposed to antipsychotic, mood stabilizer, and antidepressants alone, as well as various combinations of each. The authors not only confirmed prior indications in the literature that antipsychotic exposure was strongly associated with weight gain; they found that prolonged exposure of up to 12 months was associated with a continuous increase in BMI. In normal physiological development in late childhood and adolescence, child BMI typically increases by between 0.5 and 0.6 kg/m2; the authors found that their untreated bipolar children increased in BMI by 0.64 kg/m2. By contrast, the BMI of children on AP monotherapy nearly doubled the developmentally normal magnitude of BMI change (1.20 kg/m2).

Storebø and colleagues (2018) conducted a Cochrane review and meta-analysis of 260 non-randomized studies to assess the risk of serious and non-serious adverse events in children and adolescents taking methylphenidate (Ritalin) for ADHD. Comparative and non-comparative studies were included; studies using another drug besides methylphenidate to treat ADHD were excluded. Included patients numbered 2,283,509 across all studies and ranged in age from 3 to 20 years old.

Serious adverse events were the primary outcome, and were defined as any event that is fatal, life-threatening, requiring inpatient hospitalization or its prolongation, results in persistent or significant disability, or that requires intervention to prevent. *Non-serious adverse events*, the secondary outcome, were defined as any other event, including but not limited to common adverse events such as cardiovascular, neurological, and gastrointestinal events. Difficulty with sleep and growth retardation were other examples. Authors categorized both classes of AE by physiological system.

In comparative studies, authors found that methylphenidate use increased the risk of any serious adverse event by 36% (RR 1.36, 95% CI 1.17, 1.57), any psychotic disorder (RR 1.36, 95% CI 1.17, 1.57), and cardiac arrhythmia (RR 1.361, 95% CI 1.48, 1.74) compared to drug-untreated participants. In secondary outcome measures, the drug was estimated to increase the risk of insomnia and sleep problems from 6.2% to 8.7% (RR 2.58, 95% CI 1.24, 5.34) and decreased appetite from 1.4% to 21.5% (RR 15.06%, 95% CI 2.12 to 106.83) in untreated and methylphenidate-treated participants, respectively.

In non-comparative studies, the proportion of patients who experienced a SAE was 1.2% (95% CI 0.70%, 2.0%). The proportion of patients with any non-serious adverse event was 51.2% (95% CI 41.2%, 61.1%); these included difficulty falling asleep, abdominal pain, and decreased appetite.

The authors concluded that methylphenidate might be associated with a number of serious and non-serious AEs in people under 20; despite statistically significant risk ratios for a number of specific outcomes, the low overall quality, certainty, and reliability of the studies included prompted them to be cautious in their conclusions. The actual risk of AEs "might be higher than reported here" (3).

Wang (2018) noted contradictory findings from empirical studies in animals and humans that investigated the potential harmful effects of methylphenidate (Ritalin) on male sexual development, in particular testicular dysfunction (TD). To assess a potential association between methylphenidate use and TD, investigators compared the proportion of TD in ADHD-diagnosed and healthy boys, and also modeled the time to TD for both groups. They constructed a cohort of 52,746 boys (mean age: 9.7) born before 2000 diagnosed with ADHD between January 1999 and December

2011, and who received that diagnosis before age 20 from the Taiwanese National Health Insurance Research Database, a program tied to the country's universal health insurance. A randomly sampled control cohort of 52,008 boys (mean age: 10.6) without an ADHD diagnosis. Exposure to methylphenidate was counted on an "ever / never" basis, with any prescription record for the drug causing a youth to be counted as exposed to the drug. Duration of drug use was divided into three groups: non-use; short term use (less than one year); and long-term use (greater than one year).

The odds of a TD diagnosis between ADHD-diagnosed boys and healthy ones were calculated using logistic regressions, and the cumulative hazard of TD between drug-treated and drug-naive boys were calculated using Cox proportional hazards models. The first analysis suggested that ADHD-diagnosed boys were more likely than boys in the control cohort to develop TD (OR=1.95, 95% CI: 1.26, 3.04) after controlling for age and various neurodevelopmental disorders. In the second analysis, however, methylphenidate prescription was not associated with an increase in the risk of developing TD after controlling for age (HR=1.40, 95% CI: 0.77–2.54), nor was the duration of drug treatment significantly associated with that outcome. The authors speculated that heterogeneity in dosing strategies may account for this discrepancy, and called for future studies to focus on high-dosage administration of methylphenidate with similar outcomes of interest.

Noting that drugs given for the treatment of ADHD have been shown to have strong effects on how the central nervous system produces and regulates the neurotransmitter dopamine, and that epidemiological reports suggest that abusers of amphetamines are more likely to develop Parkinson's disease (PD), Curtin et al. (2018) conducted a retrospective cohort study of a statewide electronic medical

record database to investigate a potential association between ADHD drug use (stimulants and methylphenidate) in those diagnosed with ADHD and diseases of the basal ganglia, including PD. To maximize potential followup time for outcomes like PD, which even in their earliest-onset form do not begin to appear until a person's twenties, authors set their study's baseline to January 1996, but specified that included patients with ADHD diagnoses must be at least 20 years old by December 2011. Of 31,769 eligible ADHD-diagnosed patients, 4960 were determined to have been prescribed a stimulant; a control cohort of 158,790 people with no ADHD diagnosis and matched on sex and year of birth was randomly selected (a target control:exposed ratio = 5:1). Time to outcomes was measured from the index date to either an index diagnosis of any one of 4 ICD-9 and ICD-10 basal ganglia and cerebellum disease groups, the end of study follow-up (December 2016), a participant's death, or loss to follow-up. Hazard ratios were modeled with Cox proportional hazards regression models and adjusted for race/ethnicity, psychotic conditions, and tobacco use, the latter two of which could potentially confound the association of interest.

In drug-naive and un-diagnosed controls, the crude incidence rate of basal ganglia and cerebellum diseases was 0.19%, while in stimulant-exposed ADHD-diagnosed participants, the rate was 0.52%. The risk of disease in ADHD patients prescribed stimulants was significantly greater than matched, un-diagnosed subjects (aHR=6.0, 95% CI: 3.9–9.1; $P< 0.0001$). In the case of ADHD users of methylphenidate, the effect was more pronounced (aHR=8.0, 95% CI: 4.2, 15.1; $P< 0.0001$), while in ADHD-diagnosed participants with no record of treatment with stimulants or methylphenidate also showed an significantly increased risk of disease, though the size of the effect was smaller (aHR= 1.8, 95% CI: 1.4, 2.3; $P<0.0001$).

2.1.1.2 Other Studies

60 smaller studies of varying study design, drug exposure, outcome, and quality were also found. With the exception of single study each for antidepressants (the second-most popular psychotropic drug class prescribed to youth) and anti-anxiety drugs (including benzodiazepines), these studies focused on mood stabilizers / antiepileptic drugs, antipsychotics, and stimulants (descending order of frequency). Few papers looked at antidepressants or benzodiazepines and other anxiolytics. In papers investigating similar physiological effects for the same drug or drug class, findings were often mixed or conflicted with each other. A brief review of these articles follows here.

Mood Stabilizers / AEs

Studies of mood stabilizers and antiepileptic drugs were largely conducted by neurologists and neurological researchers on epileptic children and adolescents, and investigated the widest array of physiological effects of any drug class in articles found for this review. Their prominence here is keeping with the frequently more plentiful safety documentation for antiepileptic drugs in medical reference texts and similar sources, though the reasons for this relative abundance are unclear: it may be that "cultures" of drug safety research differ between neurology and psychiatry / mental health, but it may also be that antiepileptic drugs are simply more capable of inducing adverse reactions. Because the drugs may induce similar reactions in both antiepileptic and psychiatric applications, studies in which a mood stabilizer was used in seizure control were not excluded from this review if it met the criteria outlined above (Aronson, 2015).

In an assessment of the emergence of ADRs in epileptic children on long-term

lamotrigine treatment (144 weeks of followup), Duchowny (2002) found that 52% of participants experienced an ADR of some kind, 13.9% experienced a serious adverse event, and ADRs prompted 10.3% of participants to drop out of the study.

Several studies investigated the potential harm to child and adolescent metabolic function from mood stabilizer / AE use; two studies found suggestions of carnitine deficiencies after a year and two years of followup, respectively (Navarro-Quesada, Lluch-Fernández, Vaquero-Abellán, Marchante-Serrano, and Jiménez, 1997; Melegh et al., 1994). (Carnitine deficiencies may result in heart and liver problems, and can be addressed by L-carnitine supplementation.) Another study found no effect of valproate on BMI in 31 children after 10 months of followup (Çaksen, Deda, and Berberoglu, 2002).

Three studies implicated MS/AE use in impaired function of the thyroid gland, though some drugs (mainly carbamazepine) were more strongly implicated than others (Yüksel, Yalçin, and Cenani, 1993; Eiris-Punal et al., 1999; Çaksen et al., 2003; Alberto Verrotti, Laus, Scardapane, Franzoni, and Chiarelli, 2009). The results of two studies suggested that clinicians pay close attention to cardiovascular indicators in children taking MS/AE drugs over the long term, with one reporting alterations in serum lipid profiles (Yalçin, Hassanzadeh, and Mawlud, 1997) and another reporting both significant increases in triglycerides and significant decreases in platelet counts in children taking valproate (Amitai, Sachs, et al., 2015).

Several studies came to conflicting conclusions about their long-term effects on bone mineral density (Tsukahara et al., 2002; Dimić, Dimić, Milosević, and Vojinović, 2013) Ginige, de Silva, Wanigasinghe, Gunawardane, and Munasinghe, 2015) and renal function (Khandelwal, Varma, and Murthy, 1984; Verrotti et al., 2000).

Other studies suggested potential skin (Feliciani et al., 2003), hematologic (Brichard, Vermylen, Scheiff, Ninane, and Cornu, 1994), cognitive (Calandre, Dominguez-Granados, Gomez-Rubio, and Molina-Font, 1990), and mineral balance reactions (Armutcu et al., 2004).

Antipsychotics

The potential endocrine and metabolic effects of AP use, regardless of duration, are among the better known potential risks of these drugs in both children and adults, and investigations of them are well represented in this small group of studies. Three studies looked at the potential for APs to induce hyperprolactinemia, a state of highly elevated levels of the hormone prolactin which poses a number of short- and long-term risks to human health: in the short term, the condition can cause galactorrhea (the abnormal secretion of breast milk), gynecomastia (abnormal breast enlargement), menstrual irregularities in females, and several forms of sexual dysfunction. While the long-term sequelae of elevated prolactin are less well understood, there are indications that the risk of breast cancer and tumors of the pituitary gland, where prolactin is made, may be elevated. Short-term sexual side effects may lead to prolonged decreases in sex hormones, which in turn may lead to osteoporosis in the long term (Byerly, Suppes, Tran, and Baker, 2007). Saito (2004) found significantly elevated prolactin levels in children (n=40) taking risperidone for a mean duration of 11.2 ($\pm$2.2) weeks, but not in children taking quetiapine or olanzapine. Overall, hyperprolactinemia was present in 53% of children in the sample. In a later cross-sectional study, Buhagiar and Cassar found that 80% of subjects (n=25) taking risperidone for more than three months (mean duration: 30.4 months) had hyperprolactinemia. Migliardi (2009) found that, while prolactin levels peaked at up to four times their baseline levels at 3 and 6 months' treatment duration, prolactin

levels at 12 months remained high – at least double the baseline measurements, on average (n=42).

Of four studies investigating weight gain after long-term AP use in children, only one found no association between drug use and increased BMI (Demb, Valicenti-McDermott, Navarro, and Ayoob, 2011); the authors cited the sample sample size (n=25), the lack of a control group, the high attrition rate, and the absence of attempts to account for polypharmacy as potential reasons why. In a retrospective analysis of pharmaceutical company data, Kryzhanovskaya et al. (2012) compared amounts of weight gained by adolescents (n=179; mean age 15.8 years) and adults (n=4280, mean age 38.8) who took olanzapine, an antipsychotic, long-term (for at least 24 weeks). Mean follow-up time for adolescents was 201 days, and 280 days for adults. Adolescents gained, on average, 11.24kg (24.7lbs; 95% CI = 10.1, 12.4), and adults gained 4.81kg (10.6lbs; 95% CI = 4.57, 5.04) - a statistically significant difference. 29.1% of adolescents gained more than 25% of their baseline weight, while 8.0% of adults did. Ilies et al. (2017) reviewed the medical charts of treatment-naive Canadian children and teens (n=147) to comprare any height, weight, and fasting glucose changes after initiating AP treatment for up to 24 months. Mean weight, BMI, and fasting glucose showed a significant increase, and a notable number of subjects developed obesity and hyperglycemia (833). [2]

Pozzi et al. (2019) found that while an overall weight-gain-inducing effect had been well established for antipsychotics, particularly newer drugs, neither the trajectory of weight gain over time nor factors that influence it had been elucidated:

[2]Though not strictly related to their main analysis, the authors also noted that the most frequently-cited reason for SGA prescription was neither a mood disorder or a psychotic disorder, but a disruptive behavioral disorder and ADHD.

how much of children's weight gain is due to natural development (growth), and how much is due to the drug? In a 2-year observational study of children and teens (n=127; mean age = 12.6 years) treated with risperidone and aripiprazole, the authors mapped age- and sex-corrected BMI every 3 months. Results suggested that previous treatment with risperidone (mean = 4 months) led to a baseline BMI (normalized to national growth standards) between "excessive weight" and "obesity", and that further treatment (up to 8 months) caused further weight gain; that previous treatment with risperidone for an average of 10 months yielded an excessive baseline weight, but with slight weight loss during further treatment; and that previous treatment with aripiprazole (mean = 4 months) was associated with excessive baseline weight and continued weight gain for the duration of follow-up.

Potential long-term harm by antipsychotics to cardiovascular, neurological, sexual, and nutritional health were investigated by one study each in this group of 60. In a study by Palanca (2017), subjects (n=101) were given ECG examinations before starting AP treatment; after 1, 3, and 6 months; and every 6 subsequent months. Mean followup time was 20.0 months (±15.1), and mean duration of drug treatment was 14.0 months for risperidone (±12.8) and 11.6 months for aripiprazole (±14.5). Of the 101 participants, 7 (6.9%) had abnormal QT prolongations during followup; four of these used aripiprazole (Abilify) and three used risperidone (Risperdal). This rate is much higher than the rate in the general population, estimated to be between 0.4% and 0.5%. The appearance of prolonged QT intervals varied widely, too, with the earliest instance occurring 1 month after starting treatment and the latest occurring in month 29. No case was symptomatic, nor were there any deaths or cases of serious cardiac events.

Freedman (1994) reported on the case of 15 year-old boy with a diagnosis of

schizophrenia who had been treated with the antipsychotic clozapine (Clozaril). After 7 months taking the drug, the boy's dose was increased to address his anxiety; shortly afterwards, he began feeling nauseous and experienced "spacey feelings", later confirmed to be absence seizures by electroencephalogram (EEG). The seizures stopped when the dose of clozapine was reduced. Dunbar, Kusumakar, Daneman, and Schulz, 2004 found no disruptions to growth or sexual maturation in a combined retrospective analysis of five controlled trials of risperidone. Because iron plays a role in dopamine activity, and because antipsychotics impact dopamine as well, Calarge and Ziegler (2013) assessed whether body iron status was related to psychiatric symptom severity and antipsychotic tolerability in 115 children and teenagers who had taken risperidone for a least six months (mean=2.4 years, ±1.7). They found that a majority of subjects had either depleted or deficient iron levels (45% and 14%, respectively), and that iron levels were inversely associated with both weight gain and prolactin concentrations. The authors noted that rates of iron depletion and deficiency far exceed the base rate of these conditions in the population, and that the possible role iron deficiency plays in other known complications of antipsychotic use in children merits further research, in no small part because iron deficiency has been implicated in cognitive impairment, growth problems, and cardiovascular issues.

Stimulants

Several search results looked at the relationship between stimulants and other drugs used in the treatment of ADHD and physiological effects, particularly in children's growth and cardiac function. Taken as a whole, these smaller individual studies (n=5) showed mixed results with respect to growth (i.e. the development of height and weight through childhood and adolescence; Aarskog, Fevang, Kløve, Støa, and Thorsen, 1977; Zachor, Roberts, Hodgens, Isaacs, and Merrick, 2006; Poulton,

Briody, Melzer, and Baur, 2011; Carucci, Carta, Romaniello, and Zuddas, 2015; Diez-Suarez, Vallejo-Valdivielso, Marin-Mendez, and de Castro-Manglano, 2015). Four studies of stimulants' effects on pediatric cardiovascular function also present mixed results on blood pressure, hypertension, prolongation of the QT interval, and diastolic mitral annular motion (*E'* or e-prime; Findling et al., 2005; Popp et al., 2012; Kara, Mutlu Mıhçıoğlu, Yılmaz, and Akaltun, 2018; McCarthy et al., 2018). A 2008 review of drug safety studies of long-term stimulant treatment concluded that the drugs are reliably associated with small, statistically significant, but usually clinically non-significant increases in in blood pressure and heart rate, that reduced growth rate is typical in treatment-naive children (those taking the drug for the first time), and that this effect is most pronounced during the child's first year of taking the drug (Lerner and Wigal, 2008).

The results of a study of the effect of long-term stimulant use on children's (n=407) hematologic function were ambiguous (Wigal, Wilens, Wolraich, and Lerner, 2007). On one hand, the authors wrote that "there were no clinically significant changes from mean values" for various tested parameters (e120). On the other hand, less than 10% of participants had clinically significant changes in any measured value at any time, and for 6 measured values, greater than 10% of participants had clinically significant changes (e123). The study's conclusion that "chronic therapy with [methylphenidate] has no clinically significant impact on laboratory values" and that routine hematologic testing may not be necessary for children taking stimulants is therefore not borne out by the authors' own reporting. A serious ADR's relative rarity does not merit its dismissal – and in this case, "less than 10%" is in fact not that rare at all in a drug taken by so many children nationwide.

Konrad and colleagues (2007) investigated the long-term effects of methylphenidate

use on neural networks associated with executive attention by compared ADHD-diagnosed children with normal controls (n=30). They found that after one year of follow-up time, normal controls whose brain function was scanned had adult-like performance on executive attentional tasks, while the drug-treated children did not.

Antidepressants and Anxiolytics

Only two smaller studies investigated antidepressant and drugs prescribed for anxiety or sleep. In a case study of a 16 year-old who had been taking the antidepressant sertaline (Zoloft) for 18 months, Harel and colleagues (1995) concluded that dizziness, daytime somnolence, and insomnia - common antidepressant ADRs - may be mistaken for thyroid disorders, and urged clinicians to be aware of this. In a recent narrative review, Boafo and colleagues (2019) explored the potential for exogenous melatonin use to delay children and adolescents' sexual maturation. As justification, they cited the high estimates of the prevalence of sleep disorders in children and teens - between 15% and 25% - as well as the tremendous growth in the use of melatonin in youth in recent years. They cited strong evidence from animal studies, as well as potential signals from small studies in humans, to suggest that long-term experimental studies on children and teens are justified to investigate this phenomenon.

2.1.2 Synthesis

While a number of smaller-scale studies of longer-term psychotropic drug safety in children and adolescents, including randomized controlled trials, were found in this literature search, only 8 articles sought to maximize both sample size and follow-up time in order to detect adverse drug reactions, which in many cases occur too

infrequently for even the most rigorous RCT to detect. Of these 8, 4 correspond to 2 distinct investigations: Jerrell and McIntyre (2008) and McIntyre and Jerrell (2008), in one case, and Dalsgaard et al. (2011) and Dalsgaard et al. (2014) in the other. Strictly speaking, then, this review of the literature found 6 investigations.

Only one of these sought to assess the effects of exposure to multiple drug classes (Patel et al., 2017), and only two investigations (3 articles) looked at multiple groups of outcomes divided by physiological system (Jerrell and McIntyre, 2008; McIntyre and Jerrell, 2008; Storebø et al., 2018). Five of eight articles (62.5%) investigated stimulants and other drugs used for ADHD, 2 (25%) looked at antipsychotics, and one (12.5%) studied various drugs - antipsychotics, mood stabilizers, and antidepressants. This last study (Patel et al., 2017) was unique in studying mood stabilizers and antidepressants, which is surprising in the latter case given the predominance of antidepressant prescribing in children and adolescents, lagging only behind stimulants overall. No article looked at the long-term effects of any benzodiazepine or other anxiolytic drug.

Across all 68 studies, authors used varying definitions of "long-term" psychotropic use, as well as a wide range of potential maximum follow-up times of study subjects. Table 2.4 summarizes these characteristics for the 8 "direct hit" pharmacoepidemiological studies. In the larger group of 60 studies, investigators' definition of "long-term" duration of treatment varied widely (range = 6 months - 9.7 years).

The disproportionate number of small, relatively short empirical studies reflects an imbalance in how the drug safety researcher's toolkit is used in the real world, in which one set of necessary and potentially powerful methods - controlled trials, with and without random assignment - are used very frequently, while another equally

necessary and powerful set - observational studies employing data from large, often population-based computerized healthcare transactions and metadata - are under-used, under-valued, and in some cases avoided outright due to misconceptions about their validity (Avorn, 2007). A number of authors have critiqued current methods in drug safety research. Avorn (2007) asserted that while observational studies using large healthcare databases have their own flaws, they are able to go where controlled trials cannot. Hammad (2011) agreed, adding that apart from their small sizes and short duration, RCTs that purport to assess drug safety often simply omit ADRs from publication or reporting. Indeed, Hughes, Cohen, and Jaggi (2014) found that published journal articles based on clinical trials of antidepressants and antipsychotics reported substantially fewer serious adverse events than summaries of the same trials posted in a public registry. When RCTs do report adverse reactions, detailed information on frequency, timing, and severity is often lacking.

Observational studies of drug safety have their own potential weaknesses, of course. Studies like the 8 pharmacoepidemiological ones discussed here are susceptible to various forms of confounding whose influence may generate spurious or inaccurate associations between drug use and safety outcomes. This is especially true for drug studies, which may suffer from *confounding by indication*, a situation in which the risk for an adverse drug reaction is related to the reason a drug is prescribed (its *indication*) but not to the drug itself (Strom and Kimmel, 2006). The result is a form of selection bias: the selection of subjects to an "intervention group" - in this case, a clinician's decision to prescribe a psychotropic drug to a patient - is also associated with an outcome - in this case, an adverse drug reaction. Figure 2.1 illustrates confounding by indication using a directed acyclic graph, or DAG, where variables are mapped out and connected to each other to help determine causal re-

lationships and potential bias. Because the indication lies upstream from the drug exposure and the potential adverse drug reaction (PADR) outcome, a "backdoor path" of bias opens up between exposure and outcome, confounding the estimate of the Drug–PADR association of primary interest.

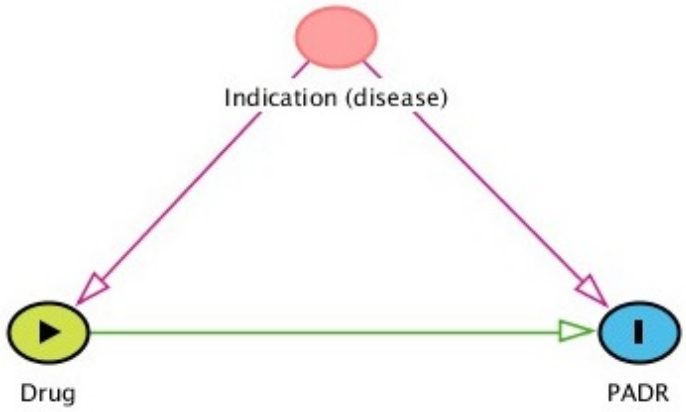


Figure 2.1. Directed acyclic graph (DAG) of confounding by indication

With drugs used in mental health contexts, confounding by indication is of special concern if the outcome of interest is psychiatric or psychological. A hypothetical association between the use of, say, and antidepressant drug and increased probability of suicide might be confounded by the reason - the *indication* - for being prescribed an antidepressant in the first place: depression, which precedes antidepressant use and is also associated with increased risk of suicide.

With physiological outcomes likes the ones in this study, the threat posed by confounding by indication is less clear. One could argue, on one hand, that psychiatric conditions are less likely to be causes of physiological outcomes than psychiatric ones: a physician would investigate several other potential causes of, say, a patient's skin rash, including potential drug reactions, before they suspected a direct causal

link to the patient's anxiety disorder. On the other hand, one could hypothesize that patients with psychiatric diagnoses are more likely to also have diagnoses of physiological illness – perhaps due to poorer overall health, or perhaps because of greater contact with the healthcare system – that may be the true cause of the suspected ADR.

In any event, say investigators, the key in observational studies of drug safety is rigor: using large healthcare or claims databases to investigate drug safety *well* can meaningfully add to our knowledge of drug safety and harm (Avorn, 2007; Westover and Halm, 2012). Westover and Halm (2012) conducted a systematic review of studies that investigated the risk of adverse cardiovascular events from prescription psychostimulant use and found a low level of overall methodological quality in the 10 studies they selected. They identified a number of ways to increase the validity of observational studies of drug safety in a systematic review of studies investigating adverse cardiovascular reactions in prescription stimulants in adults. First, they counsel the use of *hard clinical outcomes* such as death, stroke, or myocardial infarction instead of "soft" outcomes like increases in pulse or heart rate, which are less likely to be diagnosed and thus entered into a claims or medical records database.

The 8 large and long-term observational studies here, largely investigating the potential adverse effects of stimulants, each have their own strengths. But a gap appears: no single study focuses solely on younger children in their most critical stages of development; analyzes multiple drug classes of exposure (especially antidepressants) and physiological groupings of outcomes; attempts to classify outcomes by relative severity; factors in the effects of time and/or dose in their analyses; and has at least five years of potential follow-up time.

Long-term drug safety studies of psychotropics in youths are in their infancy, both in their number and in their scope. Only in very few cases - antipsychotic use leading to weight gain, for example - are the potentially serious long-term adverse reactions of psychotropic drugs in children beginning to be rigorously confirmed; in the majority of the rest, little to nothing is currently known. As reference sources and the research literature suggest, however, there are strong reasons to pursue such studies as part of formal *signal detection* in psychotropic drug safety. Meyboom et al. (1997) writes that certain situations favor signal detection efforts, and lays out a three-step framework for undertaking them in order to establish (or rule out) that a given symptom or syndrome is indeed an adverse drug reaction: *hypothesis generation*, often resulting from single instances in spontaneous reporting systems (e.g. the FDA) or published case studies; *hypothesis strengthening* using as much available data to assess a possible drug-symptom link; and *signal testing, evaluation, and explanation.*

According to Meyboom, certain situations are favorable to signal detection approaches in drug safety research. First, the clustering of a symptom or syndrome with low natural frequency, characteristic signs, potential occurrence in similar groups of people, and reasonable basis for suspecting that exposure to a drug may be a cause. Second: high frequency of exposure to the drug (e.g. daily use). Finally, symptoms or syndromes with at least one of the following: high frequency, plausible physiological mechanisms linking drug to symptom, or a plausible time or dose relationship. This project fits all three of these, and can be situated squarely within Meyboom's second phase of signal detection: *hypothesis strengthening.* The state of the knowledge is such that a variety of smaller potential signals exist for a litany of adverse reactions in various physiological systems in children in the short term, but few projects have

so far attempted to strengthen those signals using larger and more-long term data.

2.2 Statement of the problem

Psychotropic drugs are increasingly and widely prescribed to children despite meager and low-quality evidence to recommend their use in any drug class. The potential iatrogenic harm from the use of prescribed psychotropic drugs in prepubertal children is widely acknowledged in the empirical literature and by pediatric clinicians. Researchers and clinicians both supportive and critical of modern mental health research and practice have long cited the unknown long-term safety of prescribed psychotropic drugs in children, and there are numerous calls for this to be investigated empirically. However, the extent to which the long-term physiological health of young children is affected by psychotropic drug prescription, both directly and indirectly, at young ages remains largely unknown.

The aim of this study is to determine whether the long-term physiological health of children in Colorado who were first exposed to psychotropics between ages 6 and 12 differs from similar children who were never exposed to those drugs. In doing so, I hope to improve the empirical understanding of the long-term effects of prescribed psychotropic drugs on child development.

2.3 Research question(s)

The specific questions addressed in this study are:

- Is there a difference in the hazard of a group of physiological health outcomes,

understood as "potential adverse drug reactions" or PADRs, categorized by level of seriousness, between Colorado children who are first prescribed a psychotropic drug between the ages of 6 and 12, and Colorado children who are not prescribed any such drugs, controlling for age, sex, ZIP code-level median household income, epilepsy or other recurrent seizure diagnosis, and psychiatric polypharmacy?

  - Within psychotropic-exposed Colorado children, is there a difference in the hazard of PADRs between children exposed to only one psychotropic drug compared children exposed to more than one, controlling for the same variables?

2.3.1 Hypotheses

As part of Meyboom's second, *hypothesis strengthening* phase of ADR discovery, this study will build on existing suggestions of links between psychotropic drug exposure in human beings of all ages and various physiological symptoms and syndromes - in other words, *signals*. In drug safety research, signals are understood to be hypotheses that a drug may induce harm, paired with data and arguments to support them (Meyboom et al., 1997; WHO-UMC, 2019). So, while this study seeks to estimate the risk (hazard) of many physiological outcomes (harms) from many different exposures (drugs), each of these estimates hypothesizes that there *is* a statistically significant association between a given drug or drug class and a given group of outcomes, controlling for other factors.

Table 2.3

Frequency of search results by drug class and major physiological system

Drug class	Physiological system	n
Antidepressants		
	Endocrine	1
Antipsychotics		
	Cardiovascular	1
	Endocrine	5
	Hematological	1
	Metabolic	4
	Neurological	1
	Sexual function	2
	Various	5
Anxiolytics / hypnotics		
	Sexual function	1
Antimanics / mood stabilizers		
	Cardiovascular	1
	Endocrine	5
	Hematological	3
	Metabolic	8
	Musculoskeletal	2
	Neurological	1
	Nutritional	1
	Skin	1
	Urinary tract	3
	Various	2
Stimulants and drugs used for ADHD		
	Cardiovascular	6
	Hematological	1
	Metabolic	2
	Neurological	3
	Sexual function	1
	Various	6
Multiple classes		
	Metabolic	1
Grand total		68

Table 2.4

Definitions of "long-term" drug treatment and durations of follow-up in "direct hit" studies (n=8)

Study	Definition of 'long-term' drug treatment	Maximum potential duration of follow-up (years)
Jerrell and McIntyre, 2008	'6-90+ months'	8
McIntyre and Jerrell, 2008	'24-36 months'	8
Dalsgaard, Nielsen, and Simonsen, 2011	-	-
Dalsgaard, Kvist, Leckman, Nielsen, and Simonsen, 2014	-	14
Patel et al., 2017	'12 months'	1
Storebø et al., 2018	'six months or more'	11
Wang et al., 2018	'> 365 days'	12.01
Curtin et al., 2018	-	21.01

CHAPTER 3

Methods

3.1 Overview

I used population-based claims data from the state of Colorado to conduct a retrospective cohort study to examine the possible effects of psychiatric drug prescription on long-term physiological health outcomes in children whose first record of psychotropic prescription in the APCD dataset occurred between ages 6 and 12.

