EXTRA-MEDICAL PRESCRIPTION PAIN RELIEVER USE, DEPENDENCE, AND PERSISTENCE AMONG ADOLESCENTS

By

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ABSTRACT

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Background: Prescription pain reliever use to get ‘high’ or outside the boundaries of the prescriber’s intent (extra-medical use) has become a major public health concern over the past twenty years in the United States (US). In recent years prevalence has stabilized, but the US has seen increases in opioid dependence, overdoses, and related deaths. Extra-medical prescription pain reliever (EMPPR) use often starts in adolescence, a pivotal stage of development. Each of this dissertation’s three aims address a series of research questions related to adolescent-onset use, dependence, and persistence of EMPPR use among newly incident adolescent users. The first aim is to estimate peak ages of becoming a newly incident EMPPR user and a subsequent opioid dependence case among adolescents. The second aim explores alcohol involvement as might affect whether adolescents belong to one of two classes of EMPPR use: susceptible-to-persistence (STP) or not-susceptible-to-persistence (NSTP), and estimates alcohol effects on the rate of EMPPR use for adolescents susceptible-to-persistent EMPPR use. The third aim investigates latent subgroups of newly incident EMPPR-using adolescents based on alcohol and EMPPR use patterns.

Methods: Study populations are US community-dwelling adolescents 12-21 years old, with nationally representative samples for recent National Surveys on Drug Use and Health (NSDUH). For all three aims, EMPPR use, alcohol dependence, and opioid dependence were assessed via standardized, self-reported measures. The first study uses meta-analyses for independent replication samples from NSDUH 2002-2013 for summary risk estimates of

developing opioid dependence by survey year and age pair. The second study applies the zero-inflated Poisson (ZIP) approach to estimate associations of underage drinking with persistence of EMPPR use for survey years 2002-2012 among 12-20 year olds. The final study employs latent class analysis (LCA) to distinguish subgroups of adolescent-onset newly incident EMPPR users in relation to characteristics of alcohol involvement and EMPPR use.

Results: In US adolescents, the peak risk for transitioning from onset of EMPPR use to opioid dependence within 12 months is found at 14-15 years old [95% confidence interval (CI) = 6.3%, 8.7% per year], which is younger than the within-adolescence peak risk for starting EMPPR use (16-19 years old ; 95% CI = 4.1%, 5.9% per year). ZIP regressions showed that underage drinkers with alcohol dependence were more likely to be STP with an excess rate of EMPPR use (e.g., risk ratio: 1.3; 95% CI: 1.1, 1.5). Ancillary findings include associations with other levels of alcohol involvement, with shorter time since EMPPR initiation. A female excess rate of EMPPR use among the most recent initiates within the STP class is seen. Latent Class Analyses discovered three classes of newly incident users differentiated by facets of EMPPR and alcohol use: (1) Nondependent/Low level users, (2) Moderately persistent users, and (3) Persistent/Dependent users. Persistent/Dependent users were more likely to be female and younger when compared to the Nondependent/Low level class.

Conclusions: Findings from this dissertation research shed light on newly incident EMPPR use among adolescents with further identification of vulnerabilities when alcohol and dependence syndromes manifest. These results provide insights that unveil the critical time for prevention efforts focused on reducing the incidence of EMPPR use and suggest intervention strategies aimed at preventing persistence of EMPPR use and development of opioid dependence.

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KEY TO ABBREVIATIONS

ACASI – Audio Computer Self-Interviews

AIC – Akaike's Information Criterion

BIC – Bayesian Information Criterion

AD – Alcohol Dependence

CDC – Centers for Disease Prevention and Control

CPDD – College on Problems of Drug Dependence

CI – Confidence Intervals

CNS – Central Nervous System

DSM – Diagnostic and Statistical Manuals

EM – Extra-medical

EMPPR – Extra-medical Prescription Pain Relievers

IRD – Internationally Regulated Drugs

OR – Odds Ratio

PPR – Prescription Pain Relievers

NIDA – National Institute on Drug Abuse

NSDUH – National Surveys on Drug Use and Health

NSTP – Not Susceptible to Persistence

R-DAS – Restricted-use Data Analysis System

RR – Risk ratio

SAMHDA – Substance Abuse and Mental Health Data Archive

SAMHSA – Substance Abuse and Mental Health Services Administration

SNP – Single nucleotide polymorphism

STP – Susceptible to Persistence

US – United States

ZIP – Zero-inflated Poisson

ZNB – Zero-inflated Negative Binomial

CHAPTER 1

INTRODUCTION

The prevalence of prescription pain reliever (PPR) use for extra-medical purposes dramatically climbed over the past two decades in the United States (US) (i.e., to get 'high' or otherwise outside the boundaries of a prescribing clinician's intent (1). In fact, there was an almost threefold increase in those 12 years or older (2–4). While the prevalence of PPR use has become relatively stable over the last several years, PPR dependence, overdose, and related deaths have risen (5,6).

In 2013, approximately 1.5 million people in the US aged 12 years or older initiated extra-medical use of PPR within the past year, second to the numbers of initiates for cannabis in the same time frame (2.4 million) (7). That year, approximately 1.9 million people experienced opioid dependence or abuse in the past year. This estimate was also the second highest of all the internationally regulated drugs, behind only users with cannabis dependence or abuse (IRD; 4.3 million in 2013). Alcohol accounted for the highest rate of dependence among persons 12 years or older (8.0 million or 3.0% of the population in 2013) (7).

Even though PPR related disorders have plagued users of all ages, adolescence is an important time to understand extra-medical use (EM), as it represents a transition period from late childhood to early adulthood, roughly corresponding to 12-21 years old. Hereafter, this dissertation designates this age range as adolescence. Among current users of IRD, the prevalence of extra-medical prescription pain reliever use is highest among those in their late teens and twenties (EMPPR; 7). Incidence, on the other hand, reaches its peak at mid-adolescence around ages 16-17 (8,9).

1.1 Rationale

Each of this dissertation's specific aims addresses an opportunity to add epidemiological evidence by exploring use, dependence, and persistence of EMPPR among adolescents. The risk of overdose and developing dependence may be greatest when EMPPR use starts during early adolescence (8,10,11). Identifying peak ages of use and dependence for adolescents who recently began using EMPPR will address the critical age for public health intervention strategies to prevent potential hazardous consequences.

Second, although the co-occurrence of alcohol use and use of EMPPR can be harmful, there has been little research on the potential causal relationship between the two (11–16). Evidence suggests alcohol increases positive effects of EMPPR such as drug liking, pleasant bodily sensations, and euphoria when they are both co-ingested (17). Alcohol involvement plays a role in approximately one in five emergency department visits and opioid related deaths (11). There remains a gap in the knowledge base about whether alcohol dependence (AD) accelerates the rate of progression of EMPPR use and if AD affects whether people transition beyond the first occasion of EMPPR use.

Third, while some drug use subgroups have been identified among adolescents, EMPPR using adolescents have not been further characterized by facets of alcohol and EMPPR use. The work herein considers this unmet epidemiological need of the combination of EMPPR and alcohol's association at the person level.

This dissertation presents the results of a series of related studies focused on (a) newly incident cases of EMPPR (recent onset users who just started using), (b) the processes of becoming dependent after onset of EMPPR, (c) the persistence of such EMPPR use. These

studies utilize the National Surveys on Drug Use and Health (NSDUH) nationally representative sample survey data in order to accomplish these three specific aims.

1.2 Specific Aims

Specific Aim 1. To estimate the risk of becoming a newly incident case of opioid dependence within one year of beginning EMPPR use among adolescents.

Specific Aim 2. To evaluate the degree to which a recent history of active AD and sex might influence use of EMPPR by adolescents in the US.

Sub Aim 2. To estimate the relative odds of persistence after onset of use, as well as the conditional rate of use, given persistence.

Specific Aim 3. To investigate discrete classes (subgroups) of adolescents with similar profiles based on their newly incident EMPPR use and alcohol use, with empirical evaluation of the underlying structure of identified subgroups and their epidemiological distributions in the US.

Sub Aim 3. To conduct a sensitivity analysis in order to estimate the degree to which latent class inferences might change given a tangible violation of assumptions (i.e., misclassification of variables).

CHAPTER 2

BACKGROUND

2.1 Prescription Pain Relievers

Prescription pain relievers (PPR; i.e., narcotics, analgesics, pain killers) are a group of controlled substances usually prescribed for pain management. The US Controlled Substance Act places drugs into one of four schedules based on their abuse potential, likelihood to cause dependence, and accepted medical treatment. PPR are generally considered Schedule II or Schedule III controlled substances (18).

Table 2.1.1 Five schedules of controlled substances in the United States and their definitions. Data from the Drug Enforcement Administration.

Schedule I	▪ No currently accepted medical use in the United States ▪ Lack of accepted safety for use under medical supervision ▪ High potential for abuse
Schedule II/IIN	▪ High potential for abuse ▪ Abuse may lead to severe psychological or physical dependence
Schedule III/IIIN	▪ Potential for abuse less than substances in Schedules I or II ▪ Abuse may lead to moderate or low physical dependence or high psychological dependence
Schedule IV	▪ Low potential for abuse relative to substances in Schedule III
Schedule V	▪ Low potential for abuse relative to substances listed in Schedule IV ▪ Consist primarily of preparations containing limited quantities of certain narcotics

Prescription-type drugs fall into four categories: pain relievers, tranquilizers, stimulants, and sedatives (6). These psychotherapeutics encompass various medications that are available or have previously been attainable by prescription. This work focuses on pain relievers and those people who took a PPR for EM reasons (see section 2.2 and Appendix A for more information). Use of over-the-counter drugs and medical use of prescription drugs are not investigated here (6). In general, the majority of psychotherapeutics are pain relievers and most PPR are opioids, which this dissertation focuses on (7).

2.1.1 Opioids

Opioids are natural or synthetic compounds that simulate pain relieving actions by attaching to opioid receptors (19). They produce their pharmacological effects through three different receptors in the brain (i.e., mu, kappa, and delta). Agonists and antagonists interact with these receptors to reduce the perception of pain and promote calmness by blocking pain messages to the brain. Some examples of agonists are morphine or heroin, which mimic actions of endorphins and activate their reception. Naloxone and naltrexone are antagonists, which occupy opioid receptors and prevent activation of neurotransmitters. Antagonists have no effects of their own (20,21). Endogenous opioids, called endorphins, are naturally present in the body.

Opioids are usually prescribed by a clinician for their analgesic properties. Opiates are opioids naturally derived from the opium poppy (alkaloids; e.g., morphine, codeine) (22). In the past, opioids have been referred to as synthetic drugs that resemble natural opiates in their chemical and biological properties (e.g., oxycodone, heroin). Currently, the term ‘opioid’ refers to all compounds whether they are synthetic, natural, or semi-synthetic (e.g., fentanyl, methadone) (23). Opioids act by attaching to opioid receptors that are mainly found in the central nervous system (CNS; i.e., brain and spinal cord), and the gastrointestinal tract (19). Narcotic, although often synonymously used, is a legal term that should be avoided in scientific or in clinical settings (22). Narcotic comes from the Greek word ‘stupor,’ and before its reference to opioids, it was used to describe sleep medications (23).

Opioid use affects brain regions that mediate the pleasure center; some people experience a sense of euphoria with their use (21). With regard to the euphoric effects, reinforcement of repeated use occurs, and tolerance and/or dependence may develop (22). Additionally, opioid use may have other adverse effects, including respiratory depression, drowsiness, confusion, nausea,

and constipation. In fact, overdose deaths are often caused by respiratory depression resulting from overuse, and taken in combination with depressants such as alcohol may be detrimental even at non-lethal doses due to such respiratory effects (19).

2.1.2 History of Opioids

While there is some ambiguity and uncertainty as to the early history of opioid use, it is believed that the poppy plant was first cultivated, and opium first isolated, by the Sumerians of Mesopotamia in 3400 BC (24). It was named the "joy plant," and its use spread throughout the "old world" and eventually to Asia and Europe (22,24). 'Opium' refers to a mixture of poppy seed alkaloids (23). Civilizations of India, China, and portions of Europe historically used opium to treat pain, in addition to other reasons (24). In the early 19th century, morphine was isolated from opium by Friedrich Sertürner, a German scientist. Morphine became a popular pain treatment for battle injuries in the US during the Civil War. The investment of the hypodermic needle in the 1850s lead to morphine's prevalent use for minor surgeries and other medical use (24).

Like opium, morphine has a high potential for abuse and addiction. Opium related problems were primarily prevalent in China, but morphine dependence became widespread in soldiers after the Civil War ended (25). In morphine's wake, scientists synthesized heroin (a morphine derivative) as a "less addictive" and "safer" alternative at the end of the 19th century (22). In the early 20th century, heroin was distributed legally until growing rates of addiction sparked a ban on possession, sales, manufacture, and importation that ultimately extended to the control of import and export of other opioids (26,27). One notable federal law, the Harrison Act of 1914, placed a tax on 'narcotics,' regulated their use, production, and interstate commerce (25). This marked the beginning of illicit opiate sales and use in the US (25).

The 19th century was a time of change for opioids and their role in society and for medicine. New formulations became available (PPR as we now know them), various laws were passed to regulate their use, and research advances were made in maintenance therapy, addiction, and pain management (22,26,27).

2.2 Extra-medical Use

The concept of EM drug use was introduced by a university research group supported by the US National Institute on Drug Abuse (NIDA) (28). This group attempted to create a new term that would avoid the problems and ambiguities of other terms such as 'non-medical,' 'misuse,' and 'abuse' (1,28). EM can refer to use of opioid prescription drugs: (i) without a doctor's prescription, (ii) more than prescribed, (iii) more frequently than prescribed, or (iv) for any reasons other than indicated – to get high, to feel good, for curiosity, or for kicks (1). Appendix A provides a thorough description of the EM term's history, which is previously published elsewhere (28).

To understand the nature of adolescent EMPPR use, it is important to show how this use can be distinguished from terms previously used in the literature. Researchers have defined 'nonmedical' as non-prescribed use, or taking a psychotherapeutic drug only for the experience or feeling it caused (2). 'Misuse' often indicates incorrect use of a medication (29). On the other hand, 'abuse' has been defined as a "maladaptive pattern of substance use leading to clinically significant impairment or distress manifested by one or more behaviorally based criteria to fulfill major role obligations at work, school, or home" (30).

Some scientists differentiate between terms, but others use them interchangeably. Although it is common for these designations to overlap, it is important to make a differentiation between 'extra-medical' and other terms when describing PPR use. EM use can be characterized

as using a drug not only for ‘nonmedical reasons’, but also for medical reasons outside a prescriber’s boundaries or intent. For example, this could be those individuals who were prescribed an opioid for a toothache, but are using their prescription for an ailment due to back pain.

2.3 Opioid Dependence

A syndrome has been described as cluster of symptoms, signs, or lab values, which point to an underlying pathological process, but since the cause is unknown, it is not a disease. The ‘drug dependence syndrome’ embodies this definition. Drug dependence syndrome includes: disturbances of the mental life (e.g., obsession-like craving), disturbances of behavior (e.g., compulsion-like repetitive use of the drug when the user might wish not to use), and signs of neuroadaptation (e.g., tolerance, withdrawal) (31). On the other hand, dependence has been referred to as an addiction or habituation that manifests as ‘compulsive’ or ‘pathological’ behavior. Opioid dependence is an adaptive physical or physiological state that may occur with repeated exposure to opioids; it leaves the user susceptible to withdrawal when said opioid use stops (32).

Diagnosis of opioid dependence mirrors that of other drugs (e.g., alcohol, cocaine). There are seven related criteria. The Diagnostic and Statistical Manuals from the American Psychiatric Association classify drug dependence (e.g., DSM-IV, DSM-5). Clinical criteria of opioid dependence from DSM-IV are listed in Table 2.3.1. DSM-IV opioid dependence diagnosis requires three or more features to manifest during the same year (30).

Table 2.3.1 Opioid Dependence Criteria and Clinical Features. Data from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 4th Edition.

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least three of the following, occurring within a 12-month period: 1. Tolerance, as defined by either of the following: a) A need for markedly increased amounts of opioids to achieve intoxication or desired effect. b) Markedly diminished effect with continued use of the same amount of an opioid. 2. Withdrawal, as manifested by either of the following: a) The characteristic opioid withdrawal syndrome. b) Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms. 3. Opioids are often taken in larger amounts or over a longer period than was intended. 4. There is a persistent desire or unsuccessful efforts to cut down or control opioid use. 5. A great deal of time is spent on activities necessary to obtain the opioid, use the opioid, or recover from its effects. 6. Important social, occupational, or recreational activities are given up or reduced because of opioid use. 7. Opioid use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

The most recent version of the DSM was published in 2013, which created the standalone concept of 'opioid use disorder' (DSM-5) (33). In contrast, DSM-IV made a distinction between abuse and dependence. Abuse criteria included legal problems, failure to fulfill major role obligations, physically hazardous use, and continuing use despite persistent, recurrent social, or interpersonal problems (30). In DSM-5, the craving criterion, "craving, or a strong desire or urge to use," was added as a clinical feature, and opioid-related recurrent legal problems was removed. DSM-5 requires only two co-occurring clinical features (33,34); however, because the NSDUH survey questions use the DSM-IV dependence criteria, DSM-5 diagnostic criteria was not considered in this research.

2.4 The Epidemiology of Prescription Pain Reliever Use

The epidemiology of EMPPR use can be described by using the five rubrics of epidemiology proposed by Anthony and Van Etten: (i) How many?: Quantity, (ii) Where?:

Location, (iii) Why?: Causes, (iv) How?: Mechanisms, and (v) What can be done? : Prevention and control (35).

2.4.1 Quantity and Location

In regard to the rubric of quantity, EMPPR are the second most commonly used IRD behind cannabis (36). In 2014, there were roughly 32.4 million current users in the world (36). Figure 2.4.1 shows the prevalence of EMPPR use to be highest in the US, followed by Serbia, Australia and countries of the Middle East according to the 2015 World Drug Report. In Asia, PPR prevalence is stable, although reliable data does not exist in many parts of the world. The prevalence in Europe lies between that of Oceania and other continents with less use (e.g., Africa, Asia) (36). With respect to the rubric of location, the United Nations Office on Drugs and Crime estimates worldwide PPR use has been relatively stable in the past year (36).

Figure 2.4.1 Extra-medical prescription pain reliever prevalence for world countries in 2013 (or latest year available). Data from the World Health Report, 2015.

The National Comorbidity Survey estimates cumulative incidence or lifetime prevalence of EM psychoactive drug use in the US at approximately 45% (37). According to the most recent US Substance Abuse and Mental Health Services Administration (SAMHSA) report, in 2013 there were approximately 1.5 million newly incident EMPPR users aged 12 years and older.

[About 12.5% of all initiates of IRD began using PPR]. Of those users who began in the past year, 541 million started using prior to age 18 (9).

Age is an important consideration for understand the epidemiology of EMPPR especially for public health prevention and intervention efforts. Table 2.4.1 shows recent prevalence estimates from the NSDUH. Peak lifetime use of EMPPR occurs during young adulthood spanning the late years of adolescence. Similarly, past year and past month use peaks in the same age range (use in the past 12 months and past 30 days respectively).

Table 2.4.1 Prescription pain reliever prevalence trends for individuals age 12 or older (in percent). Data from the National Survey on Drug Use and Health, United States, 2014.[a]

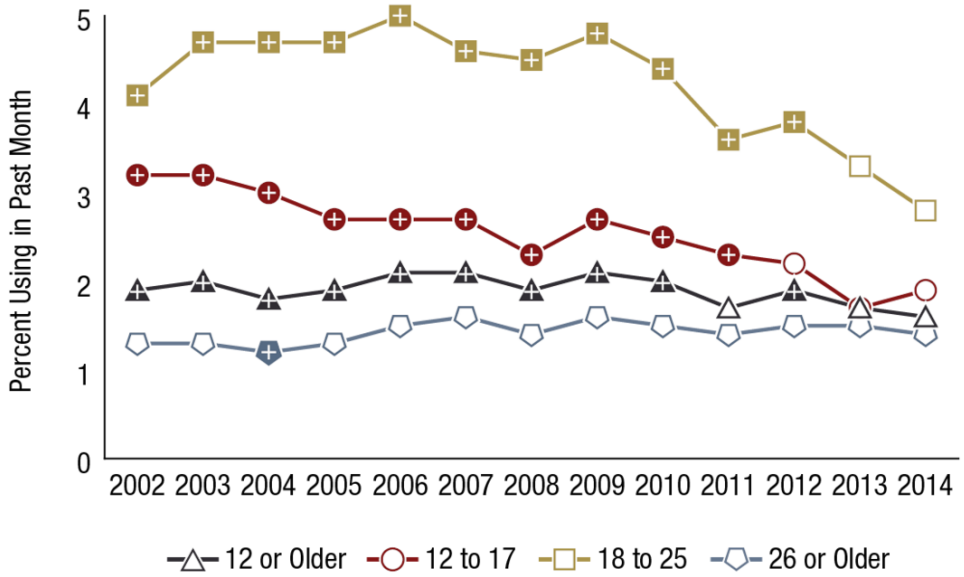
Time Period	Ages 12-17	Ages 18-25	Ages 26 or Older	Ages 12 or Older
Lifetime	7.3	20.0	13.3	13.6
Past year	4.7	7.8	3.1	3.9
Past month	1.9	2.8	1.4	1.6

[a] Adapted from https://www.drugabuse.gov/national-survey-drug-use-health.

Estimates on incident use show approximately 38% of newly incident users started using EMPPR before 18 years old (7). The mean age of first EMPPR use has been about 15 years since 2002. In 2014, for those who started their use before age 21, the average age of initiation was 16.5 years (7).

Looking across time, for past month users of EMPPR, 2014 estimates have decreased compared to prior years. Figure 2.4.2 shows the time trend of past month estimates by age group. There has been no noticeable peak across age groups since 2002, but declines are most evident in the 18-25 year old age group followed by those aged 12-17 (7).

Figure 2.4.2 Trends in past month extra-medical prescription pain reliever use among people aged 12 or older, by Age Group. Data from the National Surveys on Drug Use and Health, United States, 2002-2014.



+ Difference between this estimate and the 2014 estimate is statistically significant (p-value < 0.05).

Investigation of sex differences have disclosed that females are more likely than males to start using EMPPR (7,38,39). However, males have been found to use more frequent lifetime use (40–42). Contradictory findings have been common in the literature, some with a female excess, and vice versa (43,44).

For race/ethnicity, non-Hispanic Whites typically have the highest lifetime prevalence of EMPPR use compared to non-Hispanic Blacks and Hispanics (38,42,44). In past years though, non-Hispanic Blacks' prevalence for EMPPR use has surpassed non-Hispanic White estimates (38,45). Race/ethnicity is an important factor in epidemiological research, but is subjective and difficult to divorce from social and cultural categorizations. In the NSDUH, race/ethnicity is a self-reported measure, and recent publications have alternatively (and more accurately) described race/ethnicity as ethnic self-identification (46–49).

2.4.2 Causes and Mechanisms

Reasons have been postulated as to why some individuals begin using EMPPR and others persist to become opioid dependent. Suspected causes may be at the micro-level, occurring within the individual, may be societal, found at the mezzo- or group-level, may be global, present at the macro-level, or somewhere in between (50,51). Genetic or epigenetic influences are biological in nature and may determine the formation of susceptible drug use phenotypes. Potential psychosocial causes and mechanisms involve both psychological and social theories. Group- and macro-level emphasis mainly deals with sociological theories of drug use (50,51). This dissertation focuses on newly incident adolescent EMPPR use, which may or may not persist and eventually transition into opioid dependence.

2.4.2.1 Biological

Reviewing genetic studies of opioid use illustrated that opioid use is heritable. More specifically, twin studies have determined how genetic and environmental factors contribute to drug taking behaviors and heritability (52). Researchers show a moderate genetic contribution to opioid dependence (52). Families with probands of opioid use disorders were also investigated; relatives were ten times more likely to have opioid related disorders (53). Candidate genes have been identified to study genetic polymorphisms and how they affect opioid dependence vulnerability. Most of them are dopamine receptor genes. Dopamine is a neurotransmitter prevalent in the CNS that controls pleasure, cognition, and movement (54). In addition, several single nucleotide polymorphisms (SNPs) on genes related to opioid receptors have been associated with opioid dependence and its ethnic variation (52).

Chronic opioid use results in brain abnormalities and may produce dependence, which can involve interactions of a genetic predisposition and environmental effects such as stress,

social context and psychological conditions (32). Yet brain pathways might be abnormal before any opioid use. Central to the development of persistent EMPPR use and dependence is the pleasure center in the midbrain (32).

2.4.2.2 Psychosocial

One possible cause of EMPPR related problems may be alcohol use and the interplay between its use and EMPPR. A popular explanation put forth in many drug use studies is the gateway concept. Many believe it originated from Harry Anslinger's claims in the mid-20th century that marijuana was a precursor, or 'steppingstone', to opiate addiction (25,55). Kandel and Kandel developed the related "gateway theory" after observing repeated temporal sequences of drug use (56,57). Alcohol use has been shown to precede some drug use such as cannabis, so alcohol has been deemed a 'gateway drug' on the way to IRD use (58,59). With this in mind, alcohol use could lead to EMPPR use, and eventual opioid dependence.

Extending an the understanding of mechanisms beyond the descriptive nature of the "gateway hypothesis," other scientists have suggested theories as to why some people begin drug use and then transition to dependence. Social learning theory's concept of 'reciprocal determinism' has been proposed as affecting the relationship between socio-environmental influences and drug using behavior. Reciprocal determinism posits environmental and individual-level behaviors shape a behavior, and then they shape the related subsequent behavior (60,61). For example, adolescents who drink heavily may transition to a different social environment with more accepting peers, and those peers' alcohol drinking will influence future drinking behaviors of those adolescents (62). 'Opportunity to try' is a theory that postulates drug initiation cannot occur without an exposure opportunity (63,64). For those who eventually go on to use a drug, most transitioned from the first opportunity to use within one year (63). Work on

cocaine has demonstrated that once use begins, some users transitioned to dependence within the year (64). This dissertation will build on these transitional findings.

Peer relationships have long been an important factor in drug use. For example, the majority of adolescent EMPPR users get their PPR from friends or family (65,66). In fact, findings suggest those who got their PPR from peers drank more alcohol than those who got their PPR from family (65). One of the best predictors of drug initiation among adolescents is associating with drug using peers (67,68). Family context and parental monitoring are important predictors as well (68,69). Researchers have posited that a social learning aspect may be at play based on family member medication habits (70). The media could have a role in the acceptance of PPR especially because doctors endorse their use as "medication" (70).

Furthermore, alleviating pain has been indicated as a cause of EMPPR use. A majority of adolescents use EMPPR to treat pain; it could be either they are not benefitting from prescribed indications or they are not getting proper medical attention for the pain (71,72). Treatment of acute pain has not often been associated with EMPPR use or dependence (43,70). However, long-term PPR use that is often associated with chronic pain has been associated with dependence (73,74). Preliminary findings also suggest that motives are highly associated with adolescent persistence of EMPPR use (75,76).

While many adolescents use EMPPR for pain control, others' use is not to self-treat, but for recreational motivations (72,76). Those EMPPR users whose motivations relate to sensation-seeking have been estimated to have a greater odds of psychological disorders (e.g., affective, anxiety, somatic) (71). Moreover, these 'sensation-seekers' are more likely to engage in 'problem behaviors' (71). Problem Behavior Theory claims that problem behaviors among adolescents are highly correlated (e.g., alcohol use, sexual activity) (77,78).

Preexisting psychiatric disorders have also been associated with an increased risk of EMPPR use and dependence (79,80). In general, EMPPR use is associated with an increased risk of having mood and anxiety disorders (79,81). Hypothesized psychological causes involve individual and group level aspects that affect beginning and persisting in drug use (50).

2.4.2.3 Social-Structural

Several developmental theories have suggested there is an interaction between behavioral and environmental factors (82,83). The interaction then leads to beginning alcohol use at an early age, in adolescence, and then alcohol dependence develops soon afterward (83). EMPPR use may follow this developmental trajectory. Social networks, culture, socioeconomic factors, politics, and social change may be at play (51). For example, neighborhoods have been found to be important predictors in other drug use (84,85).

2.4.3 Prevention and Control

Prevention and treatment for beginning use of EMPPR, persisting in its use, and dependence on EMPPR could improve the health of adolescent users. Those with pain reliever disorders (abuse or dependence) have been relatively stable in the US since 2002, but there have been declines in users 12-25 years old. Still, 1.9 million users aged 12 or older had a PPR use disorder in 2014 (0.7% of this population) (7). The number of people in the US with EMPPR problems outnumbers all other IRD, besides cannabis (7).

Primary prevention would aim to stop individuals from beginning drug use and, if effective, reduce its incidence. In secondary prevention, the aim would be to reduce the duration of use, which directly relates to persistence and dependence of EMPPR use (86). Tertiary prevention would reduce the residual consequences and restore health/rehabilitate. In this research, focus is on persistence and dependence with a recent incidence of EMPPR use.

Prevalence, although helpful in identifying active cases of dependence or users, does not directly relate to the prevention goals of this dissertation. However, all three types of prevention relate to the specific aims.

Overall, identifying the peak risk and correlates for first use and the transition to opioid dependence among newly incident EMPPR users will suggest the best timing for a prevention/intervention opportunity in adolescents.

2.5 The National Surveys on Drug Use and Health

This dissertation uses the same data source to address the three specific aims. Briefly, the NSDUH is an annually completed federally funded survey, which assesses drug use and health behaviors. The NSDUH assessments are via audio computer self-interviews (ACASI). The design is a cross-sectional nationally representative survey of non-institutionalized civilian community residents in the US, with Institutional Review Board-approved protocols, completed each year. Regularized sampling, recruitment, informed consent/assent, and assessment have already been described in multiple prior reports (7,8,87,88). The Substance Abuse and Mental Health Data Archive (SAMHDA) makes NSDUH public use datasets available. Each year's dataset consists of a large sub-sample of independently drawn nationally representative samples (n~55,000 yearly). Participation levels are approximately 70%-75% of eligible participants, once appropriate consent/assent processes are complete.

2.6 Significance and Purpose

Adolescence is a key period of human development. Integral physical, psychological, sociocultural, and cognitive changes occur during this time (89). Adolescence marks the transition from childhood to adulthood and a prime time when risky behaviors and experimenting often begins (89). It continues to be a time of struggle for autonomy and identity

where drug initiation is common, including that of EMPPR use (90). If started, patterns of use and dependence can continue into adulthood. Therefore, adolescence marks a prime time for public health and prevention strategies (91).

This investigation examines the relationship between EMPPR and other risk behaviors among adolescents using the NSDUH. The purposes of this study are to (i) estimate recent incidence and dependence among those who started EMPPR within the past year; (ii) describe the relationship between EMPPR use and alcohol use; (iii) assess persistence of EMPPR use and differences over ages and between males and females; (iv) bring awareness about EMPPR to health professionals and public health experts; (v) inform prevention, intervention, and policy about EMPPR use and dependence among adolescents.

CHAPTER 3

MANUSCRIPT 1 – EPIDEMIOLOGICAL EVIDENCE ON EXTRA-MEDICAL USE OF PRESCRIPTION PAIN RELIEVERS: TRANSITIONS FROM NEWLY INCIDENT USE TO DEPENDENCE AMONG 12-21 YEAR OLDS

It is important to note that this manuscript was published in 2015, prior to the completion of this dissertation. Therefore, much of this chapter comes directly from said manuscript (28).

3.1 Abstract

Background: When 12-21 year olds start using EMPPR, some of them transition into opioid dependence within a year after such use. The main aim for this epidemiological research in the US is to estimate the risk of becoming a newly incident case of opioid dependence within 12 months after onset of EMPPR use.

Methods: Meta-analyses from multiple independent replication samples now are possible, based upon nationally representative survey samples of US adolescents age 12-21 years. All adolescents were sampled and recruited for the US NSDUH, with standardized assessments of EMPPR use and opioid dependence (2002-2013).

Results: Peak risk for a transition from start of EMPPR use to opioid dependence within 12 months is seen at mid-adolescence among 14-15 year olds (6.3%, 8.7% per year), somewhat earlier than peak risk for starting EMPPR use (seen for 16-19 year olds at 4.1%, 5.9% per year). Applied to 12-21 year olds in the US between 2002-2013, an estimated 8 million started using EMPPR. Each year, roughly 42,000 to 58,000 transitioned into opioid dependence within 12 months after onset of such use.

Discussion: These epidemiological estimates for the US in recent years teach us to expect one transition into adolescent-onset opioid dependence within 12 months for every 11-16 newly

incident EMPPR users, yielding perhaps 120 newly incident opioid dependent cases in need of practitioner attention or treatment services, each day of each year. This evidence can be used to motivate more effective public health prevention, outreach, and early intervention programs as might prevent or delay occurrence of EMPPR use and opioid dependence.

3.2 Introduction

The US has seen dramatic growth in numbers of overdoses and overdose deaths attributed to PPR, a drug subtype that consists mainly of prescription-type opioid drug compounds (see Table 3.1.1). All too often, these overdoses are occurring after 12-21 years olds have started to use PPR extra-medically.

Table 3.1.1 Comprehensive list of prescription pain reliever compounds listed in the National Surveys on Drug Use and Health (NSDUH). Data from the NSDUH, United States, 2002-2014.*

Darvocet	Darvon	Tylenol with codeine	Percocet	Percodan	Tylox
Vicodin	Lortab	Lorcet	Codeine	Demerol	Dilaudid
Fioricet	Fiorinal	Hydrocodone	Methodone	Morphine	OxyContin
Phenaphen	Propoxyphene	SK65	Stadol	Talacen	Talwin
Talwin-NX	Tramadol	Ultram			

* Many listed drugs are registered trade names.

For the most part, growth in numbers of PPR overdoses in the US can be traced back to EM use of these compounds as opposed to taking medicines exactly as prescribed (7,92–95). In recent years, more than four percent of 12-21 year olds qualify as recently active EMPPR users (7,87). As gauged by expected values based on US experiences between 1980 and 1999, it now is legitimate to speak of a 21st century ‘epidemic’ of EMPPR use among young people in this country.

Underlying fundamental conditions and processes giving rise to this epidemic are being investigated, and new interventions to prevent EMPPR use and to reduce diversion of legitimately prescribed PPR have been developed (70,96–99). In addition, once EMPPR use

occurs, there is a risk that a syndrome in the form of opioid dependence will occur, as noted elsewhere (1,100).

One recent contribution to epidemiological evidence about EMPPR use in the US was made by Meier and colleagues, who discovered a peak risk of becoming a newly incident EMPPR user during the adolescent years from ages 12-21 (8). Those estimates were based on data gathered from 2004-2008, using what Seedall and Anthony have called a 'mutoscope' approach that can be used to trace the experience of each adolescent birth cohort forward, year by year (8,69). For 12-21 year olds, results for each birth cohort showed peak values of risk at mid-adolescence (roughly age 16 years), followed by declining incidence rates across the later adolescent years (8).

In this new report on the epidemiology of EMPPR use, also with a focus on 12-21 year olds in the US, the primary aim is to estimate risk of becoming a newly incident case of DSM-IV-type opioid dependence not too long after EMPPR use starts (i.e., within 12 months). EMPPR risk estimates are also updated, extending through 2013 the prior 2004-2008 estimates of Meier et al. (8).

The value of epidemiological estimates of this type can be seen in their utility as motivators for new or renewed efforts to prevent and control the occurrence of EMPPR use. Estimates of this type also can be used to motivate early outreach and intervention efforts that are needed to identify and help the new EMPPR users who develop opioid dependence (70).

3.3 Methods

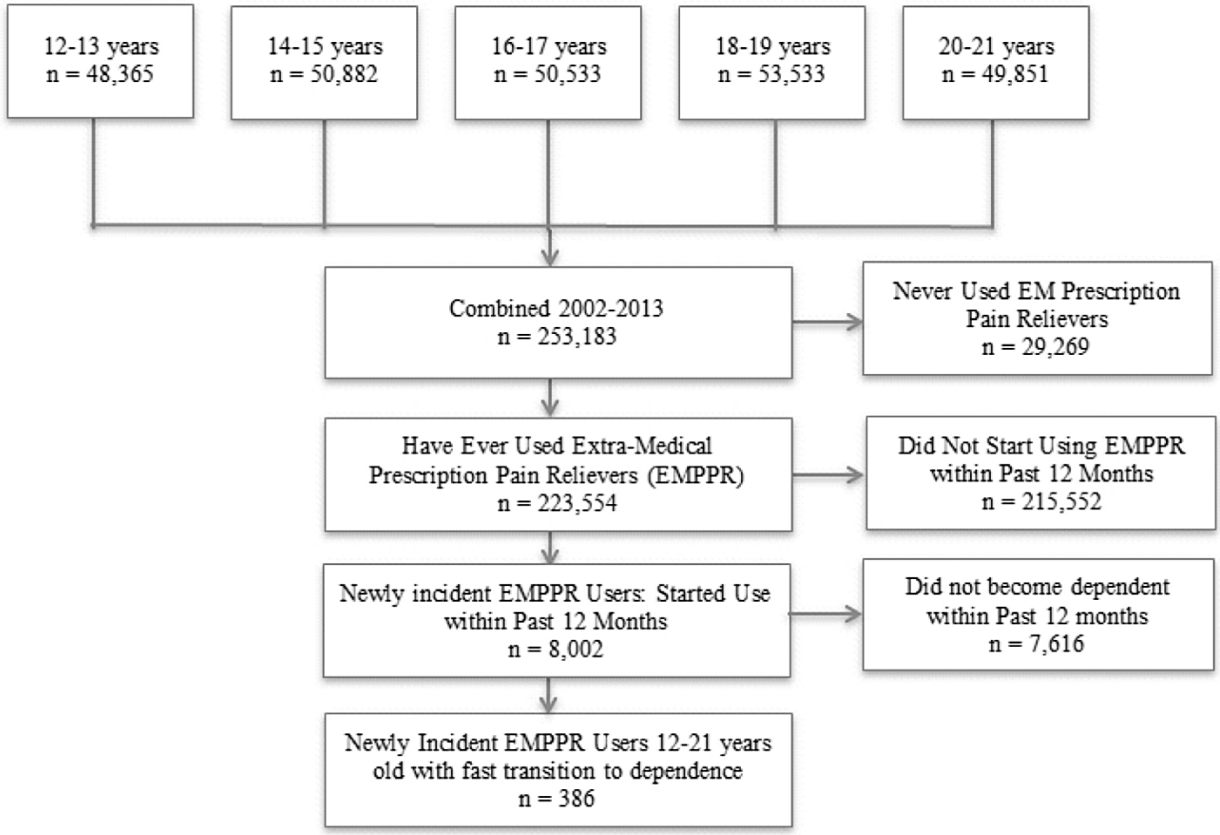
3.3.1 Sample

The study population for this investigation consists of 12-21 year old noninstitutionalized civilian residents in all 50 states and the District of Columbia during the early 21st century, as

sampled and surveyed each year by research teams supported by SAMHSA during 2002-2013. The NSDUH sampling frame is noteworthy because it encompasses noninstitutionalized adolescents irrespective of school attendance and wherever they are living, not only in households but also in non-institutional group quarters, dwelling units such as homeless shelters, and college dormitories (46).

This study's subsamples come from of the NSDUH's Restricted-use Data Analysis System (R-DAS). Unweighted numbers of designated 12-21 year old participants in each year's multi-stage area probability sample range from 41,248 to 42,864 (7). Figure 3.3.1 provides more details on approximate unweighted sample sizes.

Figure 3.3.1 Flow chart diagram of newly incident extra-medical prescription pain reliever users and those with fast transition to dependence age 12-21. Data from Restricted-use Data Analysis System subsamples of the National Surveys on Drug Use and Heath, United States, 2002-2013*



*All n are weighted in thousands. See http://www.icpsr.umich.edu/icpsrweb/SAMHDA/studies/34482 for more information

3.3.2 Measures

The NSDUH field survey assessment has multiple modules across a range of drug use and health topics, and with coverage of prescription pain relievers via PPR module items listed Appendix B. PPR module items have been used to identify newly incident EMPPR users as well as those who had become opioid dependence cases within 12 months after onset of EMPPR use (8,87,100). A generally supportive series of diagnostic reliability and validity estimates for this type of assessment has been reported by independent research teams (34,101,102).

Whereas NSDUH assessments do not ask about lifetime history of opioid dependence, the survey items have identified newly incident EMPPR users who do and do not qualify as cases of opioid dependence as observed to be present within 12 months after onset of EMPPR use. Based on these assessments, it is possible to identify the newly incident EMPPR users (i.e., those who started EMPPR use within the 12 months prior to assessment), and to measure opioid dependence that occurs after onset of EMPPR use (i.e., within the same 12 month interval).

3.3.3 Analysis Plan

The analysis plan started with Tukey-style exploratory data analysis steps and inspection of analysis-weighted marginal distributions. Thereafter, analysis-weighted estimates of annual incidence rates for EMPPR use were derived, followed by estimation of transition probabilities (with standard errors) for how often opioid dependence cases were observed after onset of EMPPR use (i.e., within 12 months).

The initial attempt to produce year-by-year estimates was thwarted by the small number of opioid dependence cases observed each year, with resulting unstable variance estimates. For this reason, year-pairs were created as well as corresponding age-pairs (103). This approach produced acceptable stability in the variance estimates.

3.3.3.1 Meta-Analysis

Resulting year-pair estimates for incidence proportions and for the variance of the incidence proportions are appropriate for meta-analysis because each year's sample can serve as a new and statistically independent replication. Accordingly, for meta-analysis purposes, each age-pair and year-pair were treated as an independent replication sample and source of meta-analysis data, building from prior work by Meier et al. and DeAndrea et al. (8,104).

Except as noted, the meta-analysis confidence intervals (CI) are from 'fixed effects' estimators. When the heterogeneity test statistic suggested potentially important variations (i.e., $p<0.05$), the 'random effects' estimator also is shown. All estimates are analysis-weighted with Taylor series linearization for variance estimation. Meta-analyses are based on Stata Version 13 'metan' commands, with a logit transformation suggested by Vsevolozhskaya and Anthony (88,105).

In a meta-analysis of estimates from multiple years, the I-squared statistic serves as a measure of heterogeneity of these year-by-year estimates. When I-squared is small (and its p-value is large), there is less year-by-year variation and a fixed effects CI can be justified. When I-squared is quite large (and its p-value is small), there is more year-by-year variation, and a 'random effects' CI can be used to take the heterogeneity of estimates into account. The default 'fixed effects' estimator was specified, but the I-squared statistic has been used as a diagnostic tool for potential year-year variation (106).

In advance, decision rules were specified for the I-squared statistic as follows: (i) When the p-value for I-squared less than 0.05, the meta-analysis is re-specified so that the 'random effects' summary estimator is reported and used in subsequent analyses; (ii) When the I-squared p-value is larger than 0.05 but less than 0.15, results based on both 'fixed effects' and 'random

effects' summary estimators are presented; (iii) Otherwise, the fixed effects summary estimate is presented, with considerable confidence that the between-year variability of estimates is acceptably small for the fixed effects approach. The 'metan' command was performed on the logit scale and transformed back to a proportion as illustrated by Vsevolozhskaya and Anthony (2014).

3.3.4 Generalizability

These study estimates might be of special interest to practitioners interested in prevention of opioid dependence, but of course constraints on generalizability deserve mention. The discussion addresses issues of generalizability, and whether this study's estimates for the nation as a whole might be useful in the context of the work of officials responsible for individual public health districts and states, given what is known about observed state-level variations in the incidence of EMPPR use (88).

3.4 Results

Table 3.4.1, Panel A describes the sample of 12-21 year olds. It cross-tabulates effective sample sizes to illustrate unweighted numbers of newly incident EMPPR users in the sample, disclosing peak values between age 14 and age 17 years. Essentially the same peaks are seen in the weighted counts of Panel B of Table 3.4.1 and in the analysis-weighted estimates of Table 3.4.2.

Table 3.4.1 Approximate unweighted numbers of newly incident adolescent onset extra-medical users of prescription pain relievers per subgroup (Panel A) and weighted population counts (Panel B) for newly incident extra-medical prescription pain reliever users by age and year-pair. Data from Restricted-use Data Analysis System subsamples of the National Surveys on Drug Use and Heath, United States, 2002-2013.