3.1.1 Social work, public health, and healthcare in the era of big data

It is widely asserted that we inhabit a world of *big data*, and healthcare is no exception. Factors such as the increased supply of large-scale clinical data; rapidly advancing technical capability to analyze, manipulate, and store clinical data while adhering to patient privacy protections; state and federal / national governments' efforts to catalyze such advancements through efforts to make data publicly available (see discussion of all-payer claims databases, or APCDs, below); and rising demand for big-data-derived insights as costs pressures in the US healthcare system all lead payers and providers to focus on lowering the cost of care, reevaluating traditional fee-for-service models for paying clinicians (Groves, Kayyali, Knott, and Van Kuiken, 2013). For nearly half a century, researchers in healthcare who desired

comprehensive, population-based healthcare data across the lifespan of entire populations had to acquire access to centralized government databases in nations with universal healthcare such as Denmark, Sweden, and Norway. The ability to do such work in the US increases yearly.

The increasing availability of high-variety and high-volume health data presents challenges and opportunities for research in social welfare. The potential for solving or attenuating social problems using computerized social service, health, and educational records, in addition to the increasing number of digital byproduct of modern human life (social media posts,sensor data from smartphones and GPS systems, etc.) is high, and the demand from policymakers, funders, and stakeholders for researchers and practitioners to prove what works (evidence-based policy and practice, in other words) is arguably even higher. This ought to be an adequate recipe for the large-scale exploitation of big data sources, but some assert that the social sector has been slow to incorporate such data into research, policy, and practice (Coulton, Goerge, Putnam-Hornstein, and de Haan, 2015).

Public health, and pharmacoepidemiology in particular, has perhaps a longer tradition of big data research than social work, but shares similar challenges (Strom and Kimmel, 2006; Mooney, Westreich, and El-Sayed, 2015). Foremost among these are new, scaled-up versions of old issues of validity in research with secondary data: missing data, measurement error, and issues of data quality; spurious statistical significance in large data sets; the potential inadequacy of researchers' knowledge of subject matter and theory compared with the sophistication of their analytical and statistical techniques; and others.

Despite these challenges, there are several potential benefits of secondary health-

care data for a project such as this one, which sits at the intersection of social welfare, pharmacoepidemiology, and quantitative data analysis. The first is the ability to study drug exposure in children over a realistically long, real-world follow-up time. While non-randomized data has disadvantages, this longitudinal superiority over RCTs of prescribed psychotropics - combined with extremely large and often population-based sample sizes - allows for assessments of drug safety that directly reflect how long psychotropics are taken for in the real world.

3.1.1.1 Observational studies using administrative claims data

While private-sector organizations possess the resources to take advantage of much of the more advanced and variable-rich data in US healthcare remains out of reach to many researchers, however - particularly in academia. Because of this, many researchers acquire and analyze the data collected during the course of administering payments for health services delivered by providers – these are administrative claims data. When someone in the US goes to a pharmacy to have a drug dispensed, the pharmacy bills the person's insurance company for the cost of the drug. In doing so, the pharmacy must identify the drug, the dose, the quantity of units of the drug (e.g. tablets), and, importantly, the patient themselves, usually by name and account number. Crucially, this information is linked back to diagnostic data given in any assessment, procedure, or clinical encounter. Thus, what is effectively an audit trail for payment processing can, in the hands of researchers, become a *de facto* longitudinal dataset of patients' interactions with their pharmacy, healthcare providers, and insurance company over time.

3.2 Data & cohort construction

3.2.1 Data overview

Healthcare and pharmacy claims data were obtained from the Center for Improving Value in Health Care (CIVHC), a not-for-profit organization that administers the Colorado All Payer Claims Database (APCD). In the late 2000's, several eastern US states began developing so-called all-payer claims database systems that systematically record all medical and pharmacy claims in a state, as well as health program eligibility and provider data from both public and private payers of health programs. These databases were usually created by legislative mandate, with payers transmitting data directly to the database, and their purpose was to increase healthcare quality and transparency while lowering costs.[1] Unlike many existing claims databases, APCDs offered information about private insurance activity that had until then been either unavailable or expensive; comprehensive information about most healthcare activity conducted in a given state; and patient information across care sites. Results of research done on APCDs are thus potentially generalizable to that state's population.

CIVHC is a public-private entity founded in 2008 whose stated goals are improving healthcare quality; lowering healthcare costs; and improving Coloradans' health by contributing to the transparency of public and private healthcare in the state. The organization generates revenue in part by temporarily licensing its non-public data to authorized organizations and individuals, including researchers, whose goals align with its own. The Colorado ACPD that CIVHC administers is a comprehen-

[1]Temporarily licensing data for research purposes, such as those outlined here, furthers these goals by providing new insight and generating revenue from the sale of the data.

sive claims dataset, representing the majority (75% to 85%, depending on year; G. Gillespie, personal communication, March 24, 2022) of publicly- and privately insured Coloradans. For each potential study participant, the APCD dataset contains health plan eligibility and enrollment status; details of inpatient and outpatient medical encounters, including International Classification of Diseases (ICD) codes; pharmacy and prescription drug information, coded as National Drug Codes (NDCs); provider information; and sociodemographic information including age and 3-digit ZIP code. Data were available for Colorado children beginning in January 2009 through June 2018.

The APCD data used in this study are a subset or "extract" of the entire APCD based on specifications given to CIVHC over several discussions about the study. This extract contains the health and pharmacy records of 1,066,005 unique Colorado minors from 2009 to 2018, comprising 4.8 million total years of person-time. Table 3.1 summarizes the number of individual members making both medical and pharmacy claims, respectively, in a given year of the extract. There are 523,240 girls (49.1%) in the extract, 541,948 boys (50.8%), and 817 (0.001%) members with gender marked "unknown". Colorado children are publicly insured more than they are commercially (privately) insured, as Table 3.2 shows.

3.2.1.1 Cohort construction & analytical sample

This study's analytical sample is a cohort of two groups: Colorado children whose first recorded exposure to a psychotropic drug took place between the ages of 6 and 12 (and who met my exposure definition), and a control group of Colorado children with no such exposures, selected at random from the same age range. In the remainder

Table 3.1

APCD Extract members making medical and pharmacy claims by year

Year	Medical claims	Pharmacy claims
2009	365,253	243,438
2010	397,437	280,225
2011	428,737	299,816
2012	493,661	302,990
2013	521,755	315,764
2014	565,975	351,587
2015	599,848	362,405
2016	584,126	358,963
2017	590,152	351,921
2018	317,293	183,864

Table 3.2

Summary of types of health insurance possessed by members in APCD extract

Insurance type	no.	%
Commercial	462,009	43.3%
Medicaid	581,312	54.5%
NA	22,684	2.1%
Total	1,066,005	100.0%

of this dissertation, I will use n_1 to refer to the exposed group, and n_2 to refer to the unexposed group.

Figure 3.1 illustrates how psychotropic-exposed and -unexposed groups were identified for descriptive and statistical analysis. Of the 1,066,005 minors in the extract, 113,299 (10.6%) received at least one psychotropic prescription between 2009 and 2018. Of these ever-exposed, 50,326 (44.4%) received their first prescription between the ages of 6 and 12, and finally, 42,362 children in this age range (83.9%) met this study's exposure definition of at least 1 prescriptions within 180 days (6 months) of that child's first psychotropic prescription (i.e. ≥ 2 total prescriptions in 6 months). 42,362 psychotropic-unexposed children employed as a control group in this study were selected from APCD members between 6 and 12 years old at the time of their first appearance in the APCD.

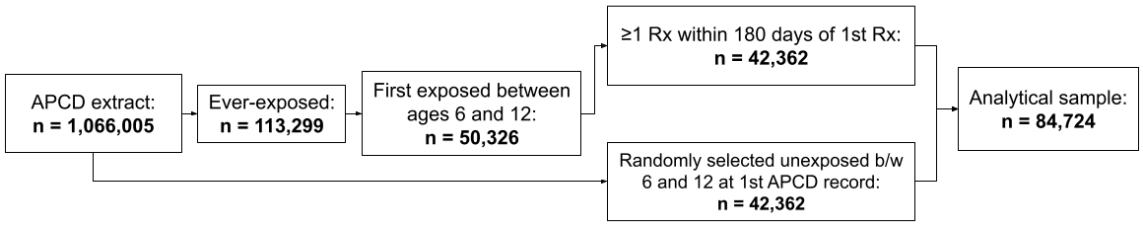


Figure 3.1. Identification and selection of exposed and unexposed groups for analysis

3.2.2 The Exposed: APCD members prescribed psychotropic drugs

3.2.2.1 Exposure definitions

Definitions of drug exposure vary considerably in pharmacoepidemiologic research with automated databases. Three approaches to exposure definition prevail: time-

Table 3.3

APCD members (all ages) with any prescription for prescribed psychotropics by drug class, 2009-2018

Drug class	no.	%
Antidepressants	58,991	35.5%
Stimulants & drugs used for ADHD	55,874	34.6%
Antipsychotics	22,256	13.4%
Antimanic / Mood stabilizers	21,026	13.6%
Anxiolytic / Hypnotic	8,166	5%
Total	166,313*	100%

*Total differs from count of ever-exposed members of any age, discussed later, due to polypharmacy.

fixed, time-varying, and nested case-control (Eskin, Eurich, and Simpson, 2018). In time-fixed approaches, medication exposure is established at a single point in time and does not change during the study's follow-up period. This study employed a time-fixed approach, establishing exposure to a given drug as the filling of at least 1 prescription for that drug within 180 days (6 months) of the first-ever prescription for that APCD member (at least 2 prescriptions in 6 months, in other words).

In the APCD data, drug prescriptions are indicated by National Drug Codes (NDC). NDCs are 11-digit numbers made up of 3 segments of smaller numbers. They are unique identifiers for all human drugs used in the United States, whether prescription or non-prescription (over-the-counter or OTC). The 3 segments in each NDC represent the labeler (the firm that manufactures and/or distributes and/or repackages the drug, e.g. "Pfizer"); the product code, which identifies the specific

product and dose (e.g. "Zoloft / sertraline, 50mg"); and the package code, which represents the size and form of the drug in question (e.g. "30 pills in a blister pack"). Table 3.4 presents some examples of NDCs and related data for two psychotropic drugs.

Table 3.4

Examples of National Drug Codes (NDC) and associated information

Brand name	Active ingredient	Manufacturer / distributor	Generic	NDC	Form	Dose
Strattera	atomoxetine hydrochloride	Eli Lilly and Co.	N	00002-3228-30	CAP	25 mg
Strattera	atomoxetine hydrochloride	Eli Lilly and Co.	N	00002-3229-07	CAP	40 mg
Celexa	citalopram hydrobromide	Dispensexpress Inc.	N	68115-0797-00	TAB	40 mg
Citalopram	citalopram hydrobromide	Mylan Pharmaceuticals	Y	00378-6231-01	TAB	10 mg

In this study, NDCs were used to define exposure. Because of the variety of information encoded in a given NDC, and the large number of potential combinations of dose, form, manufacturer, ingredient, and similar information possible for a given drug, the total number of unique NDCs found in IBM's *RED BOOK* drug database for all 104 prescribed psychotropic compounds is 36,282 (Micromedex, 2019).

3.2.3 The Unexposed

To estimate the relative hazard of potential ADRs (PADRs) after exposure to prescribed psychotropics, a group of Colorado children never exposed to these drugs was selected from the APCD extract. Following studies in the literature review that employed similar methodological features as this one (use of claims databases; drug-exposed study subjects compared to otherwise similar but *never*-exposed subjects; Jerrell and McIntyre, 2008; McIntyre and Jerrell, 2008), I used R's *sample* function

to randomly sample a control group of 42,362 unexposed members whose first record in the APCD extract appeared between the ages of 6 and 12. Unexposed members are APCD children who not only do not meet this study's exposure definition, but who have no exposure whatsoever to prescribed psychotropic drugs at *any* point in their APCD records.

In this study, my a priori interest is in a comparison between drug-exposed and never-exposed – that is, untreated – children. This contrasts with similarly structured studies which employ comparison groups who are treated in some way, but treated differently: study participants taking a new drug are compared to participants taking an existing drug, for instance. In these cases, both groups have an analogous starting point in the data because they have treatment status as an anchor. Here, the way the unexposed are selected *must* be different from the way the exposed are selected: it is not possible to select the unexposed as having first been treated between ages 6 and 12 because they are not treated by definition. As a result, in statistical analyses, followup for the unexposed began at their first record. This is one of this study's limitations, and could be mitigated in future work by including new control groups. Comparing those who begin psychotropic treatment between 6 and 12 with never-exposed children as well as, say, children who began treatment after age 12 could offer a more complete view of potential harm from psychotropics.

The exposed and unexposed groups were combined to form this study's analytical sample.

3.2.3.1 Control group size and statistical power

This study's literature review, the reference literature, and sample size calculation methods helped to determine the size of the control group. The ratio of drug-exposed group size to unexposed group size varied in 6 studies employing a 2-group comparison reviewed for this analysis, and there was no reporting of justification for investigators' choices. In their 2 papers, Jerrell and McIntyre (2008; 2008) compared antipsychotic-exposed children to never-exposed children to assess the odds of various classes of physiological adverse events. In both studies, a treatment group of 4,140 children was compared to a randomly-sampled unexposed group of 4,500 children – a 1:1.09 ratio of exposed to unexposed. While one paper (McIntyre and Jerrell, 2008) stated that there was sufficient statistical power in both groups to detect "somewhat low-incidence conditions", neither paper explicitly justified the control group size, nor were power calculations presented to the reader. Dalsgaard (2014; 2011) compared 5,482 stimulant-treated Danish minors to 2,818 untreated controls, an approximately 2:1 ratio, but they did not report a justification for this choice, either, nor was statistical power mentioned in the published study. By contrast, Patel (2017) used a 1:2 ratio to assess the effect of psychotropic exposure on BMI. While not specifically discussed, these choices appear to be artifacts of the dataset used in the study and inclusion criteria for each group. Wang (2018) compared 59,746 ADHD-diagnosed Taiwanese boys to 52,008 randomly selected and untreated controls, but did not justify that control group size.

Recommendations about overall and control group sample size in the epidemiological reference literature vary by study design. In case-control studies, where subjects are selected by outcome (disease) status and followed backwards in time to

assess potential causes (Rothman, Greenland, and Lash, 2008; Woodward, 2013), a large number of controls – at least double the number of cases – is recommended (Taylor, 1986). This is because the number of cases is often fixed at a small number in settings like hospitals where this design is frequently used. This leaves investigators with a need for statistical power they can find in non-diseased controls, who are typically much easier to locate (Woodward, 2013). Authors highlight that gains in statistical power to correctly detect an effect of a given size diminish quickly with higher numbers of controls, making ratios higher than 1:3 unnecessary for most applications (Taylor, 1986).

Recommendations for cohort studies like this one are less emphatic about the size of the control group *per se*, highlighting instead the frequent need for overall sample size to be much larger than case-control studies (Woodward, 2013). Unlike in case-control studies, where sample size requirements depend on the proportion of non-diseased controls who are exposed, sample size in cohort studies depends upon the incidence of the outcome in the unexposed (Schlesselman, 1974).

In the APCD extract, 42,362 children met this study's exposure definition. To determine an appropriate group size for unexposed controls given this study's features, I simulated several survival analysis scenarios in R using the `powerSurvEpi` and `rpact` packages (Qiu, Chavarro, Lazarus, Rosner, and Ma, 2021; Wassmer and Pahlke, 2022). These packages implement a power calculation formula designed for Cox proportional hazards regression analyses in epidemiological studies (Latouche, Porcher, and Chevret, 2004).

Tables 3.5 and 3.6 summarize required sample size and resulting statistical power, respectively, in several versions of a hypothetical two-group cohort study analyzed

Table 3.5

*Required sample sizes for various ratios of exposed to unexposed in a simulated two-group cohort study**

	Required sample size		
Exposed:Unexposed	Exposed	Unexposed	Total
3:1	38,194	12,731	50,925
2:1	28,791	14,395	43,186
1:1	19,097	19,097	38,194
1:2	14,395	28,791	43,186
1:3	12,731	38,194	50,925
1:4	11,936	47,742	59,678

*Simulation attributes: desired power: 0.8; alpha: 0.05; hazard ratio: 1.50; incidence of outcome in unexposed: 0.005.

Table 3.6

*Statistical power yielded by various sample sizes in a simulated two-group cohort study**

	Sample size			
Exposed:Unexposed	Exposed	Unexposed	Total	Power
3:1	127,086	42,362	169,448	0.9992
2:1	84,724	42,362	127,086	0.9978
1:1	42,362	42,362	84,724	0.9865
1:2	42,362	84,724	127,086	0.9979
1:3	42,362	127,086	169,448	0.9998
1:4	42,362	169,448	211,810	0.9995

*Simulation attributes: alpha: 0.05; hazard ratio: 1.50; incidence of outcome in unexposed: 0.005.

with Cox proportional hazards regression models. Table 3.5 describes various ratios of exposed to unexposed group size for a study with specified attributes (power = 0.8; alpha = 0.05; hazard ratio = 1.50; incidence of outcome in unexposed = 0.005). It suggests that changing this ratio from 1:1 in either direction increases the required sample size of the study. Table 3.6 calculates the statistical power to detect a 50% increase in the hazard of the outcome (i.e. an HR of 1.5) in the same ratios of exposed to unexposed as Table 3.6. In this table, sample size – based on multiples of the 42,362 exposed in the APCD extract – is varied in different scenarios. The reader can see that even in a 1:1 scenario, statistical power is 0.99 – substantially higher than typical requirements in observational studies. We can expect power to be somewhat lower in this study's analyses, largely because the statistical packages used in these calculations did not permit the addition of more than two covariates of interest in the hypothetical study. Still, we see that APCD data are more than capable of yielding sufficient power for this study. For this reason, I chose a 1:1 ratio for this study.

3.2.4 Outcomes

In this study, I investigated the potential effects of psychotropic drug exposure on human physiology in children. This yielded a large number of PADRs for analysis, and different ways of grouping them. In general, however, outcomes were grouped according to major physiological system according to their organization in *Meyler's Side Effects of Drugs* (2015) and *IBM Micromedex* (Micromedex, 2019), two authoritative reference collections. *Meyler's* is an encyclopedia of monographs of over 1,500 individual drugs both licit and illicit, each containing detailed information about

adverse drug reactions reported in a litany of sources, including spontaneous adverse event reporting systems in different countries, as well as the research literature. Each monograph, written by experts in that drug or class of drugs, essentially constitutes an ADR-specific literature review, lending the collection its authority. Importantly, entries report ADRs of various degrees of confirmation: one or two hints from case reports are as likely to be included as larger, controlled studies of the same possible reaction. While *IBM Micromedex* is both fully online and more expansive in scope, including drug information not related to safety, it takes a similar approach to documentation as *Meyler's*, collecting indications of known or PADRs from a wide variety of sources and presenting them to the reader in one place. As such, both overlap greatly. Three "direct hit" studies in this study's earlier literature review organized their outcomes similarly, grouping by physiological system or function (McIntyre and Jerrell, 2008; Jerrell and McIntyre, 2008; Storebø et al., 2018).

The outcomes of interest to this project are health conditions and diseases. Outcomes were drawn from two sources: the empirical research literature on psychotropic drug side effects and adverse events; and the medical reference literature, in particular *IBM Micromedex* and *Meyler's Side Effects of Drugs*[2] (15th and 16th Editions; henceforth *Meyler's*). From these sources, I developed a database of every known or suspected PADR of every prescribed psychotropic drug, grouped into 29 human physiological systems. An initial total of 1,116 adverse drug reactions of varying degrees of confirmation, across all physiological systems, were found. 293 of these were

[2]Meyler's and Micromedex are themselves partially derived from the empirical literature on drugs, side effects, and consequences, so there was some duplication of work here, and as a result I relied more on these sources – they have hundreds of contributors combing the literature in their medical specialty, whereas my reach was much more limited. New editions of the text are published every 8 to 10 years, but rolling annual updates are issued using new information from the research literature and other sources.

removed for various reasons: most (n=130) were behavioral / psychological / psychiatric effects (e.g. mania, depression) that are not of interest in this project, while others (n=63) *are* physiological but deal with types of reactions either outside of my interest, the ability of this dataset to analyze rigorously, or both (e.g. events or conditions related to death, teratogenicity,[3] withdrawal, etc.). A further 336 ADRs were identified by medical billing professionals and clinicians as duplicate conditions. For instance, "atrial dysrhythmia" and "worsening of atrial dysrhythmia" correspond to the same ICD-9 and ICD-10 codes. (See the next section on outcome conversion and validation.) Table 3.7 summarizes the remaining 587 physiological ADRs by physiological system. Nervous system/neurological reactions are by far the most common, accounting for 28.4% of ADRs; cardiovascular (9.2%), endocrine (6.6%), hematologic (6.5%), and skin reactions (6.3%) round out the top five categories, which together account for almost 60% of ADRs. Table 3.8 gives two example ADRs for each of these five categories.

3.2.4.1 ICD conversion and validation of outcomes

To be used in this project, each of the outcomes (PADRs) in my database had to be converted into a corresponding International Classification of Diseases (ICD) version 9 and version 10 code. (Both versions were required because the change from version 9 to 10 occurred in 2014, during the time span of the data under study.) This could have be done manually and for free, but since I am neither a physician, a nurse, nor pharmacist, attempts at such matching would suffer from inexperience and potentially yield misleading results in analysis. While some outcomes could be easy

[3]The ability to induce birth defects.

Table 3.7

Documented adverse psychotropic drug reactions by physiological system

Physiological system	Potential ADR (n)	Percent
Nervous/neurological	167	28.4
Cardiovascular	54	9.2
Endocrine	39	6.6
Hematologic	38	6.5
Skin	37	6.3
Sensory	36	6.1
Metabolic	32	5.5
Gastrointestinal	31	5.3
Immunologic	25	4.3
Respiratory	19	3.2
Urinary	18	3.1
Sexual function	18	3.1
Liver	17	2.9
Musculoskeletal	12	2.0
Mouth & teeth	6	1.0
Body temperature	5	0.9
Reproductive	4	0.7
Electrolyte balance	4	0.7
Mineral balance	4	0.7
Fluid balance	3	0.5
Ear, nose & throat	3	0.5
Pancreas	3	0.5
Nutrition	3	0.5
Infection risk	2	0.3
Sweat glands	2	0.3
Nails	2	0.3
Neuromuscular	1	0.2
Hair	1	0.2
Salivary glands	1	0.2

Table 3.8

Examples of adverse psychotropic drug reactions by physiological system

Physiological system	Adverse drug reaction
Nervous/neurological	Bruxism
	Parkinsonism
Cardiovascular	Hypertension
	Myocardial infarction
Endocrine	Hyperprolactinemia
	Menstrual disturbances
Hematologic	Bruising
	Hemolysis
Skin	Acne
	Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

to look up and match correctly in ICD databases, others might potentially match with more than one code or no code. Professional "translation" of descriptions of PADRs into ICD-9 and ICD-10 codes was needed.

To do this, I enlisted A.S., a certified medical billing and coding professional with extensive experience in the validation of diagnostic (ICD) and procedure (Current Procedural Terminology or CPT) coding in healthcare settings. For each PADR description (e.g. "cardiac dysfunction (due to carnitine deficiency)"), she provided matching ICD-9 and ICD-10 codes, as well as indications of duplicate conditions for cases in which two seemingly distinct descriptions actually "translated" into the same ICD code(s). An important aspect of ICD coding bears mentioning here: an individual ICD code may refer to one specific health condition, or to one of many very closely related variations on that condition. ICD entries all have a subsection on ICD *synonyms*, alternative names for the same underlying concept, including

common terms and medical jargon (World Health Organization, 2022).

Table 3.9 shows two examples of PADR to ICD translation and the potential ambiguity that can arise from related conditions – synonyms – that a clinician or biller may appropriately use to bill for a clinical encounter. The first row contains a straightforward example: the PADR description from the reference literature, "Acute myopia", is matched to ICD-9 code 367.1, whose label is "Myopia".[4] This entry has 3 synonyms, all of which match commonsensically to the label. By contrast, the second row is less straightforward. Its PADR description, "Convulsions", is matched to the ICD-9 code for "Other convulsions", which contains 104 synonyms, any of which can validly use the code 780.39 for billing.

[4]Matching ICD-10 codes are excluded from this table for brevity.

Table 3.9

Examples of PADR to ICD "translation"

PADR name	ICD diagnostic label	ICD-9 synonyms	ICD-9 Code
Acute myopia	Myopia	Bilateral myopia; Right myopia; Left myopia	367.1
Convulsions	Other convulsions	Abdominal seizure; Absence seizure; Absence seizure with atonic components; Absence seizure with autonomic components; Absence seizure with impairment of consciousness only; Absence seizure with mild clonic components; Afebrile seizure; Affective seizure; Alcohol withdrawal-induced convulsion; Alcohol-related fit; Anoxic seizure; Atonic seizure; Atypical absence seizure; Auditory seizure; Central convulsion; Clonic seizure; Cognitive seizure; Complex part seizure with impairment of consciousness only; Complex partial seizure + impairment consciousness at onset; Complex partial seizure evolving to generalized seizure; Complex partial seizure with impairment of consciousness; Convulsive syncope; Coordinate convulsion; Daily seizures; Dysmnesic seizure; Dysphasic seizure; Eclamptic seizure; Electroencephalogram abnormality with seizure; Epileptic cry; Familial febrile convulsions; Focal motor seizure; Gelastic seizure; Generalized seizure; Generalized-onset seizures; Gustatory seizure; Had a fit; Hypoglycemia-induced convulsion; Ideational partial seizure; Isolated seizures; Lowered convulsive threshold; Movement partial seizure; Non-convulsive simple partial status epilepticus; Nonspecific paroxysmal spell;Olfactory seizure; On examination - fit/convulsion; On examination - focal fit; On examination - grand mal fit; On examination - petit mal fit; Partial seizure; Partial seizure evolving to secondary generalized seizure; Partial seizure with illusions and hallucinations; Partial seizure with impaired consciousness; Partial seizure with multiple symptoms; Pattern sensitive seizure; Phonatory seizure; Post-ictal state; Postseizure delirium; Postural seizure; Puerperal convulsion; Raised convulsive threshold; Reading seizure; Secondarily generalized seizures; Seizure; Seizure after head injury; Seizure as late effect of stroke; Seizure causing illusions; Seizure disorder as sequela of stroke; Seizure related finding; Seizure undetermined whether focal or generalized; Seizure with provoking factor; Seizure with structured hallucinations; Seizure; generalized; Seizure; single; Seizures; Seizures as late effect of stroke (disorder); Seizures complicating infection; Seizures complicating intracranial hemorrhage; Seizures complicating intracranial hemorrhage in the newborn; Seizures due to metabolic disorder; Seizures in response to acute event; Seizures w provoking factor; Seizures; generalized; Seizures; late effect of stroke; Simple partial onset of seizure with automatisms; Simple partial onset seizure followed by impaired consciousness; Simple partial seizure evolving to generalized seizure; Simple partial seizure evolving to secondary generalized seizure; Simple partial seizure followed by impaired consciousness; Simple partial seizure with autonomic dysfunction; Simple partial seizure with focal motor signs with march; Simple partial seizure with focal motor signs without march; Simple partial seizure with motor dysfunction; Simple partial seizure with somatosensory or special sensory dysfunction; Simple partial seizure with special sensory symptoms; Simple partial seizure; consciousness not impaired; Single epileptic seizure; Single seizure; Somatosensory seizure; Startle partial seizure; Stress seizure; Tetanic convulsion; Tonic-clonic seizure; Versive seizure; Visual seizure	780.39

The 587 PADRs found in the reference literature were translated into 583 distinct ICD codes. With a complete list of ICD codes, I then recruited V.M., a second certified medical coder, to validate A.S.'s ratings. I randomly sampled 50 outcomes from the ADR dataset and gave them to V.M. to turn into ICD-9 and -10 codes, using the same template and instructions given to A.S.. I then compared each rater's ICD codes of those 50 outcomes (2 codes for each outcome) to calculate a percentage agreement score. For ICD-9 codes, the two raters agreed on 63.2% of outcomes, while for ICD-10 codes, raters agreed on 59.2% of outcomes. This yielded an overall agreement percentage of 61.0%. (A.S.'s codes were kept in cases of disagreement, as they have more coding experience than V.M.) While better than chance, this is not as high a degree of agreement as was expected or desired, and speaks to unanticipated ambiguities in medical coding. Given the codes' importance to this study's analysis, ICD "conversion" represents a potential source of uncertainty, and thus a potential threat to the study's internal validity. The relatively low degree of agreement between raters is a limitation of this study, and is treated further in the Discussion.

Of note, none of the empirical studies reviewed above included any description of procedures for turning outcomes (e.g., "diabetes") into accurate ICD codes ("E08.10"), nor were any analyses or validation of the reliability of those procedures included in that literature. I also searched Embase and Google Scholar for any studies, regardless of medical subject heading (MeSH), employing any methods to assign correct ICD codes to disease descriptions.[5] In reviews and validation studies, the potential inaccuracy of ICD code assignment was frequently cited as a limitation of

[5]Search terms included "ICD assignment", "assign diagnostic code", "correct ICD", and other variations.

research using administrative claims databases (Steinberg, Whittle, and Anderson, 1990). But I found no empirical studies that discussed the authors' own methods of assigning codes in a specific use of such databases. Still, some publications lent credence to the approach I took in this study. Steinberg et al. (1990) referred to a combination of "highly experienced medical coders with physician backup" as a way to establish correct ICD codes, and Schrepf et al. (2020) used expert panels to arrive at consensus on which ICD codes accurately represented chronic overlapping pain conditions (COPCs). (Though specific mechanisms for arriving at such consensus were not described, and the authors described "little to no disagreement between the experts".) I believe that these examples put my approach on solid ground.

3.2.4.2 Outcome grouping & seriousness

In the APCD dataset, outcomes of interest are expressed as ICD codes, and dependent variables in survival-analytic regression models are *groupings* of these codes by human physiological system. Instead of estimating the hazard ratio (HR) of, for instance, *diabetes mellitus* comparing psychotropic-exposed and unexposed children, models estimated HRs of the observed group of *metabolic system events* in the exposed and unexposed groups that includes diabetes and others.