Panel A: Approximate number of newly incident users in the sample

Year pair	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
2002-2003	191	625	814	564	308
2004-2005	199	520	732	477	303
2006-2007	171	476	681	532	263
2008-2009	145	546	708	514	285
2010-2011	157	446	679	426	249
2012-2013	118	353	507	313	260

Panel B: Corresponding weighted count of newly incident users in the US population

Year pair	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
2002-2003	104,000	344,000	454,000	397,000	222,000
2004-2005	113,000	301,000	430,000	351,000	224,000
2006-2007	98,000	276,000	397,000	418,000	205,000
2008-2009	81,000	313,000	408,000	392,000	215,000
2010-2011	86,000	248,000	378,000	329,000	196,000
2012-2013	66,000	202,000	290,000	254,000	208,000
Estimated analysis-weighted total (per 100)	548,000	1,684,000	2,357,000	2,141,000	1,270,000

Diagonal cells of these tables also provide what has been called an ‘epidemiological mutoscope’ view of the experience of individual cohorts. To illustrate Table 3.4.2 shows that, in 2002-2003, an estimated 1.1-1.5 percent of 12-13 year olds had just started EMPPR use. Followed forward to its 2004-2005 completely independent re-sample, that same cohort had turned 14-15 years old, and cohort-specific risk of EMPPR use had increased to 3.4-4.0 percent. Then, with a new re-sample, and observed at age 16-17 years in 2006-2007, estimated incidence of EMPPR use for the same cohort is 4.9-5.6 percent, not appreciably distant from the 4.6-5.4 percent estimates observed in 2008-2009 when the cohort had turned age 18-19 years old. Thereafter, the cohort-specific risk of becoming an EMPPR user dropped to the 2.5-3.2 percent

level in 2010-2011. Followed down its diagonal in Table 3.4.2, the cohort-specific pattern for 12-13 year olds in 2004-2005 is not appreciably different from what can be seen for 12-13 year olds observed in 2002-2003. Seedall and Anthony provide additional details about this epidemiological mutoscope view of each cohort, which complements what can be learned by studying the row and column totals of each table of this type (69).

Table 3.4.2 Estimated risk of becoming a newly incident extra-medical user of prescription pain relievers, stratified by age at assessment and survey year-pair. Age- and time-specific incidence estimates (Panel A), 95% confidence intervals (CI; Panel B), and age-specific meta-analysis summary estimates. Data from Restricted-use Data Analysis System subsamples of the National Surveys on Drug Use and Heath, United States, 2002-2013.

Panel A: Estimated risk of becoming a newly incident user (per 100)

Year pair	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
2002-2003	1.3	4.4	6.3	5.7	3.5
2004-2005	1.4	3.7	5.9	4.9	3.7
2006-2007	1.2	3.4	5.2	5.6	3.3
2008-2009	1.1	3.9	5.3	5.0	3.4
2010-2011	1.1	3.2	4.9	4.3	2.8
2012-2013	0.8	2.5	3.8	3.3	3.0

Panel B: 95% CI for Estimates in Panel A (per 100)

Year pair	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
2002-2003	1.1, 1.5	4.1, 4.8	5.9, 6.8	5.2, 6.2	3.1, 3.9
2004-2005	1.2, 1.6	3.4, 4.0	5.5, 6.3	4.5, 5.4	3.3, 4.1
2006-2007	1.1, 1.4	3.1, 3.7	4.9, 5.6	5.2, 6.1	2.9, 3.7
2008-2009	0.9, 1.3	3.6, 4.2	4.9, 5.7	4.6, 5.4	3.1, 3.9
2010-2011	1.0, 1.3	2.9, 3.5	4.6, 5.3	3.9, 4.7	2.5, 3.2
2012-2013	0.7, 1.1	2.2, 2.9	3.4, 4.2	2.9, 3.8	2.5, 3.5
Meta-analysis summary estimates & 95% CI (per 100)	1.2 (1.0, 1.3)	3.5 (3.0, 4.0)	5.2 (4.5, 5.9)	4.8 (4.1, 5.5)	3.3 (3.1, 3.5)[a]

[a] Here, the I-squared statistic has $0.05 > p > 0.15$ so the 95% CI are from 'fixed effects' estimation; the corresponding 'random effects' interval is 3.0, 3.6. All other meta-analytic 95% CI are from random effects estimation (due to I-squared $p < 0.05$).

With evidence borrowed from all years, the age-specific meta-analysis summary estimates presented in Table 3.4.2 (bottom row) make it clear that no more than about one percent of 12-13 year olds became newly incident EMPPR users in these years. The meta-

analysis summary estimates disclosed a substantial upward jump in incidence from age 12-13 years to age 14-15 years, followed by another substantial jump to peak point estimates at age 16-17 years and age 18-19 years, followed by a statistically robust decline in risk for the 20-21 year olds.

Table 3.4.2 also might be disclosing a secular trend that merits continuing attention in future years. The peak values for newly incident EMPPR use among 16-17 year olds in 2012-2013 are tangibly smaller than corresponding values for prior years, as gauged by non-overlap of CI. Forest plots presented for age-groups in Figure 3.4.1 lead to a similar conclusion.

Figure 3.4.1 Meta-analysis forest plots for newly incident extra-medical use of prescription pain relievers (a) and transition to dependence within 12 months (b). Risk estimates and 95% confidence intervals (CI; per 100) on the logit scale. Data from Restricted-use Data Analysis System subsamples of the National Surveys on Drug Use and Heath, United States, 2002-2013.

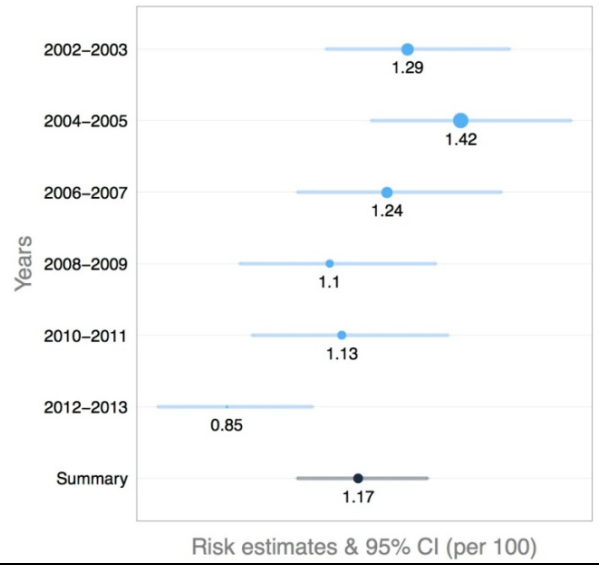
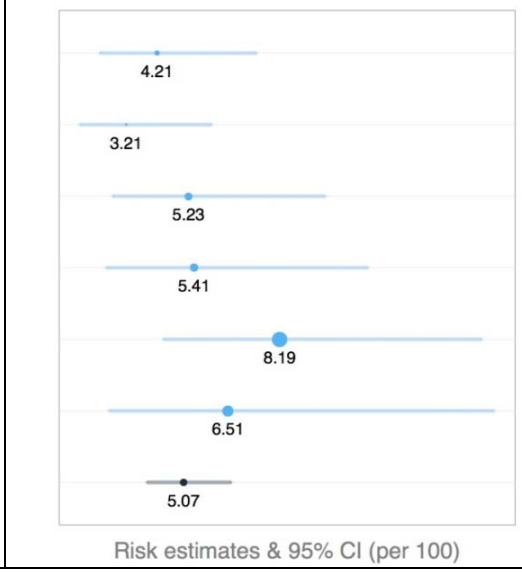
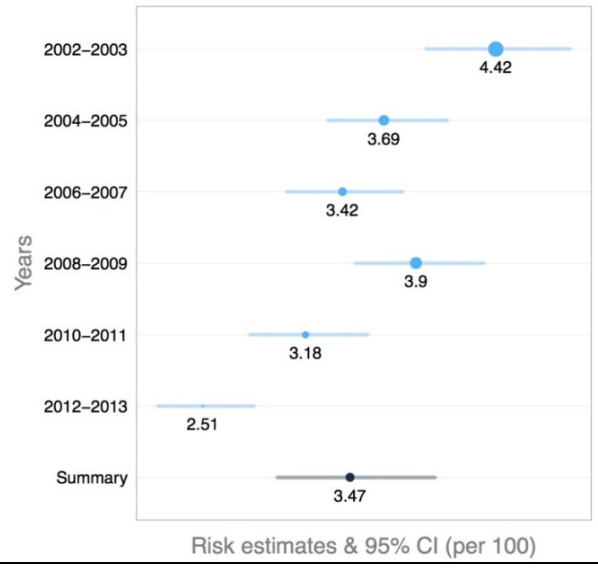
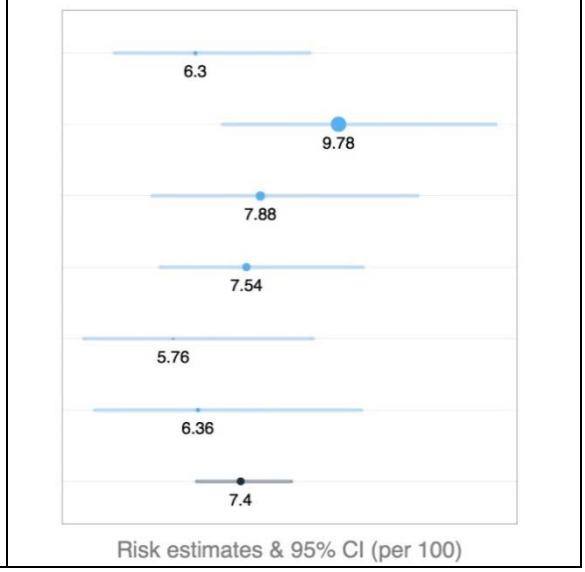
a. 12-13 year olds, becoming a user: random effects	**b. 12-13 year olds, transitioning from use to dependence: fixed effects**
	

Figure 3.4.1 (cont'd)

a. 14-15 year olds, becoming a user: random effects	b. 14-15 year olds, transitioning from use to dependence: fixed effects
	

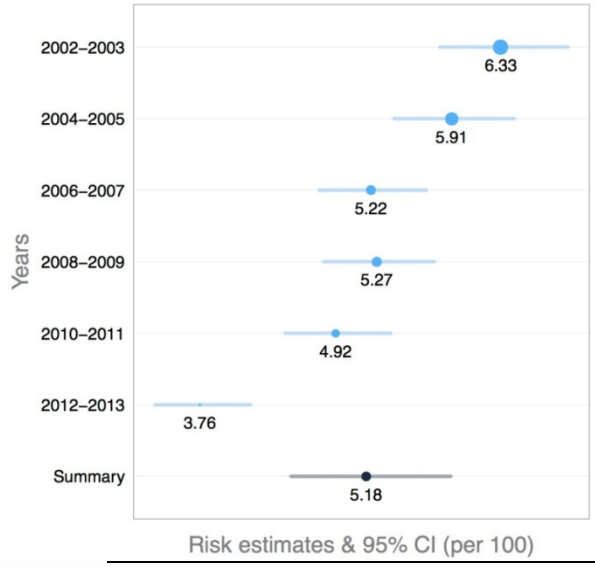
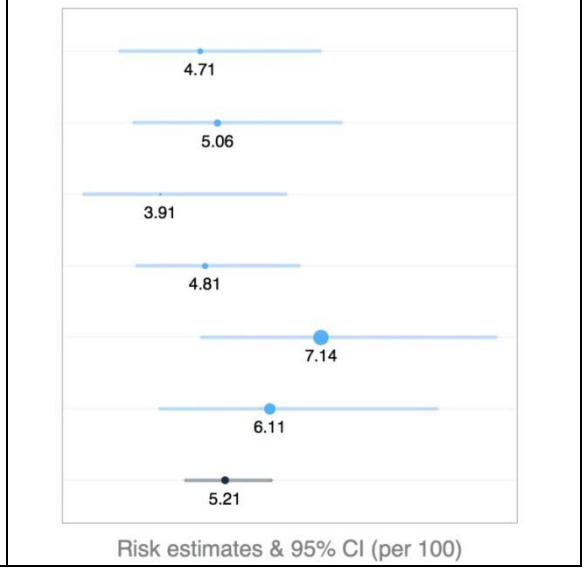
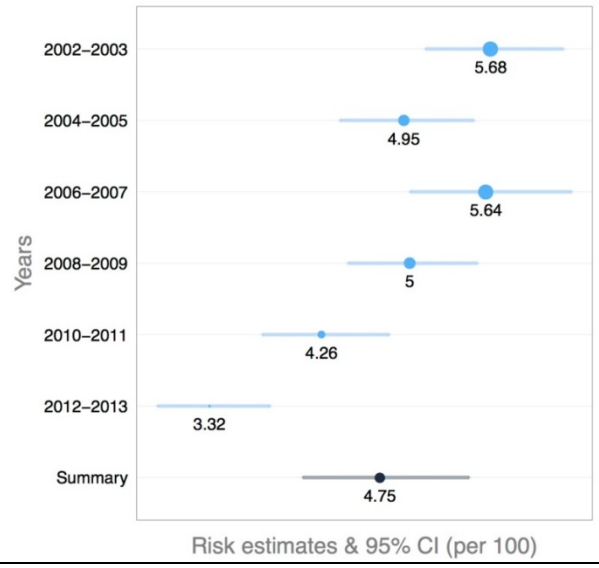
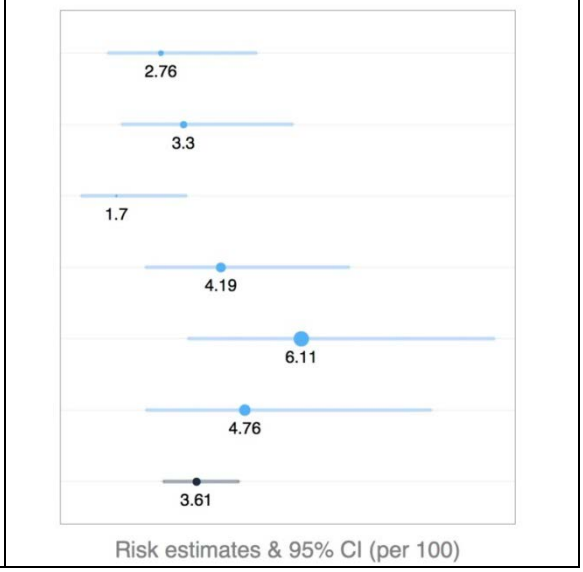
a. 16-17year olds, becoming a user: random effects	b. 16-17 year olds, transitioning from use to dependence: fixed effects
	

Figure 3.4.1 (cont'd)

a. 18-19 year olds, becoming a user: random effects	b. 18-19 year olds, transitioning from use to dependence: fixed effects
	

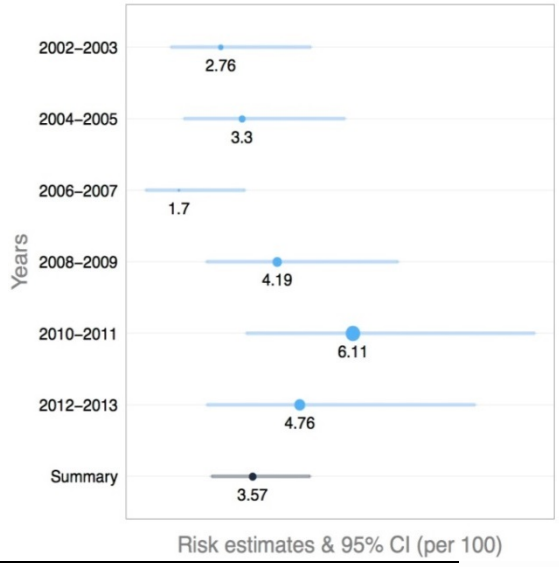
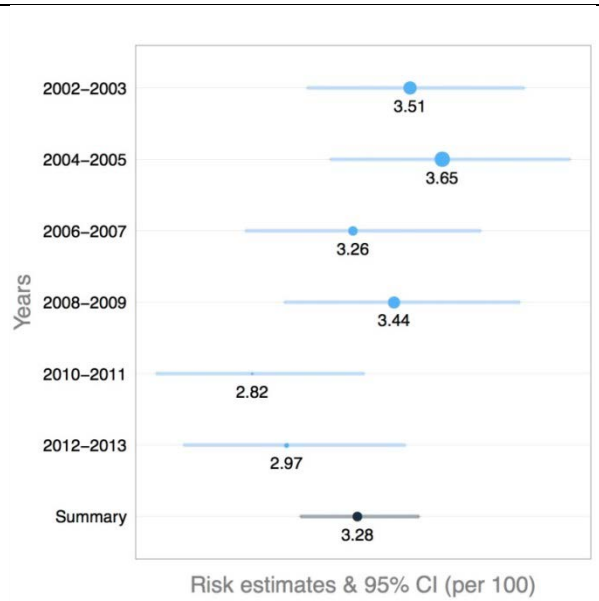
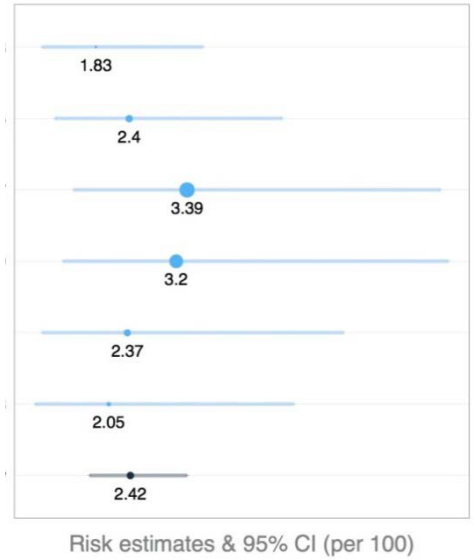
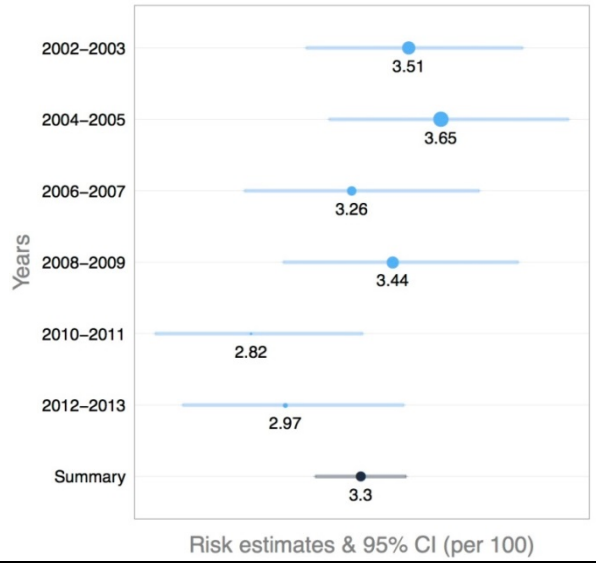
a1. (large heterogeneity test statistic with p<0.05; therefore no fixed effects approach here)	b1. 18-19 year olds, transitioning from use to dependence: random effects
	

Figure 3.4.1 (cont'd)

a. 20-21 year olds, becoming a user: random effects	b. 20-21 year olds, transitioning from use to dependence: random effects
	

a1. 20-21 year olds, becoming a user: fixed effects	b1. (small heterogeneity test statistic with p>0.10; therefore no random effects approach here)
	

Understandably, the random effects meta-analysis estimating approach tends to yield less precise 95% CI when replication samples produce heterogeneous estimates. There were

some relatively minor but potentially important survey methods differences across the years (e.g., transition to full ACASI assessments in 2004-2005; variations in US Census tables used for post-stratification adjustment factors). For this reason, the 'random effects' estimating approach was specified, but the 'fixed effects' estimating approach was substituted when the heterogeneity test statistic's p-values were appreciably larger than the 0.05 level.

When the heterogeneity test statistic's p-value was just slightly greater than 0.05, two forest plots are pictured in Figure 3.4.1, one of which is based on (and labeled as) the random effects plot and the other of which is based on (and labeled as) the fixed effects plot.

Starting with 12-13 year olds, it seems that estimated risk of becoming a user might have declined, whereas estimated risk of transitioning from EM use to dependence might have increased. However, there are wide and overlapping 95% CI. In the rightmost plots, the estimated transitions to dependence generally had small heterogeneity test statistics (and large p-values), indicating that no inference should be drawn about any secular trend toward increasing risk of dependence upon newly incident users. In addition, given the relative imprecision and overlap of 95% CI in the leftmost plots, plus the methods differences just noted, any mention of a secular trend would be speculation in the direction of reduced incidence of use, based on this evidence.

There are variations in the R-DAS post-stratification adjustment factors over time, which might well explain any observed heterogeneity. The R-DAS documentation and estimates do not make it possible to stabilize the post-stratification adjustment approaches and to rule out this source of observed heterogeneity in the estimates of becoming a newly incident EM use of these compounds.

Table 3.4.3 shifts attention to risk of becoming opioid dependent within 12 months after onset of EMPPR use. The estimated risk estimates for the age-pair at 14-15 years old is noteworthy in three ways. First, viewed row-wise, except for 2010-2011, every year-pair shown in Table 3.4.3 (Panel A) discloses a peak point estimate for becoming a case of opioid dependence at age 14-15 years. Second, meta-analysis summary estimates for the 14-15 year old newly incident EMPPR users are robustly larger than estimates observed for the other age-pairs. Third, with no more than one exception, the epidemiological mutoscope view of the table's diagonal cells shows that peak incidence of opioid dependence for birth cohorts (given newly incident EMPPR use) is larger at age 14-15 years than at other ages.

Table 3.4.3 Estimated risk of transitioning and becoming an opioid dependence case no longer than 12 months after onset of starting to use prescription pain relievers extra-medically (Panel A), 95% confidence intervals (CI; Panel B), and age-specific meta-analysis summary estimates. Data from Restricted-use Data Analysis System subsamples of the National Surveys on Drug Use and Heath, United States, 2002-2013.

Panel A: Estimated risk of becoming an opioid dependence case (per 100 newly incident EMPPR users)

Year pair	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
2002-2003	4.2	6.3	4.7	2.8	1.8
2004-2005	3.2	9.8	5.1	3.3	2.4
2006-2007	5.2	7.9	3.9	1.7	3.4
2008-2009	5.4	7.5	4.8	4.2	3.2
2010-2011	8.2	5.8	7.1	6.1	2.4
2012-2013	5.1	6.4	6.1	4.8	2.1

Panel B: 95% CI for Panel A estimates (per 100)

Year pair	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
2002-2003	2.3, 7.4	4.3, 9.1	3.1, 7.1	1.5, 5.1	0.9, 3.7
2004-2005	1.7, 6.0	6.9, 13.6	3.4, 7.6	1.8, 5.9	1.1, 5.0
2006-2007	2.8, 9.7	5.2, 11.7	2.3, 6.5	0.8, 3.4	1.5, 7.7
2008-2009	2.6, 11.0	5.4, 10.4	3.4, 6.7	2.4, 7.3	1.3, 7.8
2010-2011	4.4, 14.7	3.6, 9.2	4.7, 10.7	3.4, 10.7	0.9, 6.1
2012-2013	2.6, 15.1	3.8, 10.4	3.9, 9.5	2.4, 9.2	0.8, 5.2
Meta-analysis summary estimates & 95% CI (per 100)	5.1 (3.9, 6.6)	7.4 (6.3, 8.7)	5.2 (4.4, 6.2)	3.6 (2.5, 5.0)[a]	2.4 (1.7, 3.4)

[a] Here, the I-squared statistic has $0.05 < p < 0.15$ so the 95% CI are from 'random effects' estimation; the corresponding 'fixed effects' interval is 2.8, 4.6. All other meta-analytic 95% CI are from 'fixed effects' estimation (due to I-squared $p > 0.15$).

The epidemiological estimates presented in Tables 3.4.2 and 3.4.3 seem to be quite clear in their implications for age-specific timing of public health interventions. Delay of outreach programs and interventions until the adult years, with failure to concentrate resources on teenagers, might well be misguided, if these incidence estimates are judged to be trustworthy and actionable.

For a variety of reasons, including the technical detail known as right-censoring in the context of survival analyses, it can be difficult to estimate the mean duration of EMPPR use. By combining this study's annual incidence estimates with separately published prevalence estimates (87,90), it is possible to derive such estimates for EMPPR use via a functional relationship that expresses prevalence as a function of incidence times mean duration. Tables 3.4.4 and 3.4.5 provide details about these calculations.

Table 3.4.4 Estimated prevalence of being an extra-medical user of prescription pain relievers during the year prior to assessment, stratified by age at assessment and survey year pair. Age- and time-specific incidence estimates (Panel A), 95% confidence intervals (CI; Panel B), and age-specific meta-analysis summary estimates. Data from Restricted-use Data Analysis System subsamples of the National Surveys on Drug Use and Heath, United States, 2002-2013.

Panel A: Estimated prevalence of being a user in the year prior to assessment (per 100)

Year pair	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
2002-2003	3.2	7.6	12.1	13.3	12.5
2004-2005	3.4	6.7	11.3	13.8	13.5
2006-2007	3.0	6.8	10.7	13.7	13.2
2008-2009	2.9	6.4	9.9	12.3	12.6
2010-2011	2.9	5.8	9.5	10.7	10.9
2012-2013	2.3	4.8	7.6	9.3	9.9

Panel B: 95% CI for estimates in Panel A (per 100)

Year pair	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
2002-2003	2.9, 3.5	7.0, 8.2	11.5, 12.8	12.6, 14.1	11.7, 13.3
2004-2005	3.0, 3.9	6.2, 7.2	10.6, 12.0	13.0, 14.6	12.6, 14.4
2006-2007	2.6, 3.4	6.3, 7.3	10.1, 11.3	12.9, 14.6	12.3, 14.1
2008-2009	2.5, 3.3	5.9, 6.9	9.3, 10.6	11.5, 13.1	11.8, 13.6
2010-2011	2.6, 3.3	5.3, 6.4	8.9, 10.1	10.0, 11.5	10.2, 11.8
2012-2013	2.0, 2.7	4.4, 5.3	7.1, 8.2	8.6, 10.1	9.1, 10.8
Meta-analysis summary estimates & 95% CI (per 100)	3.7 (3.0, 3.3)[a]	6.8 (6.1, 7.6)[b]	10.8 (9.6, 12.1)[b]	13.1 (12.1, 14.2)[b]	13.0 (11.9, 14.1)[b]

[a] I-squared statistic ($0.05 > p > 0.15$); the 'random effects' 95% CI = (3.0, 3.6).
[b] I-squared statistic ($p < 0.05$); these are the 'random effects' 95% CI.

Formulated in this fashion, when EMPPR use starts during the adolescent years, its mean duration can be estimated as 2-4 years, with age variation (see Table 3.4.5).

Table 3.4.5 Mean duration of extra-medical prescription pain reliever use by age (in years). Data from Restricted-use Data Analysis Stem subsamples of the National Surveys on Drug Use and Heath, United States, 2002-2013.

Estimate	12-13 y	14-15 y	16-17 y	18-19 y	20-21 y
Incidence (per 100)	1.2	3.5	5.2	4.8	3.3
Prevalence (per 100)	3.7	6.8	10.8	13.1	13.0
Mean Duration*	3.1 years	2.0 years	2.1 years	2.8 years	3.9 years

* Estimate derived via division of the Prevalence estimate by the Incidence estimate.

3.5 Discussion

For scientists who study prescription pain relievers, policy-makers, regulatory bodies and health professionals, this report's characterization of a 21st century 'epidemic' may be useful. Consistent with prior estimates through 2008, years of peak risk for starting EMPPR use are observed during mid-adolescence (8).

When this study's epidemiological estimates are applied to population counts for 12-21 year olds in the US, the calculations suggest that roughly 8 million adolescents started using PPR extra-medically between 2002 and 2013. In addition, during each year between 2002 and 2013, roughly 42,000 to 58,000 became newly incident cases of opioid dependence within 12 months after onset of EM use (i.e., at least 120 cases per day). One can presume that all or most of these cases might be in need of advice or monitoring by a general practitioner, if not more intensive drug treatment services.

At 2.4% (95% CI = 1.7%, 3.4%), the estimated risk for becoming an opioid dependence case within 12 months after onset of EMPPR use is relatively low among 20-21 year olds. Opioid dependence risk estimates seen for newly incident 12-17 year old EMPPR users are 2-3 times larger, possibly reflecting a more general susceptibility to complications when drug use starts early, as seen elsewhere (107). An apparent peak risk for transition to opioid dependence within 12 months at age 14-15 years is noteworthy. In the US, by age 14-15 years, most teenagers have qualified for admission to the secondary school level. Perhaps PPR become more readily available once primary school years have passed. It could also be that 14-15 are more impulsive than their older counterparts (108).

In this study, by joining previously published age-specific estimates for prevalence of EMPPR use with this study's newly published age-specific estimates of incidence rates through

2013, it has been possible to discover that for the most part the mean duration of EMPPR use is on the order of 2-4 years, although an allowance for age-related variation must be made. Previously published estimates suggest that many EMPPR users try these compounds no more than a few times and then stop, with duration far shorter than the estimated mean, whereas others become persistent users, with duration considerably longer than the estimated mean (e.g., those who become opioid dependence cases). Regrettably, statistically reliable age-specific estimates for the duration of opioid dependence attributable to PPR cannot be derived from these NSDUH data.

Public health researchers, as well as practitioners interested in prevention and control of PPR use and dependence, can use this study's estimates in attempts to marshal new resources for clinical and population health initiatives. Estimates of this type might help motivate design, implementation, and evaluation of more effective public health outreach and early intervention services for adolescent-onset users and opioid dependence cases in the community.

Among study limitations the self-reported character of NSDUH data is noted, for which there is no logistically feasible alternative in nationally representative community sample surveys. While it is true that ACASI assessment protocols qualify as 'best practices' for large sample quantitative survey research on generally illegal and sensitive behaviors, some young people in these samples might fail to disclose newly incident EMPPR use or clinical features of opioid dependence once it occurs (i.e., lapses in field assessment 'sensitivity'). In addition, not all EMPPR users are assessed exactly one year after onset of EMPPR use. As such, this study's estimates fall somewhat short of 'annual' incidence rates. R-DAS estimation does not make it possible to calculate person-months from first day of EMPPR use to NSDUH assessment dates (109). In addition, the technical detail of post-stratification adjustment to US Census cell counts

is allowed to vary across R-DAS year pairs. In consequence, comparisons across NSDUH year-pairs might show variations due to variations in the US Census cell counts. As such, some degree of caution is needed when comparing R-DAS estimates across year-pairs.

With respect to the measurement issues just noted, a lack of specificity might counter-balance departures from 100% sensitivity. Some adolescents might exaggerate and boast about EMPPR experiences that never truly occurred. Alternately, some might misunderstand survey questions in a direction that creates specificity errors. Therefore, as is true for almost all epidemiological surveillance estimates, the large-sample scale for survey coverage required to achieve nationally representative probability samples tends to thwart deep probes into qualitative research issues of screening or diagnostic validity as might be achieved via drug toxicology assays or a standardized clinical reappraisal work-up of a type made feasible in research with smaller and more local samples. Nonetheless, in more than 30 years of standardized clinical reappraisal research on large sample survey-based diagnostic assessments of DSM-type drug dependence, validity evidence has generally been supportive, often more supportive than has been true for other DSM categories of neuropsychiatric disorders, as noted in articles cited within the Methods (section 3.3).

In any community sample survey of drug outcomes, there is a possibility of omissions of seriously disabled opioid-dependent users with lives so disrupted that they qualify as non-participants in the survey operations, even when their names are included on community survey sampling rosters. This is a methodological issue that pertains to the sensitivity of the surveillance operation, and is not an issue of the sensitivity of the survey measurements *per se*. To the extent that this research project involves estimation of the probability of transitioning from first onset of use into opioid dependence, there might a slight under-estimation of these probabilities, due to

left-censoring of severely affected cases of this type. A topic of continuing investigation, not yet resolved, is how often users move quickly from first use into dependence syndromes that are disabling to the point of survey non-participation. The expectation is for a small downward bias in the estimates, given that they generally are based upon users in the earliest months of the opioid dependence process. A related omission involves fatal overdose deaths as might occur on the first or second use of the drug, in which case these users can be missing from the survey denominators altogether. US vital statistics, to date, suggest that no more than a handful of such deaths would be missed by NSDUH field survey operations, given that the number of prescription opioid overdose deaths in the US totals no more than about 16,000 for the country as a whole, with a total population size of roughly 320 million individuals (94). A recent study of the potential 'Len Bias' bias suggests negligible error from this theoretically interesting source of epidemiological bias (110).

Those interested in dependence that occurs after strictly medical use of PPR may be disappointed that NSDUH focuses exclusively on EMPPR use. One must look elsewhere for opioid dependence estimates when users stay well within boundaries of a prescribing clinician's instructions. It seems reasonable that this study's estimates of opioid dependence transition probabilities might be larger than what would be observed in research on PPR use exactly as prescribed, because the susceptibility traits giving rise to adolescent-onset EM drug use almost certainly overlap with those influencing adolescent-onset drug dependence. Nonetheless, there now are no definitive nation-level estimates for these transition probabilities in the context of medically prescribed use. Estimates of this type will be needed to make a direct comparison of dependence risks across these different contexts of medical and EMPPR use.

The relationship between PPR use and opioid dependence can be complex, with feedback loops. Quite clearly, EM use can lead to dependence, but dependence that develops during medically prescribed use also can lead to EMPPR use, as discussed elsewhere (111).

Another question is whether these estimates for the US as a whole might generalize to sub-units as small as public health districts, to jurisdictions as large as states or regions within the US, or to other countries. There is substantial evidence of state-level variations in the occurrence of EMPPR use (88). Observed variations in those estimates lead to hesitation before recommending application of this study's estimates to state or sub-state units. Fortunately, R-DAS 10-year datasets (2002-2011) make provisions for sub-state estimates. For the larger sub-states (and for states), it is possible to pool data across 10 years in order to derive summary estimates. As for applicability elsewhere (i.e., in other countries), use caution.

Notwithstanding limitations of this type, and the fact that the transition probabilities for onset of opioid dependence within 12 months actually might be somewhat larger than estimated, the epidemiological estimates observed here are not trivial. These estimates deserve both clinical and public health attention. These estimates should help encourage and motivate NIDA, Centers for Disease Prevention and Control (CDC), and others to focus or renew attention to 12-21 year olds in current efforts to prevent and control EM use of prescription pain relievers and associated opioid dependence risks.

CHAPTER 4

MANUSCRIPT 2 – BEYOND AN ADOLESCENT'S FIRST OCCASION OF USING PRESCRIPTION PAIN RELIEVERS EXTRA-MEDICALLY: ZERO-INFLATED POISSON REGRESSIONS FOR HYPOTHESIZED INFLUENCES ON PERSISTENCE AND RATES OF USE

In writing this dissertation, this manuscript was in the review process of a peer-reviewed journal. As a result, a majority of this chapter has been reproduced from the 'under review' version (112).

4.1 Abstract

Objective: Evidence from double blind experiments suggests two classes of individuals starting EMPPR, with young alcohol dependence (AD) cases as potentially vulnerable population subgroups. Evoking a latent class of youthful EMPPR users who are susceptible-to-persistence (STP) of such use versus an alternative class not-susceptible-to use (NSTP), we posit an under-representation of AD cases in the NSTP class, as well as an excess rate of EMPPR use (given membership in the STP class). Well-characterized zero-inflated Poisson regression models are used to evaluate these hypotheses.

Method: Nationally representative samples of community-dwelling 12-20 year olds in the US are studied, all with standardized assessments for NSDUH, 2002-2012 (n = 21,037 newly incident EMPPR users).

Results: Underage drinkers with AD are less likely to be in an EMPPR not-susceptible-to-persistence (NSTP) class. Moreover, given STP class membership, there is AD-associated excess rate of EMPPR use (e.g., risk ratio: 1.3; 95% CI=1.1, 1.5). Ancillary findings disclose a female excess rate of EMPPR use among the most recent initiates within the STP class.

Conclusions: Underage drinking is a signal of persistent EMPPR use once it starts. Given membership in the STP class, rates of EMPPR use are greater for alcohol dependence cases. A prudent course of action might be adjustment of pain relief plans or greater vigilance when underage drinking is in the background (e.g., adjustments in numbers of dosage units dispensed refill constraints).

4.2 Introduction

4.2.1 Background

With a start during an era of high priority research on the current US epidemic of heroin and other opioids use (113), this study's origin begins with evidence from double blind laboratory experiments on heroin administered to humans, as well as other compounds in the class of PPR, primarily opioids. The laboratory evidence makes one posit existence of two differentiable latent classes of PPR users: (i) those who are more susceptible-to-persistence of use (i.e., an STP class), and (ii) those who are not-susceptible-to-persistence of use (i.e., an NSTP class). From the lab experiments, membership in these two classes is expected to be determined, in part, by histories of serious alcohol or other drug involvement (i.e., before or concurrent with EMPPR use).

4.2.2 Heterogeneity in Response to Opioid Use

An early heroin study in this line of research was conducted in an opioids laboratory directed by pharmacologists Lasagna and Beecher. Their work disclosed that as many as 50% of 'normal' human volunteers might respond to heroin and other opioids with an initially dysphoric or otherwise negative response, with a description of the drug experience as one they never wished to repeat (114). These lab experiment findings help substantiate epidemiological

estimates that no more than about one in four young people develop heroin dependence, once heroin use starts (1).

After the pioneering lab studies of the 1950s, subsequent research in behavioral pharmacology labs bolstered an early idea that susceptibility to persistence of opioid use might be influenced by whether experimental volunteers come to the lab with recently active histories of concurrent alcohol and/or other drug use. In a 2003 review article, Griffiths and colleagues summarized these studies, and suggested that experimentalists might anticipate greater 'drug liking' and related manifestations of subjectively favorable drug responses among other alcohol- and other drug-involved volunteers in their studies (115).

Recent field survey evidence gathered just before and during the current epidemic of prescription pain reliever use in the US falls in a coherent pattern with evidence from the laboratory. A clear implication is that prior or concurrent alcohol and other drug use are potential determinants of initial EMPPR use, and might influence post-onset trajectories of EMPPR use leading toward opioid dependence syndromes (38,116,117).

4.2.3 Specific Aims for this Initial Project

In this study, these lines of research are brought together by investigating what happens to adolescent EMPPR users within the relatively short interval of 12 months after the first occasion of EMPPR use, defined as in prior research to encompass use of a PPR compound 'to get high' or otherwise beyond boundaries of the prescribing clinician's intent (1,28). In contrast with investigations of how often an opioid dependence syndrome emerges soon after young people initiate EMPPR use (118), this investigation works forward from the first occasion of EMPPR use and studies steps that are occurring in the process of developing a dependence syndrome, more proximal to the onset of initial EMPPR use.

One way to conceptualize these steps is to count up the number of occasions or days of EMPPR use during an interval of observation that starts as soon as newly incident EMPPR use has occurred. Thereafter, suspected determinants of the resulting 'rate of use' for that interval of time can be studied using standard Poisson 'count' regression models. Standard Poisson regression modeling was the statistical approach in mind in an effort to estimate the degree to which co-occurring alcohol dependence (AD) might influence a young person's rate of EMPPR use during a one year interval after onset of EMPPR use. As described in the methods (section 4.3), an adaptation of this planned use of the Poisson regression model was made. A zero-inflation of the count distribution was detected (i.e. more newly incident EMPPR users with zero days of use after the first occasion of use). To accommodate this departure from the standard Poisson distribution, the zero-inflated Poisson regression model was used.

4.3 Methods

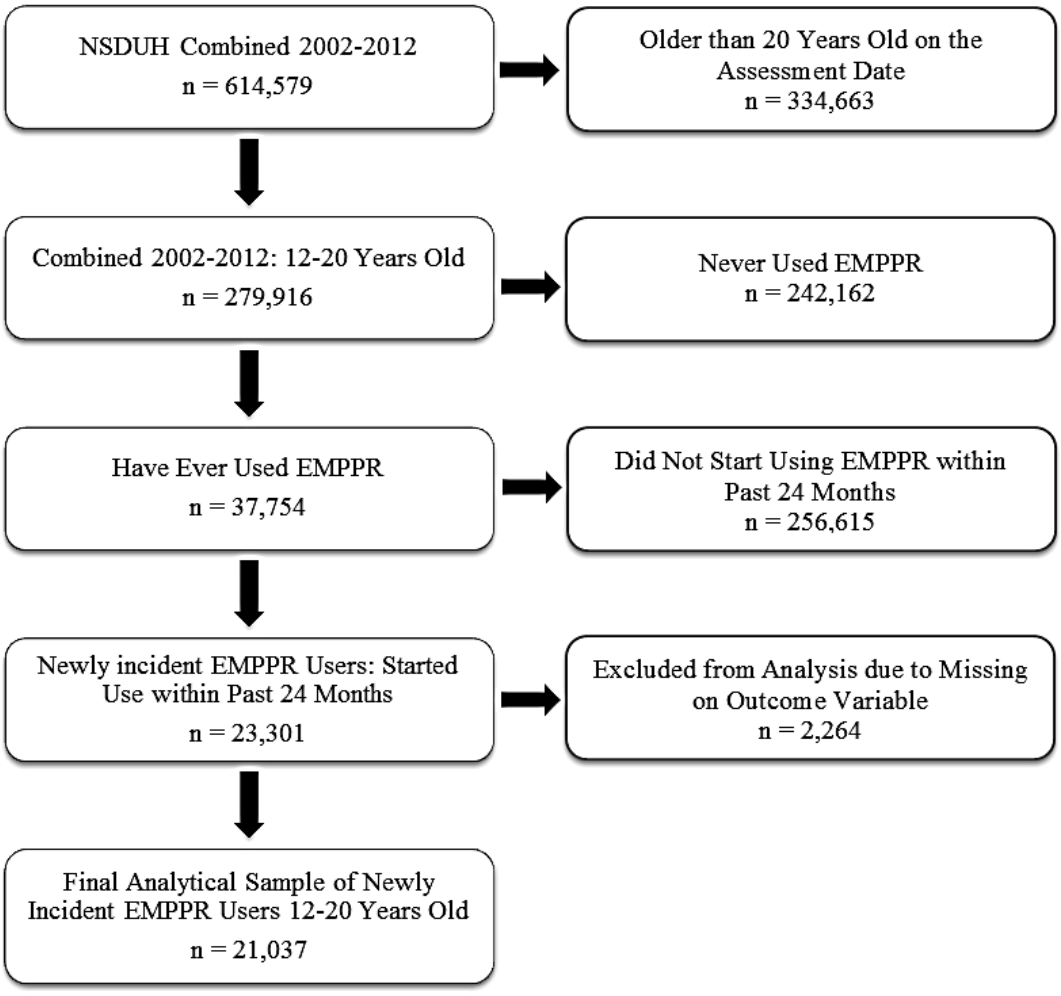
4.3.1 Research Design and Study Population

Estimation of the study parameters required either a cross-sectional or prospective research design with a large epidemiologically credible unselected series of newly incident EMPPR users in the age range from 12-20 years. For each EMPPR user, it was necessary for a sufficient amount of time to pass since first use in order to characterize the number of days of use in the 12 month interval prior to assessment. The focus on 12-20 year olds was dictated by the idea that earlier-onset AD might be of greatest importance when EMPPR use starts before the adult years. Adolescents who began drinking at the legal drinking age (e.g., 21 years) were suspected to be different than underage drinkers. Lacking large enough samples in currently available prospective studies of EMPPR users, the NSDUH publicly available datasets were used (2002-2012).

4.3.2 Sample

Figure 4.3.1 sums across years and shows that the NSDUH yearly samples included 279,916 participants age 12-20 years old. A total of 21,037 newly incident EMPPR users were ascertained at age 12-20 years, all with EMPPR use started within 24 months prior to assessment. Only 2,264 were excluded, due to unanswered EMPPR items (e.g., days of use).

Figure 4.3.1 Flow chart showing the process used to enumerate newly incident extra-medical prescription pain relievers (EMPPR) in the sample of 12-20 year olds. Data from the National Surveys on Drug Use and Health (NSDUH), United States, 2002-2012.