In analyzing groups of outcomes instead of individual conditions, a trade-off was made in favor of breadth (with a loss of specificity). By grouping outcomes together, the number of observed outcomes used in statistical analyses are increased, leading to more precise estimates of ADR hazard. As a signal detection exercise, an analogy could be made to photography: before taking a close-up of an individual tree, we might first want to make a wide-angle shot of the forest. Given a strong "signal" in

a given physiological system in this study, future studies might look at that system's PADRs in more detail.

Built-in outcome grouping by physiological system is useful, but the issue of seriousness is untouched: reporting a hazard ratio for central nervous system outcomes is not of much value if that outcome grouping contains both mild dizziness and intracerebral hemorrhage. Inspired by Storebø and colleagues' (2018) use of International Conference on Harmonization (ICH) guidelines in their review of methylphenidate-related adverse events, I made groupings of "serious" PADRs for each physiological system for use as dependent variables in separate statistical analyses. Serious and non-serious ADRs are defined by the ICH as follows:

- *Serious Adverse Drug Reactions* are any untoward medical occurrences that at any dose
  - result in death,
  - are life-threatening,
  - require inpatient hospitalization or prolongation of existing hospitalization,
  - result in persistent or significant disability/incapacity, or
  - are a congenital anomaly/birth defect.
- *Non-serious Adverse Drug Reactions* are all other ADRs, including but not limited to common adverse events such as cardiovascular, neurological, and gastrointestinal events (ICH, 1995, 1996).

To identify which PADRs are serious according to the ICH definition, I recruited

3 healthcare providers to assign a rating of either "serious" or "not serious" to every outcome:

- Rater 1, a Certified Pediatric Nurse Practitioner (C.P.N.P) currently working in pediatric neurosurgery and with experience in pediatric primary care.
- Rater 2, a Certified Pediatric Nurse Practitioner (C.P.N.P) with clinical experience in pediatric primary care and pediatric psychiatry.
- Rater 2, a Pharmacist (PharmD) currently employed in a Northeastern US children's hospital, and with extensive experience in pediatric pharmacology and pharmacotherapy.

These clinician-raters were given a document containing an introduction to the project, the ICH definition of ADR seriousness, and detailed instructions for rating. A Microsoft Excel template containing each outcome description along with fields for their rating (serious or non-serious) and notes (for questions, comments, similarities to other outcomes, etc.) was also included. Raters were asked to conceive of each outcome description as a separate, miniature clinical case description, and to base their evaluation of either "serious" or "non-serious" on it: a hypothetical minor older than age 6 presents with their caregiver to the rater's clinic with the condition listed in that row of the Excel sheet.

Table 3.10

Inter-rater reliability (Fleiss's κ) for clinician ratings of PADR seriousness

Rating tasks (N)	Raters (n)	Value	Statistic	p-value
587	3	0.44	z = 8.13	p<0.001

Table 3.11

Benchmarks for interpretation of Fleiss's κ proposed by Shrout (1998)

Kappa	Strength of agreement
0.00 - 0.10	Virtually none
0.11 - 0.40	Slight
0.41 - 0.60	Fair
0.61 - 0.80	Moderate
0.81 - 1.00	Substantial

Completed ratings were then combined into a single dataset to perform inter-rater reliability (IRR) analysis, and to decide on a final seriousness rating for each PADR from the 3 given by the independent raters. To estimate IRR for seriousness ratings, I used Fleiss's κ, a popular method of assessing agreement reliability in situations with categorical ratings and more than 2 raters (Fleiss, Levin, and Paik, 2013; Landis and Koch, 1977). Like its more popular cousin, Cohen's κ (which works only with 2 raters), Fleiss's κ can be interpreted as the proportion of observed agreement about N rating tasks by n raters, compared to the agreement expected if ratings were allocated randomly. Table 3.10 shows that the value of κ for clinician seriousness ratings is 0.44 (N=587, n=3, $p<0.001$), which indicates a fair level of agreement according to benchmarks proposed by Shrout (1998), replicated in Table 3.11. Complete ratings for all 587 PADRs are summarized in Appendix Table A.1.

3.3 Data management

The APCD extract acquired from CIVHC is a relational database: a collection of tables, each consisting of rows and columns, that describe different data and are connected to each other using relational operators. As constructed by CIVHC, the

APCD consists of 13 distinct tables, each describing an aspect of the business of healthcare in Colorado: a list of eligible members of the data (i.e. users of healthcare, in this case children); records of pharmacy claims; records of medical claims; tables corresponding to different data about healthcare providers; diagnoses, etc.

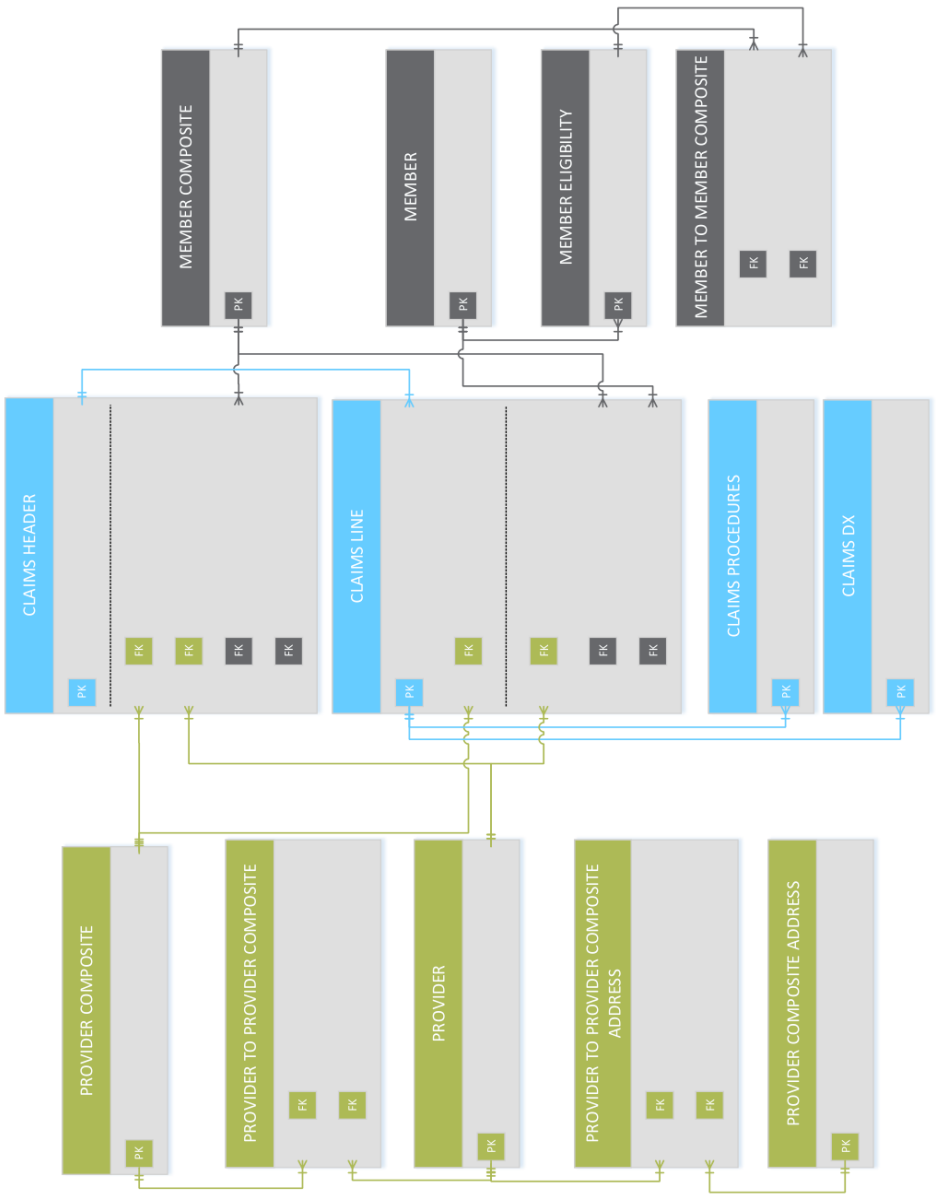


Figure 3.2. Entity relationship diagram (ERD) for the APCD dataset

Figure 3.2 shows the APCD's *entity relationship diagram* or ERD, a map that explains the logical structure of relational databases, with the labeled squares each representing a single table and the lines connecting them describing the specific relation one table's variables have to another table's. To these 13 tables, two tables were added, both of my own creation: a "master" list of all prescribed psychotropic drug National Drug Codes, which served as study exposures; and a similar list of PADRs grouped by physiological system, which served as outcomes.

Table 3.12

Summary of dependent variables in analytical sample

Variable name	Variable label	Description	Measurement level	Coding
adr_indicator	PADR (Overall)	PADRs of either level of ICH seriousness (serious and non-serious) in any physiological system.	Binary categorical	0 = no ADR 1 = ADR
adr_cns	PADR (CNS)	Nervous/neurological PADRs of either level of ICH seriousness (serious and non-serious).	Binary categorical	0 = no ADR 1 = ADR
adr_gi	PADR (GI)	Gastrointestinal (GI) PADRs of either level of ICH seriousness (serious and non-serious).	Binary categorical	0 = no ADR 1 = ADR
adr_sensory	PADR (Sensory)	Sensory PADRs of either level of ICH seriousness (serious and non-serious).	Binary categorical	0 = no ADR 1 = ADR
adr_ent	PADR (ENT)	Ear, nose, & throat (ENT) PADRs of either level of ICH seriousness (serious and non-serious).	Binary categorical	0 = no ADR 1 = ADR
adr_serious_any	Serious PADR (Overall)	Serious PADRs in any physiological system	Binary categorical	0 = no ADR 1 = ADR
adr_serious_cns	Serious PADR (CNS)	Serious nervous/neurological PADRs	Binary categorical	0 = no ADR 1 = ADR
adr_serious_sensory	Serious PADR (Overall)	Serious sensory PADRs	Binary categorical	0 = no ADR 1 = ADR
adr_serious_cardio	Serious PADR (Overall)	Serious cardiovascular PADRs	Binary categorical	0 = no ADR 1 = ADR
adr_serious_resp	Serious PADR (Overall)	Serious respiratory PADRs	Binary categorical	0 = no ADR 1 = ADR

Table 3.13

Summary of independent variables in analytical sample

Variable name	Variable label	Description	Measurement level	Coding
exposed	Psychotropic exposure	2-level indication of 1st psych. prescription between 6 and 12, with ≥2 total prescriptions within 180 days of the 1st.	Binary categorical	0 = unexposed 1 = exposed
age_whole	Member age	APCD member age, rounded to the nearest whole number.	Ratio	E.g. 6, 7, 8, etc.
member_gender_cd	Gender / sex	Member's gender	Binary categorical	0 = female 1 = male
psych_poly	Psychiatric polypharmacy	Indicates whether an exposed member has >1 psych. drug in their APCD records.	3-level categorical	0 = 1 drug 1 = 2 drugs 2 = 3 or more drugs
hh_income_zip	ZIP-code-level household income	Median income category of member's ZIP code.	Ordinal	0 = Low income 1 = Middle income 2 = High income
epilepsy	Epilepsy disorder diagnosis	Indicates whether an APCD member's records contain >1 of 65 ICD codes for epilepsy.	Binary categorical	0 = No epilepsy 1 = >1 epilepsy Dx
exposure*time	Psychotropic exposure by time interaction	Checks whether relationship between exposure and ADR hazard varies with time.		

3.3.1 Multiple events or repeating diagnoses? Challenges in managing the APCD data

Getting the APCD dataset into a form ready for descriptive and statistical analysis was challenging, and important decisions about this study's methodological approach were made as a result. During this data preparation, early attempts at exploratory data analysis and simple survival models yielded suspicious results: implausibly high numbers of PADRs per exposed subject, for instance, and very large hazard ratios for ADRs for drug-exposed children compared to controls. Closer investigation revealed critical – and until that point, unnoticed – details about how the APCD database organizes information.

The first relates to how information is organized on claims forms. As Figure 3.2 shows, claims information (represented by the 4 blue boxes) is divided into 4 categories: header, line, procedures, and DX (diagnoses). The first two – header and line – represent the main categories of information in a medical claim. The *header* is a higher-level summary of claim information that includes patient information like name and date of birth as well as a primary diagnosis code and the identification code of the clinician providing care. The *line* section contains more detail about the specific care provided on the dates specified, including any procedure codes and corresponding diagnosis codes. This means that a patient given a diagnosis for a single health condition on a specified day, but who sees several different clinicians, each of whom does a different kind of work, may have repeated entries of the same diagnosis when their insurance company receives their claim. For example, a person's broken arm may be initially diagnosed and treated by a physician in an emergency room, but shortly afterward may be sent to get an X-ray. In this scenario, both the

ER physician and the X-ray technicians would be represented on the patient's claim form as having provided care – each with a different procedure code, but each with the same diagnosis of a fractured humerus. By the time this claim's data is added to Colorado's APCD, the ER doctor and X-ray tech each have their own row, each with a mention of the same diagnosis. The upshot is that, without careful removal of these "duplicate" diagnoses, descriptive and statistical analysis of the APCD data in the context of this study may "reveal" many more instances of PADRs than actually occurred.

The second wrinkle builds on the first: subjects may have "repeat" diagnoses several days, weeks, or months later. In the example above, it is likely that the subject will again seek medical care, perhaps with their primary care physician, to follow up on their broken arm. This encounter, which takes place 14 days after the initial ER visit, also yields a medical claim – one with (potentially) the same diagnosis. Of course, it is the same fractured humerus as 2 weeks prior, but the claim information may not say so. A closer look at the APCD extract showed that cases of same- and multiple-day "repeated diagnostic codes" were common.

Therefore, for the above reasons, the decision was made for this study's analyses to only count the first instance of a given diagnostic code as a potential outcome of interest in both descriptive and regression contexts. This was a trade-off: on the one hand, information about PADRs that I would want to include may be lost (continuing the analogy above, the hypothetical patient may fracture their humerus again 3 years after the first time), but on the other hand, I ensured a more conservative and meaningful approach to the data. Importantly, this decision did not attenuate or threaten one of this study's central ambitions: to account for psychotropic drugs' potential to cause more than one form of harm to the human body. In other words, the

de-duplication procedures used to handle repeating instances of the same diagnosis still allowed analyses to "see" that a hypothetical subject may experience tachycardia 3 months after drug exposure and impaired vision 7 months after exposure.

This puzzle served as a good reminder that using administrative claims data in biomedical research is fundamentally improvisational. These datasets are not purpose-built to investigate human health; they are made to transmit, validate, and process health insurance claims and payments. This dissertation project has shown several times how different these two purposes are.

3.3.2 Variables of interest

Tables 3.12 and 3.13 described the variables in the analytical sample employed in survival analytic models. Ten models were specified – one for each dependent variable described in Table 3.12 – and each used the independent variables described in Table 3.13.

3.3.2.1 Age & gender

The chosen age-range for prescribed psychotropic exposure – ages 6 to 12 – is a special time in the human lifespan. Not only is it a "critical period" of explosive but vulnerable physiological and psychological development, as discussed above; it is also the cusp of puberty, the stage of life during which human beings become capable of reproduction. Boys and girls become young men and women around this time period, and they do so in different ways and at a different pace: the onset of puberty in girls is as low as 9 years of age, while boys begin later, around age 12 (Venes, 2017). With little known about long-term harms of psychotropics first prescribed in this stage of

life, age and gender are an important part of the methodological approach in this study. Each are used as lenses through which to describe the APCD data, and both are also used as control variables in statistical analyses.

The majority of clinical research studies report basic demographic characteristics about their subjects, and how many participants were male or female, boys or girls, or men and women is often one of the first reported. The variable is sometimes referred to as "sex", and other times as "gender", but it is often unclear what is meant by these terms (Deutsch, Keatley, Sevelius, and Shade, 2014). This is especially the case in light of the current advances in the scientific understanding and social and political awareness of the distinction between sex and gender. Generally, sex is defined as a biological characteristic that differentiates men and women at the level of chromosomes, sex organs, and hormonal profiles. Gender refers to socially constructed behaviors and roles that take place in specific social and historical contexts, and which vary over time and between cultural groups (National Institutes of Health, 2022). These include how people perceive and present themselves (identity); explicit or unspoken norms and attitudes about gender; and how people of different gender identities relate to each other, especially in the context of power (Clayton and Tannenbaum, 2016). The APCD contains a variable `member_gender` that indicates whether members are *Male*, *Female*, or *Unknown*. Since the APCD is a synthesis of Colorado's many public and private insurers' claims data, it is unclear to what degree this variable refers to biological sex or aspects of gender such as identity. For the years included in the APCD extract, the database contained no other sex- or gender-related variables for members.

3.3.2.2 Psychiatric polypharmacy

As discussed in the introduction, the concurrent use of more than one prescribed psychotropic drug in US minors has increased in the last 3 decades with little empirical justification for the practice. In older people, polypharmacy has been established as a risk factor for several forms of potential iatrogenic harm, including ADRs. The potential risks of polypharmacy in adults and the elderly are substantially better understood than in children (Zito, Zhu, and Safer, 2021). Because of this, I believe that polypharmacy is an essential dimension to describe in the APCD data and to use in statistical analyses of ADR hazard. I created a 3-level categorical variable of polypharmacy in psychotropic-exposed Colorado children, with the reference level indicating no polypharmacy (i.e., an exposed member only has prescription records of a single psychiatric compound), and the second two levels referring to 2 drugs and 3 or more drugs, respectively (see Table 3.13). Of note, all other drugs besides psychotropics were not organized or identified because of resource limitations.

This approach contrasts with some in the literature on psychiatric polypharmacy. Other studies look at polypharmacy at the level of drug class; *multi-class* polypharmacy would described a person who takes an antidepressant and a stimulant, for instance. In this study, I define polypharmacy at the level of the drug or compound, not the class. Here, a child prescribed fluoxetine (Prozac) and venlafaxine (Effexor), both antidepressants, would be a child with polypharmacy.

3.3.2.3 ZIP code-level median household income

Several epidemiological studies suggest that the prevalence of psychotropic prescription depends in part on socioeconomic status. Zito et al. (2003) showed substantially

higher rates of psychotropic prescription in children in two US states' Medicaid programs compared to children with HMO health insurance. Zito et al. (2008) further suggest that American foster children – largely members of lower socioeconomic strata – not only have a 3 to 11 times higher prevalence of psychotropic prescription than otherwise poor non-foster youth on Medicaid, but that their rates of psychiatric polypharmacy across drug classes were extremely high: 41.3% of their sample (n=472) had been prescribed psychotropic drugs of 3 or more classes, and 15.9% received drugs from 4 or more classes.

I used members' ZIP code as a proxy for median household income in analyses. My primary aim was to be able to control for any potential economic or geographical effects that could contribute to an exposed-unexposed difference in ADR hazard. To do so, I mapped median household income data for Colorado ZIP codes from the 2013 American Community Survey (ACS) to APCD members' ZIP codes (Bureau of the Census, 2013). The year 2013 was chosen because it constitutes a middle point in the APCD extract's 2009 to 2018 chronology. I then grouped ZIP code-level median household income into 3 income tiers – low, middle, and high – using Pew Research's definition of middle income for US households: households with an income between two-thirds to double the US median household income, which in 2013 was $52,250 (Pew Research Center, 2021). This variable was included as a covariate in all 10 of this study's statistical models.

3.3.2.4 Epilepsy & recurrent seizure disorders

For several decades, antiepileptic drugs have been prescribed as mood stabilizers for people diagnosed with variants of manic depression and bipolar disorder (Harris

et al., 2003). Today, these medications are in wide use in psychiatric contexts, and many users may not be aware of their original purpose. Anti-seizure medications' parallel classification as prescribed psychotropic drugs, and their presence in the analytical dataset, pose a challenge in my analyses: since I seek to model the relationship between these drugs (among other psychiatric drugs) and PADRs of the central nervous system (among other physiological systems), epilepsy and other recurrent seizure disorders are an indication for antiepileptic drug use that could confound the assessment of this relationship. In my database of PADRs of prescribed psychotropics, the subsection of Central Nervous System (CNS) effects includes several seizure- and seizure-related phenomena: for instance, "aggravated epilepsy syndromes" and "complex partial seizure". While these were cited in the reference literature as *potential* effects of prescribed psychotropics, they are certainly potential effects of the idiopathic or traumatic seizure disorders, as well. Without accounting for them, a finding in this study purporting to show that psychotropic exposure increases the hazard of serious CNS events compared to the unexposed may be *confounded by indication* – skewed by the unacknowledged presence of children with seizure disorders in the dataset. (As discussed, confounding by indication is a central concern in studies of drug safety, and the topic is given extended consideration in Chapter 5, this dissertation's Discussion section.)

To account for this, 4 of 10 statistical models include a binary indicator of epilepsy and recurrent seizure disorder diagnoses, `epilepsy_dx`: members with any of a list of 18 ICD-9 or 47 ICD-10 codes for epilepsy disorders (65 in total) in their APCD data are marked 1 on this variable, and marked 0 otherwise. The 4 models that accounted for epilepsy were ones in which PADRs of the central nervous system were included in – or simply were – the regressands.

3.4 Data analysis

This project consists of two main analyses: a descriptive analysis of the exposed and unexposed groups, henceforth called the *analytical sample*; and comparative survival analyses of the hazard of PADRs between drug-exposed and drug-unexposed children. Each of these will be summarized in the following subsections.

Data were cleaned and managed using PostgreSQL, a popular (and free) relational database management system (RDBMS; PostgreSQL Global Development Group Core Team, 2022). All analysis took place in R, with the `survival`, `coxme`, and `Tidyverse` libraries enabling the bulk of descriptive and statistical analysis (R Core Team, 2021; Therneau, 2020, 2021; Wickham et al., 2019). The majority of data visualization was also done in R, using the `ggplot2` and `ggsurvplot` packages (Wickham, 2016).

3.4.1 Descriptive analyses

The APCD dataset provided an opportunity to make a uniquely generalizable, high-level description of a population of minors' use of prescribed psychotropic drugs over a 9-year-long recent time period. Such a description is a useful pharmacoepidemiological exercise in its own right, and not just as an intermediate step before the "proper" statistical analysis in the second phase of this project. Descriptive analyses of the APCD data consisted of database (SQL) queries and statistical observations of the overall APCD data and the smaller groups of drug-exposed ($n_1 = 42{,}362$) and drug-unexposed children to be used in later random effects survival analyses.

Of central interest in descriptive analyses were thorough looks at drug exposure

and outcome (PADR) distribution. First, univariate descriptive analyses were conducted on Colorado youth who met this study's criteria for exposure, characterizing this group by age group, sex, major psychotropic drug class, seizure disorder status, and polypharmacy status. Multivariate descriptions of the exposed followed, looking at psychotropic drug class through the other 3 variables. Outcomes were described similarly, with univariate summaries generated for major physiological system, as well as sex, age, and polypharmacy.

3.4.2 Semi-parametric survival analysis of PADR hazard

Since this study's research questions focus on drug exposure over longer periods of time than other studies, attempting to answer them is a task well suited to survival analysis, a large group of statistical methods for the occurrence and the timing of events (Allison, 2010; Cleves, Gould, Gutierrez, and Marchenko, 2008; Cox and Oakes, 2018; Therneau and Grambsch, 2000). Generally, survival analysis (also known as event history analysis, time-to-event analysis, or reliability analysis, depending on the field) focuses on a group or groups of people for each of whom there is a defined event that occurs after a precisely defined interval of time. In healthcare research, the event of interest is often death; "survival" analyses are thus commonly used to assess how long a group or groups of patients survive after receiving or undergoing an intervention. In epidemiological and pharmacoepidemiological settings, survival analysis is a common and robust method of comparing rates of outcomes or disease between two groups using observational or randomized data (Rothman et al., 2008).

In this study, I fit Cox proportional hazards regression models (henceforth *Cox*

models) to estimate hazard ratios of "serious" and "non-serious" outcomes both overall and in major human physiological systems for children who took drugs, compared to children who did not. While different from an odds ratio (OR) in a logistic regression analysis, the HR is interpretable in an analogous way. For instance, a hypothetical HR of 1.38 for the psychotropic exposure coefficient in a hypothetical Cox model estimating the hazard of ADRs while controlling for other covariates would be interpreted as follows: *the instantaneous relative risk of PADRs between children exposed to prescribed psychotropic drugs is 38% greater than those not exposed, given that both have survived until time t and holding other variables constant.*

Cox regression is an extension of basic survival analytic methods (e.g. the Kaplan-Meier estimator) that, like multiple linear or logistic regression methods, allow an investigator to compare outcomes between groups while accounting for additional characteristics of the participants that may affect or confound those outcomes (Allison, 2010; Klein and Moeschberger, 2006). In short, Cox regression allows for the estimation of the effect of a linear combination of covariates (e.g. exposure to drugs, age, sex) on the time it takes for an outcome (e.g. a suspected ADR) to occur.

3.4.2.1 General concepts of survival analysis

Here, the building blocks of survival analysis are presented to the reader.

Time, events, and **basic notation.** In survival analyses, the dependent variable is time, usually referred to as *survival time*,[6] and is defined the length of time between a specified starting point and endpoint of interest. In this study, a simplified definition of survival time would be "the time from a subject's first exposure to a

[6]It is also commonly known as *failure time* or *event time*.

prescribed psychotropic drug until their first instance of a PADR, the end of their APCD records, or until the end of the study."[7] Survival time is a continuous random variable whose value must be greater than or equal to zero, and is usually denoted T. The symbol t, by contrast, denotes any specific value of T. Both variables have a range of $(0, \infty)$.

Events[8] are phenomena of interest defined by the researcher that mark one of two ways for a subject's survival time to end. The event, typically denoted d, is a binary random variable indicating whether a subject has the event or is censored (more on which below):

$$d = (0, 1) = \begin{cases} 1 & \text{if event} \\ 0 & \text{if censored} \end{cases} \tag{3.1}$$

In common applications, the event of interest is often death, relapse or disease recurrence, or the first appearance of disease. Here, the event of interest is the occurrence of any of a list of potential physiological ADRs. In many survival analyses, the event of interest is terminal, either by nature (death) or because of researchers' specific interest (time to first cancer recurrence). Many health phenomena, however, may recur several times in a single person; a person may also experience several related phenomena. Because exposure to a psychotropic drug may cause multiple ADRs during use, this study seeks to account for a subject's potential for *recurrent events* during the time after psychotropic exposure.

The survival and **hazard functions.** If T is a non-negative random variable

[7]Because of this study's attempt to model the effects of subsequent PADRs in addition to one's first instance, this definition is reductive. More on multiple ADRs per subject, or *recurrent events* in survival analysis terms, in the relevant section below. Further, a subject whose APCD records end before the end of the study would be a *censored* subject; more on that below, as well.

[8]Also known as *failures*.

describing the time that elapses until an event of interest, and t is a specific value of T, the probability of a subject or subjects surviving past a given time t can be described using the *survival function*, $S(t)$:

$$S(t) = Pr(T > t) \tag{3.2}$$

At time $t = 0$, $S(t) = 1$. Put differently, the probability of *not* having the event (surviving, in other words) at time 0 is 1.0. By contrast, as t approaches infinity, the probability of survival decreases, ending like so: when $t = \infty$, $S(t) = 0$.

The *hazard function* $h(t)$ is the survival function's close cousin, and will be at the core of this study's statistical analyses. It represents the instantaneous potential for the event to occur given that a subject has survived to time t. Importantly, the hazard function is a *rate*: it is the probability that the event occurs in a given interval, given that the subject has survived to the beginning of that interval, divided by that interval (Cleves et al., 2008). In simpler terms, the hazard of an event is akin to the inverse of the survivor function:[9] the former is interested in the probability that an event will occur, while the latter focuses on the probability of the event *not* occurring — that is, the probability of surviving. The higher the hazard, the worse the outlook for survival becomes. There is a close relationship between the probability of surviving past a certain time – $S(t)$ – and the amount of risk of the event that has accumulated up until that that time. The function $h(t)$ measures the rate at which that risk grows (Cleves et al., 2008).

The actual shape of the survival and hazard functions are determined by the data-

[9]In fact, each is mathematically derivable from the other.

generating process – the phenomenon under study in the real world. For example, several real-world phenomena appear to follow a so-called "bathtub curve" of the hazard of failure, including human mortality over the lifespan (Bebbington, Lai, and Zitikis, 2007; Cleves et al., 2008). As illustrated in the graph from Bebbington et al. (2007) below, the hazard of mortality in human beings begins somewhat elevated since, despite profound worldwide reductions in infant mortality in the past 150 years, being born remains somewhat dangerous. The hazard falls after birth and plateaus for some time during youth, after which the mortality hazard begins to rise steadily again as the decades pass.

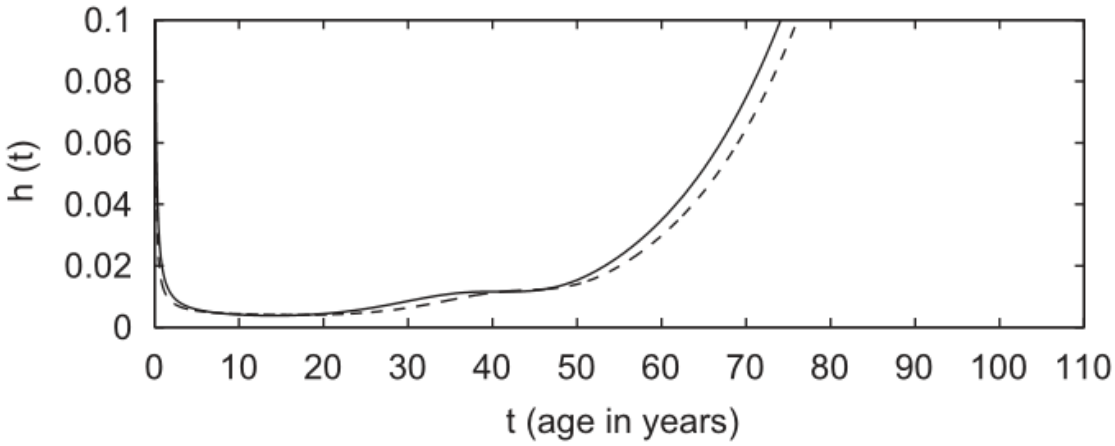


Figure 3.3. Average hazard $h(t)$ of human mortality, from Bebbington, Lai, and Zitikis (2007)

Censoring. Datasets like the APCD which contain information about drug exposures, outcome events, and the times at which each of these occur are subject to censoring, a core problem addressed by survival analysis that broadly refers to uncertainty about survival time for a specific person, subject, or patient (Cox and Oakes, 2018; Rich et al., 2010). In plain English: a subject is considered censored

when we do not know their survival time *exactly* (Kleinbaum and Klein, 2010).

A subject can be considered censored for 3 reasons:

1. A person does not experience the event of interest before the end of the study period.

2. A person is *lost to follow-up* during the study period. For instance, they may cease contact with investigators without warning or explanation.

3. Withdrawal from the study may occur if a person dies (if death is not the outcome of interest), or for some other reason.