4.3.3 Measures

After consent, NSDUH ACASI assessments cover multiple standardized multi-item modules on background variables, drug use, and health topics, including EMPPR use and alcohol involvement. See Appendix C for items.

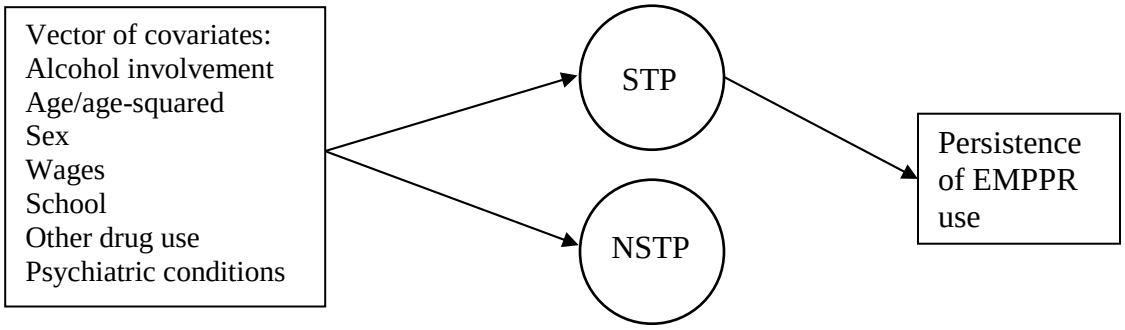
The ZIP modeling response variable is based on answers to ACASI questions about the number of days of EMPPR use during the 12 month interval prior to survey assessment, and the primary covariate as active AD, measured via a multi-item module based on the DSM-IV (30). NSDUH does not assess past or lifetime AD history.

Recently active AD cases are contrasted with three other forms of alcohol involvement: (i) Never drank in lifetime (reference subgroup), (ii) Drank at least once in lifetime, but not in the past year, (iii) Drank in the past year, but AD-negative (mindful that EMPPR use might influence drinking status, as mentioned above, and this uncertainty about temporal sequencing thwarts firm cause-effect inferences.)

Participants can mark multiple categories of ethnic self-identification, but it was not associated with newly incident EMPPR use. ZIP estimates changed little with this adjustment.

Before analysis, the conceptual model was simplified by starting with a covariate for elapsed time between onset of EMPPR use and the assessment. Then, we introduced our main covariate of interest (alcohol involvement), with male sex and age terms as covariates. For age, both a quadratic and linear term were included to evaluate whether there was a non-linear relationship with the number of EMPPR use days. Due to the cross-sectional nature of our data and our focus on estimation of associations rather than cause-effect inference, all potentially endogenous covariates that might be EMPPR-influenced were excluded (e.g., school achievement, current employment, disposable income levels; see Figure 4.3.2).

Figure 4.3.2 General conceptual model of the zero-inflated process for adolescent newly incident extra-medical prescription pain reliever (EMPPR) users susceptible-to-persistence (STP) and not-susceptible-to-persistence (NSTP).



4.3.4 Statistical Analysis

For newly incident EMPPR users with onset during the 12 months prior to survey assessment, the first day of use was subtracted from total 'days of use' in order to form the response variable for this study of 'persistence' of use after trial use. For newly incident EMPPR users with onset during months 13-24 prior to assessment, the trial use had occurred before the most recent 12 months and for this reason, the response variable was the actual number of days of EMPPR use during the 12 months prior to assessment.

The Tukey-style pre-estimation step disclosed zero inflation in these count distributions of EMPPR usage after onset of EMPPR use (42.4% zeroes), and thwarted our planned use of the standard Poisson regression model. The presence of this zero inflation was evaluated, and prompted positing two latent classes of zeroes: one set of zeroes due to membership in the 'susceptible-to-persistence' (STP) class and the other zeroes due to membership in a 'not-susceptible-to-persistence' (NSTP) class. Akin to the 'normal' volunteers in the experiment conducted by Lasagna and colleagues, the NSTP class would encompass individuals who tried the drug and never wanted to try it again. In contrast, the STP latent class is one whose members

either have tried EMPPR on a second (or subsequent) day, or are anticipated to have engaged in EMPPR use if they were to be evaluated again after some additional interval of time.

Based upon this theoretical formulation and the zero inflation, we were prompted to use the two-equation zero-inflated Poisson (ZIP) model in order to estimate the degree to which early alcohol involvement might influence progression of EMPPR use after the initial day of EMPPR use. In ZIP regression, responses $\mathbf{Y} = (Y_i, \ldots, Y_n)'$are independent, $\pi_i$is the probability of excess zeroes, λ_i is the expected Poisson count for the *i*th individual, and the distribution is given by:

$$\Pr(Y = y)\begin{cases} \pi_i + (1-\pi_i)e^{-\lambda_i};\ y = 0 \\ \frac{(1-\pi_i)e^{-\lambda_i}{\lambda_i}^y}{y!};\ y \geq 1 \end{cases}.$$

Briefly, the ZIP regression model applied to individuals with one occasion of EMPPR use is one that produces two parameter estimates: (i) a regression slope to estimate the degree to which subgroups might be mal-represented in the NSTP class, and (ii) a regression slope to estimate the excess rate of EMPPR use, given membership in the STP class, with an allowance for the possibility that some STP class members might be observed with zero days of use (119). Here, it is hypothesized that underage AD cases might be under-represented in the NSTP class, and that given membership in the STP class, they might have greater rates of EMPPR use during the observation interval after initial onset of EMPPR use.

4.3.4.1 ZIP Inflate Equation

Here, the first of the two ZIP equations indexes subgroups that are more or less likely to be in the NSTP class, for whom the only possibility is zero days after trial use. It is the presence of the NSTP class members and the mixture of the NSTP zeroes with the STP zeroes that gives rise to the inflated number of zeroes in the observed count distribution, relative to the standard Poisson count distribution. The NSTP zeroes are said to ‘inflate’ the number of zeroes expected

under the standard Poisson distribution. For this reason, this ZIP equation can be called an 'inflate' equation, which is a reminder that this equation can show which subgroups are inflating the count of zeroes above what is expected under the standard Poisson distribution. Here, NSTP versus STP class membership is a binary variable, and the familiar logistic regression model provides slope estimates for each subgroup, which can be exponentiated to yield the familiar odds ratio (OR) as a measure of association. An OR greater than 1.0 means that the subgroup is over-represented in the NSTP subgroup, or more generally, is helping to inflate the number of zeroes.

4.3.4.2 ZIP Count Equation

The second ZIP equation is for estimation of variation in rates of EMPPR use, given membership in the STP class. It is a standard regression equation for count distributions that follow the Poisson distribution, and for this reason it is known as the 'count' equation. As with standard Poisson regression, this count equation estimates event rate ratios in a contrast of one subgroup versus another, conditional on membership in the class that includes zero counts but that does not inflate the zero count (i.e., here, the STP class). Solving the 'count' equation yields the estimated rate ratio (RR) on the natural log scale. After exponentiation, the resulting familiar RR conveys the degree of excess or reduced rate in one covariate-denoted subgroup versus a designated reference subgroup, with standard interpretation of RR greater or less than the null (1.0). Appendix D further explains the ZIP model.

There are alternatives to the ZIP model, as well as simpler models that ignore the heterogeneity of zeroes and the possible existence of susceptible versus not susceptible latent classes. These alternatives can be used to analyze count data with inflated zeroes, including an approach that starts with a logistic regression with a manifest binary response coded 1 for having

a zero count and 0 for having a non-zero count, and finishes with a Poisson regression for those with a count greater than zero. As shown in Appendix D via a simulated dataset, this simpler logistic+Poisson approach can lead to erroneous inferences about subgroup variation. Appendix D also covers more appropriate zero-inflation models that can be evaluated using goodness of fit statistics.

4.3.4.3 Analysis Plan

Analysis and estimation steps were conducted using Stata Version 13 software procedures for ZIP models and complex analysis-weighted survey data (105). These steps addressed the NSDUH complex sample design, interdependence of survey observations, and analysis weights, with 'subpopulation' focus on 12-20 year old newly incident EMPPR users. In these analyses, precision of the informative study estimates with a focus on 95% CI was stressed; p-values may aid interpretation and inference.

4.4 Results

4.4.1 Features of the Sample of Newly Incident EMPPR Users

Table 4.4.1 describes study sample characteristics, with analysis-weighted estimates for US 12-20 year olds. The mean age of the 21,037 NSDUH participants in this nationally representative sample of newly incident EMPPR users was approximately 17 years old; a balanced male-female ratio can be seen. Overall, roughly 11% had never consumed an alcoholic beverage; an estimated 12% qualified as recently active cases of AD (i.e., adolescent-onset AD). The ethnic self-identification distribution was unremarkable, as discussed in Section 4.3.3.

Table 4.4.1 Selected characteristics of newly incident extra-medical prescription pain reliever users (EMPPR; n = 21,037). Data from the National Surveys on Drug Use and Health, United States, 2002-2012.

Sample characteristics	Newly incident users (n)	Unweighted %[a]	Weighted %[a]
Sex			
Female	10,802	51.4	50.3
Male	10,235	48.7	49.7
Age in years (when interviewed)[b]	21,037	16.8	17.1
Ethnic Self-Identification			
Non-Hispanic White	14,536	69.1	70.2
Non-Hispanic Black	1,840	8.75	9.4
Non-Hispanic Native American	399	1.9	<1.0
Non-Hispanic Pacific Islanders (incl. Hawaiian)	80	<1.0	<1.0
Non-Hispanic Asian Americans	306	1.5	1.6
Non-Hispanic more than one race/ethnicity	866	4.1	2.0
Hispanic	3,010	14.8	15.8
Alcohol involvement			
Never drank in lifetime	2,139	11.0	10.8
Drank at least once, but not in past year	1,464	7.0	6.9
Drank in past year, no alcohol dependence	14,718	70.0	70.4
Drank in past year, alcohol dependent case	2,536	12.0	11.9
Number of days used EMPPR in the past year[b]	21,037	18.3	19.1
Survey year, 2002-2012	~2,000/year	~10%/year	~10%/year

[a] Due to rounding, percentages may not add to 100%.
[b] Mean.

4.4.2 The Alcohol Dependence Hypothesis

Table 4.4.2 provides a display of covariate-adjusted estimates from the ZIP inflate equation and from the ZIP count equation with respect to the primary hypothesis about the role of AD in the persistence of EMPPR use, once it has started. The inflate estimates speak to membership in the NSTP class, and with never-drinkers as the reference category, AD users and non-dependent recent drinkers were less likely to be in the NSTP class (OR = 0.5 and 0.7, respectively; 95% CI do not trap the null value of 1.0). Also with the never-drinkers as reference, underage drinkers with a past history of drinking but no recent drinking were more likely to be in the NSTP class (OR = 1.5; Model 2 95% CI = 1.2, 1.7).

The ZIP count equation, also with never-drinkers as the basis for comparison and conditional on being STP, shows that the AD EMPPR users had a higher rate of EMPPR use during the 12 month interval prior to assessment (RR = 1.3; 95% CI = 1.1, 1.5), but this was not the case for recent drinkers with no AD (RR = 1.0; 95% CI = 0.8, 1.1). The 95% CI for the rate of EMPPR use for recent drinkers without AD, AD cases, and that of never drinkers touch in Table 4.4.2. However, performing a linear combination reveals a tangible gradient in strength of the rate of EMPPR use among newly incident users: (1) AD cases have the highest conditional rate; (2) the conditional rate of use for recent drinkers without AD is intermediate between that of AD cases and that of never drinkers (p-value < 0.05). The excess RR for the past drinkers with no recent drinking came as a surprise, but a possible explanation is provided in the Discussion section (section 4.5; RR = 1.3; 95% CI = 1.1, 1.6).

Table 4.4.2 Estimated covariate-adjusted Zero-inflated Poisson model associations linking elapsed time, age, sex, and alcohol involvement with persistent extra-medical use of prescription pain relievers (EMPPR). Data from the National Surveys on Drug Use and Health, United States, 2002-2012.

	Model 1[a]			Model 2[b]		
Inflate	*OR*[c]	*95% CI*	*p-value*	*OR*[c]	*95% CI*	*p-value*
Alcohol involvement						
Never drank in lifetime (reference)	1.0	--	--	1.0	--	--
Drank at least once, but not in the past year	1.5	1.3, 1.9	<0.001	1.5	1.2, 1.7	<0.001
Drank in the past year, no alcohol dependence	0.8	0.7, 0.9	<0.001	0.7	0.6, 0.8	<0.001
Drank in the past year, alcohol dependent case	0.4	0.4, 0.5	<0.001	0.5	0.4, 0.5	<0.001
Count	*RR*[d]	*95% CI*	*p-value*	*RR*[d]	*95% CI*	*p-value*
Alcohol involvement						
Never drank in lifetime (reference)	1.0	--	--	1.0	--	--
Drank at least once, but not in the past year	1.4	1.2, 1.8	0.001	1.3	1.1, 1.6	0.009
Drank in the past year, no alcohol dependence	1.1	0.9, 1.2	0.260	1.0	0.8, 1.1	0.482
Drank in the past year, alcohol dependent case	1.5	1.3, 1.7	<0.001	1.3	1.1, 1.5	<0.001

[a] Model 1 included terms for alcohol involvement, time elapsed, age, and age-squared (but not a term for sex). Age and age-squared were not required for inclusion in the inflate part of the model.
[b] Model 2 included terms for alcohol involvement, time elapsed, sex, and an interaction term for sex and elapsed time. Neither sex nor the interaction term were required for inclusion in the inflate part of the model.
[c] Odds ratio (OR) estimate from the inflate part of the model (transformed log odds of being a member of the not-susceptible-to-persistence class.
[d] Rate ratio (RR) estimate from the count part of the model, conditional on susceptible-to-persistence class membership.

4.4.3 Ancillary Findings Offered as Leads for Future Research

Among 12-20 year olds with no prior history of EMPPR use, an estimated 3.2% qualify as newly incident EMPPR users each survey year. Among the most recent newly incident users (defined with onsets of EMPPR use within 12 months before the assessment), roughly 25.5% had used on one day and one day only (unweighted = 0.26); roughly 13.7% had used on just two days (unweighted = 0.14). Among the newly incident users with EMPPR onset 13-24 months before assessment, roughly 50.7% had not used within the 12 months prior to assessment (unweighted = 0.50); roughly 3.9% had used on just one day (unweighted = 0.04), and 4.5% had used on just two days (unweighted = 0.04).

For the newly incident users, the mean number of days of EMPPR use was about 18-19 in the past year (Table 4.4.1). As shown in Table 4.4.3, the estimated mean days of EMPPR use varied by level of alcohol involvement, and were largest for AD cases. Moreover, more than 60% of the AD-affected EMPPR users had more than two days of EMPPR use in the 12 month interval of interest; among recent drinkers without AD, this estimate is roughly 50%. Smaller estimates were observed for the other alcohol involvement categories.

Table 4.4.3 Days of extra-medical prescription pain reliever (EMPPR) use after initial use, stratified by levels of alcohol involvement. Data from newly incident EMPPR users age 12-20 years old identified in the National Surveys on Drug Use and Health, United States, 2002-2012 (n = 21,037).

	Number of EMPPR Use Days (%)[a]		
	0	1	>1
Alcohol involvement			
Never drank in lifetime	46.6	7.6	45.8
Drank at least once, but not in the past year	59.8	5.3	34.9
Drank in the past year, no AD[b]	41.3	8.5	50.3
Drank in the past year, AD[b] case	30.0	6.4	63.6

[a] Some rows do not add to 100% due to rounding.
[b] AD refers to alcohol dependence.

The covariates in the AD analyses had an interesting pattern of associations with NSTP class membership and with EMPPR rates, conditional on STP class membership. In a ZIP model with no covariate adjustment for level of alcohol involvement, neither age nor being male were associated with being in the NSTP class; the only association was with elapsed time since onset of EMPPR use, with the most recent newly incident EMPPR users being under-represented in the NSTP class (see Table 4.4.4). As for the count equation in that model, age *per se* was not influential, given membership in the STP class (e.g., RR = 1.2; 95% CI = 1.0, 1.6), and greater elapsed time since onset of EMPPR use was associated with a smaller rate (RR = 0.5; 95% CI = 0.4, 0.5).

Table 4.4.4 Estimated covariate-adjusted Zero-inflated Poisson model associations linking elapsed time, age, and sex with persistent extra-medical prescription pain reliever use (EMPPR). Data from the National Surveys on Drug Use and Health, United States, 2002-2012.

Inflate	*OR*[a]	*95% CI*	*p-value*
Time elapsed since assessment[b]	0.41	0.38, 0.44	<0.001
Count	*RR*[c]	*95% CI*	*p-value*
Time elapsed since assessment[b]	0.46	0.41, 0.52	<0.001
Male	0.93	0.84, 1.03	0.182
Time elapsed x Male	0.85	0.73, 0.99	0.041
Age (at assessment)	1.22	0.96, 1.56	0.109
Age-squared	0.99	0.98, 1.00	0.050[d]

[a] Odds ratio (OR) estimate from the inflate part of the model (transformed log odds of having zero days of EMPPR use).
[b] Began use within 12 months of assessment. Reference group is onset of EMPPR use between 13-24 months prior to assessment.
[c] Rate ratio (RR) estimate from the count part of the model, conditional on persistence of EMPPR use. The inflate part of the model is not shown, but was adjusted for time elapsed since assessment.
[d] Including alcohol involvement in this model changes the significance of this relationship ($p > 0.05$).

Male-female variations of note can be found in the rate of EMPPR use, among the STP class, even though a male-female balance in the NSTP class membership was observed (data not shown in a table). In specific, there is a female excess rate, when males and females in the STP class are compared. For newly incident EMPPR users with fewer than 12 months between onset and assessment, the RR estimate is 0.8 (95% CI = 0.7, 0.9), signifying that the male rate is 80%

of the female rate. For newly incident EMPPR users with 13-24 months between onset and assessment, females and male rates do not differ appreciably.

4.4.4 Post-estimation Exploratory Data Analyses

Some examples and a basic introduction to the ZIP model can be found in Appendix D. Knowledgeable investigators might prefer the negative binomial model, but Table 4.4.5 provides post-estimation exploratory data analyses that suggest better fit of the ZIP model in this sample of EMPPR users. In addition, results from the zero-inflated negative binomial (ZNB) model tend to support choice of ZIP modeling, in this instance. While estimates from the ZNB count part of the model are similar to ZIP estimates, estimates from the ZNB inflate part of the model have either very large or small values (Table 4.4.5).

Table 4.4.5 Comparing estimated coefficients linking alcohol involvement with sustained extra-medical use of prescription pain relievers (EMPPR; Conventional, Zero-inflated Poisson (ZIP), and Zero-inflated negative binomial (ZNB))[a]. Data from the National Surveys on Drug Use and Health, United States, 2002-2012.

	Conventional			ZIP			ZNB		
Inflate	*OR*[b]	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Alcohol involvement									
Never drank in lifetime (reference)	1.0	--	--	1.0	--	--	1.0	--	--
Drank at least once, but not in the past year	1.0	0.5, 2.0	0.930	1.8	1.5, 2.1	<0.001	7.6	3.2, 18.3	<0.001
Drank in the past year, no AD[c]	1.0	0.5, 2.0	0.881	0.7	0.6, 0.8	<0.001	0.00	0.0, 0.0	<0.001
Drank in the past year, AD[c] case	1.7	0.97,3.16	0.065	0.5	0.4, 0.5	<0.001	0.00	0.0, 0.0	<0.001
Count	*RR*	*95% CI*	*p-value*	*RR*	*95% CI*	*p-value*	*RR*	*95% CI*	*p-value*
Alcohol involvement									
Never drank in lifetime (reference)	1.0	--	--	1.0	--	--	1.0	--	--
Drank at least once, but not in the past year	1.0	0.8, 1.3	0.797	1.3	1.1, 1.6	0.005	1.4	1.1, 1.8	0.005
Drank in the past year, no AD[c]	1.1	0.9, 1.2	0.462	0.9	0.8, 1.1	0.346	1.0	0.9, 1.1	0.958
Drank in the past year, AD[c] case	1.7	1.5, 2.0	<0.001	1.4	1.2, 1.6	<0.001	1.7	1.4, 1.9	<0.001

[a] So as to compare the column-wise estimates, no covariates are included in this comparison.
[b] These are the ratios of the mean number of days used prescription pain relievers in the past year.
[c] AD refers to alcohol dependence.

Another unresolved question was whether or not important covariates from the ZIP model varied by duration of EMPPR use until interview. Table 4.4.6 explores time elapsed from onset of EMPPR use until the quarter of assessment. Elapsed time in months is similar between sexes and over levels of alcohol involvement. There is only a slight gradient between never drinkers and current drinkers who are AD-cases.

Table 4.4.6 Summary of estimates for newly incident males versus females and for levels of alcohol involvement with respect to elapsed time in months from onset of extra-medical use of prescription pain relievers (EMPPR) until quarter of assessment[a]. Data from the National Surveys on Drug Use and Health, United States, 2002-2012.

	Mean	Median	Interquartile range (IQR)	Minimum[b]	Maximum
Sex					
Male	4.64	0	8	-1	25
Female	4.59	1	4	-1	25
Alcohol involvement					
Never drank in lifetime	3.30	0	4	-1	24
Drank at least once, but not in the past year	4.01	0	6	-1	25
Drank in the past year, no AD[c]	4.84	1	9	-1	25
Drank in the past year, AD[c] case	5.10	2	9	0	25

[a] These elapsed time values are approximations based on the National Surveys on Drug Use and Health public use datasets, with the mid-point of the month-year of first EMPPR use subtracted from the mid-point of the quarter-year of assessment.
[b] A negative value occurs when the mid-point value of the quarter-year of assessment was the month prior to the onset of EMPPR use.
[c] AD refers to alcohol dependence.

The summary estimates of duration warranted further analyses. Table 4.4.7 combines age, sex, and quarter of assessment in two ZIP models with interaction terms.

Table 4.4.7 Zero-Inflated Poisson (ZIP) model parameter estimates by elapsed time from onset of extra-medical use of prescription pain reliever (EMPPR) use until quarter of assessment. Data from the National Surveys on Drug Use and Health, United States, 2002-2012.

Model 1	IRR	Linearized Std. Err.	t	P>t	[95% Conf.	Interval]
Count						
Age	0.95	0.01	-5.13	<0.001	0.93	0.97
Quarter_1 (ref)	1.00					
Quarter_2	1.50	0.11	5.52	<0.001	1.30	1.74
Quarter_3	1.59	0.13	5.62	<0.001	1.35	1.86
Quarter_4	1.88	0.14	8.43	<0.001	1.62	2.18
male	1.04	0.09	0.46	0.647	0.87	1.24
Quarter_2Xmale	0.80	0.10	-1.89	0.061	0.63	1.01
Quarter_3Xmale	0.88	0.11	-0.99	0.324	0.69	1.13
Quarter_4Xmale	0.85	0.10	-1.43	0.154	0.67	1.07
constant	57.78	9.47	24.76	<0.001	41.77	79.92
	OR	Std. Err.	t	P>t	[95% Conf.	Interval]
Inflate						
AGE	1.05	0.01	4.28	<0.001	1.02	1.07
Quarter_1 (ref)	1.00					
Quarter_2	1.49	0.08	5.27	<0.001	1.28	1.73
Quarter_3	1.74	0.09	6.13	<0.001	1.46	2.09
Quarter_4	2.18	0.08	9.18	<0.001	1.84	2.58
male	1.05	0.09	0.51	0.611	0.88	1.25
Quarter_2Xmale	0.79	0.13	-1.84	0.068	0.61	1.02
Quarter_3Xmale	0.98	0.13	-0.15	0.880	0.75	1.28
Quarter_4Xmale	1.03	0.13	0.22	0.828	0.80	1.32
constant	0.20	0.18	-9.00	<0.001	0.14	0.28

Model 2	IRR	Linearized Std. Err.	t	P>t	[95% Conf.	Interval]
Count						
Age	0.94	0.01	-5.67	<0.001	0.93	0.96
male	0.92	0.04	-1.84	0.068	0.85	1.01
Quarter_1 (ref)	1.00					
Quarter_2	1.31	0.08	4.38	<0.001	1.16	1.49
Quarter_3	1.41	0.10	4.96	<0.001	1.23	1.62
Quarter_4	1.66	0.12	7.22	<0.001	1.45	1.91
Alcohol dependence (AD)	1.14	0.11	1.31	0.193	0.94	1.39
Quarter_2XAD	1.19	0.16	1.36	0.177	0.92	1.54
Quarter_3XAD	1.39	0.24	1.95	0.054	0.99	1.95
Quarter_4XAD	1.27	0.17	1.76	0.082	0.97	1.66
constant	66.92	11.31	24.87	<0.001	47.89	93.52
	OR	Std. Err.	t	P>t	[95% Conf.	Interval]
Inflate						
Age	1.05	0.01	4.88	<0.001	1.03	1.08
male	0.98	0.04	-0.54	0.590	0.90	1.06
Quarter_1 (ref)	1.00					
Quarter_2	1.31	0.06	4.51	<0.001	1.16	1.48
Quarter_3	1.70	0.06	8.37	<0.001	1.50	1.93
Quarter_4	2.23	0.06	12.41	<0.001	1.96	2.53
Alcohol dependence (AD)	0.50	0.15	-4.56	<0.001	0.37	0.67
Quarter_2XAD	1.02	0.20	0.10	0.917	0.69	1.52
Quarter_3XAD	1.21	0.20	0.98	0.330	0.82	1.78
Quarter_4XAD	0.94	0.21	-0.27	0.784	0.62	1.44
constant	0.20	0.18	-9.12	<0.001	0.14	0.28

As shown in Table 4.4.7, there is little evidence of subgroup variation in the ZIP model parameter estimates for newly incident users when the subgroups are formed on the basis of

elapsed time from the month of onset of EMPPR use until the quarter of assessment during each NSDUH survey year. With one exception, involving a male-female contrast, the product-terms have p-values that are quite large, and the null hypothesis of 'no subgroup variation' cannot be rejected**.**

4.5 Discussion

In order to evaluate the proposition that underage drinkers with AD might be more susceptible to persist in their EMPPR use once it starts, this study turned to a nationally representative US sample of 12-20 year old newly incident EMPPR users. As disclosed via ZIP modeling for complex survey data, AD underage drinkers were less likely to be found in the hypothesized class of EMPPR users labeled as 'NSTP' and that these AD-affected underage drinkers had higher rates of EMPPR use when they were in the 'STP' class.

Ancillary discoveries also were made. For example, AD was not a requirement for the association with underage drinking. Recent underage drinkers without AD also were under-represented in the NSTP class of EMPPR users. An unexpected alcohol finding was that young people with a past history of underage drinking (without recent drinking) were more likely to be in the NSTP class of those who tried EMPPR once but not again. The study speculates, but cannot confirm, that these young people might be in school athletics or other activities with regular testing for alcohol consumption, but with infrequent testing for other drugs such as opioids. This possible explanation, among others, deserves investigation, if the unexpected finding is found to be reproducible. However, once EMPPR use persisted, past drinkers had an excess rate of EMPPR use.

In addition, extending recent evidence that females are over-represented among adolescents who are newly incident EMPPR users (39), this work discovered that females in the

STP class have a higher rate of EMPPR use, when observed within 12 months after the first occasion of such use. However, there was male-female balance with respect to class membership.

Before detailed discussion, some limitations should be noted. All newly incident EMPPR users are from cross-sectional surveys with a simulated prospective design. Longitudinal extension of this research, building from these initial estimates, will be useful, but will face complexities not encountered here, such as sample attrition and measurement reactivity that sometimes complicate repeated measures research (8,69).

This is a study of associations; the observed AD association may not be a manifestation of any cause-effect relationship. There may be potential model misspecification and absence of full information about the AD history. To illustrate, EMPPR use might have predated drinking onset as well as alcohol problems in this sample. As a check, onset ages were compared and showed that 97% of these newly incident EMPPR users started drinking before EMPPR onset. Nonetheless, EMPPR use might have exacerbated or accelerated onsets of AD problems that had not existed before such use.

Another potential complication for both cross-sectional and longitudinal research is left-truncation such that some newly incident EMPPR users in the population are not observed in the sample. For example, in any population's newly incident users, fatal overdose at first 'trial' use implies missed non-persistent users. Rapid onset of severely disabling opioid dependence might promote exclusion from sampling rosters or non-participation, implying missed persistent users. Adolescents with the most severe AD might be similarly excluded.

Self-report measurement artifacts might prompt over-reporting of zeroes when drug use is recalled over a 12 month interval. Under-reporting can be present with respect to yes/no

history of EMPPR use and drinking involvement. However, empirical research substantiates that self-reported epidemiological studies provide both reliable and valid estimates of occurrence of drug use and the ages of onset (46).

This study is not the first health research making use of ZIP models, which have been used to study patients seeking treatment in a given year, with estimation of treatment-seeking rates conditional upon the initial treatment episode (120,121). For previous health services research applying ZIP models, a count of events during a given time interval (e.g., visits to a doctor in a year) has been taken as the response variable. Tobacco applications also can be seen with the most recent using ZIP models to estimate smoking rates conditional on membership in the latent class of those susceptible-to-persistence of smoking (119,122–125). Elsewhere in the drug dependence literature, ZIP models are not often seen. Still, the findings show zero inflation thwarts use of simpler regression models when estimating influences on counts (Table 4.4.5).

Notwithstanding limitations of the type just mentioned, there is an implication that alcohol involvement, including AD, may be a potentially modifiable causal determinant of using EMPPR, or deserves consideration as a signal or marker of potential persistence of EMPPR use, once it starts. In addition, these new epidemiological findings, from a large well-measured sample of 12-20 year olds, support the idea that the conditional rate of EMPPR use is greater among young women with newly incident EMPPR use. If there is, in fact, female excess in the conditional probability of becoming dependent on EMPPR, then the origins of the dependence process might be traced back to this early stage of EMPPR involvement.

These findings set the stage for future longitudinal research on these topics. With shorter follow-up intervals (e.g., less than one year, possibly monthly), it will become possible to

approximate what might be found in both nationally representative samples and health plan settings to encompass both medically prescribed and EMPPR use.

In future research of this type, it also should be possible to clarify roles of chronic and acute pain, as well as other covariates such as peer and family histories of EMPPR use. It would be useful to tease apart reasons certain adolescents begin use and persist in their use while others do not, although this domain of inquiry is more social-psychological than epidemiological in its reliance on what young people say about their motives for drug use (76).

Probes for potentially common genetic vulnerability traits for AD and excess EMPPR rates might shed light on associations between these phenotypes, with EMPPR rate as an alternative to the commonly used opioid dependence or addiction syndrome phenotype. It is possible that alcohol involvement and EMPPR use are influenced by similar sets of underlying genetic influences on AD and excess EMPPR rates.

A more biostatistical line of future research also can be helpful. For example, integration of persistence, conditional rates of use, and risk of becoming opioid dependent within the framework of simultaneous equations modeling may produce important prediction equations and parameter estimates required for more effective planning of alcohol and EMPPR prevention initiatives for adolescent-onset EMPPR use.

Even without additional research, clinical surveillance of EMPPR use, as well as down-regulation of prescription rates for 12-20 year olds will continue to be practical public health practices that can be modified to take advantage of epidemiological findings of this type. Little harm would come if these findings were to influence guidelines for clinical diagnosis, therapeutics, and case management for pediatric patients in pain. In mind are guidelines that note potential vulnerabilities of adolescents susceptible to persistent EMPPR use. This might include

young female patients as well as those with past or recently active drinking histories, particularly if those histories include presenting clinical features of the AD syndrome. Along these lines, when clinicians write prescriptions for pain relievers for pediatric patients, consideration of history of alcohol involvement, including past use, is not always included. This aspect of pediatric practice can be changed without additional research, and could include more deliberate surveillance after prescribing pain relievers, constrained numbers of dosage units per prescription, and caution in response to refill requests regardless of alcohol involvement.

In closing, there is a prior finding from Jones and colleagues (66), who reported that a patients with frequent EMPPR use (200+ days per year) are getting their EMPPR directly from a prescribing physician (not via diversion or street purchases), as well as emerging evidence on EMPPR-associated transitions into heroin use (126). This form of 'polydrug use' in sequence deserves greater attention in epidemiological research, and the evidence from the present investigation draws attention to consideration of alcoholic beverage consumption as a drug in future research on this sequenced 'polydrug use' process.

CHAPTER 5

MANUSCRIPT 3 – PERSISTENCE OF EXTRA-MEDICAL PRESCRIPTION PAIN RELIEVER USE AMONG UNITED STATES ADOLESCENTS: A LATENT CLASS ANALYSIS

5.1 Abstract

Aims: To investigate discrete classes (subgroups) of adolescents with similar profiles based on their newly incident EMPPR use and alcohol use, with empirical evaluation of the underlying structure of identified subgroups and their epidemiological distributions in the US.

Methods: US NSDUH, 2002-2013, sampled, recruited, and assessed 24,749 12-20 year old newly incident EMPPR users, with self-interviews on PPR, alcohol, and covariates. Latent classes were formed based on EMPPR and alcohol status variables. Then, age and sex were studied as potentially important covariates of class membership. Analysis-weighted estimates and delta method variances were derived.

Results: Three classes were distinguished by EMPPR and alcohol use patterns: (1) Nondependent/Low level users, (2) Moderately persistent users, and (3) Persistent/Dependent users. Being female and younger were associated with greater odds of being in the Persistent/Dependent user class compared to the Nondependent/Low level class; being younger was associated with being in the Moderately persistent user class compared to the Non/Low level class; being male was associated with being in the Moderately persistent user class compared to the Persistent/Dependent user class.

Discussion: Persistent adolescent EMPPR and alcohol users' characteristics require tailored public health prevention and intervention strategies based on their vulnerability to continue use over time. Underage recency of drinking can be an indicator of persisting in EMPPR use,

particularly if presenting clinical features of alcohol dependence and/or PPR dependence already have become manifest at or near time of first onset of such EMPPR use.

5.2 Introduction

EMPPR use remains a serious public health concern in the US (127). While estimates claim the use of EMPPR has been stable in recent years, dependence and overdose increases indicate a persistent US problem (5,87). Some research suggests EMPPR use is declining and heroin is on the rise (128). In fact, recent studies show that EMPPR use is a strong risk factor for using heroin and more severe outcomes such as overdose (129).

Not only has the use of EMPPR associated morbidity and mortality persisted, but also underage drinking continues to be a threat for adolescents and young adults alike (i.e., drinking before age 21) (130–132). Here, the focus is on an array of EMPPR use and the complex relationship between alcohol and EMPPR use to address this opioid epidemic. Although there are harmful consequences associated with the co-occurrence of alcohol use disorders and use of EMPPR (94), there has been little research on the relationship between the two. Studies have shown that use of EMPPRs is highly associated with heavy drinking and other drug behaviors (133,134).

The importance of alcohol dependence (AD) and recency of alcohol use leading to EMPPR use and eventually opioid dependence are unclear among adolescents and young adults. When co-ingested, alcohol increases drug liking, pleasant bodily sensations, and euphoric effects of EMPPR (17). Alcohol has also been considered a ‘gateway drug’ on the way to IRD use such as opioids (58,59). Work on recently active use of alcohol as a predictor and correlate among 12-17 year olds who have initiated EMPPR use is implicative of a causal relationship (38,116), as well as a strong association between alcohol use disorders and EMPPR use in both men and

women (135). It could be that facets of alcohol and EMPPR use are influenced by the same sets of underlying genes that predispose one to AD or EMPPR use/opioid dependence (136).

As such, drug use behaviors tend to cluster among groups, so examining groups can help understanding how use and dependence are related. Latent Class Analysis and Latent Profile Analysis allow researchers to group individuals based on similar criterion and then enables estimation of the degree to which these 'classes' or 'profiles' differ on other characteristics (LCA and LPA respectively) (137,138). These person-centered analyses are based on a measurement theory that posits a 'latent class/profile' exists as an unobserved grouping variable, which can be created by a set of categorical or continuous variables (139,140). LCA uses categorical variables to form the 'latent classes' as part of a measurement model. LPA, another approach, uses continuous variables to form the 'latent profiles' in a comparable way. These multivariate statistical models lend well to the study of drug use behaviors. Several researchers have used the latent class/profile approach to study different drug use behaviors among adolescents and young adults (69,75,141–143).

This study illustrates the latent class/profile approach in the study of this important contemporary problem of drug dependence research--namely, initiation and persistence of EMPPR. The purpose of this research is to identify distinct profiles of EMPPR and alcohol use among adolescents. To determine individual characteristics that are associated with these classes and examine patterns of drug use, covariates for age and sex are included in the LCA/LPA. The focus is on 12-20 year olds because mid-adolescence is the estimated peak risk of first EMPPR use (8,28). This peak often occurs after beginning underage alcohol use. In addition, many newly incident EMPPR users transition to opioid dependence in the first year after onset of such use. Among adolescents, approximately 5-6% of EMPPR users manifest the syndrome of opioid

dependence within the first year (28). If dependence criteria (i.e., opioid and alcohol) or underage recency of drinking can predict continuing use of EMPPR, public health intervention and prevention strategies can be catered for this vulnerable young population.

5.3 Methods

5.3.1 Design

The design is that of a nationally representative cross-sectional survey of non-institutionalized civilian community residents in the US, with Institutional Review Board-approved protocols for NSDUH, completed each year between 2002 and 2013 (4). In aggregate, summed across years, the samples included 303,330 participants age 12-20 years old. Participation levels are close to 75% among adolescents. Publications and online reports provide detailed descriptions of the NSDUH methods (e.g., as last accessed 30 March 2016: http://www.samhsa.gov/data/population-data-nsduh/reports).

5.3.2 Sample

From among the sampled 303,330 12-20 year olds in 2002-2013, a total of 24,749 newly incident EMPPR users were identified via IRB-approved computerized self-interviews (i.e., those whose EMPPR use had started within 24 months prior to the date of assessment). A majority of 12-20 year olds never used EMPPR (n = 263,000). This amounts to an incidence rate of 9.4% among adolescents between 2002-2013.

5.3.3 Measures

Most participants agree to complete the NSDUH assessment via ACASI after consent and instructions from a field staff member. Each assessment includes multiple standardized multi-item modules used to assess topics of drug use and health, including the number of days of

EMPPR use in the 12 months prior to the assessment date, alcohol and opioid dependence as well as alcohol recency.

For the number of EMPPR use days, it was important to differentiate between users whose onset of use began in the past 12 months and those who began 13-24 months ago. For newly incident EMPPR users with onset during the 12 months prior to survey assessment, the first day of use was subtracted from total 'days of use' in order to form the latent class of 'persistence status'. For newly incident EMPPR users with onset during months 13-24 prior to assessment, the trial use had occurred before the most recent 12 months and for this reason, the measurement variable was the actual number of days of EMPPR use during the 12 months prior to assessment.

Alcohol and opioid dependence were both measured using a standardized NSDUH multi-item module based on the DSM-IV clinical feature criteria of the American Psychiatric Association (30). Alcohol recency was classified as (i) Drank within the past month, (ii) Drank more than 30 days ago but within the past year, (iii) Drank more than a year ago, and (iv) Never used alcohol.

The primary expectation for this application of LCA/LPA was subgroup membership might depend upon concurrent EMPPR use and alcohol involvement. Measures of EMPPR use included both opioid dependence and number of days used EMPPR in the past year. Measures of alcohol involvement included both alcohol dependence and recency of alcohol use in the past year. Covariate terms for sex and age were included for empirical evaluation of the underlying structure of identified subgroups.

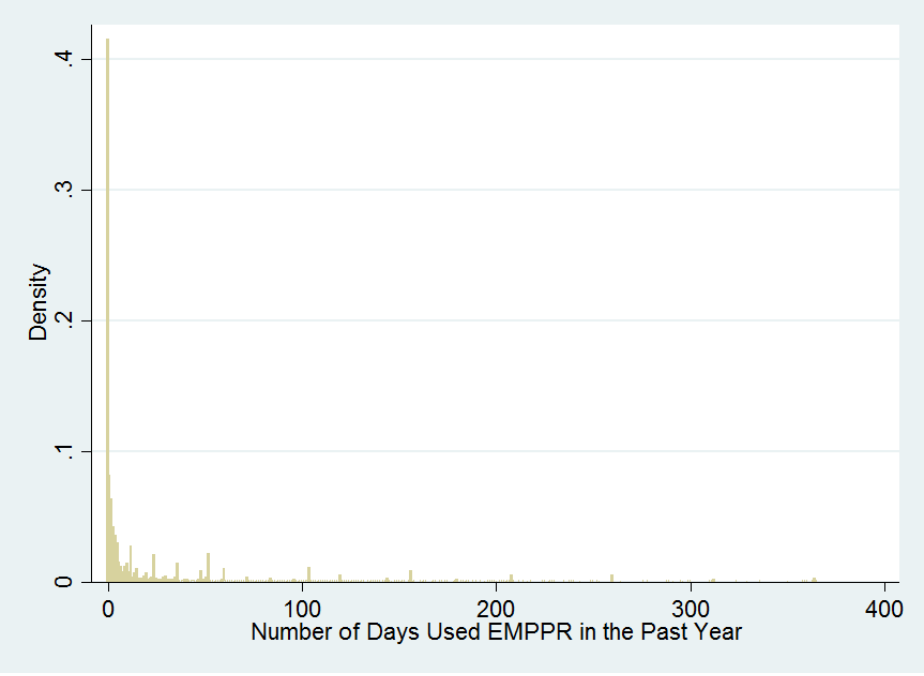
5.3.4 Analysis Plan

LCA measurement models use observed variables as indicators of one or more categorical variables. Although this analysis uses one count variable as an indicator, for simplicity the term LCA is used rather than LPA. In general, LCA attempts to identify subgroups or "classes" of individuals within the observed data. The guiding conceptual model is one in which a grouping variable exists but was not directly observable. The standard latent class model notation for the response vector of p variables ($i = 1, \ldots, p$) with K classes ($j = 1, \ldots, K$):

$$f(x_i) = \sum_{j=1}^{K} \eta_j \prod_{i=1}^{p} \pi_{ij}^{x_i} (1 - \pi_j)^{1-x_i}.$$

Here, it is posited that alcohol and EMPPR involvement may precipitate future persistence of EMPPR use. The number of days of EMPPR use in the 12 months was designated as a zero-inflated count variable due to an abundance of observed zeroes. In the past year, 41.5% of the sample had used EMPPR zero days after their first trial use (see Figure 5.3.1).

Figure 5.3.1 Histogram showing the distribution of the number of extra-medical prescription pain reliever (EMPPR) use days in the past year for newly incident EMPPR users aged 12-20. Data from the National Surveys on Drug Use and Health, United States, 2002-2013.



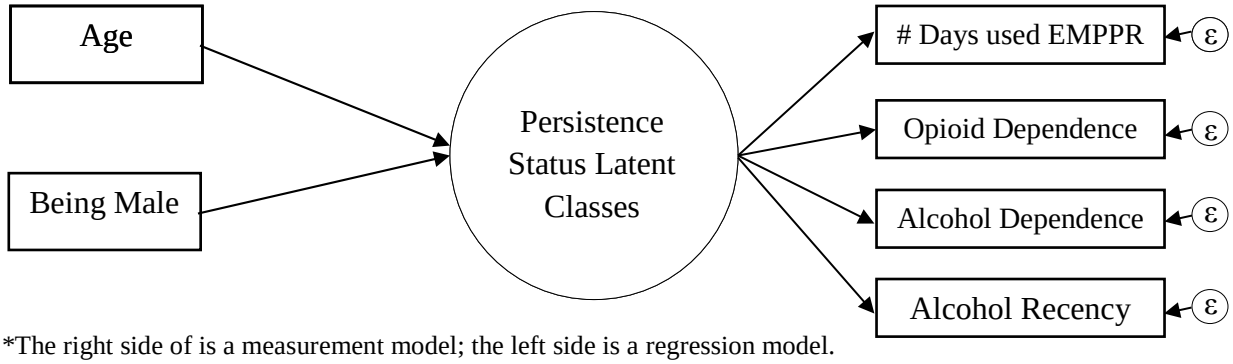
The plan for data analysis was organized in relation to standard "explore, analyze, explore" cycles, in which the first exploratory steps involve Tukey-style box-and whisker plots and other exploratory data analyses to shed light on the underlying distributions of each response variable and covariate of interest. In the initial analysis step, the task was to estimate latent classes of ‘persistence status’, for which the statistical approach was to form them based on the two EMPPR and two alcohol status variables. Building the latent class model started with a parsimonious one class model (‘all newly incident EMPPR users the same’). Next, successive models were fit with increasing numbers of classes. The optimal number of classes was identified based on (a) Akaike’s Information Criterion (AIC); (b) Entropy; (c) Subject matter. AIC is a statistical criteria with lower values indicating a better model fit. Entropy is a measure of classification certainty and values close to 1 are better. High posterior probabilities are also preferable (144–146). Subject matter is a more subjective measure of model fit typically based on theory and/or literature review. Bayesian information criterion (BIC), an alternative to AIC is preferable in some instances, so has been presented as well (146).