The first example is the most common in survival analysis. Because the incompleteness of the observation occurs on the right-hand side, so to speak, of that person's timeline, this is considered an instance of right-censoring, when the true survival time is greater than or equal to the observed survival time.

Censoring is critically important to this study, and to survival analysis generally, because it is a kind of *missing data* problem. Like all missing data, finding a way to deal with it is critical if analyses are to be as unbiased as possible. Some approaches to censoring might take a *complete-case* view, simply ignoring study subjects with any censoring and analyzing only uncensored, complete observations (Leung, Elashoff, and Afifi, 1997). While streamlined, this would be less efficient (one might lose a substantial proportion of sample size). It would also potentially introduce systematic error. Say, for instance, that subjects dropping out of a study (censored as "lost to followup") were doing so because their experimental treatment was injuring them, preventing their return to the clinic, but researchers decided to analyze only those subjects who completed all their appointments. Resulting analyses might show the

treatment to be effective at extending survival time – the opposite of the truth. *Imputation approaches*, common to other missing data problems, encounter similar problems of bias: one could propose a theory of how censoring works and use that to impute complete survival times to censored subjects, but one would then need to justify that model, which would be difficult to check.

Survival methods, by contrast, neither ignore censoring nor try to fill in the blanks, so to speak. Instead, they give censored data its own term in the *likelihood function* underlying a specific survival-analytic model or estimator (Leung et al., 1997). The result is that analyses keep everyone who contributed any survival time, regardless of whether their final outcome status is known. While it is beyond the scope of this dissertation to discuss the details of how this is done, it suffices to say that the likelihood function describes the fit between the observed data and the parameters the data are being used to estimate. Methods that use *maximum likelihood estimation* (MLE) are statistical approaches that seek the values of the parameters p that maximize the probability of the observed data given p (Bayarri and DeGroot, 1992; Rosner, 2015). Logistic regression makes its estimates with MLE, and survival models like the Kaplan-Meier estimator and Cox proportional hazards regression do, as well. But only the latter 2 have a term for censored data built in.

Figure 3.4 displays the survival time of 5 subjects in a hypothetical survival analysis simulated using R. Here, Subject 1 survives to the end of the study without experiencing the event, and Subject 5 is lost to followup after 7.5 years; both subjects are considered censored.

That they account for censoring represents a key advantage of survival-analytic

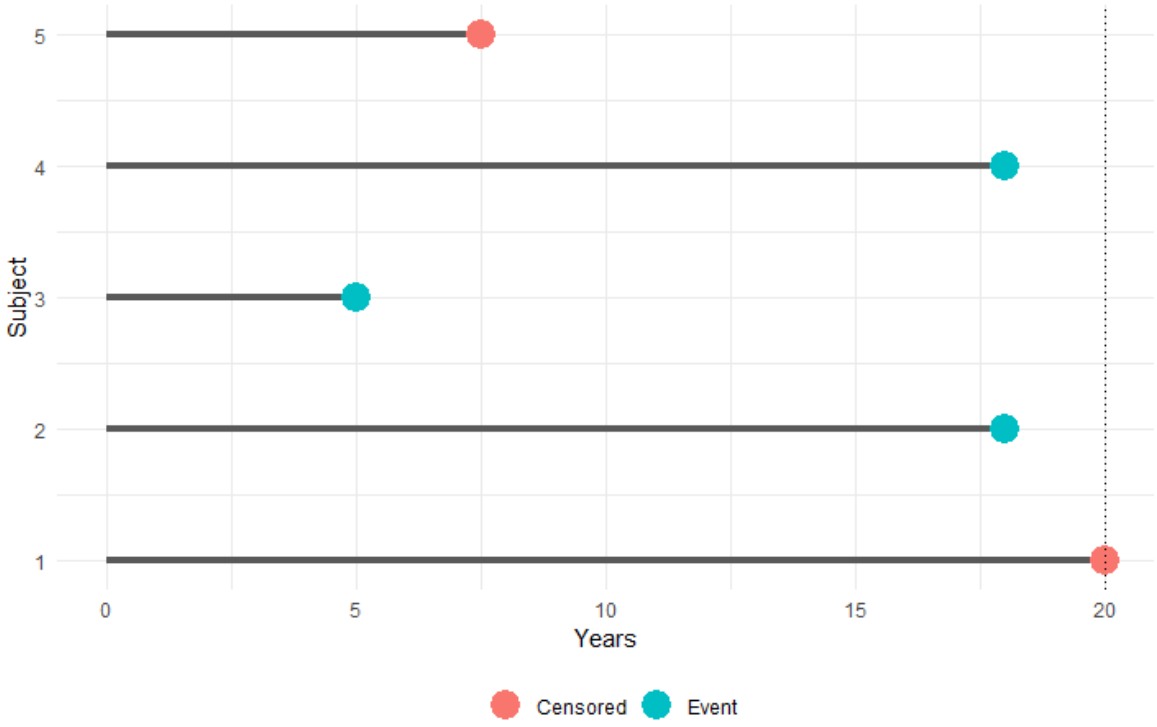


Figure 3.4. Censoring in a simulated 20-year study, n=5

methods over other potentially appropriate analytic methods, several of which do not (or do not without modification).

3.4.2.2 Cox proportional hazards regression

In simple applications of survival analytic methods, only one group of subjects may be of interest: for this group of lung cancer patients treated with chemotherapy, what is the expected hazard of cancer recurrence? But for research questions that concern the comparison of the survival experience (or hazard of the outcome) of two or more groups of people – and want to adjust for potential confounding factors in doing so – other methods are required.

The most popular of these is the Proportional Hazards model developed by David Cox (Cox, 1972; Cox and Oakes, 2018), arguably because of the conceptual components it shares with other regression-based tools many social scientists and biomedical researchers are already familiar with. Like those, the Cox proportional hazards model (often simplified to "Cox regression" or "Proportional hazards regression") features a linear combination of predictor variables on which an outcome of interest is regressed. This allows researchers and readers to carry over some of the same intuition they are accustomed to using in linear or logistic regression scenarios.

The Cox model is attractive to this project for several reasons. First, unlike other regression models, it accounts for information in which the APCD data is quite rich: survival time and censoring. Second, the model allows for the estimation of the effects of several different covariates on the hazard of the outcome, similarly to other regression applications. Third, regression coefficients are interpretable in analogous terms to odds ratios in logistic regression analyses, or risk ratios in cohort studies.

The Cox model is semi-parametric: while part of the model is specified like linear or logistic regression models, and carries similar assumptions about underlying distributions, no parametric form of the survival or hazard functions needs to be specified. This makes implementing a Cox model much simpler than analogous parametric survival methods, and is likely a second reason for its evergreen popularity. The baseline hazard, $h(t)$, does not actually need to be estimated, which in practical terms means that the model makes no assumptions about the "shape" of the hazard of the outcome over time – it might increase at first, then decrease, for instance. The central assumption is merely that the general shape of the hazard is the same for everyone.

This basic form of the model is:

$$h_i(t) = \lambda_0(t)exp(\beta_1 x_{i1} + \ldots + \beta_k x_{ik}) \tag{3.3}$$

Many will recognize the exponentiated portion as the same linear combination of predictors and coefficients from other regression applications. This model states that the hazard of the event for the subject i at time t is the product of 2 components: $\lambda_0(t)$, the hazard function for a subject whose covariates in the linear combination all equal zero; and a linear combination of a set of k covariates which is exponentiated (Allison, 2010). The function $\lambda_0(t)$ is called the *baseline hazard function* and, as stated above, is left unspecified.[10]

[10]The reason that $\lambda_0(t)$ is able to be left unspecified has to do with how the β's are estimated in Cox models – not with the maximum likelihood estimation (MLE) used by logistic regression or the ordinary least squares (OLS) in linear regression, but a procedure developed by Cox called partial likelihood estimation. The details of partial likelihood estimation may be beyond the scope of this dissertation, but it suffices to say that Cox's innovation was to show that the baseline hazard $\lambda_0(t)$ is not necessary to produce robust estimates of regression coefficients.

The primary effect measure in Cox models is the *hazard ratio* (HR):

$$e^{\beta_{exposure}} = \frac{h_{exposed}(t)}{h_{unexposed}(t)} \tag{3.4}$$

It is calculated simply by exponentiating the value of one of the values of β, as shown. In this analysis of the APCD data, the primary β of interest is first exposure to prescribed psychotropic drugs between the ages of 6 and 12, while the outcome is the hazard of PADRs of a physiological nature.

3.4.2.3 The proportional hazards assumption

The central assumption made in Cox models is that the hazard of the outcome for a single subject i at a given time t is a fixed proportion of the hazard of the outcome for another subject j at the same time t. Subject i's hazard may rise, fall, or remain constant over the course of survival time, but subject j's hazard is assumed to behave similarly.

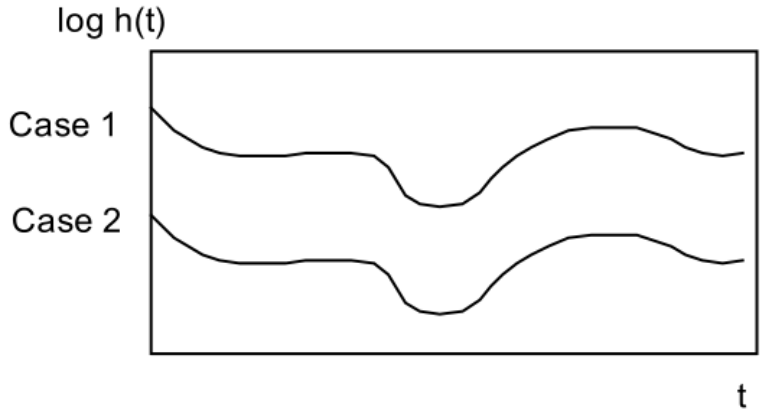


Figure 3.5. Proportional hazards of 2 subjects, from Allison (2010)

Figure 3.5 illustrates this assumption graphically between two hypothetical subjects, with the log-hazard functions of each moving in parallel over time (Allison, 2010).

3.4.2.4 Accounting for multiple events per APCD member using random effects

One of this study's unique features is its attempt to account for a reality thus far little considered in pharmacoepidemiological investigations of psychotropic drug safety in children, namely that human beings who take prescribed psychotropics may experience more than one instance of the same discrete ADR (e.g. headache), or more than one distinct ADR during the time they take the drug (e.g. headache shortly after initial use, then weight gain 4 months later). The issue of *multiple events per subject* or *recurrent events* has drawn substantial interest from researchers and statisticians seeking to extend survival models to different clinical situations, and several tools have been developed to deal with it (Austin, 2017; Balan and Putter, 2020; Crowder, 2012; Therneau and Grambsch, 2000). In this study's main statistical modeling of the relationship between psychotropic exposure and the hazard of PADRs, we employed *shared frailty* terms in models' exposure variables to account for potential recurrent events.

There are two challenges posed by the possibility of a subject having multiple events of interest during their survival time. The first concerns how a Cox model treats subjects with respect to the characteristics that make them different. In a standard Cox model, the hazard function described above describes the distribution of a subject's time to event; different study subjects will inevitably have different

hazard functions because their hazard of the outcome will be different for various reasons. Sicker patients tend to have bad outcomes sooner than healthy patients (disease severity), for instance, and women tend to live longer than men (sex). Cox models account for these sources of *heterogeneity* among study subjects (Balan and Putter, 2020) by being able to include these factors as other independent variables in the linear combination $\beta_1 x_{i1} + \ldots + \beta_k x_{ik}$. Given the value of these variables for a subject in a perfectly specified model (one that measured and included all possible sources of heterogeneity between subjects), the baseline hazard function $\lambda_0(t)$ would reflect, without any "noise", the randomness of the event (outcome) time.

But models cannot be perfectly specified: it is not possible to include all possible sources of between-subject heterogeneity, in large part because it is not possible to know them. This means that a model's independent variables only account for *observed* heterogeneity. Some quantity of *unobserved* heterogeneity is left out of the model, unexplained, but still affecting survival times. The effects of unobserved heterogeneity on survival times are known as *frailty* (Balan and Putter, 2020; Therneau and Grambsch, 2000).

The second challenge is *intrasubject correlation*: because subject i's state at $t+1$ can be assumed to depend at least in part on their state at t, all of subject i's observations will be shown to be correlated even if they remain independent of subject j's. Since Cox proportional hazards models, like other regression models, treat observations as independent, we run the risk of misspecifying models of ADR hazard if, in wanting to model multiple events per person, we do not account for intrasubject correlation. Seen in this light, the APCD dataset looks *clustered* into different levels: (potentially) many observations of one subject (level 2) are nested inside a larger group of observations of many different subjects (level 1). Cox models that

include frailty terms, known as *shared frailty* models, are able to account for the dependence of survival times inside a specified cluster – in this study, a child from the analytical sample – while correctly treating survival times between APCD children as independent. The two challenges are related, as the unknown factors that influence a subject's having multiple or recurring outcome events can be seen as unobserved heterogeneity – a frailty – within a single person. Accounting for this frailty can thus improve a model's internal validity.

In its basic (univariate) form, a frailty model modifies the baseline hazard by including a multiplicative random effect, Z, in describing the hazard of the outcome in an individual i:

$$\lambda_i(t|Z) = Z\lambda(t) \tag{3.5}$$

If individual i has a higher frailty Z, they can be expected to have experienced the outcome sooner than other individuals with the same values of measured covariates but different values of Z. Adding frailty to the whole proportional hazards model works similarly:

$$\lambda(t|Z) = Z\lambda_0(t)exp(\beta_1 x_{i1} + \ldots + \beta_k x_{ik}) \tag{3.6}$$

In this study, I applied the shared frailty term Z to individual APCD members in Cox proportional hazards models to account for potentially recurring ADRs.

3.4.2.5 10 models of potential ADR hazard

With 29 physiological systems into which PADRs were categorized, and 2 levels of ADR seriousness, I faced the prospect of running upwards of 58 separate Cox models. Despite its goal of capturing a wide breadth of types of potential reactions to prescribed psychotropics, calculating, reporting, and discussing that number of models would have proved too resource-intensive for this analysis. At the same time, the number of PADRs observed in several of those physiological systems (in both exposed and unexposed children) may have been too small for models to run validly. Faced with a large number of models, I required a way of paring the number of statistical analyses down while remaining in keeping with the innovations of the study. I decided to specify 10 models, 5 each for ADRs of any ICH seriousness and serious ADRs only, that reflected the most common kinds of PADR by physiological system visible in the analytical dataset.

CHAPTER 4

Results

4.1 Results of descriptive analyses of psychotropic drug exposure in the APCD data

Descriptive analyses are divided into two parts: first, a brief characterization of the larger APCD extract (N = 1,066,005); second, a detailed description of the analytical sample, which only contains drug-exposed and drug-unexposed Colorado children.

4.1.1 APCD extract (N = 1,066,005)

The APCD extract contains records of healthcare claims for the majority of Colorado minors between 2009 and 2018: the 1,066,005 in the extract comprise 86.9% of the 1,225,609 Coloradans under 18 in the 2010 US Census (KIDS COUNT Data Center, 2020). While this is an approximate percentage, owing to the years included in the dataset and the growth in Colorado's population between 2009 and 2018, it demonstrates the APCD's wide coverage of Colorado residents. There were 523,396 girls, 542,100 boys, and 509 members with unknown gender in the extract. On average, these APCD youths remained in the extract for 6.9 years (SD = 2.4).

Table 4.1 outlines exposed Colorado children's psychotropic use by major drug

Table 4.1

Minors with any psychotropic exposure in overall APCD extract (n = 113,299) by major drug class

Drug class	n	Percent*
Antidepressants	58,991	52.1%
Stimulants and ADHD	55,874	49.3%
Antipsychotics	22,256	19.6%
Antimanic / mood stabilizers	21,026	18.6%
Anxiolytic / hypnotic	8,166	7.2%

* Percentages do not sum to 100% because of polypharmacy.

class, showing that stimulants and antidepressants represent a substantial proportion of the distribution. Of the 113,299 minors aged 0 to 18 ever prescribed a psychotropic drug, the average age at fist prescription was 12.4 years (SD = 4.1), and the average duration of psychotropic treatment was 3.1 years (SD = 2.7).[1]

[1]This estimate of treatment duration for the 113,299 ever-exposed minors *does* include minors who had only one psychotropic prescription in their APCD records. Analogous figures, presented below, for mean psychotropic treatment duration in the 42,362 children meeting the study's exposure definition do not, as such children do not meet that exposure definition.

4.1.2 Analytical sample (n = 84,724)

The 84,724 psychotropic-exposed and unexposed children that make up the analysis dataset had a mean follow-up time (defined as the average difference between children's first and last APCD record) of 7.7 years (SD = 2.1 years). In the exposed, mean follow-up time was 7.9 years (SD = 1.9), and in the unexposed it was 6.7 years (SD = 2.5). Children meeting exposure criteria were 8.8 years old (SD = 1.99), on average, on the day of their first psychotropic prescription, and psychotropic treatment lasted, on average, 4.0 years (SD = 2.9). Exposed children experienced an average of 13.7 (SD = 37.5) PADRs during their time in the analytical sample, while unexposed children experienced 3.47 (SD 8.87) per child. On average, most of these were serious: 11.0 (SD = 36.6) serious PADRs in the exposed, and 3.46 (SD = 8.89) in the unexposed.[2] Table 4.2 describes the mean (SD) number of PADRs experienced by exposed APCD members in the first 5 years after their first psychotropic exposure, and shows a declining number of ADRs per year.

[2]In the unexposed, calling them potential *adverse drug reactions* is something of a misnomer, of course: these diagnoses cannot be potential reactions to psychotropic drugs in the absence of such drugs. To keep nomenclature consistent, however, I will continue this usage throughout. The potential influence of non-psychotropic drugs is raised in the Discussion (Chapter 5).

Table 4.2

Mean number of ADRs (any seriousness level) per exposed APCD member in the 5 years after first exposure

	Exposed	
Year	Mean	SD
1	1.94	0.35
2	1.51	0.31
3	1.21	0.28
4	1.01	0.26
5	0.84	0.24

Table 4.3

Exposed members (n=42,362) in analytical sample by major drug class

Drug class	n	Percent
Stimulants and ADHD	32,668	47.5
Antidepressants	15,107	22.0
Antipsychotics	10,406	15.1
Antimanic / mood stabilizers	7,980	11.6
Anxiolytic / hypnotic	2,596	3.8
Total	68,757[a]	100.0

[a] Because of psychiatric polypharmacy, sum of APCD members is greater than 42,362.

There were substantially more children (n=32,668) first prescribed a psychotropic between ages 6 and 12 who were prescribed a stimulant or other drugs used in ADHD than other psychotropic drug classes, with antidepressants a distant second (n=15,107). This stands in contrast to the mix of drug classes in ever-exposed minors of all ages in the larger APCD extract (Table 4.1), where users of antidepressants slightly outnumbered those using stimulants and other ADHD drugs (58,991 and 55,874, respectively). Further stratifying drug class counts by gender (Table 4.5) shows that for each major drug class, boys with prescriptions for a drug in that class outnumbered girls. In the most prescribed class, stimulants and other drugs used in ADHD, exposed boys outnumbered girls by 24,170 to 8,486, respectively. Only in the least-prescribed class, Anxiolytics / Hypnotics, did prescriptions to females approach parity with males.

Of 104 prescribed psychotropic compounds identified in preparation for this study,

75 appeared in the exposed group. Across the 42,362 exposed, 1,332,690 psychotropic prescriptions were given. Table 4.4 summarizes the 15 most frequently prescribed psychotropic compounds by drug class, which comprised 89.8% of all prescriptions given. Stimulants and other drugs prescribed for ADHD comprise 4 of the 5 most prescribed drugs

Looking at the distribution of distinct NDC codes, both psychotropic and non-psychotropic, extends the view of prescription drug use in the analytical sample (Table 4.6). Overall, 8.6% of the distinct NDCs of any kind were psychotropic, and within the exposed, 12.3% were psychotropic. Children who are exposed to psychotropics between 6 and 12 years old also appear to be given substantially more prescription drugs in general. The figure is roughly double the number in the unexposed: 22,556 of 32,454 NDCs (69.5%) in the analytical sample were given to exposed children. Due to resource limitations, I was not able to look at polypharmacy more broadly (i.e., in non-psychotropic drug classes) in the same detail.[3]

[3]Specifically, I was not able to match non-psychotropic NDC codes in the APCD data to drug names and classes.

Table 4.4

Most prescribed psychotropic compounds (n=15) in exposed members (n=42,362) by number of prescriptions

Compound	Drug class	n	%
Methylphenidate	Stimulants and ADHD	193,058	14.5
Lisdexamfetamine	Stimulants and ADHD	164,352	12.3
Amphetamine	Stimulants and ADHD	163,597	12.3
Aripiprazole	Antipsychotics	115,712	8.7
Guanfacine	Stimulants and ADHD	105,896	7.9
Risperidone	Antipsychotics	102,538	7.7
Sertraline	Antidepressants	95,847	7.2
Trazodone	Antidepressants	42,525	3.2
Fluoxetine	Antidepressants	37,254	2.8
Valproate	Antimanic / Mood Stabilizers	37,107	2.8
Oxcarbazepine	Antimanic / Mood Stabilizers	35,599	2.7
Topiramate	Antimanic / Mood Stabilizers	28,291	2.1
Quetiapine	Antipsychotics	28,179	2.1
Lamotrigine	Antimanic / Mood Stabilizers	27,159	2
Citalopram	Antidepressants	20,409	1.5
Total		1,197,523	89.8

Table 4.5

Exposed members (n=42,362) in analytical sample by psychotropic drug class and gender

Drug class	Gender	n	%
Stimulants and ADHD	Female	8,486	12.3
	Male	24,170	35.2
Antidepressants	Female	5,508	8.0
	Male	9,593	14.0
Antipsychotics	Female	3,010	4.4
	Male	7,394	10.8
Antimanic / mood stabilizers	Female	3,136	4.6
	Male	4,843	7.0
Anxiolytic / hypnotic	Female	1,098	1.6
	Male	1,497	2.2
Total	-	68,735[a]	100.1

[a] Because of psychiatric polypharmacy, sum of APCD members is greater than 42,362.

Table 4.6

Distinct National Drug Codes (NDC) by exposure group in analytical sample (n=42,362)

	Psych NDCs	All NDCs
Exposed	2,774	22,556
Unexposed	-	9,898
Total	2,774	32,454

While the particular order differed between exposed and unexposed children in the analytical sample, CNS, gastrointestinal, ENT, and sensory events were the most frequent in both groups. Overall, however, exposed children experienced substantially more events (582,003) than unexposed children (218,741), as is summarized in Table 4.7. Similar patterns obtained for serious PADRs stratified by physiological system. Table 4.8 is structured like Table 4.7, but summarizes the frequency of *serious* PADRs. There, too, we see the same 3 most common systems in the exposed and unexposed, but ordered differently in each: CNS, Sensory, and Respiratory PADRs. For serious PADRs, the overall difference between groups was even more pronounced than in the combined-seriousness counts: in the latter, the exposed were diagnosed with 2.7 times as many PADRs as the unexposed; in the former, the ratio was 5.7 times as many serious ADRs. Despite the uneven distribution of physiological systems in the frequency of ADRs by exposure group, the substantially greater frequency of PADRs in the exposed compared to the unexposed still obtained in physiological systems with much fewer ADRs in either group. For instance, there were 4.1 times as many serious Skin ADRs – the system with the 11th-highest frequency – in the exposed (n=1841) as in the unexposed (n=446).

In exposed Colorado children, 44.7% of PADRs were non-behavioral central nervous system diagnoses, more than double the proportion in the unexposed (21.4%), where CNS events were also the most frequent of the physiological outcomes. In both groups, the decrease in proportion from CNS ADRs to the systems with the next-largest share was pronounced, especially in the exposed: gastrointestinal ADRs account for 10.7% of ADRs in the exposed. After the nervous system, the rest of the body shares more evenly in ADR counts. The skewed share of ADR frequency in a small number of physiological systems, compared to the others, remained the

case when looking at serious ADRs only, where the combination of CNS, Sensory, Respiratory, Cardiovascular, Musculoskeletal, Immunologic, and Hematologic (7 of 29 systems) account for 94.4% of ADRs in the exposed.

I also counted individual members with PADRs in a given physiological system, for all levels of seriousness and for serious ADRs only (Tables 4.9 and 4.10, respectively). In both tables, more psychotropic-exposed APCD members in the analytical sample experienced PADRs than unexposed members. As with Tables 4.7 and 4.8, there were no physiological systems in the unexposed that outnumbered their analogous frequencies in the exposed.

Table 4.7

Count of potential ADRs by physiological system in psychotropic-exposed and unexposed children (n=84,724)

Exposed (n=42,362)			Unexposed (n=42,362)		
Physiological system	n	%	Physiological system	n	%
CNS	260,167	44.7	CNS	31,457	21.4
GI	62,193	10.7	GI	23,071	15.7
ENT	38,465	6.6	ENT	19,132	13.0
Sensory	37,716	6.5	Sensory	14,987	10.2
Urinary	37,258	6.4	Skin	12,267	8.3
Respiratory	31,696	5.4	Body temperature	11,026	7.5
Cardiovascular	24,152	4.1	Respiratory	10,114	6.9
Skin	19,765	3.4	Cardiovascular	7,539	5.1
Body temperature	17,580	3.0	Urinary	5,495	3.7
Musculoskeletal	12,754	2.2	Endocrine	2,550	1.7
Endocrine	12,118	2.1	Immunologic	2,317	1.6
Immunologic	8,335	1.4	Hematologic	2,303	1.6
Metabolism	7,175	1.2	Metabolism	1,773	1.2
Hematologic	6,320	1.1	Liver	632	0.4
Mouth and teeth	1,625	0.3	Mouth and teeth	585	0.4
Liver	1,318	0.2	Reproductive	581	0.4
Reproductive	898	0.2	Musculoskeletal	434	0.3
Electrolyte balance	504	0.1	Sexual function	193	0.1
Sexual function	419	0.1	Hair	137	0.1
Pancreas	367	0.1	Mineral balance	136	0.1
Mineral balance	333	0.1	Fluid balance	83	0.1
Fluid balance	263	0.0	Nails	76	0.1
Hair	222	0.0	Pancreas	55	0.0
Nails	176	0.0	Electrolyte balance	45	0.0
Infection risk	70	0.0	Infection risk	32	0.0
Neuromuscular	58	0.0	Salivary glands,	23	0.0
Sweat glands	24	0.0	neuromuscular,		
Nutrition	18	0.0	sweat glands,		
Salivary glands	14	0.0	and nutrition		
Total	582,003	99.9	Total	147,043	99.9

Table 4.8

Count of serious potential ADRs by physiological system in psychotropic-exposed and unexposed children (n=84,724)

Exposed (n=42,362)			Unexposed (n=42,362)		
Physiological system	n	%	Physiological system	n	%
CNS	171,963	58.9	Sensory	14,299	27.8
Sensory	35,031	12.0	CNS	13,049	25.4
Respiratory	23,315	8.0	Respiratory	8,972	17.5
Cardiovascular	20,092	6.9	Cardiovascular	6,600	12.8
Musculoskeletal	12,160	4.2	Immunologic	2,119	4.1
Immunologic	7,874	2.7	Hematologic	1,619	3.1
Hematologic	4,989	1.7	Skin	1,049	2.0
GI	4,959	1.7	Metabolism	755	1.5
Urinary	2,874	1.0	Urinary	736	1.4
Metabolism	2,619	0.9	GI	666	1.3
Skin	1,841	0.6	Endocrine	446	0.9
Endocrine	1,303	0.4	Musculoskeletal	331	0.6
Electrolyte balance	504	0.2	Reproductive	247	0.5
Liver	480	0.2	Mineral balance	113	0.2
Body temperature	393	0.1	Liver	107	0.2
Reproductive	389	0.1	Sexual function	82	0.2
Pancreas	367	0.1	Body temperature	70	0.1
Mineral balance	242	0.1	Pancreas	55	0.1
Sexual function	211	0.1	Electrolyte balance	45	0.1
Infection risk	70	0.0	Infection risk,	43	0.1
Fluid balance	22	0.0	mouth and teeth,		
Mouth and teeth,	15	0.0	fluid balance,		
nails			and nails		
Total	291,713	99.9	Total	51,402	99.9

Table 4.9

Count of members of analytical sample with PADRs by physiological system

Exposed (n=42,362)			Unexposed (n=42,362)		
Physiological system	n	%	Physiological system	n	%
CNS	22,913	17.8	GI	10,415	15.5
GI	17,056	13.2	ENT	10,049	14.9
ENT	16,468	12.8	CNS	9,238	13.7
Skin	10,875	8.4	Skin	7,263	10.8
Sensory	10,640	8.3	Body temperature	6,922	10.3
Cardiovascular	9,528	7.4	Sensory	5,284	7.9
Body temperature	9,442	7.3	Cardiovascular	4,205	6.2
Urinary	7,534	5.8	Respiratory	3,887	5.8
Respiratory	7,418	5.8	Urinary	3,018	4.5
Endocrine	4,143	3.2	Endocrine	1,454	2.2
Immunologic	3,030	2.4	Immunologic	1,453	2.2
Metabolism	2,763	2.1	Hematologic	1,148	1.7
Hematologic	2,536	2.0	Metabolism	848	1.3
Mouth and teeth	1,200	0.9	Mouth and teeth	514	0.8
Musculoskeletal	900	0.7	Liver	413	0.6
Liver	553	0.4	Reproductive	365	0.5
Reproductive	542	0.4	Musculoskeletal	270	0.4
Sexual function	363	0.3	Sexual function	157	0.2
Mineral balance	218	0.2	Mineral balance	104	0.2
Fluid balance	214	0.2	Fluid balance	77	0.1
Electrolyte balance	152	0.1	Hair	68	0.1
Nails	144	0.1	Nails	58	0.1
Hair	101	0.1	Infection risk	30	0.0
Pancreas	64	0.0	Electrolyte balance	22	0.0
Infection risk	52	0.0	Pancreas,	34	0.0
Neuromuscular	46	0.0	salivary glands,		
Sweat glands	14	0.0	neuromuscular,		
Salivary glands	19	0.0	sweat glands,		
and nutrition			and nutrition		
Total	128,928*	99.9	Total	67,296*	100.0

* Because they could experience >1 PADR, sum of APCD members is greater than 42,362.

Table 4.10

Count of members of analytical sample with serious potential ADRs by physiological system

Exposed (n=42,362)			Unexposed (n=42,362)		
Physiological system	n	%	Physiological system	n	%
CNS	14,641	28.4	Sensory	5,049	23.5
Sensory	10,034	19.5	CNS	4,111	19.2
Cardiovascular	8,749	17.0	Cardiovascular	3,895	18.2
Respiratory	6,396	12.4	Respiratory	3,506	16.3
Immunologic	2,796	5.4	Immunologic	1,314	6.1
Hematologic	1,886	3.7	Skin	869	4.1
Skin	1,413	2.7	Hematologic	790	3.7
GI	1,372	2.7	Urinary	374	1.7
Urinary	876	1.7	GI	335	1.6
Metabolism	858	1.7	Endocrine	272	1.3
Musculoskeletal	682	1.3	Metabolism	244	1.1
Endocrine	564	1.1	Musculoskeletal	192	0.9
Body temperature	304	0.6	Reproductive	168	0.8
Reproductive	276	0.5	Mineral balance	99	0.5
Mineral balance	188	0.4	Sexual function	79	0.4
Sexual function	188	0.4	Body temperature	67	0.3
Electrolyte balance	152	0.3	Infection risk	30	0.1
Pancreas	64	0.1	Electrolyte balance	22	0.1
Infection risk	52	0.1	Pancreas	16	0.1
Liver	39	0.1	Liver,	22	0.1
Fluid balance	15	0.0	mouth teeth,		
Mouth and teeth,	13	0.0	fluid balance,		
nails			and nails		
Total	51,558*	100.1	Total	21,454	100.1

* Because they could experience >1 PADR, sum of APCD members is greater than 42,362.

Tables 4.11 to 4.14 stratify the ADR frequency by the 5 most frequent individual ADRs (as ICD diagnostic descriptions) within the 4 most frequent physiological systems for PADRs of both seriousness levels and serious PADRs, respectively. Table 4.15 filters the analysis dataset to users of a single psychotropic drug (psychotropic "monotherapy") and identifies the 5 most frequent ADRs and serious ADRs by users of a given drug class. Note that this table describes users of a given drug class *only*; in other words, users with no polypharmacy.[4]

[4]Including polypharmacy would have made these counts ambiguous, as "stimulant users" may have also been "stimulant and antidepressant users", for instance.

Table 4.11

5 most frequent diagnoses in 4 most frequent phys. systems, exposed (n=42,362), all seriousness levels

Phys. system	ICD diagnostic label	ICD-9 Code	n
CNS	Lack of coordination	781.3	36,572
	Other convulsions	780.39	32,652
	Other developmental speech or language disorder	315.39	25,497
	Epilepsy, unspecified, without mention of intractable epilepsy	345.9	14,875
	Headache	784.0	13,472
	Subtotal		123,068
GI	Abdominal pain, unspecified site	789.00	18,361
	Constipation, unspecified	564.00	12,564
	Vomiting alone	787.03	9,331
	Other and unspecified noninfectious gastroenteritis and colitis	558.9	5,579
	Diarrhea	787.91	4,982
	Subtotal		50,817
ENT	Cough	786.2	26,899
	Allergic rhinitis, cause unspecified	477.9	9,664
	Other disease of nasal cavity and sinuses	478.19	1,902
	Subtotal		38,465
Sensory	Acute Myopia	376.1	18,169
	Bilateral Myopia	376.1	12,972
	Unspecified hearing loss	389.9	2,694
	Esotropia, unspecified	378.00	1,306
	Presbyopia	367.4	427
	Subtotal		35,568

Table 4.12

5 most frequent diagnoses in 4 most frequent phys. systems, unexposed (n=42,362), all seriousness levels

Phys. system	ICD diagnostic label	ICD-9 Code	n
CNS	Other developmental speech or language disorder	315.39	5,437
	Headache	784.0	4,013
	Other and unspecified Creutzfeldt-Jakob disease	046.19	3,791
	Lack of coordination	781.3	2,824
	Other convulsions	780.39	1,541
		Total	17,606
GI	Abdominal pain, unspecified site	789.00	6,792
	Vomiting alone	787.03	4,237
	Constipation, unspecified	564.00	4,117
	Other and unspecified noninfectious gastroenteritis and colitis	558.9	3,170
	Diarrhea	787.91	2,470
		Total	20,786
ENT	Cough	786.2	13,872
	Allergic rhinitis, cause unspecified	477.9	4,374
	Other disease of nasal cavity and sinuses	478.19	886
		Total	19,132
Sensory	Acute myopia	376.1	6,966
	Bilateral myopia	376.1	6,293
	Unspecified hearing loss	389.9	706
	Esotropia, unspecified	378.00	429
	Presbyopia	367.4	110
		Total	14,504

Table 4.13

5 most frequent diagnoses in 4 most frequent phys. systems, exposed (n=42,362), serious PADRs only

Phys. system	ICD diagnostic label	ICD-9 Code	n
CNS	Lack of coordination	781.3	36,572
	Other convulsions	780.39	32,652
	Epilepsy, unspecified, without mention of intractable epilepsy	345.9	14,875
	Other speech disturbance	784.59	9,782
	Other and unspecified Creutzfeldt-Jakob disease	‘046.19	9,352
		Total	103,233
Sensory	Acute myopia	376.1	18,169
	Bilateral myopia	376.1	12,972
	Unspecified hearing loss	389.9	2,694
	Visual discomfort	368.13	333
	Optic atrophy, unspecified	377.10	176
		Total	34,344
Respiratory	Pneumonia, organism unspecified	486	8,959
	Asthma, unspecified type, with (acute) exacerbation	493.92	8,746
	Acute respiratory failure	518.81	2,371
	Other pulmonary insufficiency, not elsewhere classified	518.82	1,187
	Pulmonary congestion and hypostasis	514	987
		Total	22,250
Cardiovascular	Other respiratory abnormalities	786.09	5,896
	Chest pain, unspecified	786.50	4,866
	Epistaxis	784.7	2,800
	Cardiac dysrhythmia, unspecified	427.9	1,628
	Nonspecific abnormal electrocardiogram [ECG] [EKG]	794.31	1,310
		Total	16,500

Table 4.14

5 most frequent diagnoses in 4 most frequent phys. systems, unexposed (n=42,362), serious PADRs only

Phys. system	ICD diagnostic label	ICD-9 Code	n
Sensory	Acute myopia	376.1	6,966
	Bilateral myopia	376.1	6,293
	Unspecified hearing loss	389.9	706
	Visual discomfort	368.13	110
	Unspecified visual loss	369.9	59
		Total	14,134
CNS	Other and unspecified Creutzfeldt-Jakob disease	046.19	9,352
	Lack of coordination	781.3	2,824
	Other speech disturbance	784.59	1,206
	Other convulsions	780.39	971
	Other generalized ischemic cerebrovascular disease		438
		Total	14,791
Respiratory	Asthma, unspecified type, with (acute) exacerbation	493.92	4,151
	Pneumonia, organism unspecified	486	3,893
	Other pulmonary insufficiency, not elsewhere classified	518.82	328
	Acute respiratory failure	518.81	290
	Pulmonary congestion and hypostasis	514	113
		Total	8,775
Cardiovascular	Other respiratory abnormalities	786.09	2,095
	Chest pain, unspecified	786.50	1,746
	Epistaxis	784.7	1,279
	Cardiac dysrhythmia, unspecified	427.9	362
	Other specified cardiac dysrhythmias	427.89	284
		Total	5,766

Table 4.15

PADRs by drug class, exposed members on psychotropic monotherapy

All seriousness levels				Serious PADRs only			
ICD diagnostic label	ICD-9 Code	n	%	ICD diagnostic label	ICD-9 Code	n	%
Stimulants & ADHD							
Cough	786.2	6,131	30.4	Acute myopia	376.1	1,238	24.3
Lack of coordination	781.3	5,380	26.7	Other and unspecified Creutzfeldt-Jakob disease	046.19	1,207	23.7
Other developmental speech or language disorder	315.39	4,828	23.9	Bilateral myopia	376.1	1,053	20.6
Fever, unspecified	780.60	3,829	19	Pneumonia, organism unspecified	486	820	16.1
Myopia	376.1	3,243	13.9	Asthma, unspecified type, with (acute) exacerbation	493.92	783	15.3
Total		20,168	100	Total		5,101	100
Antidepressants							
Cough	786.2	1,410	25.3	Other and unspecified Creutzfeldt-Jakob disease	046.19	311	26.3
Abdominal pain, unspecified site	789.00	1,383	24.8	Acute myopia	376.1	266	22.5
Lack of coordination	781.3	1,115	20	Bilateral myopia	376.1	234	19.8
Fever, unspecified	780.60	873	15.7	Asthma, unspecified type, with (acute) exacerbation	493.92	189	16
Other developmental speech or language disorder	315.39	795	14.3	Pneumonia, organism unspecified	486	182	15.4
Total		5,576	100.1	Total		1,182	100
Antipsychotics							
Lack of coordination	781.3	914	30.6	Acute myopia	376.1	90	24.5
Other developmental speech or language disorder	315.39	797	26.7	Bilateral myopia	376.1	84	22.9
Other speech disturbance	784.59	509	17	Other and unspecified Creutzfeldt-Jakob disease	046.19	78	21.3
Cough	786.2	408	13.7	Other convulsions	780.39	60	16.3
Urinary incontinence, unspecified	788.30	360	12	Pneumonia, organism unspecified	486	55	15
Total		2,988	100	Total		367	100
Antimanics & mood stabilizers							
Other convulsions	780.39	2,167	31.1	Other convulsions	780.39	476	34.9
Headache	784.0	1,378	19.8	Epilepsy, unspecified	345.9	337	24.7
Epilepsy, unspecified	345.9	1,234	17.7	Acute myopia	376.1	200	14.7
Lack of coordination	781.3	1,136	16.3	Other and unspecified Creutzfeldt-Jakob disease	046.19	188	13.8
Urinary incontinence, unspecified	788.30	1,046	15	Transient alteration of awareness	780.02	161	11.8
Total		6,961	99.9	Total		1,362	99.9
Anxiolytics & hypnotics							
Other convulsions	780.39	803	32.2	Other convulsions	780.39	114	35.1
Other specified cerebral degenerations in childhood	330.8	716	28.7	Epilepsy, unspecified	345.9	65	20
Epilepsy, unspecified	345.9	361	14.5	Epilepsy, unspecified	345.9	56	17.2
Pneumonia, organism unspecified	486	327	13.1	Transient alteration of awareness	780.02	46	14.2
Lack of coordination	781.3	286	11.5	Pneumonia, organism unspecified	486	44	13.5
Total		2,493	100	Total		325	100

Psychotropic compound polypharmacy

Psychiatric compound polypharmacy in the analytical sample was divided into 3 levels: exposed members either had 1, 2, or 3 or more unique psychotropic prescriptions in their APCD records. Table 4.18 shows that substantial proportions of children meeting this study's exposure criteria were prescribed either 2 (25.7%) or 3 or more (33.5%) psychotropics. Among the exposed, 59.2% were prescribed more than 1 psychotropic. Looking at a distribution of counts of distinct psychotropic compounds by counts of individual members, as in Figure 4.1, shows that polypharmacy ranged from 1 compound (i.e. monotherapy) in 17,287 exposed children to 20 compounds in 3 children. Of the 14,203 members with 3 or more distinct psychotropics, 12,060 (85.0%) had between 3 and 6 compounds in their APCD records.

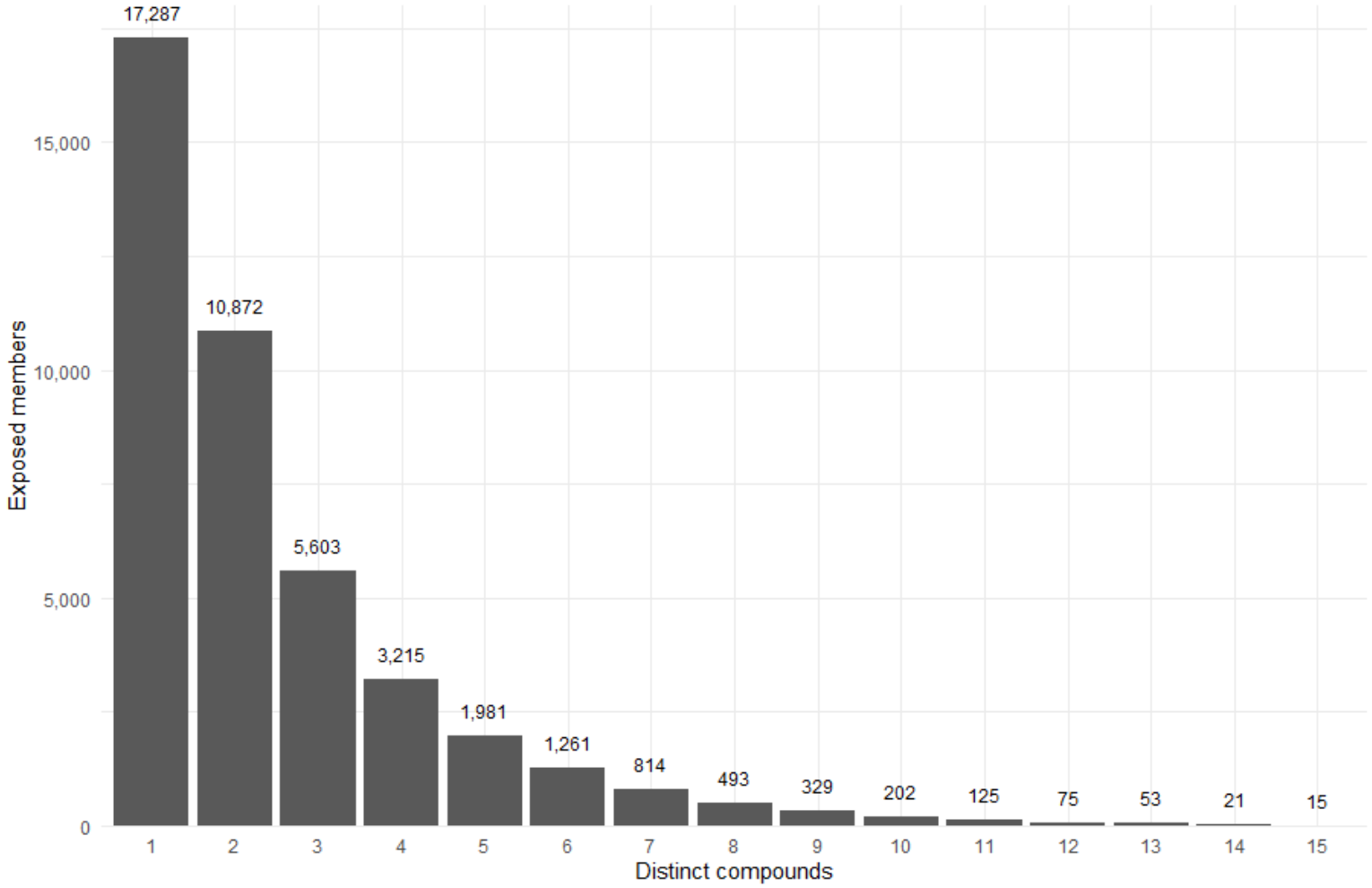


Figure 4.1. Exposed members by count of distinct psychotropic compounds in APCD records

Breaking out polypharmacy in the exposed by APCD member gender shows that males had over twice the proportion of polypharmacy as females for each polypharmacy category (Figure 4.2). Alternatively, looking at polypharmacy by the age of exposed members' first psychotropic prescription (Table 4.16) shows that, within levels of polypharmacy, 6 and 12 year-olds generally had fewer prescriptions than members of ages 7 to 11.

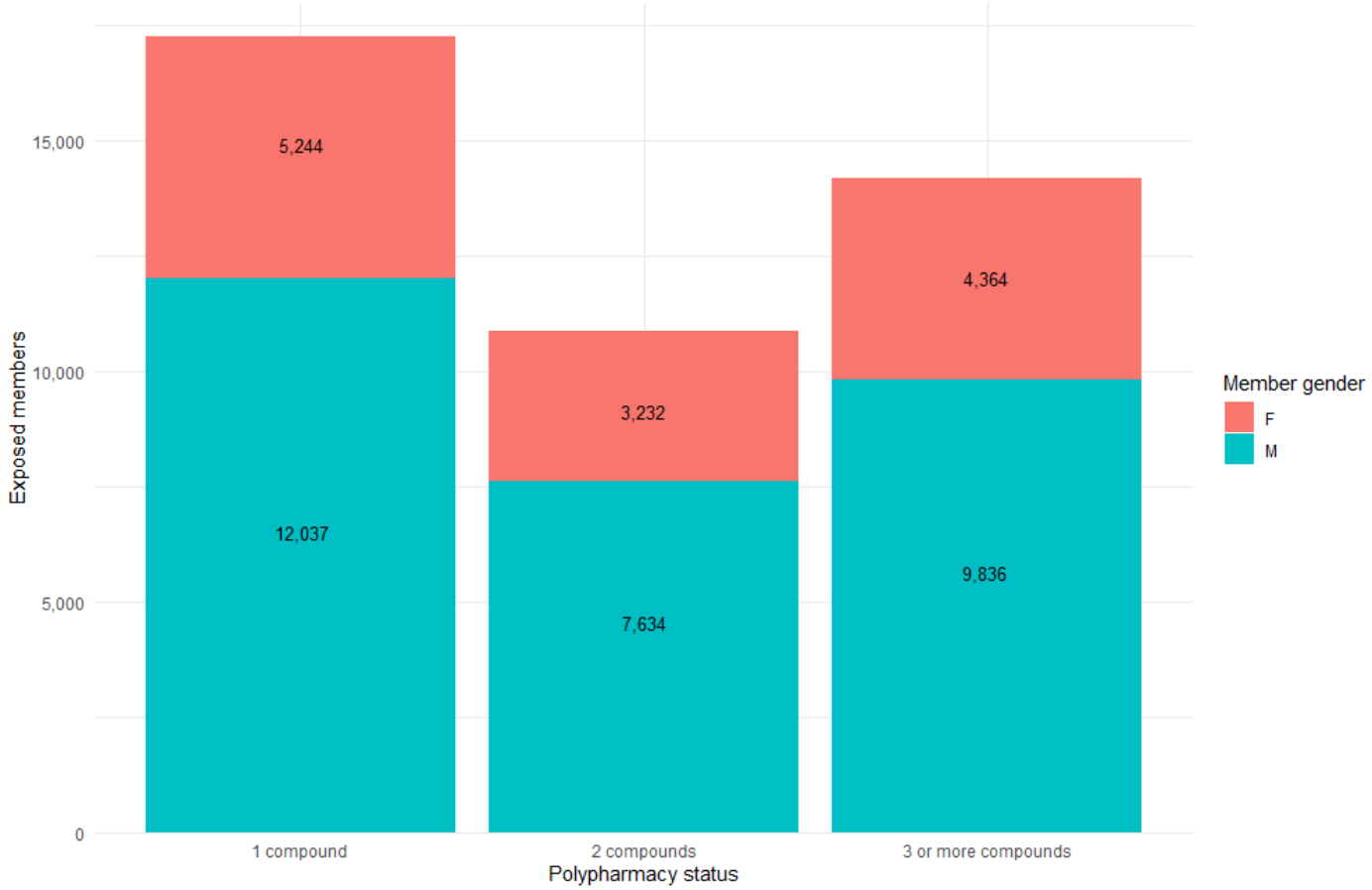


Figure 4.2. Exposed members by polypharmacy status and gender in analytical sample (n=42,362)

Table 4.16

Exposed members by polypharmacy status and age at first psychotropic prescription in analytical sample (n=42,362)

Polypharmacy	Age at first psych. Rx	n	%
1 compound	6	1,189	2.8
	7	2,556	6
	8	2,943	6.9
	9	3,121	7.4
	10	3,116	7.4
	11	2,857	6.7
	12	1,505	3.6
2 compounds	6	1,075	2.5
	7	1,896	4.5
	8	1,826	4.3
	9	1,825	4.3
	10	1,745	4.1
	11	1,678	4
	12	827	2
3 or more compounds	6	1,938	4.6
	7	2,522	6
	8	2,266	5.3
	9	2,208	5.2
	10	2,101	5
	11	2,075	4.9
	12	1,093	2.6
Total		42,362	100.1

4.2 Results of multivariate, frailty-adjusted Cox regression analyses of ADR hazard

I fit two groups of 5 multivariate Cox proportional hazards regressions of PADR hazard on psychotropic exposure: in the first 5 analyses, the regressands (dependent variables) were PADRs *of both seriousness levels*; in the second 5, regressands were serious PADRs only. The first analysis in each group sought to estimate the hazard of ADRs in all physiological systems, while the next 4 had as their dependent variable the 4 most frequently occurring physiological systems in each of the 2 groups. Table 4.17 summarizes the physiological systems included in each group of 5 Cox models. All Cox regression analyses employed a shared frailty term Z on the exposure variable to account for intra-subject correlation, and an `exposure*time` term to account for interactions between time and psychotropic exposure.

Table 4.17

Regressands in adjusted Cox models (n=10) by group

Group 1 (Serious & non-serious ADRs)	Group 2 (Only serious ADRs)
All physiological systems	All physiological systems
CNS	Sensory
Gastrointestinal	CNS
Sensory	Cardiovascular
ENT	Respiratory

Table 4.18

Characteristics of exposed and unexposed members in analytical sample (n=84,724)

	Exposed		Unexposed	
	n	%	n	%
Age (years)				
Mean (SD)	6.4 (3.3)	-	6.8 (5.1)	-
Median [min, max]	6.8 [0.0,11.9]	-	6.2 [0.0, 11.9]	-
Gender				
Male	21,234	50.1	12,840	30.3
Female	21,094	49.8	29,507	69.7
Unknown	15	0.0	34	0.1
Psychiatric polypharmacy				
1 compound	17,287	40.8	-	-
2 compounds	10,872	25.7	-	-
3 or more compounds	14,203	33.5	-	-
Median HH income (ZIP)				
Low	3,069	7.2	3,049	7.2
Medium	35,562	84.0	35,549	83.9
High	1,740	4.1	1,744	4.1
NA	1,991	4.7	2,020	4.8
Epilepsy disorder				
Yes	3,314	7.8	201	0.05

Table 4.19

Multivariate Cox models of potential ADR hazard, all physiological systems

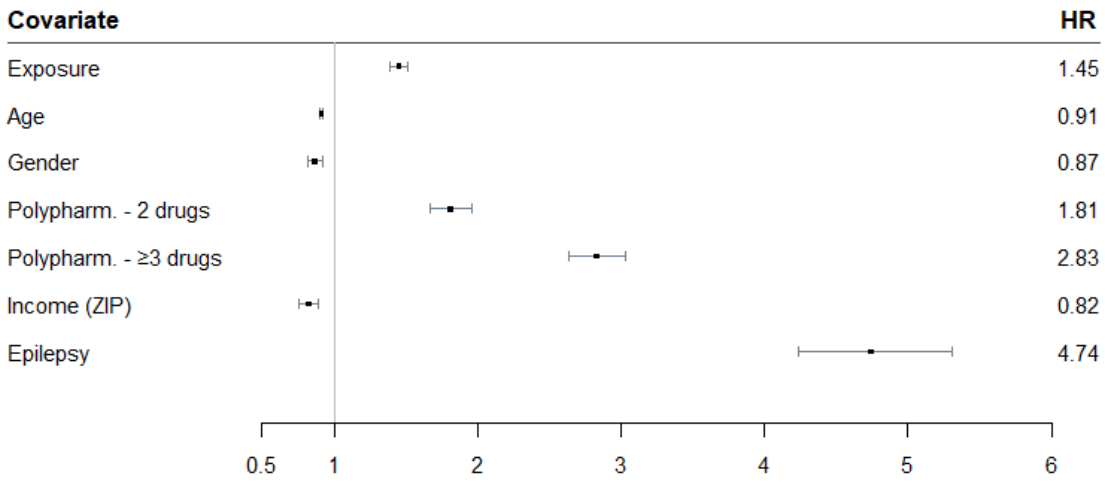
	All seriousness levels				Serious potential ADRs			
	HR	95% CI	SE	*p*	HR	95% CI	SE	*p*
Exposure	1.45	[1.39, 1.52]	0.02	<.001	1.60	[1.51, 1.70]	0.03	<.001
Age (years)	0.91	[0.90, 0.92]	0.001	<.001	0.94	[0.93, 0.95]	0.02	<.001
Gender[a]								
Male	0.87	[0.82, 0.92]	0.009	<.001	0.87	[0.80, 0.94]	0.01	<.001
Polypharmacy[b]								
2 drugs	1.81	[1.67, 1.97]	0.01	<.001	1.90	[1.70, 2.1]	0.02	<.001
3 or more drugs	2.83	[2.64, 3.04]	0.01	<.001	3.23	[2.93, 3.57]	0.01	<.001
Income[c]	0.82	[0.76, 0.89]	0.01	<.001	0.81	[0.70, 0.90]	0.02	<.001
Epilepsy[d]								
Yes	4.74	[4.23, 5.30]	0.01	<.001	8.20	[7.20, 9.30]	0.02	<.001
Frailty (Exposure)	-		-	<.001	-		-	<.001
Exposure*Time	0.99	[0.99, 0.99]	0.00	<.001	0.99	[0.99, 0.99]	0	<.001

[a] Reference level for gender is "female"
[b] Reference level for polypharmacy is "1 drug"
[c] Median 2013 household income in APCD members' ZIP code
[d] Reference level for epilepsy is "no epilepsy disorder diagnosis"

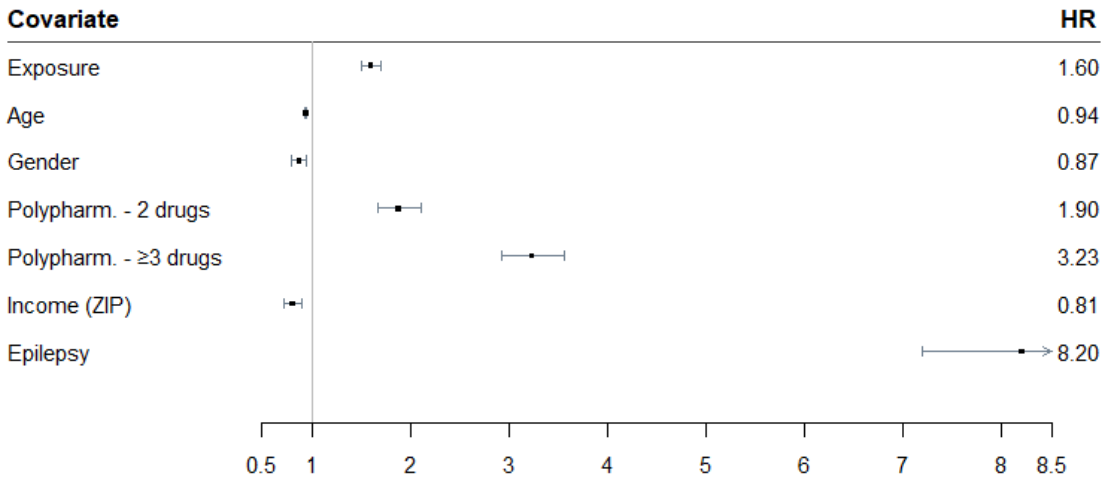
4.2.1 Group 1: Hazard of potential ADRs, combined seriousness

Table 4.18 describes the exposed and unexposed groups at baseline across the characteristics used as covariates (control variables) in statistical analyses. Exposed and unexposed children were similar on all characteristics except psychiatric polypharmacy, epilepsy and gender. In the case of polypharmacy, the unexposed could not have had any by definition: they were not exposed to prescribed psychotropipcs.

Figure 4.3. Forest plots of Cox models for all physiological systems



All levels of seriousness



Serious potential ADRs

With respect to epilepsy and other seizure disorders, the large difference (3,314 children in the exposed, compared to 201 in the unexposed) is due to there being very few children with such disorders in a medical and pharmacy claims database who have never been given an anti-seizure drug. By the same token, selecting a group of children on the basis of their having been prescribed psychotropic drugs, including anti-seizure drugs, will naturally yield a large number of children with epilepsy and related conditions. In the case of gender, the 50.1% to 49.8% ratio of males to females in the exposed contrasts with the 30.3% to 69.7% ratio in the unexposed. The imbalance is an artifact of R's pseudorandom `sample` function, which selected the unexposed group from the larger APCD extract.

The first column of Table 4.19 summarizes an "overall" Cox model of the relationship between psychotropic exposure and ADR hazard, as compared to non-exposure and controlling for several covariates, as well as within-subject correlation (frailty). The first (top) forest plot in Figure 4.3 visualizes the same information, displaying HRs and confidence intervals for each covariate on a number line. The dependent variable in this model was a grouping of all ADRs of both levels of seriousness. Compared to drug-unexposed APCD members, psychotropic exposure increased the hazard of PADRs by 45% (*HR* 1.45, 95% CI [1.39, 1.52]) within the same levels of age, gender, income, and epilepsy diagnosis. Higher age (*HR* 0.91, 95% CI [0.90, 0.92]), being male (*HR* 0.87, 95% CI [0.82, 0.92]), and higher median household income by member ZIP code (*HR* 0.82, 95% CI [0.76, 0.89]) suggested decreased hazard of ADRs of 9.0%, 13.0%, and 18.0%, respectively, compared to being younger, female, and in a lower median-income ZIP code, respectively, controlling for the other covariates.

The 4 physiological systems with the most ADRs of combined seriousness (in

descending order) were the central nervous system (CNS), gastrointestinal (GI) system, sensory system (comprising visual, auditory, and other symptoms), and ear, nose, and throat (ENT) system. Tables 4.20 and 4.21 summarize the results of the these systems' Cox regression models. Meeting this study's exposure definition was associated with significantly increased hazard of ADRs in 3 of these these systems (CNS, GI, and Sensory) compared to the unexposed, while controlling for age, gender, ZIP code-level income, and epilepsy diagnoses. However, the magnitude of these effects varied, as Tables 4.20 and 4.21 show: a small increase in the hazard of serious and non-serious gastrointestinal ADRs (*HR* 1.28, 95% CI [1.13, 1.46]), and greater than doubling of hazard for CNS (*HR* 2.19, 95% CI [2.05, 2.34]) and sensory ADRs (*HR* 2.46, 95% CI [2.11, 2.87]). The hazard of ENT ADRs (*HR* 1.15, 95% CI [1.13, 1.46]) was elevated by 15.0% compared to the unexposed, but the association was not statistically significant.