5.3.4.1 Exploratory Analyses

In subsequent analysis steps, the statistical approach involved including important explanatory variables in the LCA. Initially, the predictors of persistence profiles/classes studied were continuous age and sex (see Figure 5.3.2). Later, stratified analysis was performed for the time elapsed from onset of EMPPR use to assessment to see if LCA estimates differed between groups (coded 1 for onset of use in the 12 months prior to assessment, and coded 0 for onset of use during the prior 12 months). In addition, a term for age-squared was included in the model to evaluate whether the relationship of persistence with age was non-linear as seen in prior work

(28). Modifications to the model were considered including direct pathways from all three covariates to specific measurement variables to account for residual variance.

Figure 5.3.2 Conceptual model to depict hypothesized age and sex differences in 'Persistence Status' for newly incident extra-medical prescription pain reliever (EMPPR) use among 12-20 year olds. Data from the National Surveys on Drug Use and Health, United States, 2002-2013.*



*The right side of is a measurement model; the left side is a regression model.

The final exploratory analyses compared the final LCA model changing the 'days of EMPPR use' as continuous, without zero-inflation, and setting the zero-inflation as equivalent over all three classes to see if findings significantly differed.

Analysis and estimation steps in the statistical analysis plan are based on Mplus version 7. The software addresses the complex NSDUH sample design, interdependence of survey observations, and analysis weights, including use of a 'subpopulation' command focused on the subset of 12-20 year old newly incident EMPPR users. In these analyses, precision of the informative study estimates is stressed with a focus on 95% CI; p-values are intended to aid interpretation. Analysis-weighted estimates and delta method variances were derived.

5.4 Results

Table 5.4.1 offers a description of the study sample (n = 24,749). For example, approximately half of the sample was male (51.3%). The average age was 16.7 years. The majority of adolescents were White, non-Hispanic (67.0%). About 11.6% were alcohol dependent and 4.7% were opioid dependent. The mean number of days used prescription pain

relievers extra-medically in the past year was 19, with use ranging from 0-365 days. Most newly incident EMPPR users aged 12-20 were also current alcohol drinkers (57.7%).

Table 5.4.1 Selected characteristics of newly incident extra-medical prescription pain reliever users (EMPPR; n = 24,749). Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

Sample characteristics	Unweighted n	%[a]
Sex		
Male	12,066	48.8
Female	12,683	51.3
Age (at interview)[b]	16.7	2.1
Time elapsed[c]		
0-12 months	15,656	63.3
13-24 months	9,093	36.7
Race/ethnicity		
Non-Hispanic white	16,583	67.0
Non-Hispanic black	2,384	9.6
Hispanic	3,744	15.1
Other	2,038	8.2
Number of days used EMPPR in the past year[b]	19.0	45.4
Opioid dependent	2,864	11.6
Alcohol dependent	1,162	4.7
Recency of alcohol use		
Drank within the past month	14,287	57.7
Drank more than 30 days ago, but within the past year	5,488	22.2
Drank more than a year ago	1,796	7.3
Never used alcohol	3,178	12.8

[a] Due to rounding, some percentages may not add to 100%.
[b] Mean with standard deviation.
[c] Time from onset of EMPPR use to interview.

5.4.1 Latent Classes

Three classes were indicated by EMPPR and alcohol use patterns: (1) Nondependent/Low level users, (2) Moderately persistent users, and (3) Persistent/Dependent users. The majority of newly incident EMPPR users belonged to the first class (79.2%), 15.0% fit into the second class, and the last 5.6% were designated to the third class. The main estimates of the study are presented in Table 5.4.2. Item response probabilities for Latent class 1 show a paucity of newly incident 12-20 year old EMPPR users who are opioid or alcohol dependent as

belonging in this Nondependent/Low level users class (1.5% opioid dependent and 10.1% AD). The majority of dependent users were classified as belonging to Latent class 2 or Latent class 3. Probabilities of alcohol recency were similar across classes. Mean number of EMPPR use days used in the past year varied between classes with the lowest estimated average in Latent class 1 and the highest in Latent class 3 (1.6 versus 5.1 days). Inflating the number of EMPPR use days was only necessary for Latent class 1 because the majority of users with zero number of days used EMPPR in the past year were classified as Nondependent/Low level users. The mean estimate for the inflated number of EMPPR use days was 0.113 (standard error = 0.02).

Table 5.4.2 Item response probabilities for latent class membership for newly incident extra-medical prescription pain reliever users (EMPPR). Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

	Latent Classes		
Item	(1) Nondependent/Low level users	(2) Moderately persistent users	(3) Persistent/Dependent users
Opioid dependent	0.015	0.108	0.274
Alcohol dependent	0.101	0.154	0.203
Recency of alcohol use			
Drank within the past month	0.583	0.618	0.606
Drank more than 30 days ago, but within the past year	0.216	0.191	0.213
Drank more than a year ago	0.076	0.053	0.072
Never used alcohol	0.124	0.138	0.109
Number of days used EMPPR in the past year[a]	1.622	3.728	5.129

[a] Means

Figure 5.3.3 presents the item response probabilities from Table 5.4.2 in a different way. The three classes are visually depicted by the estimated proportion of the categorical indicators. It appears the pre-specified LCA model differentiated three classes of newly incident EMPPR users aged 12-20 quantitatively. These classes do not seem qualitatively different from one another as their graphed proportions follow a similar trajectory.

Figure 5.3.3 Estimated proportion of individual categorical indicators for persistence, by latent class of newly incident extra-medical prescription pain reliever using adolescents. Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

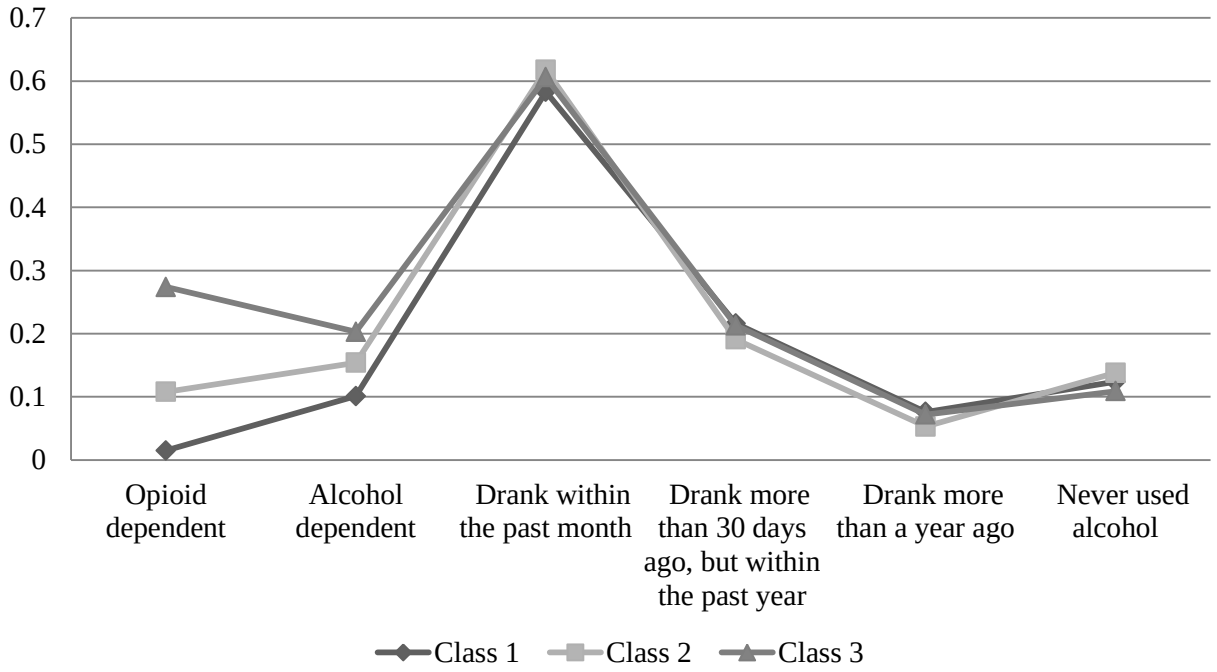


Table 5.4.3 compares two indicators of model fit starting with a one class model up to a seven class model. The entropy for the three class model was 0.945. This value is near 1.0, which suggests a good model fit (145). The entropy was highest for the four class model at 0.952. On the other hand, the AIC decreased by increasing the number of classes. The decrease in AIC tapered as the number of classes grew higher. The smallest difference in AIC was between a model with six classes and a model with seven classes (219780 versus 216593). On further examination, the fourth class appeared to divide all members of the third class into two from the 3 class model. This indicated that a fourth class may be an artifact and, therefore, the three class model was preferred.

Table 5.4.3 Indicators of fit for models with one through seven latent classes. Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

Number of Classes	Entropy	AIC	BIC
1	-	1067367	1067456
2	0.949	391472	391602
3	0.945	271570	271774
4	0.952	243985	244269
5	0.929	225295	225652
6	0.934	219780	220210
7	0.881	216593	217096

Adjusted OR from the LCA are shown in Table 5.4.4. Unadjusted OR were not estimated due to the pre-specified conceptual model (see Figure 5.3.2). In other words, hypothesized subgroups designated by the LCA are based on a conditional model. The first two columns of Table 5.4.4 use Latent class 1 as the reference group (Nondependent/Low level users). Latent class 1 had significantly less opioid and alcohol dependent users than Latent classes 2 and 3. In addition, Latent class 2 had significantly less opioid and alcohol dependent users than Latent class 3. In this way, the OR for both opioid and alcohol dependence are less than unity. Compared to Latent class 2, Latent class 1 also had more current drinkers (Drank within the past month; OR = 1.16; 95% CI = 1.05, 1.27).

Table 5.4.4 Latent class adjusted odds ratios for newly incident extra-medical prescription pain reliever users.[a, b] Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

	Latent Class Comparisons Adjusted Odds Ratio (95% Confidence Interval)		
Item	Class 1 vs. Class 2	Class 1 vs. Class 3	Class 2 vs. Class 3
Opioid dependent	**0.13 (0.10-0.16)**	**0.04 (0.03-0.05)**	**0.32 (0.26-0.38)**
Alcohol dependent	**0.62 (0.53-0.70)**	**0.44 (0.37-0.53)**	**0.72 (0.58-0.88)**
Recency of alcohol use			
Drank within the past month	**1.16 (1.05-1.27)**	1.10 (0.94-1.29)	0.95 (0.79-1.15)
Drank more than 30 days ago, but within the past year	1.06 (0.94-1.21)	1.13 (0.92-1.40)	1.07 (0.84-1.34)
Drank more than a year ago	0.89 (0.74-1.06)	1.16 (0.89-1.50)	1.31 (0.98-1.75)
Never used alcohol	1.00	1.00	1.00

[a] Adjusted for age and sex.
[b] Bolding denotes significance at the alpha = 0.05 level.

Other results not shown in a table depict being in Latent class 3 compared to Latent class 2 associated with a significantly greater odds of being female and younger (OR = 1.3; 95% CI = 1.1, 1.5 and OR = 1.1; 95% CI = 1.04, 1.1). Being younger was also significantly associated with being in Latent class 2 compared to Latent class 1 (OR = 1.08; 95% CI = 1.05, 1.10). Finally, being male was significantly associated with being in Latent class 2 compared to Latent class 3 (OR = 1.2; 95% CI = 1.05, 1.5).

5.4.2 Exploratory Analyses

5.4.2.1 Subgroup Variation

Post-estimation exploratory analyses to probe variation in subgroup estimates disclosed that including a term for age-squared in the LCA wiped out any significant age differences between the three latent classes. There were also differences between those who started EMPPR use within the past 12 months and those who started within the past 13-24 months. For those whose time elapsed between onset of EMPPR use and assessment was 13-24 months, item response probabilities did not differ appreciably from the main estimates of Table 5.4.2 (see Table 5.4.5). All 95% CI for item response probabilities overlapped with the 95% CI of the item response probabilities found in Table 5.4.2 for each covariate (data not shown in a table).

Table 5.4.5 Item response probabilities for latent class membership of newly incident extra-medical prescription pain reliever users (EMPPR) whose time elapsed between onset of EMPPR use and assessment was between 13-24 months. Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

	Latent Classes		
Item	(1) Nondependent/Low level users	(2) Moderately persistent users	(3) Persistent/Dependent users
Opioid dependent	0.008	0.095	0.269
Alcohol dependent	0.094	0.150	0.203
Recency of alcohol use			
Drank within the past month	0.559	0.625	0.613
Drank more than 30 days ago, but within the past year	0.214	0.175	0.208
Drank more than a year ago	0.091	0.057	0.069
Never used alcohol	0.136	0.143	0.110
Number of days used EMPPR in the past year[a]	1.709	3.769	5.162

[a] Means

Furthermore, for those whose time elapsed between onset of EMPPR use and assessment was within the past 12 months, all covariate item response probabilities' 95% CI also fell within the range of the main LCA estimates found in Table 5.4.2 (see Table 5.4.6).

Table 5.4.6 Item response probabilities for latent class membership of newly incident extra-medical prescription pain reliever users (EMPPR) whose time elapsed between onset of EMPPR use and assessment was within the past 12 months. Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

	Latent Classes		
Item	(1) Nondependent/Low level users	(2) Moderately persistent users	(3) Persistent/Dependent users
Opioid dependent	0.024	0.126	0.249
Alcohol dependent	0.112	0.158	0.191
Recency of alcohol use			
Drank within the past month	0.627	0.610	0.557
Drank more than 30 days ago, but within the past year	0.223	0.205	0.224
Drank more than a year ago	0.050	0.050	0.075
Never used alcohol	0.100	0.135	0.123
Number of days used EMPPR in the past year[a]	1.419	3.495	4.861

[a] Means

Similar to the main OR estimates from Table 5.4.4, Tables 5.4.7 and 5.4.8 show adjusted OR for newly incident EMPPR users depending on the time elapsed from onset of EMPPR use to assessment. Both Tables 5.4.7 and 5.4.8 show that Latent class 1 had significantly less opioid and alcohol dependent users than Latent classes 2 and 3 regardless of time elapsed between onset of EMPPR use and interview. On the other hand, for those newly incident EMPPR users whose time elapsed between onset of EMPPR use and survey assessment was between 13-24 months, compared to Latent class 3, Latent class 2 also had less opioid and alcohol dependent users (OR = 0.29 and OR = 0.70 respectively; see Table 5.4.7).

Table 5.4.7 Latent class adjusted odds ratios for newly incident extra-medical prescription pain reliever users whose time elapsed between onset of EMPPR use and assessment was between 13-24 months.[a, b] Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

	Latent Class Comparisons Adjusted Odds Ratio (95% Confidence Interval)		
Item	Class 1 vs. Class 2	Class 1 vs. Class 3	Class 2 vs. Class 3
Opioid dependent	**0.08 (0.06-0.11)**	**0.02 (0.02-0.03)**	**0.29 (0.22-0.37)**
Alcohol dependent	**0.59 (0.49-0.71)**	**0.41 (0.33-0.52)**	**0.70 (0.55-0.88)**
Recency of alcohol use			
Drank within the past month	1.31 (1.15-1.50)	1.25 (1.03-1.52)	0.95 (0.76-1.19)
Drank more than 30 days ago, but within the past year	1.17 (0.97-1.41)	1.35 (1.06-1.71)	1.15 (0.86-1.54)
Drank more than a year ago	0.95 (0.76-1.18)	1.28 (0.94-1.73)	1.35 (0.94-1.94)
Never used alcohol	1.00	1.00	1.00

[a] Adjusted for age and sex.
[b] Bolding denotes significance at the alpha = 0.05 level.

In contrast, for those newly incident EMPPR users whose time elapsed between onset of EMPPR use and survey assessment was within the past year, Latent class 3 had more opioid dependent users than Latent class 2 (see Table 5.4.8). Table 5.4.8 shows several significant comparisons between Latent class 1 and Latent classes 2 and 3 in regard to recency of alcohol use. Those in Latent class 2 had less newly incident EMPPR users who drank more than 30 days ago, but within the past year as well as those who drank more than a year ago (OR = 0.78 and

OR = 0.71 respectively). Those who never used alcohol are the reference group. Moreover, there were more newly incident EMPPR users who drank within the past month in Latent class 3 compared to Latent class 1 (OR = 0.75; 95% CI = 0.59, 0.95).

Table 5.4.8 Latent class adjusted odds ratios for newly incident extra-medical prescription pain reliever users whose time elapsed between onset of EMPPR use and assessment was within the past 12 months.[a, b] Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

	Latent Class Comparisons Adjusted Odds Ratio (95% Confidence Interval)		
Item	Class 1 vs. Class 2	Class 1 vs. Class 3	Class 2 vs. Class 3
Opioid dependent	**0.17 (0.13-0.23)**	**0.08 (0.05-0.11)**	**0.44 (0.31-0.65)**
Alcohol dependent	**0.67 (0.53-0.86)**	**0.54 (0.38-0.76)**	0.80 (0.54-1.17)
Recency of alcohol use			
Drank within the past month	0.93 (0.79-1.09)	**0.75 (0.59-0.95)**	0.80 (0.59-1.08)
Drank more than 30 days ago, but within the past year	**0.78 (0.62-0.98)**	0.71 (0.48-1.06)	0.92 (0.59-1.42)
Drank more than a year ago	**0.71 (0.55-0.93)**	0.79 (0.47-1.32)	1.11 (0.66-1.86)
Never used alcohol	1.00	1.00	1.00

[a] Adjusted for age and sex.
[b] Bolding denotes significance at the alpha = 0.05 level.

In a comparison between Table 5.4.7 and 5.4.8, there were some differences in those whose time elapsed between onset of EMPPR use and assessment. However, both subgroup OR estimates' 95% CI overlap with the main OR estimates' 95% CI found in Table 5.4.4. For example, for Latent class 1 versus Latent classes 2 and 3, the OR for newly incident EMPPR users who are opioid dependent was lower for those whose time elapsed between onset of EMPPR use and assessment was 13-24 months prior compared to those whose time elapsed between onset of EMPPR use and assessment was within 12 month prior to assessment (OR = 0.08; 95% CI = 0.06, 0.11, and OR = 0.02; 95% CI = 0.02, 0.03 respectively; see Table 5.4.6). On the other hand, compared to Latent class 1, the OR was lower for those who drank within the past month for Latent class 3 if the time elapsed was 13-24 months before assessment rather than within 12 months (OR = 0.75; 95% CI = 0.59, 0.95).

The last exploration of subgroup variation fell within the estimation routine of Mplus. Mplus modification indices suggested adding another pathway to the latent class model. The variability in Latent Class 1 after including the zero-inflated count specification suggested a direct path between the number of days used EMPPR in the past year and age. The direct path between inflated EMPPR use days and age was significant (Beta = -0.02; p-value = 0.01). The path connecting uninflated EMPPR use days and age was significant as well (Beta = 0.04; p-value <0.001). Despite this, other estimates from the LCA changed very little.

5.4.2.2 Sensitivity Analysis

The final set of exploratory analyses compared models using the days of EMPPR use as continuous, without zero-inflation (count), and setting the zero-inflation as equivalent over all three classes showed that findings differed slightly (see Table 5.4.9). Changing the EMPPR use days from an inflated variable changed the entropy of the three class model. The designation of EMPPR use days as continuous slightly increased the entropy to 0.973. However, Mplus indicated there was some residual variance for the number of days used EMPPR in the past year. Furthermore, the AIC from the original zero-inflated model remained the lowest compared to using EMPPR use days as continuous or without zero-inflation (AIC = 271570). With equivalence of zero-inflation, there was not good model fit because the entropy value was not near 1 (Entropy = 0.651).

Table 5.4.9 Indicators of fit for different three class models based on extra-medical prescription pain reliever use days. Data from the National Surveys on Drug Use and Health, United States, 2002-2013.

Variable designation	Entropy	AIC	BIC
Zero-inflated	0.945	271570	271774
Continuous	0.973	283311	283514
Count	0.929	304854	305049
Zero-inflated equivalent	0.651	272382	272585

5.5 Discussion

The main findings of this study may be summarized succinctly. First, three distinct classes were designated by EMPPR and alcohol use patterns. (1) Nondependent/Low level users, (2) Moderately persistent users, and (3) Persistent/Dependent users. Using large nationally representative survey data allowed exploration of sex and age variation. Being female and younger were associated with greater odds of being in the Persistent/Dependent user class compared to the Nondependent/Low level class; being younger was associated with being in the Moderately persistent user class compared to the Non/Low level class; being male was associated with being in the Moderately persistent user class compared to the Persistent/Dependent user class.

Before discussing these results in detail, several of the more important study limitations warrant attention. Of central concern is the cross-sectional nature of the data which makes it so that causal interpretations of findings cannot be made. The findings provide a population-averaged snapshot of the nationally representative sample. Although the analysis might be described as person-centered rather than variable-centered, the sample is not person-centered and, therefore, does not follow one individual over time. With respect to the population under study, the relatively homogenous age distribution (12-20 years) does not capture what happens when drinking becomes legal and may miss an important transition that happens between ages 20 and 21.

With respect to the sampling approach, study sample, and sample size, some limitations are inherent to the NSDUH survey methods in general and have been explained elsewhere (147). With respect to study participation, left-truncation is possible such that some newly incident EMPPR users in the population are not observed in the sample. For example, a very rapid onset

of severe opioid dependence might lead to non-participation. Similarly, those with the most severe AD might not be captured in a community sampling design (i.e., due to non-response).