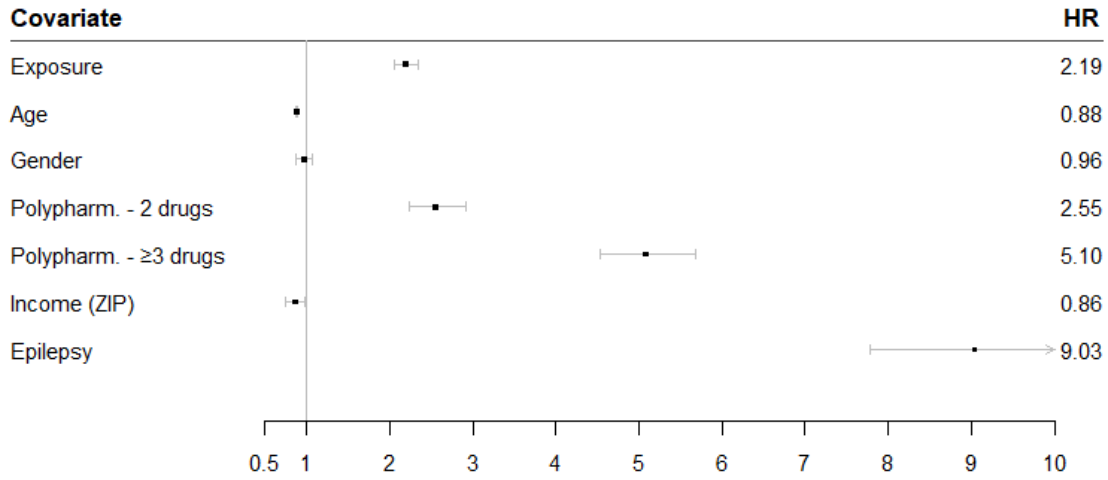
Table 4.20

Multivariate Cox models of potential ADR hazard in CNS and GI systems, all levels of seriousness

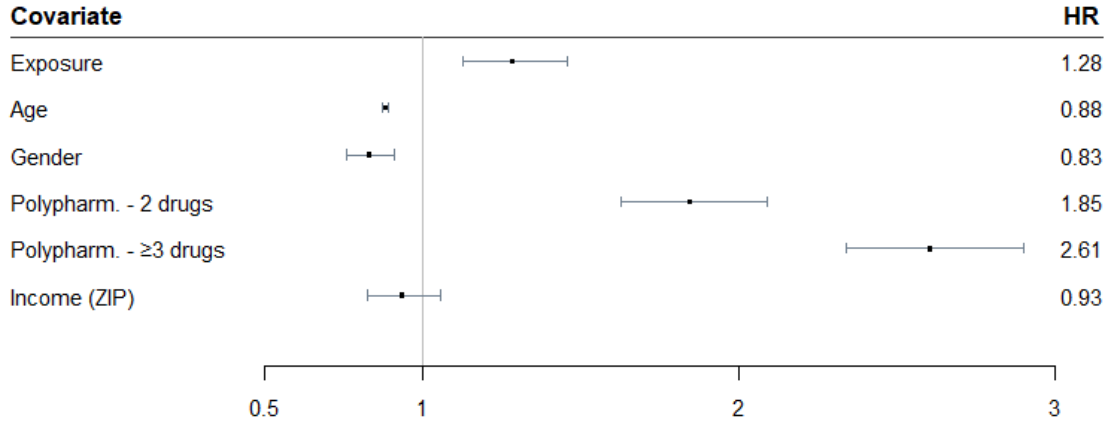
	CNS				Gastrointestinal			
	HR	95% CI	SE	*p*	HR	95% CI	SE	*p*
Exposure	2.19	[2.05, 2.34]	0.003	<.001	1.28	[1.13, 1.46]	0.06	<.001
Age (years)	0.88	[0.87, 0.89]	0.003	<.001	0.88	[0.87, 0.89]	0.003	<.001
Gender[a]								
Male	0.96	[0.87, 1.06]	0.017	0.48	0.83	[0.77, 0.91]	0.02	<.001
Polypharmacy[b]								
2 drugs	2.55	[2.23, 2.91]	0.019	<.001	1.85	[1.63, 2.10]	0.03	<.001
3 or more drugs	5.10	[4.53, 5.68]	0.015	<.001	2.61	[2.34, 2.90]	0.03	<.001
Income[c]	0.86	[0.74, 0.98]	0.024	<.001	0.93	[0.82, 1.05]	0.03	0.27
Epilepsy[d,e]								
Yes	9.03	[7.8, 10.50]	0.024	<.001	-		-	-
Frailty (Exposure)	-		-	<.001	-		-	<.001
Exposure*Time	0.99	[0.99, 0.99]	0	<.001	1	[0.99, 1.00]	<.001	0.1

[a] Reference level for gender is "female"
[b] Reference level for polypharmacy is "1 drug", i.e. no polypharmacy
[c] Median 2013 household income in APCD members' ZIP code
[d] Reference level for epilepsy is "no epilepsy disorder diagnosis"
[e] Epilepsy diagnoses not controlled for in GI, ENT, and Sensory models

Figure 4.4. Forest plots of Cox models for CNS and GI system ADRs, all levels of seriousness



Central nervous system



Gastrointestinal

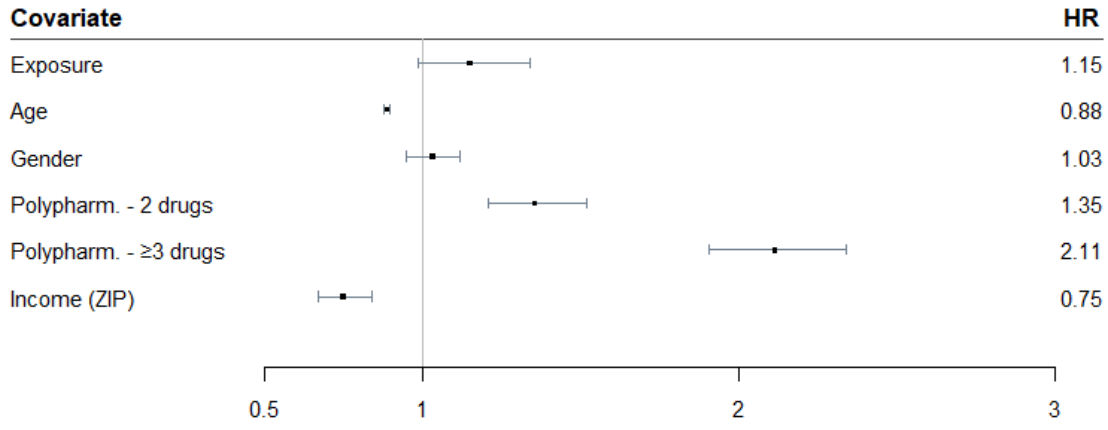
Table 4.21

Multivariate Cox models of potential ADR hazard in ENT and Sensory systems, all levels of seriousness

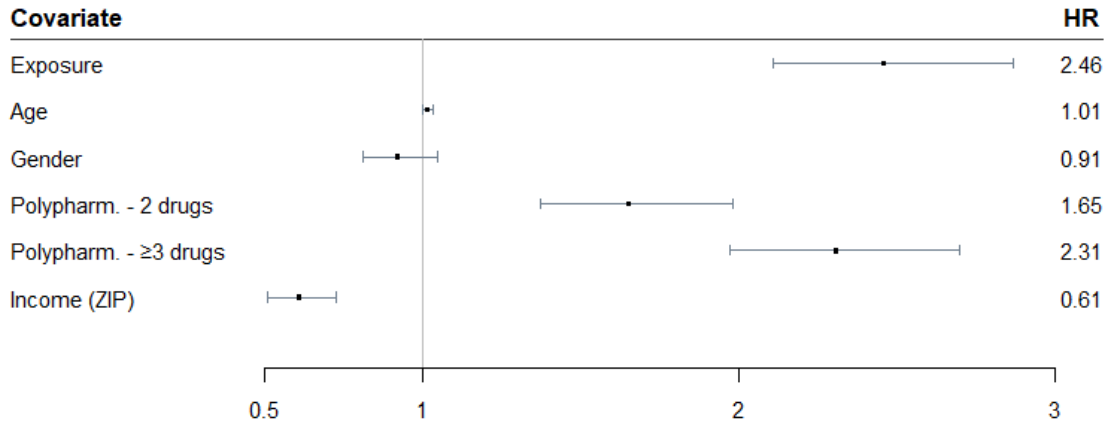
	ENT				Sensory			
	HR	95% CI	SE	p	HR	95% CI	SE	p
Exposure	1.15	[0.98, 1.34]	0.07	0.08	2.46	[2.11, 2.87]	0.07	<.001
Age (years)	0.88	[0.87, 0.89]	0.004	<.001	1.01	[0.99, 1.03]	0.004	0.11
Gender[a]								
Male	1.03	[0.95, 1.11]	0.03	0.48	0.91	[0.81, 1.04]	0.03	0.21
Polypharmacy[b]								
2 drugs	1.35	[1.20, 1.52]	0.04	<.001	1.65	[1.37, 1.98]	0.04	<.001
3 or more drugs	2.11	[1.90, 2.34]	0.04	<.001	2.31	[1.97, 2.70]	0.04	<.001
Income[c]	0.75	[0.67, 0.84]	0.04	<.001	0.61	[0.51, 0.73]	0.04	<.001
Epilepsy[d,e]								
Yes	-		-	-	-		-	-
Frailty (Exposure)	-		-	<.001	-		-	<.001
Exposure*Time	0.99	[0.99, 1.00]	<.001	0.15	0.99	[0.99, 0.99]	<.001	<.001

[a] Reference level for gender is "female"
[b] Reference level for polypharmacy is "1 drug", i.e. no polypharmacy
[c] Median 2013 household income in APCD members' ZIP code
[d] Reference level for epilepsy is "no epilepsy disorder diagnosis"
[e] Epilepsy diagnoses not controlled for in GI, ENT, and Sensory models

Figure 4.5. Forest plots of Cox models for ENT and Sensory system ADRs, all levels of seriousness



Ear, nose, & throat



Sensory

4.2.2 Group 2: Hazard of serious potential ADRs

The 5 Cox models fitted on serious PADRs followed similar overall trends for exposure, but with larger HRs for psychotropic exposure in every case. The second column of Table 4.19 and second (bottom) forest plot in Figure 4.3 summarize the model for all *serious* ADRs from all physiological systems. Here, the HR for psychotropic exposure was 1.60 (95% CI [1.51, 1.70]), 15.0% greater than that of its sister model of ADRs of all levels of seriousness. HRs for age (*HR* 0.94, 95% CI [0.93, 0.95]), gender (*HR* 0.87, 95% CI [0.80, 0.94]), and ZIP-level median household income (*HR* 0.81, 95% CI [0.70, 0.90]) show HRs of similar magnitude and direction as the equivalent HRs for all levels of seriousness. Compared to that model, the relative hazard of serious ADRs between children diagnosed with epilepsy and those not so diagnosed, holding other covariates constant, was 8.20 (95% CI [7.20, 9.30]).

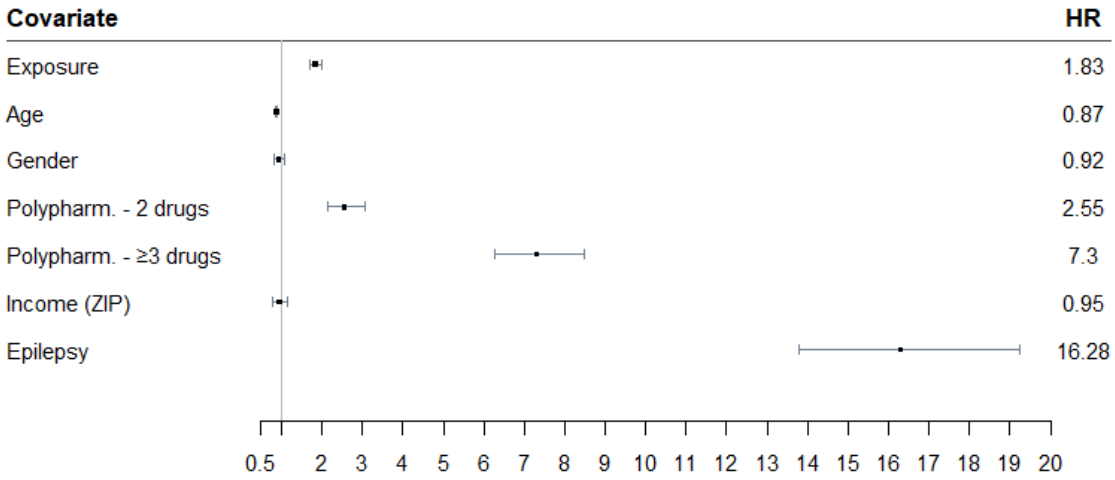
Table 4.22

Multivariate Cox models of potential ADR hazard in CNS and Sensory systems, serious ADRs only

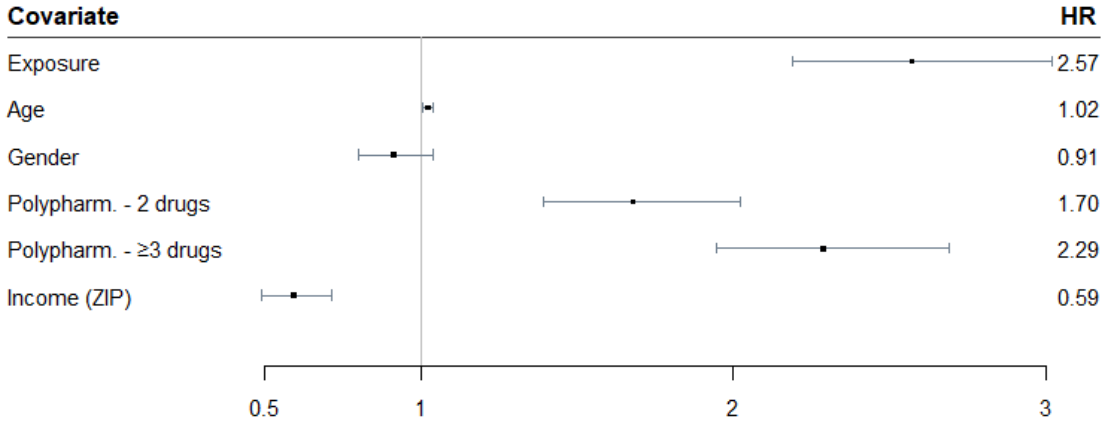
	CNS				Sensory			
	HR	95% CI	SE	*p*	HR	95% CI	SE	*p*
Psychotropic exposure	1.83	[1.69, 1.99]	0.045	<.001	2.57	[2.2, 3.02]	0.08	<.001
Age (years)	0.87	[0.85, 0.88]	0.004	<.001	1.02	[1, 1.04]	0.003	0.001
Gender								
Male	0.92	[0.81, 1.06]	0.02	0.27	0.91	[0.8, 1.04]	0.03	0.16
Polypharmacy								
2 drugs	2.55	[2.14, 3.05]	0.03	<.001	1.7	[1.4, 2.02]	0.04	<.001
3 or more drugs	7.3	[6.29, 8.48]	0.019	<.001	2.29	[1.94, 2.7]	0.04	<.001
Income	0.95	[0.79, 1.14]	0.03	0.59	0.59	[0.5, 0.71]	0.04	<.001
Epilepsy								
Yes	16.28	[13.77, 19.26]	0.03	<.001	-		-	-
Frailty (Exposure)	-		-	<.001	-		-	<.001
Exposure*Time	0.99	[0.99, 0.99]	0	<.001	0.99	[0.99, 0.99]	<.001	<.001

[a] Reference level for gender is "female"
[b] Reference level for polypharmacy is "1 drug", i.e. no polypharmacy
[c] Median 2013 household income in APCD members' ZIP code
[d] Reference level for epilepsy is "no epilepsy disorder diagnosis"
[e] Epilepsy diagnoses not controlled for in GI, ENT, and Sensory models

Figure 4.6. Forest plots of Cox models for CNS and Sensory system ADRs, serious ADRs only



Central nervous system



Sensory

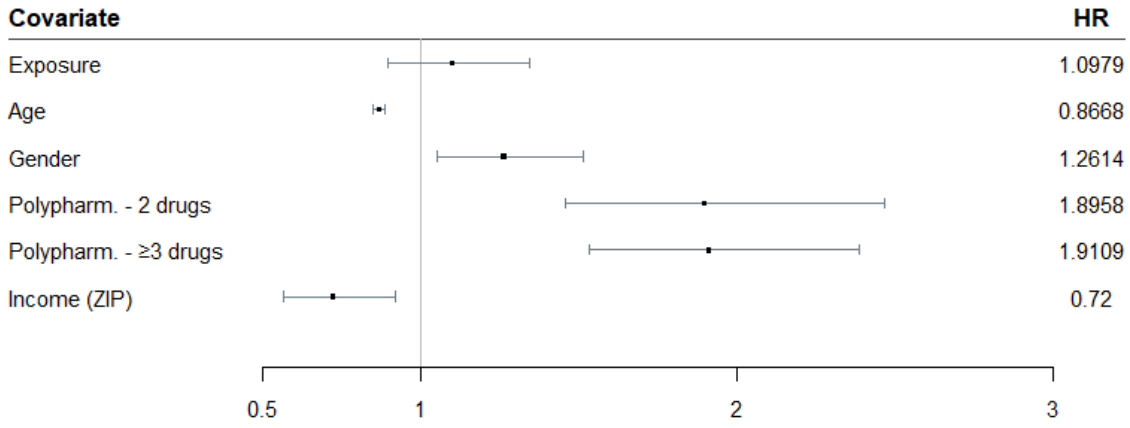
Table 4.23

Multivariate Cox models of potential ADR hazard in Respiratory and Cardiovascular systems, serious ADRs only

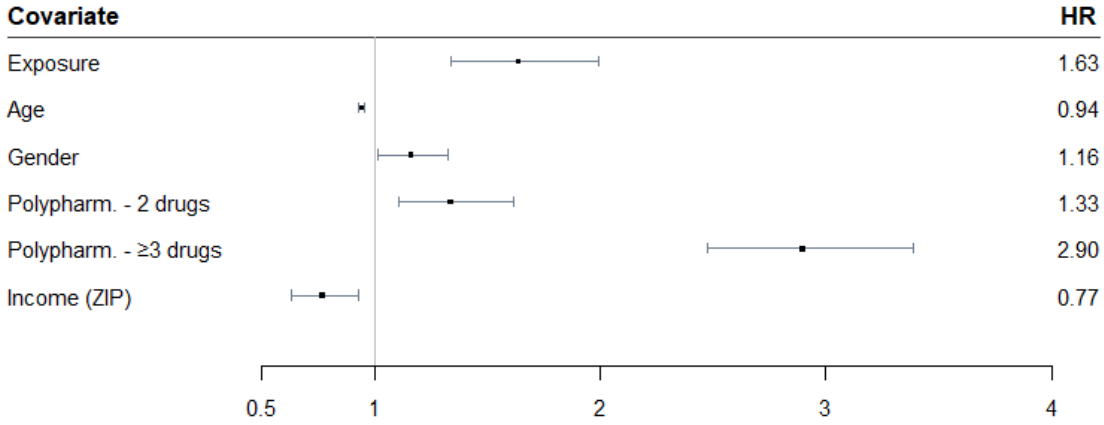
	Respiratory				Cardiovascular			
	HR	95% CI	SE	p	HR	95% CI	SE	p
Psychotropic exposure	1.10	[0.89, 1.34]	0.09	0.37	1.63	[1.34, 1.99]	0.09	<.001
Age (years)	0.87	[0.85, 0.88]	0.01	<.001	0.94	[0.92, 0.95]	0.005	<.001
Gender								
Male	1.26	[1.05, 1.51]	0.04	0.01	1.16	[1.01, 1.32]	0.04	0.03
Polypharmacy								
2 drugs	1.90	[1.5, 2.47]	0.05	<.001	1.33	[1.10, 1.64]	0.06	0.003
3 or more drugs	1.91	[1.53, 2.40]	0.05	<.001	2.90	[2.47, 3.39]	0.05	<.001
Income	0.72	[0.56, 0.91]	0.05	<.001	0.77	[0.63, 0.93]	0.060	0.007
Epilepsy								
Yes	-		-	-	-		-	-
Frailty (Exposure)	-		-	<.001	-		-	<.001
Exposure*Time	0.99	[0.98, 1.00]	<.001	0.75	0.99	[0.99, 0.99]	<.001	<.001

[a] Reference level for gender is "female"
[b] Reference level for polypharmacy is "1 drug", i.e. no polypharmacy
[c] Median 2013 household income in APCD members' ZIP code
[d] Reference level for epilepsy is "no epilepsy disorder diagnosis"
[e] Epilepsy diagnoses not controlled for in GI, ENT, and Sensory models

Figure 4.7. Forest plots of Cox models for Respiratory and Cardiovascular system ADRs, serious ADRs only



Respiratory



Cardiovascular

4.2.3 Polypharmacy

As shown in the descriptive results, psychotropic polypharmacy was widespread in exposed members of the analytical dataset, occurring in the majority (59.2%) of the 42,362 children. Inherently a phenomenon of the exposed, it was not compared to the unexposed, as in the 10 models' other covariates. Instead, HRs for polypharmacy compare the hazard of ADRs in exposed children prescribed 2 drugs, or 3 or more drugs, to those prescribed only 1 psychotropic drug (monotherapy) in their APCD records, holding the model's other covariates constant. Each model therefore generated 2 hazard ratios for polypharmacy, making 20 total in this project. In all 20, there was a statistically significant increase in hazard for each polypharmacy group, compared to children on monotherapy. In several cases, these hazard ratios were the largest in each model save for some HRs for epilepsy. In each model, the HR for "3 or more drugs" was greater than that model's HR for "2 drugs". Taken together, these findings show a consistent effect of additional psychotropics on the short- and long-term hazard of ADRs both overall and by several physiological systems, and constitute this project's second central finding.

4.2.4 Frailty and interaction

In all models, the Chi-Square test for frailty effects was statistically significant, suggesting the presence of frailty effects in each model and validating my thinking about within-subject heterogeneity.

In several initial iterations of statistical models, the exposure term was shown to

violate the proportional hazards assumption for Cox models.[5] Since indications of non-proportional hazards suggest that the hazard of the outcome for a given variable (psychotropic exposure, in this case) varies with time, I addressed these violations by including an interaction term for psychotropic exposure and time, `exposure*time`, in each model (Therneau, Crowson, and Atkinson, 2021).

This *time-dependent coefficient* was statistically significant in 7 of 10 models (all except models for ENT and GI ADRs of all seriousness levels, and the model for serious respiratory ADRs), supporting my hypothesis that the effect of psychotropic exposure on PADR hazard varies with time. Hazard ratios for this coefficient, modeled as a linear function, were below 1.0 in all 10 models, suggesting a decrease in ADR hazard for the exposed over time in each one. Table 4.24 displays the number of years it would take for the additional hazard of psychotropic exposure to decrease to parity with the same hazard in the unexposed (i.e. an HR of 1.00), given each model's HRs for psychotropic exposure and exposure-time interaction. The table shows a range of estimates, from 2.7 years (serious respiratory ADRs) to 14.1 years (combined-seriousness Sensory ADRs), and suggests that while greater early in psychotropic use, the hazard of ADRs continues for substantial periods of time after first prescription between 6 and 12 years old.

[5]From the Methods section, recall that Cox models assume that while Subject i's hazard of the outcome may rise, fall, or remain constant over time, Subject j's may differ in value but rises, falls, or remains constant as Subject i's does. Subject i's hazard, in other words, is proportional to Subject j's.

Table 4.24

Time (years) to hazard ratios of 1.0 in exposed compared to unexposed children by statistical model

Any seriousness level		Serious ADRs only	
Model	Years to 1.0 HR	Model	Years to 1.0 HR
Overall	6.42	Overall	8.50
CNS	8.80	CNS	8.10
Gastrointestinal (GI)	3.99	Sensory	11.60
ENT[a]	4.11	Respiratory[a]	2.70
Sensory	14.10	Cardiovascular	8.99

[a] HRs for psychotropic exposure in these models were not statistically significant.

CHAPTER 5

Discussion

5.1 Overview

In the literature review, I found disparate studies of potential adverse drug reactions to prescribed psychotropic use in children, which analyzed a small number of specific outcomes in relatively short-term trials – a sparse base of long-term safety evidence for such widely used treatments in a vulnerable population. To address this, I conducted long-term descriptive and statistical analyses of psychotropic-exposed and unexposed Colorado children and 587 physiological ADRs. Two main conclusions follow. First, that potential physiological adverse drug reactions occur with greater frequency in the exposed, and that the hazard of PADRs in the exposed is generally higher in the exposed when controlling for age, gender, psychiatric polypharmacy, ZIP code-level median household income, epilepsy diagnostic status, multiple-event heterogeneity (frailty), and time-dependent exposure. The hazard of serious ADRs alone was, on balance, greater than the hazard of looking at serious and non-serious ADRs combined. The magnitude of these effects are as high as a 150.0% increase in hazard compared to drug-unexposed children, and 8 of 10 were statistically significant at the 0.05 level of α. While a large proportion of the hazard occurred in the first 5 years after psychotropic exposure, and decreases over time, it does so slowly –

in some cases longer than the dataset captured chronologically. The relative hazard in the exposed takes up to 14.1 years to equalize with that in the unexposed.[1]

The bulk of PADR risk is driven by PADRs in a subset of physiological systems: non-behavioral CNS, GI, ENT, and Sensory for effects of any seriousness level; and CNS, Sensory, Respiratory, and Cardiovascular systems for serious PADRs. Expressing PADR frequency by system as a count of APCD members who experienced effects in a given system shows that increased ADR frequency in the exposed was not just a matter of raw counts of diagnoses: there were also substantially more exposed *people* who experienced ADRs by a given physiological system than unexposed people. In fact, there were no physiological systems with greater frequency, regardless of definition (count of ADRs or count of people with ADRs) in the unexposed than in the exposed. This applies to both ADRs at the combined seriousness and serious-only levels.

Similarly to other epidemiological studies of psychotropic prescription prevalence in pediatric settings, Stimulants and Antidepressants represented the bulk of psychotropic prescriptions to young Coloradans between 2009 and 2018. However, the degree to which stimulant use outpaced all other classes in Colorado was perhaps even more pronounced than in those other studies. Boys were prescribed substantially more drugs than girls, and led prescription counts in the exposed for all drug classes.

The second main conclusion is that in every physiological system examined here, psychotropic polypharmacy greatly (and in every case, statistically significantly) elevated the relative hazard of ADRs, serious and combined-serious, compared to

[1]This calculation assumes a linear reduction in hazard.

children only prescribed one psychotropic in their APCD records. The range of these magnitudes was as low as a 33.0% increase, and as high as a 630.0% increase. As with psychotropic use more broadly, polypharmacy was more prevalent in boys than in girls. These findings are even more powerful in light of how widespread psychotropic polypharmacy was in the the APCD data between 2009 and 2018; 59.2% of Colorado children meeting this study's exposure criteria were prescribed at least two psychotropics in that time. Overall, this study's findings imply that polypharmacy being the rule, rather than the exception, is cause for immediate clinical and policy concern.

One of this study's central aims was to account for many users' long duration of psychotropic use in across the human lifespan, and to describe how the expected hazard of physiological adverse drug reactions was distributed over time. While I found that, on average, exposed children experienced the most ADRs in their first year of use, with ADR hazard decreasing over time after that, that decrease had a "long tail" in the APCD data, with relative hazard in the exposed taking over a decade in some cases to be the same as the unexposed. While this result of this signal-detection analysis requires further elaboration in future projects, it points prescribed psychotropic drug research and clinical practice more strongly in the direction of the chronological *totality* of users' experience with these compounds. An increasing amount of research on prescribed psychotropics has taken a similar turn in the last decade, with new or revived interest in the *end* of people's psychotropic use revealing critical information about withdrawal syndromes and discontinuation practices being a good example (Cohen and Recalt, 2019; Recalt and Cohen, 2019 ; Hengartner, Jakobsen, Sørensen, and Plöderl, 2020).

An innovation of this analysis was to incorporate a specific classification of the

clinical *seriousness* of ADRs into my analyses. My aim was to give abstract estimates of average ADR hazard more real-world clarity, and to do so I devoted 5 of 10 statistical models to estimating ADR hazard only in those PADRs that this study's clinician-raters assessed as serious: those ADRs that could result in death, be life-threatening, require or prolong hospitalization, or result in significant dysfunction or disability. This stratification proved valuable, as I showed that while there were 2.7 times as many ADRs of any seriousness level overall in the exposed, there were 5.7 times as many *serious* ADRs. Analyses also showed that the effects of psychotropic exposure may go far beyond those described very quickly and *sotto voce* in television advertisements for antidepressants and other psychotropics. While those effects – gastrointestinal disturbances, headache – appeared with great frequency in this analysis, and are likely responsible for a substantial proportion of increased hazard, other physiological systems and the effects grouped in them may not yet be the subject of widespread awareness or scrutiny. Several serious, non-behavioral CNS effects related to human movement appeared in exposed APCD members in substantially greater numbers than in the unexposed, and translated into excess hazard compared to the unexposed in statistical models even when epileptic disorders were controlled for. Asterixis (flapping tremor of the hand), Creutzfeld-Jacob-like syndrome (characterized by lack of coordination), and convulsions appear more frequently in exposed users, in users of different drug classes.

Serious and non-serious ADRs appeared in physiological systems critical to human functioning and thriving. On one hand, as a non-physician, I may perhaps not be qualified to make judgments about the relative importance of cardiovascular function compared to that of the mouth and teeth. On the other hand, consideration of the descriptive and statistical results suggests that psychotropic drugs may be

acting on extremely important functions of the human body and not solely on the nervous system, even if they appear to be acting more frequently or substantively on it (which is common sense: they are intended to act on the CNS). The physiological systems that most frequently contributed to overall counts of ADRs in the APCD data are essential ones, even to a lay reader: the sensory system, responsible for receiving and processing information about our world and our place in it; the cardiovascular system, which transmits blood and nutrients throughout our bodies; and the respiratory system, ensuring we exchange oxygen for carbon dioxide and enabling our lives in the process. Put plainly, prescribed psychotropics given to children in a critical period of human development appear to affect parts of bodily functioning responsible for keeping us alive and aware of our surroundings.

This study is unique in research on psychotropic drug safety. No other single study in this study's literature review described ADR risk or hazard across multiple physiological systems, with different levels of seriousness, for all drug classes, and include polypharmacy at the same time. It is critical to underscore that this study's approach to *time* was also unique: few similar studies employ analytic methods that explicitly account for time and its potential interaction with exposure, as I did here, and no study I identified in any age group attempted to account for the real-world possibility of users experiencing multiple adverse reactions during their time on a prescribed psychotropic. This study's findings validate its methodological choices: I built a detailed, population-based picture of prescribed psychotropic use beginning early in life that shows strong signals of elevated physiological ADR hazard at multiple levels of analysis, widespread and potentially harmful polypharmacy, and variable effects of exposure across time, all while accounting robustly for multiple outcomes within the same person.

5.2 Frailty, multiple events, & time

One of this study's central methodological innovations for research about prescribed psychotropic drug safety in pediatric settings was the decision make time a cornerstone of statistical analysis. This followed from my primary interest, which was a chronological one: not only is it crucial, I claimed above, to understand *what* can happen to the physiology of minors first prescribed a psychotropic in childhood or early adolescence, but *when* can that happen – how early?, how late?, etc. This began by using survival analysis as the analytic foundation. Other studies of potential harm from psychotropics in children, discussed in the Literature Review, employed logistic regression to estimate the relationship between psychotropic exposure and ADR hazard. I built on this foundation by specifying that regression models first account for individuals' potentially experiencing more than one ADR over time – what I called a random effect or *frailty* above – and that they next test for any interaction between psychotropic exposure and time.

All 10 models found a statistically significant frailty effect in their Chi-square tests of the Z frailty term, suggesting the presence in each model of within-subject interdependence across multiple events – what I called heterogeneity in the discussion of frailty. As stated in the results, both the exposed and unexposed experienced multiple potential ADRs, on average (13.7, SD = 37.5; and 3.47, SD = 8.87, respectively). 8 of 10 models – all save ENT ADRs in both ICH seriousness levels and serious Respiratory ADRs – found statistically significant interactions between exposure and time, and all described a similar direction: the effect of psychotropic exposure on ADR hazard, holding age, gender, polypharmacy, ZIP-level income, an epilepsy status constant, depends on time, and that effect *decreases* over time in all

8 cases. These have important implications for our understanding of psychotropics' effects on young people's rapidly developing (and *ipso facto* vulnerable) physiology, because it suggests that the hazard of ADRs, within and across key physiological systems, is highest early in a minor's "time on drug".

5.3 A conservative approach

I took an explicitly conservative approach to this signal detection study, deciding in the project's planning phases that if given a choice, it was preferable to underestimate a hypothesized relationship between prescribed psychotropic exposure and physiological ADRs than to overestimate one. The motivation for this was a desire for rigor: to remove, as much as possible, any statistical noise that may point measures of effect farther away from the null than they might otherwise merit. I liken this to astronomy: to detect the oldest, farthest light in the universe – light which may be extremely faint – we need to remove the younger and closer light, shining at us from innumerable sources, that sits between us. If we do not, that closer light, being much brighter, could conceal the real target.

Two of this study's features best embody this thinking: one in design, the other in analysis. The former is the decision to exclude a substantial proportion of APCD member records because of the possibility of duplication in the APCD. While CIVHC goes to great lengths to ensure that researchers' APCD extracts are "clean" from a data management point of view, they do not make diagnostic decisions about claims. Nor can we, of course. No one can tell by looking at the APCD tables whether Jane Smith's diagnosis of hearing loss at her doctor's visit yesterday is a different hearing loss than the one she was diagnosed with two weeks ago. It could be, of course

(perhaps two weeks ago it was in the other ear), and, if counted as such, would move hazard ratios that much higher than 1.0, showing increased ADR hazard overall. Then again, it might not be different: maybe yesterday's visit was Jane's followup visit, scheduled two weeks ago when she first saw her doctor. Because I don't know – in fact, because we can't ever know from claims data alone – I chose to treat these "subsequent day" instances of the same potential drug reaction as duplicates, and remove them. Trimming the data this way *before* analysis began was an effort to have only the surest signals, no matter how faint, show up when they did.

The analytic feature is the use of a frailty term Z in fitting proportional hazards models. In introducing survival analysis above, I discussed the central role of the hazard function $h(t)$, describing it as the instantaneous potential for the outcome to occur at a given time, given that the subject has survived (gone without the outcome) until that time. I wrote further that in proportional hazards models, the hazard of the outcome at time-zero (the beginning of the study), now called the *baseline* hazard function or $\lambda_0(t)$, is equivalent to a person's hazard of the outcome if all their covariate values were zero), and it isn't actually estimated. I cited this as one of the Cox model's strengths: it allows a researcher to have valid and robust regression coefficients in a package that combines the benefits of survival analysis and familiar regression methods, all without the heavy computational work of estimating every subject's $\lambda_0(t)$. The drawback, however, is an elision of a critical feature of the real world: at the start of a study, not everyone has the same susceptibility to the outcome. This could be for reasons the researchers have measured (age, say) or ones they haven't, but it remains that some people are *more frail* to the outcome, so to speak, than others.

A Cox model without a frailty term, then, is a Cox model that assumes that

people in the study with the same values of the measured covariates (in this case age, gender, polypharmacy, etc.) have the same hazard of the outcome of interest at the beginning of followup, and we know this is not true. A model with Z, by contrast, is one that allows for different subjects to have different values of baseline susceptibility ($\lambda_0(t)$) to the outcome, whether or not the reasons for that susceptibility have been measured. In statistical terms, this difference in frailties is a variance, a source of noise that left unaccounted for could have biased models' estimates. Because of the choice to fit models conservatively, though, the frailty terms get us that much closer to seeing the "oldest light".

5.4 COVID-19

Even though the APCD extract did not include data after 2018, it is important to look at this study through the lens of the global COVID-19 pandemic, a public health emergency that as of this writing has claimed over 6 million lives worldwide, and 1 million in the United States.

The rapid and profound changes to society brought on by the pandemic and authorities' responses in the first half of 2020 stoked widespread concern about the potential impacts to mental health of a deadly global pandemic and the isolation that accompanied it. Concerns in early 2020 about the potential worsening of existing psychiatric symptoms, or the emergence of new ones in those previously unaffected (Luykx, Vinkers, and Tijdink, 2020), had by the end of the year been shown to be well founded, with studies suggesting increases of symptoms of post-traumatic stress in hospitalized COVID patients and healthcare workers, and higher rates of symptoms of depression in COVID patients (Vindegaard and Benros, 2020).

It remains unclear whether the pandemic has had a lasting effect on rates of psychotropic drug prescription. A search of Embase in June of 2022 for the indexing terms "psychoactive agent", "child", and "coronavirus disease 2019" yielded 19 results, 5 of which were relevant to assessing prescription rates of psychotropics in youth related to COVID-19. None of the 5 studies analyzed US youth. Of these, 4 reported a decline in psychotropic prescription in the immediate weeks and months after March 2020 (Leith et al., 2022; Leong et al., 2022; Nason, Stein, Frank, and Stein, 2021; Ong and Roberts, 2022), but 3 reported a subsequent return to pre-pandemic rates (Leith et al., 2022; Leong et al., 2022; Ong and Roberts, 2022). One study of Canadian youth in Manitoba identified an increase in antidepressant prescriptions above pre-pandemic rates, but the difference was not statistically significant (Leong et al., 2022). Investigators explained the initial decline as a result of a delay in the transition from in-person doctor's visits to telehealth in the initial lockdown period.

5.5 Limitations

5.5.0.1 Fundamental limitations of pharmacoepidemiological studies of claims databases

Conducting pharmacoepidemiology studies carries some risks (Strom and Kimmel, 2006). Studies may find spurious associations between drugs and outcomes, leading investigators and readers to potentially indicate the possibility of either harm or benefit when none exists. This is especially true if pharmacoepidemiological studies are interpreted causally; while recent methodological advances have made causal

inference from observational data more feasible, many studies make unjustified claims of causal relationships (Bareinboim and Pearl, 2016; Hernan and Robins, 2010).

The central limitation of this study, however, is the limited internal validity of its results. In a dataset as large as the Colorado APCD, and with as many exposures and outcomes as I propose, spurious significant results are likely to appear. Furthermore, due to the inherent dearth of potentially useful covariates in administrative datasets such as the APCD, researchers' ability to effectively control for confounding factors is lower than it otherwise would be in the case of "wider" datasets such as EMR. Useful or interesting covariates that do appear in claims databases are often incomplete. The reader may have wondered why the descriptive and statistical analyses in this study featured some sociodemographic variables common to social science and biomedical research, such as age, gender, and median household income, but did not include others, like race or ethnicity, which would have been highly relevant given known disparities in psychotropic prescription between these groups. The APCD does have a variable for ethnicity, but I did not include it because those data were missing in 87.0% of members in the APCD extract. Communication with CIVHC revealed that the problem lay upstream of their collection and cleaning of Colorado insurers' claims: for the years in the dataset, many of the professionals creating and processing medical and pharmacy claims simply did not fill out the "ethnicity" field very often. The APCD dataset also contained a "race" variable, but this did not include an option for "Hispanic", which would have been essential for this study. (Data were also missing for 65% of members.) This is a notable limitation of this study.

Challenges like these underscore the fact that administrative claims datasets are created for financial purposes, and not for research. While researchers have made insightful use of them in a variety of medical and economic contexts, their use in

these cases has always been fundamentally improvisational, borne out of an absence of an ideal way to study health phenomena in large populations as well as their sudden availability beginning in the late 1980's. EMR datasets are not built for research, either, but they are a step up from claims databases in that their level of analysis is a patient and their health, and not a transaction between a payer and a healthcare provider. A study similar to this one, methodologically identical but employing an EMR dataset instead of a claims dataset like the APCD, might have higher internal validity by being able to account for characteristics of patients' health and sociodemographic characteristics that a dataset like the APCD simply does not feature. Race and ethnicity are good examples: owing to their largely incomplete status in the APCD, I am not able to account for these basic and important variables in the study as currently conceived.

Relative to such alternatives, then, there is a lower ceiling on this study's internal validity, and one could justifiably ask, if such a ceiling exists, and if the study's results are not causal, how conducting it contributes to knowledge. The answer lies in situating a study like this one as an intermediate step in a broader process of pharmacoepidemiological signal detection. Drug safety research in 2022 is a patchwork quilt of imperfect tools, and the degree to which we have a useful picture of a drug's benefits and harms is the result of those tools working together to account for each others' weaknesses across many individual studies and efforts. Above, I outlined the limitations of controlled trials in drug safety, but I would not argue for not conducting them at all. Adverse event reporting systems, not addressed in detail here, have their own flaws, incomplete and inconsistent reporting among them. By itself, a study like this one may at best represent a modest contribution to the overall knowledge of psychotropic drug safety in pediatric settings, useful to further test

and filter out preliminary signals gathered from other sources like reference volumes, smaller studies, and adverse event reporting systems. "Psychotropic drugs are not meaningfully associated with PADR Grouping A, but it is strongly associated with PADR Grouping B" may not make for the grandest of claims, but it is a valuable signpost for future efforts: *don't look over there; look over here instead.*

Other limitations concern the outcomes under study. In a study like this one, in which a wide array of serious and non-serious outcomes in pediatric health are investigated, including death as a serious outcome would make sense; in this study, though, it is not included. The main reason for this is that the APCD dataset is not yet fully linked to state death records, so attempting an accounting of the risk of death due to long-term psychotropic use in children would admit at least some bias (misclassification). One might reasonably wonder, too, why this study limits itself to physiological outcomes, excluding psychological or psychiatric adverse reactions – especially when such reactions have been widely reported on and discussed (see e.g. suicidal ideation and behavior in pediatric use of antidepressants). The central reason is one of interest: at this stage, I am mainly curious about the potential effects of prescribed psychotropics on human bodily health, especially considering how little attention such effects have received in the drug safety literature.

5.5.0.2 Confounding by indication.

In this dissertation project's Methods section, I described the need to handle epilepsy diagnoses with a certain care in statistical analyses, outlining a plan to control for them in Cox models. The reason for this was the risk of *confounding by indication*: when the risk for an adverse drug reaction is related to the reason a drug is prescribed

(its *indication*) but not to the drug itself (Strom and Kimmel, 2006). I hypothesized that because of the unique position that Antimanic and Mood Stabilizer drugs have in terms of the indications for which they're prescribed, prescribed as they are for both seizure disorders *and* psychiatric disorders like bipolar, the risk of epilepsy diagnoses confounding the estimate of the relationship between exposure to these drugs and PADRs (in particular, "non-behavioral" ADRs of the central nervous system (CNS)) was particularly high. Analyses showed that this concern was well founded: controlling for other variables, the estimated hazard of ADRs (and CNS ADRs in particular) for children with epilepsy diagnoses, compared to children without them, in the 4 models that included epilepsy were extremely high.

This seeming success points to a crucial limitation of this study, though: the possibility of confounding by indications (diagnoses) I have *not* explicitly identified. I felt comfortable proceeding with less control for this sort of confounding because broadly speaking, psychiatric diagnoses do not have a long list of direct physiological sequelae that could serve to confound the estimation of a drug's effect on the human body. There are exceptions, of course: depression, for instance, is frequently associated with increased or decreased sleep, which could be considered non-psychiatric CNS or even pulmonary effects. But the causal relationship remains unclear, especially in the absence of valid and reliable pathophysiology for any psychiatric disorder. Did the depression *cause* the increased sleep, or vice-versa? Did an unknown variable, upstream from both symptoms, cause both?

Since my lists of physiological systems (n=29) and PADRs (n=587) were so large, I thought at the outset that a substantial amount of confounding by indication was unlikely because of the structure of the research question: a built-in division between indication (*mental* disorders) and outcomes (groups of *physiological* diagnoses) made

the latter's association with exposure to drugs which affect the body easier to establish than it would have been had the indication been physiological as well. Put plainly, I believed it was unlikely that whatever physiological process lie underneath ADHD (if any) were unlikely to directly cause a symptom like asterixis (hand tremor). However, a case might be made for such an association, and dozens or hundreds like it, for the drug indications (psychiatric diagnoses) and PADRs in this study.

Outside of epilepsy, I did not account for these possibilities. Indeed, a look at the high HRs for the Epilepsy (and other recurrent seizure disorders) variables in statistical models suggests that the choice to control for these conditions in the HRs of primary interest (exposure) was correct, and thus that confounding by indication would have been present because of the inclusion of anti-seizure drugs in my list of prescribed psychotropics. The HRs for epilepsy show that the relative hazard of PADRs in those with seizure diagnoses compared to those without them, controlling for other variables (including psychotropic exposure), was significantly higher.

This might prompt the reader to wonder about the psychotropic-exposed children in the APCD more broadly. While I do not know exactly which ones they were prescribed, Table 4.6 shows that children in the APCD who were exposed to psychotropics were also exposed to the bulk of *all* prescription drugs in the dataset: of the 32,454 distinct NDCs prescribed to psychotropic exposed and unexposed children together, 22,556 (69.5%) were prescribed to children meeting psychotropic exposure criteria, suggesting that a child exposure to psychotropics was substantially more likely to be prescribed other, non-psychotropic drugs than an unexposed child. From this we might conclude that psychotropic-exposed children in the APCD were more unhealthy overall, with psychiatric conditions as well as other physiological ones unaccounted for in this study's analyses.

5.5.0.3 A mismatch with the literature?

Another critique might be made against this study: the sorts of ADRs and PADRs discussed in the Literature Review are in some ways quite different from the PADRs found in this study's analyses. A reader familiar with the risks of psychotropic treatment in children may justifiably wonder, for instance, where the mentions of metabolic conditions like diabetes mellitus are in this analysis. These effects are one of the few widely accepted and recognized ADRs of antipsychotic use in children, with substantially increased risk in published studies (Galling and Correll, 2015), so why do they not appear?

One response would be liken psychotropic safety in children to a jigsaw puzzle: in the literature review, I found several very detailed pieces, each asking whether *this* specific population subgroup had *that* specific ADR. But there ultimately weren't very many of these. My analyses, by contrast, attempted to start from scratch by making new pieces, looking at the bulk of human physiological functioning. Because of the quantity of outcomes under study here, I could not feasibly fit 587 survival models for each outcome, nor did I feel comfortable choosing a small number among them. My solution was to follow the two studies by Jerrell and McIntyre (2008; McIntyre and Jerrell, 2008) and group outcomes together according to their physiological system.

Gaining breadth in this way may have resulted in a loss of depth, however. This may have been further compounded by other choices about what to analyze and present in a study this large, namely the selection of which physiological system-groups to model statistically. With 29 physiological systems, and without *a priori* reasons to focus statistical analyses on one physiological system over another, I chose

a simple "Top 4", frequency-based approach in choosing how to narrow my focus in proportional hazards models. While commonsensical, this choice represents a limitation, in that clinically important or serious effects residing in systems with lower ADR frequencies in the APCD analysis dataset may have been overlooked in analyses and findings. But since this study's aim was comprehensiveness – an attempt to detect signals based on a collection of *all* mentions of potential adverse reactions to psychotropics, ever, in any part of the human body – I would respond by saying that other approaches to outcome selection and presentation would have been equally arbitrary. I also acknowledge that my decision to use an "any class" definition of exposure instead of looking at specific drug classes as exposures in statistical models represents another limitation of this study. Readers may note a contrast between "direct hit" Literature Review studies that in 7 of 8 cases looked at a single drug class, and this study's results, which collapsed drug classes into a universal psychotropic exposure variable, and object that this loss of detail obscures important differences between drug classes with different chemical structures and effects. This is a valid critique.

The last potential source of mismatch that merits mention here sits further upstream from my decisions in this study and lies instead in the APCD itself: clinical recognition of potential ADRs in the context of clinicians' well established and substantial under-reporting of the phenomenon. A diagnosis of a health condition only enters the APCD after a clinician has made a decision about what they are seeing. An invisible (to us) but critical negotiation occurs between potentially appropriate diagnoses for the condition being observed. Broadly, society trusts clinicians to make these decisions and we invest time and resources into training doctors and nurses to make the right ones. But clinicians are human beings, too, susceptible to the same

pressures as anyone else. In the United States, they are generally given very little time to spend with patients, and because of drug marketing practices may not know as much about drugs' drawbacks as they hear about their benefits. Psychological mechanisms like denial and cognitive dissonance may play a role as well (Beggelman, 2016; Varallo, Guimarães, Abjaude, and Mastroianni, 2014). In this line of thinking, the psychological tendency to prioritize internal consistency and positive self-regard may blind physicians to the idea that their interventions and clinical decisions could result in harm. While it is impossible to measure in a study like this one, and is thus speculative, I consider this possibility in light of work that suggests that treatment-induced or *iatrogenic* harm of different kinds is consistently underreported to authorities, with one estimate suggesting that as few as 1% of serious adverse events are ever shown to the FDA (Kessler et al., 1993). A 1987 study is directly relevant to my own, showing high rates of non-recognition by doctors of neurological movement disorders known as extrapyramidal symptoms (EPS) that appear after antipsychotic use (Weiden, Mann, Haas, Mattson, and Frances, 1987). Analyses like ours rest as much on the decision-making of doctors, nurses, and pharmacists as on other factors outlined here. I wonder if human frailty and under-reporting of ADRs affect my estimates of ADR hazard, biasing them toward the null.

Despite these drawbacks, the Literature Review and Results are not entirely mismatched – in fact, this study's results fit well into the 5 of the 8 "direct hit" studies cited above, with a partial connection to 1 more. To start, recall the Jerrell and McIntyre studies of antipsychotic exposure in children (2008a; 2008b), which in addition to Type II diabetes mellitus also found increased rates of cardiovascular, CNS, and sensory conditions, as well. While metabolic PADRs (the physiological grouping that would contain Type II diabetes) were not one of the 4 most frequent

groupings in the APCD analytic sample, and thus were not focused on in these analyses, the descriptive and statistical results also showed increased proportions and hazard, respectively, of CNS, sensory, and cardiovascular effects.

Dalsgaard and colleagues (2014; 2011) also looked at cardiovascular ADRs, here in Danish children who used stimulant drugs. Like us, they estimated HRs of a grouping of cardiovascular outcomes using Cox proportional hazards models – and found a similar hazard to ours: they found an HR of 1.83 (95% CI [1.10, 3.04]) while I found an HR of 1.63 (95% CI [1.34, 1.99] p <.001). Even specific effects identified in their study overlap with ours: while I did not see ischemic heart disease or hypertension in the 5 most frequent cardiovascular effects, like Dalsgaard and colleagues did, arrythmias did, which they saw in 23% of their exposed group. Results were partially similar to Storebø and colleagues' (2018), as well. In the only study I found to specifically focus on *serious* ADRs of psychotropics, the authors found that methylphenidate (Ritalin) use increased the risk of any serious adverse event by 36% (RR 1.36, 95% CI 1.17, 1.57). While not a one-to-one comparison because of differences in exposure (1 drug class vs. 5) and outcomes (this study looked at many more), it bears mentioning that estimates of the hazard of serious PADRs was also significantly elevated (HR = 1.60, 95% CI [1.51, 1.70] p = <.001). Curtin et al. (2018) found significantly greater risk of diseases of the basal ganglia (conditions which alter motor function such as Parkinson's disease)in ADHD patients prescribed stimulants than matched, un-diagnosed subjects (aHR=6.0, 95% CI: 3.9–9.1; $P<$ 0.0001). While this study showed a large proportion of CNS PADRs, and increased hazard of them in statistical models, tabulation of individual CNS effects did not show similar disorders. Considering the relative wealth of knowledge on conditions like tardive dyskinesia in the literature on prescribed psychotropic use, I expected

to see more movement disorders show up as CNS PADRs in this study. The closest individual diagnoses that showed up, though, were forms of *lack of coordination* like ataxia and dyspraxia (what medical coders selected for "asterixis", a type of hand tremor which appeared in the ADR reference literature and thus made it into my database).

Overall, while it may be fairly said that in this study, some PADRs that readers familiar with prescribed psychotropics might expect to see did not appear, the results align substantially with the small body of similar prior literature in this field.

5.5.0.4 Ambiguity and agreement in raters' evaluation of ICD codes and ADR seriousness

I used expert medical billers (n=2) and pediatric clinicians and pharmacists (n=3) to translate PADR descriptions into ICD codes, and to rate PADRs according to ICH definitions of adverse drug reaction seriousness, respectively. With the limited resources available to a graduate student, I succeeded: in the former case, I developed a comprehensive database of potential ADR signals able to be electronically integrated into the APCD data and matched to its diagnostic information; and in the latter case, I made consensus ratings of ADR serious for all 587 of these. But within this success lie two of this project's weak points, both of which concern the less-than-ideal amount of agreement between raters on each task. In the ICD translation task, a validation exercise yielded only a 61.0% overall agreement on codes matched to descriptions. In the seriousness rating task, a formal calculation of inter-rater reliability produced a Fleiss's κ value of 0.44, considered on the lower end of "fair" agreement strength (Shrout, 1998). In my view, both of these processes

can be significantly improved in future endeavors, but doing so will require more substantial investigation into best practices for classification and reliability in any applicable fields, biomedical or otherwise. In this project, an effort was made to enlist experienced assistance in these matters, but it did not come to fruition.

There was another source of ambiguity in the organizational daisy-chain from "short description of potential ADR found in the reference literature" to "ICD code merged and matched to the APCD data", namely that what I thought were very distinct and precise ICD codes could in some cases actually be groupings of their own. This is the issue of *ICD synonyms* mentioned briefly in the Methods section of this study. In many cases, an ICD code's synonyms will conform to the plain-English understanding of that word. For instance, take the ICD-9 entry for *epistaxis*, or nosebleed (ICD-9 code 784.7): its synonyms are "Anterior epistaxis"; "Epistaxis (nosebleed)"; "Epistaxis, anterior"; and "Posterior epistaxis". Aside from an allowance for where the nosebleed occurs (at the front or back of the nasal cavity), these appear to be variations on phrasing that do not stray from the code's label. But other codes are not as straightforward: in the case of "Other convulsions" (ICD-9 code 780.39), there are 104 synonyms. While I am not a physician, an search through a medical dictionary suggests that "tonic-clonic seizures" and "eclamptic seizures" are not exactly the same phenomenon – but they could be appropriately given the same ICD code.

5.5.0.5 Absence of other prescription drug use.

For this study, I built a database of approximately 36,282 National Drug Codes (NDCs) for 104 psychiatric compounds available in the United States in the past

5 decades. Doing this consisted of manual searches through US Government and private databases (IBM Micromedex) for each psychotropic compound and later, collation into a single table. I used this database to identify psychotropic prescriptions in APCD children meeting exposure criteria for this study. To my knowledge, no similar database for pharmacoepidemiological investigations of psychotropic drug safety has been built.

Despite this, this study leaves non-psychotropic prescription drugs unaccounted for in descriptive and statistical analysis. This is one of the study's central limitations, since I feel confident in saying that the kinds of potential psychotropic ADRs I gathered from the literature and analyzed here may also be caused by drugs other than stimulants, antidepressants, antipsychotics, and the like. If that can be shown to be the case, it means that this study has not controlled for important potential contributors to the reported findings. Querying the APCD data shows that of a total of 40,432 unique NDCs of any kind that appear, only 3,217 (7.9%) corresponded to the psychotropic compounds in my database of 36,282 codes. This leaves 37,215 (92.1%) non-psychotropic NDC codes without description or account.

Resource limitations are the primary reason for why a larger database of *all* NDCs, psychotropic or otherwise, could not be brought into this dissertation project. Manually creating such a database in a manner analogous to my psychotropic NDC database was out of the question for one PhD candidate's project; building the psychotropic database for a mere 104 compounds required several dozens of hours of labor over the course of 3 months. Doing so for thousands of other compounds may have prevented the project from ever coming to fruition. This left only the acquisition of, or direct electronic access to, an already existing database of NDCs accessible directly over the web from my computer's database environment. Such

a database would have allowed for code to be written to link the database and "translate" NDCs into descriptions of compounds and drug categories. However, searches for such a database yielded no results, at any price.

Without an *a priori* list of compounds of interest before undertaking a project like this one, matching cryptic or obscure claims database fields to detailed descriptions of drugs and medications is prohibitively difficult without more personnel, funding, or extant database link designed for this kind of purpose. I remain fairly confident that databases with the ability to connect directly do exist, but have yet to find them. Future, better-resourced iterations of this study's broader scope and aims will endeavor to be able to account more fully for all drugs that database members may be prescribed.

5.6 Conclusion

The results of this study suggest that there is significant potential for long-term physiological harm as a result of prescribed psychotropic use that begins in childhood. Its broad view of drugs and outcomes must be followed by more focused, rigorously validated, and longer-term work by researchers (at specific drug classes and systems of the body, for instance) and by cultural shifts in psychotropic use by policymakers, clinicians, and families.

This work has two broad implications for researchers. First, short-term studies no longer suffice for a true picture of psychotropic safety. Estimates of average duration of psychotropic use, in both the analytic sample of Colorado children and Americans more broadly, are several years long in the lowest case – "long term" by any reasonable definition. As this study's review of the literature shows, few

studies of psychotropic drug harm in children seek to maximize followup time, and definitions of what constitute "long term" vary widely, from weeks to years. Second, long-term psychotropic drug safety research in children and minors must go *deeper* and *wider*. "Deeper" here applies to specific harms: with statistically significant HRs appearing in some unexpected physiological systems (e.g. sensory), and diagnostic summaries showing unexpected conditions (e.g. lack of coordination, respiratory failure), future research ought to focus on specific symptoms while maximizing followup and confounding control. Other work must go "wider": if drug safety research is a patchwork quilt, observational studies of claims data like this one cannot be the only square. Other sources of data and other methodological approaches are essential, as one design's weaknesses may be mitigated by another's strengths.

Studies similar to this one but which instead employ electronic medical record (EMR) data instead of claims data could have some advantages, particularly with respect to outcome identification and confounding control. EMR datasets often have more complete diagnostic information about patients, designed as they are to collect medical information, as opposed to payment information in the case of claims datasets. But even the largest EMR datasets face similar constraints as their claims-based cousins: in the first place, they are not designed for research, either, so investigators still must spend time adapting, cleaning, and "translating" different sources of data. This in turn increases the potential for the kinds of uncertainty introduced into this study, PADR seriousness ratings and ICD code validation being salient examples. Needed innovation in psychotropic drug safety research could come from the kind of approach taken in the Framingham Heart Study, for instance: prospective, multi-decade studies of specific cohorts of drug-exposed children would be able to look comprehensively at their lives in ways that analyses of observational data like

this one could never hope to mimic.

For families, practitioners, and patients themselves, this study suggests that prescribed psychotropic use of indefinite or unscrutinized duration can no longer be an acceptable clinical default. Current practice guidelines for psychotropics in children and minors either recommend long-term treatment (12 months or more for anxiety disorders; Walter et al., 2020) or do not discuss treatment duration in detail. In a memorandum to state and tribal authorities concerning the use of psychotropic drugs in children in foster care, the US Department of Health and Human Services' (HHS) Administration for Children and Families cites the large increase in prescription rates in recent decades to caution against "too many [psychotropic drugs], too much [dose], and too young" by prescribers and administrators (Samuels, 2012). Given the rates of psychotropic polypharmacy in non-foster youth, as well the potential harms to human physiology over the long term, I would suggest extending this advice to all youth and adding "for too long" to the end of the HHS's expression.

I follow Yoder (2014) and Whitaker (2016) in advocating for the kind of "selective use" model of psychotropic prescription pioneered in Open Dialogue treatment approaches to psychosis (see e.g. Bergström et al., 2017), and specifically for it to be adapted to child and minor populations. On the one hand, prescribed psychotropic drugs may in some instances be helpful in providing relief from acute distress. When recommended in the context of a collaborative, informed, and dignified relationship with a prescriber, they can form part of a broader journey towards healing. On the other hand, little and often low-quality empirical evidence supports these drugs' use in children at all, and studies like this one strongly suggest that using them may have damaging consequences to physiological health in a critical period of human physiological, psychological, and social development. A cautious yet caring approach to

threading this needle might suggest *the least amount of medication beneficial, in the lowest dose necessary, for the briefest amount of time possible.*

Appendix A

Supplementary material

A.1 Individual ratings of PADR seriousness

Table A.1 summarizes the 3 clinician-raters' evaluations of PADR seriousness for each of the 587 PADRs analyzed in this study. Ratings were binary, with 0 equaling "non-serious" and 1 equaling "serious". To restate the definitions presented in Chapter 3, serious and non-serious ADRs are defined by the ICH as follows:

- *Serious Adverse Drug Reactions* are any untoward medical occurrences that at any dose
  - result in death,
  - are life-threatening,
  - require inpatient hospitalization or prolongation of existing hospitalization,
  - result in persistent or significant disability/incapacity, or
  - are a congenital anomaly/birth defect.
- *Non-serious Adverse Drug Reactions* are all other ADRs, including but not limited to common adverse events such as cardiovascular, neurological, and gastrointestinal events (ICH, 1995, 1996).

Table A.1

ICH seriousness ratings of individual PADRs (N=587) by rater (n=3)

Phys. system	Outcome	R1	R2	R3
Body temp.	Benign transient increases in body temperature	0	0	0
Body temp.	Heat stroke	1	1	1
Body temp.	Hypothermia	1	1	1
Body temp.	Increased hypothermic episodes in existing hypothalamic dysfunction	1	1	1
Body temp.	Labile blood pressure	1	0	1
Cardiovascular	Abnormal electrocardiogram	0	1	1
Cardiovascular	Abnormal ST segments	0	1	1
Cardiovascular	Acute massive pulmonary thromboembolism	1	1	1
Cardiovascular	Acute myocardial ischemia (in patient with known angina and mild coronary artery disease)	1	1	0
Cardiovascular	Angina	0	1	1
Cardiovascular	Apical cardiomyopathy	0	1	0
Cardiovascular	Arrhythmia	0	1	0
Cardiovascular	Asystole	1	1	1
Cardiovascular	Atrial fibrillation	0	0	1
Cardiovascular	Atrioventricular block	0	1	1
Cardiovascular	Bradycardia	1	0	1
Cardiovascular	Brain stem stroke	1	1	0
Cardiovascular	Bundle branch block	0	0	1
Cardiovascular	Cardiac dysfunction (due to carnitine deficiency)	1	1	0
Cardiovascular	Cardiac muscle pathology	0	1	0

Cardiovascular	Cardiac shock	1	1	1
Cardiovascular	Cardiomyopathy	1	1	1
Cardiovascular	Chest pain	0	0	0
Cardiovascular	Complete heart block	1	1	1
Cardiovascular	Congestive heart failure	1	1	1
Cardiovascular	Depressed cardiac conduction	1	1	1
Cardiovascular	Dilated cardiomyopathy	1	1	1
Cardiovascular	Dyspnea	0	1	1
Cardiovascular	Eosinophilic myocarditis	1	1	0
Cardiovascular	Epistaxis (severe)	0	0	1
Cardiovascular	Exacerbation of previous heart failure	1	1	1
Cardiovascular	Fatal myocarditis	1	1	1
Cardiovascular	Focal myocarditis	0	1	1
Cardiovascular	Gangrene	0	1	1
Cardiovascular	Hypertension	0	0	0
Cardiovascular	Hypertensive crisis	1	1	1
Cardiovascular	Hypotension	0	0	0
Cardiovascular	Hypotension (severe orthostatic)	1	0	1
Cardiovascular	Increased heart rate	0	0	0
Cardiovascular	Intermittent asystole	1	1	0
Cardiovascular	Pacemaker failure	1	1	1
Cardiovascular	Palpitations	0	0	0
Cardiovascular	Pericardial effusion	0	1	1
Cardiovascular	Pericarditis	0	1	1
Cardiovascular	Peripheral edema	0	0	0
Cardiovascular	Potentially fatal polymorphic ventricular tachycardia	1	1	1
Cardiovascular	Prolonged QT interval	0	1	1
Cardiovascular	Raynaud's phenomenon	0	0	1
Cardiovascular	Reduced cardiac output	1	1	0

Cardiovascular	Serious cardiac dysrhythmias (some fatal)	1	1	0
Cardiovascular	Serositis	0	0	1
Cardiovascular	Sinoatrial block	0	1	1
Cardiovascular	Sinus arrest	1	1	1
Cardiovascular	Stroke	1	1	1
Cardiovascular	Vasculitis	0	0	1
Cardiovascular	Venous thromboembolism	1	1	1
Cardiovascular	Ventricular fibrillation	1	1	1
Cardiovascular	Vertebral artery dissection	1	1	0
Cardiovascular	Worsening of existing heart failure	1	1	1
Electrolyte balance	Acute hypokalemic paralysis	0	1	1
Electrolyte balance	Hypernatremia	0	1	1
Electrolyte balance	Hyponatremia	0	1	0
Electrolyte balance	Severe hyponatremia	1	1	1
Endocrine	Abnormal thyroid function	0	0	0
Endocrine	Altered cortisol concentration	0	1	0
Endocrine	Altered dehydroepiandrosterone concentration	0	1	0
Endocrine	Amenorrhea	0	0	1
Endocrine	Anovulatory cycles	0	0	0
Endocrine	Bone mineral density loss	0	0	0
Endocrine	Breast cancer	1	1	1
Endocrine	Breast tenderness	0	0	0
Endocrine	Depressed ACTH / cortisol concentration	0	1	1
Endocrine	Drug-induced hyperprolactinemia	0	0	0
Endocrine	False-positive pregnancy	0	0	1
Endocrine	Galactorrhea	0	0	0
Endocrine	Goiter	0	0	1
Endocrine	Gynecomastia	0	0	0
Endocrine	Hirsutism	0	0	0

Endocrine	Hypercalcemia	0	0	0
Endocrine	Hyperparathyroidism	0	0	1
Endocrine	Hyperthyroidism	0	0	0
Endocrine	Impaired spermatogenesis	0	0	0
Endocrine	Inappropriate ADH secretion	1	0	1
Endocrine	Inappropriate prolactin secretion	0	0	0
Endocrine	Increased androstenedione	0	0	0
Endocrine	Increased plasma melatonin	0	0	0
Endocrine	Increased serum SHBG	0	0	0
Endocrine	Increased TSH	1	0	0
Endocrine	Incresed growth hormone concentration	1	0	0
Endocrine	Low TSH concentration	1	0	0
Endocrine	Menstrual disturbances	0	0	0
Endocrine	Osteoporosis	0	0	0
Endocrine	Polidipsia	1	0	0
Endocrine	Prolactin release	0	0	0
Endocrine	Pubertal growth arrest	0	1	0
Endocrine	Reduced plasma cortisol	1	0	0
Endocrine	Reduced serum progesterone concentration	0	0	0
Endocrine	Sick euthyroid syndrome	1	0	1
Endocrine	Subclinical hypothyroidism	0	0	0
Endocrine	Suppresion of endogenous melatonin secretion	0	0	0
Endocrine	Thyroiditis	0	0	1
Endocrine	Weight loss	0	0	1
ENT	Intractable coughing	0	0	0
ENT	Nasal burning	0	0	0
ENT	Rhinitis	0	0	1
Fluid balance	Edema	0	0	0
Fluid balance	Leg edema	0	0	0

Fluid balance	Water intoxication	1	1	0
GI	Abdominal distension	0	0	1
GI	Abdominal distress	0	0	0
GI	Abdominal tenderness	0	0	0
GI	Acute intestinal pseudo-obstruction (Ogilvie's syndrome)	1	1	1
GI	Colitis	0	0	1
GI	Constipation	0	0	0
GI	Constipiation (significant)	0	1	1
GI	Diarrhea	0	0	0
GI	Drug-induced acute hepatitis	1	1	1
GI	Dyspepsia	0	0	0
GI	Eosinophilic esophagitis	0	1	0
GI	Fatal constipation	1	1	0
GI	Gastric intolerance	0	0	0
GI	Gastritis	0	0	0
GI	Gastrointestinal disturbances	0	0	0
GI	Gingival hyperplasia	0	0	0
GI	Hiatus hernia	0	1	1
GI	Loose stool	0	0	0
GI	Loss of appetite	0	0	0
GI	Lymphocytic colitis	0	0	0
GI	Microscopic colitis	0	0	0
GI	Minor bowel disturbances	0	0	0
GI	Oligurgic renal insufficiency	1	1	1
GI	Paralytic ileus	1	1	1
GI	Parotid gland enlargement	0	0	1
GI	Peripheral eosinophilia	1	0	1
GI	Raised aminotransferase	1	0	0
GI	Rapid bowel ischemia	1	1	1

GI	Reflux esophagitis	0	0	0
GI	Upper gastrointestinal bleeding	1	1	1
GI	Vomiting	0	0	0
Hair	Hair loss	0	0	0
Hematologic	Abnormal bleeding	1	1	1
Hematologic	Acquired von Willebrand's disease	0	1	0
Hematologic	Acute marrow aplasia	1	1	1
Hematologic	Acute myeloblastic leukemia	1	1	1
Hematologic	Afibrinogenemia	1	1	1
Hematologic	Agranulocytosis	1	1	1
Hematologic	Anemia	1	0	0
Hematologic	Blood dyscrasia	1	1	0
Hematologic	Bone marrow failure (lethal)	1	1	1
Hematologic	Bone marrow suppression	0	1	0
Hematologic	Bruising	0	0	0
Hematologic	Easy bruise-ability	0	0	0
Hematologic	Erythroblastopenia	0	1	1
Hematologic	Gingival bleeding	0	0	0
Hematologic	Granulocytopenia	1	1	1
Hematologic	Hematuria	0	0	1
Hematologic	Hemolysis	1	1	1
Hematologic	Hemolytic anemia	1	0	1
Hematologic	Increased prothrombin time	1	1	1
Hematologic	Leucopenia	1	1	0
Hematologic	Leukocytosis	1	1	0
Hematologic	Lymphoma	1	1	1
Hematologic	Lymphopenia	0	1	0
Hematologic	Melena	0	1	1
Hematologic	Myeloid hyperplasia	0	0	1
Hematologic	Pancytopenia	1	1	1

Hematologic	Pseudolymphoma	0	0	1
Hematologic	Pure red cell aplasia	0	1	1
Hematologic	Purpura	0	0	1
Hematologic	Reduced factor VII concentraion	0	1	1
Hematologic	Reduced factor XIII	0	1	1
Hematologic	Reduced fibrinogen	0	1	1
Hematologic	Reduced platelet count	1	1	0
Hematologic	Reduced protein C	1	1	1
Hematologic	Reticulocytosis	1	0	0
Hematologic	Reversible intravascular hemolysis	1	1	1
Hematologic	Thrombocytopenic purpura	0	1	1
Hematologic	Thrombocytosis	1	1	1
Immunologic	Anaphylactic reaction	1	1	1
Immunologic	Anticonvulsant hypersensitivity syndrome	1	1	1
Immunologic	Antiphospholipid syndrome	1	1	1
Immunologic	Arthralgia	0	0	0
Immunologic	Cervical lymphadenopathy	0	0	1
Immunologic	Cryoglobulinemia	0	1	1
Immunologic	Dificulty swallowing and breathing	1	1	1
Immunologic	Drug-induced lupus-like syndrome	0	0	1
Immunologic	Excess of interferon-gamma	0	0	1
Immunologic	Guillain-Barre-like syndrome	1	1	1
Immunologic	Herpes simplex reactivation	0	1	0
Immunologic	Hypersensitivity syndrome	1	1	1
Immunologic	Hypocomplementemia	0	1	1
Immunologic	Hypogammaglobulinemia	0	1	1
Immunologic	Immunoblastic lymphadenopathy	1	0	1
Immunologic	Kikuchi disease	0	0	1
Immunologic	Lupus erythematosus	0	1	1
Immunologic	Lupus-like syndrome	0	0	1

Immunologic	Lymphadenopathy	0	0	0
Immunologic	Lymphocytosis	0	0	1
Immunologic	Membranoproliferative glomerulonephritis	0	1	1
Immunologic	Pleural effusion	1	1	1
Immunologic	Rowell's syndrome	0	0	1
Immunologic	Serum sickness-like reaction	0	1	1
Immunologic	Splenomegaly	0	0	1
Infection risk	Increased infection risk	1	0	1
Infection risk	Increased viral load of HIV	1	1	0
Liver	"Reye-like syndrome"	1	1	1
Liver	Acute hepatic necrosis	1	1	1
Liver	Acute liver damage	1	1	1
Liver	Autoimmune hepatitis	1	1	1
Liver	Cholangitis	1	0	1
Liver	Cholestatic hepatitis	0	0	1
Liver	Cytolitic reactions	1	1	1
Liver	Drug-induced liver damage	1	1	1
Liver	Fatal hepatic failure	1	1	1
Liver	Granulomatous hepatitis	0	1	1
Liver	Hepatitis	0	1	1
Liver	Hepatotoxicity	1	1	1
Liver	Jaundice	0	0	1
Liver	Non-alcoholic fatty liver disease	0	0	0
Liver	Obstructive jaundice	1	1	1
Liver	Post-liver-transplant hepatitis	1	1	1
Liver	Pruritus	0	0	0
Metabolism	Abnormal glucose homeostasis	0	1	0
Metabolism	Alkalosis	0	1	0

Metabolism	Atherogenic metabolic triad (hyperinsulinemia, raised apolipoprotein B, raised small-density LDL concentration)	0	0	0
Metabolism	Carnitine deficiency	1	1	0
Metabolism	Cerebrospinal fluid acidosis	0	1	1
Metabolism	Diabetes insipidus	1	0	1
Metabolism	Diabetes mellitus	0	1	0
Metabolism	Diabetic ketoacidosis	1	1	1
Metabolism	Exacerbation of existing diabetes mellitus	1	1	0
Metabolism	Excessive weight gain	0	0	0
Metabolism	High cholesterol	0	0	0
Metabolism	High LDL cholesterol	0	0	0
Metabolism	High plasma homocysteine	0	0	0
Metabolism	High plasma triglyceride concentration	0	0	0
Metabolism	Hyperammonemia	1	0	1
Metabolism	Hyperglycemic coma	1	1	1
Metabolism	Hyperglycinuria	0	0	1
Metabolism	Hyperinsulinemia	0	0	0
Metabolism	Hypersmolar coma	1	1	1
Metabolism	Impaired glucose tolerance	0	0	0
Metabolism	Increased HDL	0	0	0
Metabolism	Increased uric acid concentraiton	0	0	1
Metabolism	Ketoacidosis	1	1	0
Metabolism	Ketonuria	1	0	1
Metabolism	Low blood sugar	1	0	0
Metabolism	Low HDL cholesterol	0	0	0
Metabolism	Low serum erythrocyte concentration	0	1	0
Metabolism	Polyphagia	0	0	0
Metabolism	Polyuria	1	0	0
Metabolism	Reduced body weight (->anorexia)	0	0	0

Metabolism	Reduced insulin sensitivity	0	0	0
Metabolism	Type 3 (mixed) renal tubular acidosis	1	1	1
Mineral balance	Increased calcium metabolism	1	0	0
Mineral balance	Increased urinary calcium	0	0	1
Mineral balance	Increased urinary hydroxyproline	0	1	0
Mineral balance	Reduced urinary alkaline phosphatase	0	0	0
Mouth teeth	Cavities / caries	0	0	0
Mouth teeth	Dental wear / tooth wear	0	0	0
Mouth teeth	Hypersalivation / sialorrhea	0	0	0
Mouth teeth	Mouth ulcers	0	0	0
Mouth teeth	Sensation of burning mouth	0	0	0
Mouth teeth	Severe, unremitting gingival pain	0	1	0
Musculoskeletal	Altered bone metabolism	0	0	0
Musculoskeletal	Bone pain	0	0	0
Musculoskeletal	Enthesitis	0	0	1
Musculoskeletal	Increase creatine kinase activity	1	0	0
Musculoskeletal	Increased risk of fracture in patients with Rett syndrome	1	1	1
Musculoskeletal	Low speed of sound transmission in radius and phalanges of hand	0	1	0
Musculoskeletal	Myokimia	0	0	0
Musculoskeletal	Myopathy	0	0	0
Musculoskeletal	Myotonia	0	0	1
Musculoskeletal	Rhabdomyolysis	1	1	1
Musculoskeletal	Strength deficit	0	0	1
Musculoskeletal	Tendon sheath abscess	1	1	1
Nails	Onychomadesis	0	0	0
Nails	Photo-onycolisis	0	0	1
Nervous system	Abnormal electroencephelographic changes	1	1	1
Nervous system	Abnormal involuntary movements	0	0	0

Nervous system	Absence seizures	0	1	1
Nervous system	Acute delirium	1	1	1
Nervous system	Acute dystonia	0	0	1
Nervous system	Acute laryngeal dystonia	1	0	1
Nervous system	Acute psychosis	0	1	1
Nervous system	Aggravated epilepsy syndromes	1	1	1
Nervous system	Aggravation of existing seizures or seizure disorder	1	1	1
Nervous system	Aggressive behavior	0	0	1
Nervous system	Agitation	0	0	1
Nervous system	Akathisia	0	0	0
Nervous system	Akinesia	1	1	0
Nervous system	Altered consciousness	1	1	1
Nervous system	Altered visual evoked potential	0	0	1
Nervous system	Anorexia	0	0	0
Nervous system	Arteriovenous malformation	1	1	1
Nervous system	Aseptic meningitis	0	1	1
Nervous system	Asterixis	0	0	1
Nervous system	Ataxia	1	0	1
Nervous system	Autonomic dysfunction	1	1	1
Nervous system	Babisnki reflexes	0	0	0
Nervous system	Ballismus	0	1	1
Nervous system	Behavioral changes	0	0	0
Nervous system	Bilateral foot-drop with peroneal nerve involvement	1	1	1
Nervous system	Blurred vision	0	0	0
Nervous system	Brainstem hemorrhage	1	1	1
Nervous system	Bruxism	0	0	0
Nervous system	Cataplexy	1	0	1
Nervous system	Catatonia	1	1	1

Nervous system	Central pontine myelinolysis	1	1	1
Nervous system	Central visual processing changes	0	0	1
Nervous system	Cerebellar ataxia	1	1	1
Nervous system	Cerebellar deterioration	1	1	1
Nervous system	Cerebral edema	1	1	1
Nervous system	Cns toxicity	1	1	1
Nervous system	Cognitive dysfunction	1	1	1
Nervous system	Cogwheeling	0	0	0
Nervous system	Coma	1	1	1
Nervous system	Coma (deep)	1	1	1
Nervous system	Complex partial seizure	1	1	1
Nervous system	Confusion	0	0	0
Nervous system	Convulsions	1	1	1
Nervous system	Cramps	0	0	0
Nervous system	Creutzfeld-Jakob-like syndrome	1	1	1
Nervous system	Daytime sleepiness	0	0	0
Nervous system	Delusions	0	1	0
Nervous system	Dementia (reversible)	0	1	0
Nervous system	Diffuse sensorimotor peripheral neuropathy	0	1	0
Nervous system	Diplopia	0	0	0
Nervous system	Disorders of mood and behavior	0	0	0
Nervous system	Disturbed gait	0	0	0
Nervous system	Dizziness	0	0	0
Nervous system	Downbeat nystagmus	0	0	1
Nervous system	Dream-like state	0	0	0
Nervous system	Drug-induced dystonia	1	1	0
Nervous system	Drug-induced seizure	1	1	1
Nervous system	Dysarthria	1	0	0
Nervous system	Dysgeusia	0	0	0
Nervous system	Dyskinesia	1	1	0

Nervous system	Electric shock sensation (in hands, neck, and arms)	0	0	0
Nervous system	Electroencephalographic deterioration	1	1	1
Nervous system	Encephalopathy (drug-induced hyperammonemic encephalopathy)	1	1	1
Nervous system	Exacerbation of myoclonic seizures	1	1	1
Nervous system	Exacerbation of seizure	1	1	1
Nervous system	Exarcebation of existing parkinson's disease or parkinsonism	1	1	0
Nervous system	Excessive tiredness	0	0	0
Nervous system	Excessive yawning	0	0	0
Nervous system	Explosive behavior	0	0	1
Nervous system	Extrapyramidal movement disorders	1	1	0
Nervous system	Fasciculation	0	0	0
Nervous system	Fatigue	0	0	0
Nervous system	Focal myoclonic jerks of the left arm	0	1	0
Nervous system	Fragmented sleep	0	0	0
Nervous system	Frontal atrophy	1	1	0
Nervous system	Hallucinations	0	1	1
Nervous system	Headache	0	0	0
Nervous system	Hemiparesis	1	1	1
Nervous system	Horizontal and vertical gaze nystagmus	0	0	1
Nervous system	Hyperactivity	0	0	0
Nervous system	Hyperhidrosis	0	0	0
Nervous system	Hyperthermia	1	0	1
Nervous system	Hypokinetic disorders of motion	1	0	0
Nervous system	Hyposalivation / dry mouth	0	0	0
Nervous system	Impaired driving ability	1	1	0
Nervous system	Impaired psychomotor performance	1	0	0
Nervous system	Inability to walk	1	1	1

Nervous system	Increased REM density	0	0	0
Nervous system	Increased seizure activity	1	1	1
Nervous system	Insomnia	0	0	0
Nervous system	Intellectual deterioration	1	1	0
Nervous system	Intoxication	0	0	1
Nervous system	Intracerebral hemorrhage	1	1	1
Nervous system	Intractable headache	0	1	1
Nervous system	Irritability	0	0	0
Nervous system	Lack of balance	0	0	0
Nervous system	Lethal catatonia	1	1	1
Nervous system	Lingual writhing	0	0	0
Nervous system	Lisp	0	0	0
Nervous system	Loss of dexterity (right hand)	1	1	0
Nervous system	Major neuropathy (with high-stepping gait and inability to dorsiflex the foot)	1	1	1
Nervous system	Marked hangover effect	0	0	0
Nervous system	Mask-like facial features	0	0	0
Nervous system	Meige's syndrome	1	1	0
Nervous system	Mesencephalic ischemia	1	1	1
Nervous system	Monoplegia	1	1	1
Nervous system	Motor tics	0	0	0
Nervous system	Myasthenia	1	1	1
Nervous system	Myoclonic seizure	0	1	1
Nervous system	Neuroleptic drug-induced hyperpyrexia	1	1	1
Nervous system	Neuroleptic malignant syndrome	1	1	1
Nervous system	Neurological impairment leading to injuries	1	1	1
Nervous system	Neuronal losss	0	1	0
Nervous system	Obsessive-compulsive symptoms	0	0	0
Nervous system	Oculogyric crisis	0	1	1
Nervous system	Oral dyskinesia	0	1	0

Nervous system	Parenchymal hematoma (intraparenchymal hemorrhage)	1	1	1
Nervous system	Parkinsonian gait	1	1	0
Nervous system	Parkinsonism	1	1	0
Nervous system	Peripheral nerve dysfunction	1	0	0
Nervous system	Persistent neuronal damage	1	1	1
Nervous system	Personality changes	0	0	0
Nervous system	Phonic tics	0	0	0
Nervous system	Posturing	0	0	0
Nervous system	Pseudoparkinsonism	0	1	0
Nervous system	Pseudotumor cerebri (benign intracranial hypertension)	0	1	1
Nervous system	Radial nerve palsy	0	0	0
Nervous system	Repetitive hand and finger movements	0	0	0
Nervous system	Respiratory difficulty	1	1	1
Nervous system	Restless leg syndrome	0	0	0
Nervous system	Retinal / optic nerve disorders	0	1	1
Nervous system	Retrograde amnesia	1	0	0
Nervous system	Sedation	1	0	0
Nervous system	Seizure	1	1	1
Nervous system	Serotonin syndrome	1	1	1
Nervous system	Severe mental deterioration (cortical atrophy; drug-induced pseudoatrophy of the brain)	1	1	1
Nervous system	Shivering	0	0	1
Nervous system	Shock-like sensations in the head	0	0	1
Nervous system	Sleep apnea	0	0	0
Nervous system	Sleep driving	0	1	1
Nervous system	Sleep-wake cycle disturbances	0	0	0
Nervous system	Sleepwalking	0	0	0

Nervous system	Slow speech	0	0	0
Nervous system	Slurred speech	0	0	1
Nervous system	Stammer	0	0	0
Nervous system	Status migrainosus	0	1	1
Nervous system	Stupor	1	0	1
Nervous system	Subarachnoid hemorrhage	1	1	1
Nervous system	Subcortical dementia	1	1	0
Nervous system	Suboptimal choices on computerized decisionmaking task	0	0	0
Nervous system	Suicidality	1	1	1
Nervous system	Tardive tremor	0	1	0
Nervous system	Tension	0	0	0
Nervous system	Tinnitus	0	0	0
Nervous system	Tongue heaviness	0	0	0
Nervous system	Tongue protrusion	0	0	0
Nervous system	Tonic-clonic seizure	1	1	1
Nervous system	Torticollis	0	0	0
Nervous system	Tourette-like syndrome	0	0	0
Nervous system	Trismus / lockjaw	0	1	0
Nervous system	Trunk stiffness	0	0	0
Nervous system	Uncontrollable laughter	0	0	0
Nervous system	Vasculitic bleeding	1	1	1
Nervous system	Visual hallucinations	0	0	0
Nervous system	Worsening of dementia	1	1	0
Nervous system	Worsening of disability in Multiple Sclerosis	1	1	1
Nervous system	Worsening of seizure	1	1	0
Neuromuscular	Hyperflexia	0	0	0
Nutrition	High active vitamin b6	0	0	0
Nutrition	Low pyridoxine (vitamin B6) concentration	0	0	0
Nutrition	Vitamin B12 deficiency	0	0	0

Pancreas	Acute pancreatitis	0	1	1
Pancreas	Hemorrhagic pancreatic necrosis (fatal)	1	1	1
Pancreas	Overt exudative pancreatitis	1	1	1
Reproductive	Menorrhagia	1	0	1
Reproductive	Menstrual abnormalities	0	0	0
Reproductive	Polycystic ovary syndrome	0	0	0
Reproductive	Vaginal bleeding	0	0	0
Respiratory	Acute hypersensitivity reactions	1	1	1
Respiratory	Acute respiratory failure	1	1	1
Respiratory	Aspiration asphyxia	1	1	1
Respiratory	Drug-induced infiltrative lung disease	1	1	0
Respiratory	Eosinophilic infiltration	0	1	0
Respiratory	Eosinophilic pneumonia	1	1	1
Respiratory	Exercise-induced bronchospasm	1	0	0
Respiratory	Hypercapnia	1	1	1
Respiratory	Idiopathic pulmonary fibrosis	1	1	1
Respiratory	Pneumonia	1	1	1
Respiratory	Pulmonary edema (fatal)	1	1	1
Respiratory	Pulmonary embolism without primary focus	1	1	1
Respiratory	Pulmonary hemorrhage (fatal)	1	1	1
Respiratory	Pulmonary hypertension	1	1	1
Respiratory	Respiratory complications of diaphragmatic, laryngeal, and glottal dyskinesias	1	1	1
Respiratory	Respiratory depression	1	1	1
Respiratory	Reversible diffuse alveolar hemorrhage without thrombocytopenia	1	1	1
Respiratory	Serious complications of asthma	1	1	1
Respiratory	Truncal weakness	0	0	0
Salivary glands	Salivary stones	0	0	1

Sensory	[adverse effects of bright light due to TCAs enhancing that effect?]	0	0	0
Sensory	Abnormal color perception	0	0	0
Sensory	Acute angle-closure glaucoma	1	1	1
Sensory	Acute myopia	0	0	1
Sensory	Anisocoria (unequal pupils)	0	0	1
Sensory	Bilateral severe uveitis	1	1	1
Sensory	Blue-green blindness	0	1	1
Sensory	Cataract	0	0	0
Sensory	Concentric visual field constriction	0	0	0
Sensory	Conjunctival metaplasia	0	0	0
Sensory	Corneal deposits	0	0	1
Sensory	Damage to corneal epithelium	0	0	1
Sensory	Drug-induced bilateral papilledema	1	0	1
Sensory	Esotropia	0	0	0
Sensory	Extraocular muscle abnormalities	0	0	1
Sensory	Hearing loss	1	1	0
Sensory	Higher pitch perception (auditory disturbance)	0	0	0
Sensory	Impaired vision	1	0	1
Sensory	Increased intraocular pressure	0	0	1
Sensory	Increased visual evoked potential / visual evoked response	0	0	0
Sensory	Lens deposits	0	0	0
Sensory	Loss of ability to taste	0	1	0
Sensory	Loss of vision	1	1	0
Sensory	Night blindness	1	1	0
Sensory	Oculomotor palsy	0	1	1
Sensory	Optic atrophy	0	1	1
Sensory	Optic neuritis	0	1	1

Sensory	Oscillopsia	1	0	0
Sensory	Papilledema with visual impairment	1	0	1
Sensory	Photophobia	0	0	1
Sensory	Pigmentary retinopathy	1	0	1
Sensory	Presbyopia	0	0	0
Sensory	Retinal damage	1	1	1
Sensory	Retinal hemorrhage	1	1	1
Sensory	Secondary angle-closure glaucoma	1	1	1
Sensory	Transient myopia	0	0	1
Sexual function	Abolished ejaculation	0	0	0
Sexual function	Absent orgasm	0	0	0
Sexual function	Anorgasmia	0	0	0
Sexual function	Clitoral engorgement	0	0	0
Sexual function	Decreased libido	0	0	0
Sexual function	Delayed ejaculation	0	0	0
Sexual function	Heightened sexual performance	0	0	0
Sexual function	Impaired potency	0	0	0
Sexual function	Irreversible priapism	1	1	1
Sexual function	Low sperm count	0	0	0
Sexual function	Male infertility	0	0	0
Sexual function	Male sexual dysfunction	0	0	0
Sexual function	Painful ejaculation	0	0	1
Sexual function	Penile anesthesia	0	0	1
Sexual function	Priapism	1	1	0
Sexual function	Retrograde ejaculation	0	0	0
Sexual function	Sexual dysfunction	0	0	0
Sexual function	Spontaneous orgasm	0	0	0
Skin	Grey discoloration of the skin in light-exposed areas	0	0	1
Skin	Aceniform eruption	0	0	0

Skin	Acne	0	0	0
Skin	Aggravation of existing psoriasis	0	0	0
Skin	Angioedema	1	0	1
Skin	Blisters	0	0	0
Skin	Contact dematitis	0	0	0
Skin	Contact urticaria	0	0	0
Skin	Cutaneous pseudolmphoma	0	0	1
Skin	Cutaneous reaction	0	0	1
Skin	Darier's disease (follicular keratosis)	0	0	1
Skin	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome	1	1	1
Skin	Erythema	0	0	0
Skin	Erythema multiforme	0	0	1
Skin	Erythematous eruption	0	0	1
Skin	Exaggerated sunburn	0	0	0
Skin	Exfoliative dermatitis	0	0	0
Skin	Folliculitis	0	0	0
Skin	Generalized erythematous maculopapular eruption	0	0	0
Skin	Generalized lichenoid eruption	0	0	1
Skin	Generalized pustular psoriasis	0	0	1
Skin	Hidradenitis suppurativa	0	0	1
Skin	Hyperkeratosis	0	0	0
Skin	Ichthyosiform desquamation of the skin	0	0	0
Skin	Melanosis / blue-grey skin discoloration	0	0	1
Skin	Nail dystrophy	0	0	1
Skin	Parakeratosis	0	0	0
Skin	Photosensitivity	0	0	0
Skin	Pityriasis versicolor	0	0	0
Skin	Rash	0	0	0

Skin	Seborrheic dematitis	0	0	0
Skin	Secondary prurigo	0	0	0
Skin	Sweet's syndrome	0	0	0
Skin	Toxic pustuloderma	0	1	1
Skin	Ulcerative genital lesions	0	0	1
Skin	Ulcerative oral lesions	0	0	1
Skin	Vesicular plaques and erosions on the penis	0	1	1
Sweat glands	Hypohidrosis	0	0	0
Sweat glands	Topiramate-associated blue pseudochromhidrosis	0	0	0
Urinary	Acute dysuria	0	0	0
Urinary	Acute interstitial nephritis	1	1	1
Urinary	Acute renal insufficiency	1	1	1
Urinary	Azotemia	1	1	0
Urinary	Chronic renal insufficiency	1	1	0
Urinary	Fanconi syndrome	1	1	0
Urinary	Gross hematuria	0	0	1
Urinary	Hematuria with acute renal insufficiency	1	1	1
Urinary	Hemorrhagic cystitis	1	0	0
Urinary	Impaired renal concentrating ability	0	0	0
Urinary	Nephrogenic diabetes insipidus	1	1	1
Urinary	Nephrolithiasis	0	1	0
Urinary	Nephrotic syndrome	1	1	1
Urinary	Retroperitoneal fibrosis	0	0	1
Urinary	Urinary hesitancy	0	0	0
Urinary	Urinary incontinence	0	0	0
Urinary	Urinary retention	1	0	0
Urinary	Urolithiasis	0	0	1

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