With respect to assessment of the key response variables, the experiences of the sample of 12-20 year olds are self-reported drug use and dependence responses. Users must recall over the past year how many times they have used PPR extra-medically. Therefore, there may not be stability and generalization of the classes for these newly incident users whose first use was within the past 24 months. Considering the very sensitive nature of questions related drug use for some and the cost and accuracy of drug tests, self-reported data is one of the best assessment types available (46,64,148).

With respect to assessment of the key covariates of interest, this study did not consider other drugs and/or combinations, or psychiatric conditions as important predictors of EMPPR persistence. In addition, neither alcohol abuse nor opioid abuse were integrated as indicators within the LCA. This approach is consistent with Anthony's clarification that the phenomena of (a) the drug dependence syndrome and (b) social maladaptation secondary to drug use (sometimes termed pejoratively as 'abuse') can be specified in a multi-dimensional framework on strictly theoretical and scientific grounds, even when the fallible empirical latent variable approach might suggest a single dimension (111,149). In addition, the hypothesized relationship might be extended to consider other drug use such as benzodiazepine use.

Nevertheless, gauged in relation to the standards of the most recent DSM (i.e., DSM-5), a limitation might be that opioids-related socially maladaptation has not been studied. That is, while abuse was specified as a separable diagnostic construct from DSM-III through DSM-IVR, the DSM-5 expert committees judged otherwise, and DSM-5 no longer makes a distinction between dependence and abuse (30,34). Furthermore, dependence was specified with a binary

indicator of interest and the separate criteria were not considered. As it happens, in the sample under study, it appears the dependence criteria ‘Spent a great deal of time’ and ‘Tolerance’ drive the dependence syndrome (between 87%-88% of newly incident opioid dependent users 12-20 years old display these features). A future line of research could tease apart dependence symptoms as indicators in a LCA, and might incorporate the indicators for ‘abuse’ as in the prior DSM criteria that were used to devise the NSDUH assessment of opioid dependence phenomena. However, it should be noted that less common clinical DSM criteria such as ‘Using more often than intended’ or ‘Inability to cut down’ may produce data sparseness and convergence problems.

With respect to the conceptual model, in some rare instances, drinking onset and alcohol related problems may come after first EMPPR use in the cases under study. This limitation has been explained elsewhere (112). With respect to the data analysis plan, the optimal number of classes in LPA or LCA is subject to investigator interpretation. While a lower AIC is preferred, the distinctness of classes drawn by latent class separation and homogeneity are subjective. In general, when response probabilities are high in one class, they should be low for another class (144). There is also a potential issue in using the estimated class membership in the second stage regression where the latent classes are treated as fixed, known, or estimated without error, sometimes manifest in a " label-switching" problem (150,151).

Despite limitations such as these, the study findings are of interest because they serve as evidence that there might well be distinct subgroups of newly incident EMPPR users defined by readily measured characteristics such as their past year involvement with EMPPR and alcohol. The LCA method allows empirical grouping of adolescent newly incident EMPPR users by their recent use, which provides a context for the distinctions made. The results from this study may

have important implications in seeking to account for what makes persistent users different from the Nondependent/Low level and Moderately Persistent users.

Persistent adolescent EMPPR and alcohol users may require differentially tailored public health prevention and intervention strategies based on subgroup vulnerability to continue use over time. In future research that builds from findings such as these, it may be possible to use underage recency of drinking as an indicator of vulnerability to persist in EMPPR use, particularly if presenting clinical features of alcohol dependence and/or PPR dependence already have become manifest at or near time of first onset of such PPR use.

CHAPTER 6

FINAL DISCUSSION

6.1 Summary of Findings

This dissertation presents research on EMPPR use among adolescents found in the nationally representative samples of US study populations surveyed in 2002-2013 for the NSDUH. The overall goal of this work was to provide updated and novel epidemiological evidence on adolescents who qualify as newly incident EMPPR users. In this research, each specific aim was designed to address various facets of adolescent EMPPR use.

The main findings may be summarized concisely. The first study identified the peak risk for starting EMPPR use as between 16-19 years old in this US nationally representative sample of adolescents. For this adolescent population, the peak risk for becoming opioid dependent within a year of first EMPPR use happened at a younger age (14-15 years old). For newly incident users in mid-adolescence, the average duration of EMPPR use is estimated as two to three years.

In the investigation of individual-level differences, the second study found that females who were newly incident EMPPR users (all starting within a year prior to assessment) had higher rates of use, given their membership in the class of STP users. Among newly incident EMPPR users, active AD cases were most likely to persist, followed by non-AD recent drinkers, when compared to those adolescents who had no underage drinking. However, never drinkers were more likely to persist in their EMPPR use compared to those who had not drank alcohol recently. In any case, conditional on persistence of EMPPR use, recent drinkers without AD and never drinkers had lower rates of EMPPR use compared to AD cases and past drinkers. About one in two adolescents persist in their EMPPR use after onset of such use.

Taking this evidence a step beyond the work in the first two studies, the third study attempted to discover latent classes of newly incident EMPPR users, as might be aligned in relation to prior or concurrent alcohol involvement as well as indicators of EMPPR involvement (e.g., whether opioids dependence had developed). These LCA evoked three different latent classes. The classes, each with a distinct use pattern, were designated as: Nondependent/Low level users, Moderately Persistent users, and Persistent/Dependent users. More specifically, the Persistent/Dependent user class was associated with greater odds of being female and younger while the Moderately Persistent user class was only associated with greater odds of being younger compared to the Nondependent/Low level class. The Moderately Persistent user class was associated with a greater odds of being male compared to the Persistent/Dependent user class.

6.2 Limitations and Strengths

Several important study limitations should be considered before a more detailed discussion of these results. As mentioned in prior sections of this dissertation report, one concern is the self-reported nature of the NSDUH data. Adolescents' truthfulness and memory affect responses (152). Drug use may be over or underreported for various reasons (e.g., recall bias, social pressure, legal ramifications). For the NSDUH, validity and reliability of these measures as well as age at first use have been substantiated (46).

With respect to the cross-sectional design, although cause-effect inferences cannot be drawn, epidemiological predictions for EMPPR use among US adolescents can be made, based on the estimates from these studies. Potential left-truncation may have resulted in exclusion of some newly incident EMPPR users from the sample. Left truncation might be present due to events such as fatal overdose at the first occasion or onset of EMPPR use. Likewise, severe

opioid dependent and AD cases in the population may not have participated, or could have been inside institutions and excluded from the population sampling frame or by definition. Due to this limitation, there may be a small downward bias of the study estimates with respect to occurrence rates and transition probabilities. However, as part of the dissertation research, an exploration was made to see whether characteristics of newly incident users who developed opioid dependence in the first quarter after initiation might be different from the characteristics of cases that appeared in subsequent quarters after first EMPPR use; few differences were seen.

A more serious limitation might be that the dissertation research does not address those newly incident users who use PPR for medical reasons under their doctor's direction. Since susceptibility traits related to adolescent-onset EM drug use most likely correspond to those for opioid dependence, estimates for occurrence rates might well be larger for those who initiate EM use, as compared with those using PPR strictly as prescribed and not for extra-medical reasons. Quite clearly, persistence of use and opioid dependence (or DSM-5 addiction syndromes) clearly can occur within the context of medically indicated PPR use, and some researchers have explored this differentiation between the two types of PPR users (43,153). The NSDUH does not, at present, identify those who use PPR exactly as prescribed and within boundaries of the prescriber's intent, and it cannot be determined whether the EMPPR use might have followed a clinician's prescription of pain relievers during treatment of pain connected to general medical conditions or to neuropsychiatric conditions (e.g., major depression), which might have some connection to the emergence of EMPPR use (46,79,81).

6.3 Implications and Future Directions

This dissertation's results might have significant implications in exploring the role of incidence, persistence, and dependence of EMPPR use among adolescents. The findings are of

interest because they indicate that although the peak risk for starting EMPPR use happens in mid-adolescence, the highest risk for persisting in said use and developing opioid dependence is earlier. Persistent/dependent newly incident users were also more likely to be female, predicted by AD, and younger compared to Nondependent/Low level users. Once EMPPR use persisted, females who began their use in the past year, past drinkers, and AD cases had higher rates of use as well.

The nationally representative results suggest that any efforts directed to prevent or intervene in adolescent EMPPR use should consider EMPPR use, alcohol involvement, sex, and age. There is an implication for prevention efforts directed toward EMPPR use might start earlier than secondary school, with due attention to unintended consequences (e.g., encouraging curiosity and earlier-onset use before secondary school). Knowledge about this co-occurrence of EMPPR use and underage drinking can help inform pediatricians, family doctors, dentists, oral surgeons, and others who now write pain relief prescriptions for adolescents. The study's evidence also might be used as a guide to the refinement of public health or treatment service programs and their EMPPR prevention or opioid dependence management strategies.

Given the press of time during each clinician's short office visit with adolescent patients, detailed assessment of these topics might be beyond the scope of the clinician's cross-examination before each prescription is written. Nonetheless, a general rule of thumb might be to prescribe opioid PPR with no more than a few dosage units or a supply limited to no more than a few dosing cycles, with over-the-counter pain relievers substituted as soon as possible, and with instructions for proper disposal of any left-over opioid supply that otherwise will create an 'exposure opportunity' for EMPPR use by the patient or by others with access to that supply.

Clearly, parental vigilance is needed, and when newly incident EMPPR is discovered, appropriate interventions are in order.

In addition, underage alcohol use may be a modifiable causal determinant of persisting in EMPPR use. Dissemination of this crucial information should not only be aimed at adolescents who engage in EMPPR use but also family members and friends. After one's own prescription, relatives are a common source of PPR that may be used extra-medically (65,66,154). Therefore, school-level interventions aimed at educating students about the dangers of EMPPR use and sharing prescriptions may help. Educating parents about keeping prescriptions safeguarded, adhering to medical use in the home as indicated by a prescribing physician, and discussing the risks of 'problem behaviors' is advisable. Consistent with alcohol and EMPPR use patterns discovered herein, often problem behaviors like EMPPR use and underage drinking do not occur in isolation (50,77,78). Alcohol use predating onset of EMPPR use is consistent with the popular though controversial gateway idea (58,59,155).

Some individual level differences were found in this research. In support of recent findings, the female excess rates indicate a vulnerability of progressing from first EMPPR use to dependence (10,38,69). Adolescent girls who are 14-15 may be at particular risk especially if there is a history of alcohol involvement leaning toward a dependence syndrome. With this in mind, prevention efforts may benefit from replication studies for future years and in subpopulations of adolescents. Further studies identifying other individual, interpersonal, and community level predictors might be useful to guide more tailored public health actions (e.g., the role of pain, protective factors, and family dynamic).

In future research that builds from findings such as these, it may be possible to alter expectations of adolescents regarding EMPPR use. Longitudinal studies with causally

informative designs can inform best practices for newly incident adolescent users. A prospective design would address the process from first taking a PPR extra-medically to eventual opioid dependence. In addition, temporal sequencing of other important characteristics could be probed as many of these characteristics had to be trimmed from this dissertation research project due to uncertainty of event sequences (e.g., school or income values that might have post-dated rather than pre-dated the EMPPR use). That is, some variables could have influences on PPR or, alternatively, PPR may influence them. To date, there is very little longitudinal research focused on newly incident adolescent EMPPR users (156).

Other future directions involve investigation of sources of PPR and diversion of PPR as might change with increased duration, persistence, and development of dependence (66). Availability of PPR for adolescents as well as opportunity to use are areas of research integral to extending our understanding of the epidemiology of EMPPR use in adolescent populations. Improved clinical guidelines and prescription practices informed by empirical evidence on these topics may be required to encourage health professionals, researchers, policy-makers to change their protocols and regulations that guide pain relief practices as applied to adolescents and other vulnerable populations.

During the years to follow, there will be continuing need for epidemiological surveillance of trends in the incidence rates for EMPPR use and for occurrence of opioid dependence-related syndromes. While prevalence proportions for EMPPR use have been declining in recent years, the newly incident users who fall into the persistent/dependent subgroup may have different using practices in future years, especially given increased availability and lower cost of opioids such as heroin (128,129,157). Continuation of the NSDUH surveys year after year will make it

possible for researchers to track these trends and help guide public health practices intended to promote the health of adolescents in our country.

6.4 Conclusions

In conclusion, the dissertation research has identified several correlates of EMPPR use that merit consideration in studies of contemporary adolescents in the US. The evidence on these correlates might not be 'game-changing' with respect to guidance of future prevention, intervention, and policies related to PPR. Nevertheless, the inter-connections of underage drinking and alcohol dependence with EMPPR use have not previously been studied in detail, and these new epidemiological findings may well prove to be useful in their application.

The dissertation research also draws attention to persistence of EMPPR use among newly incident users, as distinct from the prevalence of use per se, and as distinct from estimation of incidence rates. The dissertation research findings help confirm the proposition that once EMPPR use begins an important fraction of adolescents will persist in their use and transition quite rapidly to develop opioid dependence in processes that are not occurring at random; rather, they are occurring in relation to underage drinking and manifestations of alcohol dependence, as well as associated characteristics. The work builds upon progress that already has been made in efforts to bring attention to adolescent EMPPR use, overdoses, and surveillance of such use (5,158,159).

It will be necessary to conduct additional research that builds from this body of evidence. More comprehensive prediction models are needed to identify adolescents at highest risk for initiating EMPPR use, and for developing an opioid dependence syndrome soon after onset of

EMPPR use. These models can build from the cross-sectional approximations derived from the dissertation research.

Surveillance and monitoring adolescents in the clinical setting are public health actions that can happen now, without delay. The nationally representative samples studied in this dissertation research provide incidence rate estimates and dependence transition probability estimates that can be used to identify target audiences for clinical and public health interventions. Useful discriminations now can be made, based on what has been learned about the relationships linking EMPPR use with alcohol involvement, and about differences between males and females during adolescence. It is hoped that practical public health interventions for adolescents will be modified so as to take advantage of the new epidemiological findings that have emerged from this dissertation research project's three studies.

APPENDICES

APPENDIX A

'Extra-Medical' or 'Extramedical' Drug Use in Drug Dependence Epidemiology

The concepts of 'extra-medical' (or 'extramedical') drug use were introduced in 1989 by a Johns Hopkins University research work group supported by the United States National Institute on Drug Abuse and led by James C. Anthony, then Professor with appointments in the Johns Hopkins University School of Hygiene and Public Health (Mental Hygiene; Epidemiology) and its School of Medicine (Psychiatry and Behavioral Sciences). The research group provided a set of operational specifications for epidemiological field surveys, and proposed a set of pre-written standardized survey items for use in the first United States National Comorbidity Survey (NCS-1), scheduled for completion in 1990-92.

By creating a new term, the research group was trying to avoid ambiguities and other problems of signification encountered when terms such as 'drug misuse' and 'non-medical drug use' and 'drug abuse' appeared in the scientific literature. The group thought that these ambiguities and signification problems might be avoided by introducing a completely new term with clear operational specifications.

The team offered this introduction, to be presented to survey participants before its set of proposed standardized survey items on extra-medical drug use:

> We are interested in the extra-medical use of these prescription-type drugs.
>
> Extra-medical use is any use on your own; that is, either:
> **One**, without a doctor's prescription, or
> **Two**, in greater amounts than prescribed, or
> **Three**, more often than prescribed, or
> **Four**, for any reasons other than a doctor said you should take them-- such as for kicks, to get high, to feel good, or curiosity about the pill's effect (28).

The term ‘extramedical drug use’ first appeared in the peer reviewed scientific literature during 1994, within a journal article on drug dependence epidemiology (1). This article has been cited more than 1000 times, and at present is cited at a rate of 35-50 citations per year (according to Google Scholar). The term has been adopted by multiple US and international research groups.

Drug researchers growing up during the interval from 1960 through 1990 had to deal with many shifts in the meaning of basic terms such as ‘drug’ and ‘drug misuse,’ as well as the more stigma-laden ‘drug abuse’ and ‘drug addiction’ terms. As time passed, the meanings of these terms became more and more ambiguous. In consequence, what philosopher John Locke described as the ‘signification’ of words became a problem. Ambiguity prevailed.

These ambiguities can be seen clearly in a simple comparison. First, presented is what the Canadian ‘Le Dain’ Commission said in 1972 about ‘drug misuse’ and ‘drug abuse’ and it is compared with what a recent US Food and Drug Administration (FDA) official said about these concepts. First, this is the excerpt from the Commission report:

> We do not find the notion of drug "abuse" (or "misuse" for that matter) very helpful. In some cases it seems to be equated with the use of any drug which has a potential for producing dependence, physical or psychological. If it is equated with the drug use that actually produces dependence, then it is equated with only one potential aspect of harm. Certain kinds of drug use may produce harm quite apart from dependence, and in some cases, any use of a particular drug may involve the risk of harm. (http://druglibrary.eu/library/reports/ledain/ldc6a-2.htm)

In contrast, Dr. Klein’s more recent FDA view was as follows:

> When a person takes a legal prescription medication for a purpose other than the reason it was prescribed, or when that person takes a drug not prescribed to him or her, that is misuse of a drug. Misuse can include taking a drug in a manner or at a dose that was not recommended by a health care professional. This can happen when the person hopes to get a bigger or faster therapeutic response from medications such as sleeping or weight loss pills. It can also happen when the person wants to “get high,” which is an example of prescription drug abuse. (http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM220434.pdf)

By the late 1980s, the diversity of definitions and the loss of word signification for ‘drug misuse’ and ‘drug abuse’ prompted the John’s Hopkins research group to abandon these terms in scientific reports. Stigma-laden terms such as ‘drug abuse’ and ‘drug addiction’ also became problems rather than solutions in scientific communication. For these reasons, the group advocated a substitution with a more or less clear distinction between ‘medical’ and ‘extra-medical’ use of a drug.

Medical use of the drug was stipulated as use within the boundaries of a clinician-intended prescription or the equivalent as applied to over-the-counter non-prescription compounds. Extra-medical use of the drug (as conveyed by the adjective stem ‘extra’) was stipulated as use ‘outside’ the boundaries of a clinician-intended prescription or the equivalent as applied to OTC non-prescription compounds. After deciding to create a new term, the operational specification for ‘extra-medical use’ was framed.

APPENDIX B

National Surveys on Drug Use and Health (NSDUH) Assessment: Manuscript 1

Newly incident users of extra-medical prescription pain relievers can be identified by the variable RECANL_B from the 2-year Restricted-use Data Analysis System (R-DAS). Year pairs from 2002 to 2003, 2004 to 2005, 2006 to 2007, 2008 to 2009, 2010 to 2011, and 2012 to 2013 are obtained via the year pair indicator (YRPRIND). Outlined in the 2011 NSDUH Summary of National Findings for 2002-10, the control totals are from analysis weights derived from the 2000 census data. For NSDUH weights after 2010, the 2010 census was used. Therefore, researchers should be cautious in the comparisons between prescription pain reliever use estimates across these survey years (2).

Those who were eligible for past year initiation of pain reliever use can be identified using the R-DAS variable ELGANL_B. Those 'at risk' to become newly incident users were evaluated on the basis of the lifetime history of using prescription pain relievers extra-medically during an interval prior to the 12 months preceding the date of survey assessment. 'Ever users' who had a month and year of first use that pre-dated the interval were excluded from this 'at risk' population. Those eligible to become newly incident extra-medical prescription pain reliever users are designated by the RDAS variable ELGANL_B, coded with a value of 1.

RECANL_B and ELGANL_B pertain to 12 months before the assessment date and allow differentiation of newly incident users who started (or were eligible to start) using during that time interval, versus those who were 'at risk' but did not start using. For both RECANL_B and ELGANL_B, the NSDUH asks, "Have you ever, even once, used any type of prescription pain

reliever that was not prescribed for you or that you took only for the experience or feeling it caused?"

All NSDUH questions about the use of pain relievers are not about "over-the-counter" pain relievers that can be obtained without a doctor's prescription. When asking about such use, the survey method involves presentation of a supplementary 'Card A' image to show pictures and names of various prescription pain relievers (see Figure B.1 below).

Figure B.1 Card A: pictures of pain relievers with tradenames from the National Surveys on Drug Use and Health supplement.

Dependence upon these compounds (DEPNDANL) was evaluated when there was extra-medical use of a prescription pain reliever in the 12 months prior to the date of assessment. The diagnostic criteria are those of the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994). A user qualifies as a case of opioid dependence after evaluation in relation to standard DSM-IV criteria, including the withdrawal criterion, for opioid dependence: three or more of these seven criteria must be

fulfilled as in the DSM-IV specifications. The withdrawal question was asked when opioid-specific withdrawal manifestations had lasted for longer than a day after cutting back or stopping use. DEPNDANL is a binary variable with only "Yes" or "No/Unknown (Otherwise)" as the alternative value labels.

Prevalence of recently active EMPPR use can be derived from the RDAS recoded variable IRANLRC. The original variable ANALREC asks, "How long has it been since you last used any prescription pain reliever that was not prescribed for you or that you took only for the experience or feeling it caused?" Answers vary between "Within the past 30 days," "More than 30 days ago but within the past 12 mos," "More than 12 months ago," or "Never used pain relievers." Combining the first two answer categories allowed estimation prevalence of being a recently active user (within 12 months prior to assessment). Numerators for prevalence include those who used within the past 12 months.

Beginning with the 2002 NSDUH, missing values for the sex question (QD01) were not allowed so no imputation was required. This variable has the prefix 'IR', which stands for 'Imputation Revised', only for the sake of consistency with data sets from earlier surveys (pre-2002). The sex variable IRSEX has two values, "Male" and "Female".

The 2-year RDAS file allows users to indicate age with the final edited age variable (AGE). After the respondent has entered his/her birthdate in the first part of the questionnaire, he/she has multiple opportunities to change his/her age in response to consistency checks throughout the questionnaire. The final age variable is determined using multiple survey questions. Age pairs were of interest in this analysis (e.g., 12-13; 14-15; 16-17; 18-19; 20-21) to match the paired nature of the years and ensure there would be no confidentiality issues due to small sample sizes. These age values pertain to the participant's age on the date of assessment.

APPENDIX C

National Surveys on Drug Use and Health (NSDUH) Assessment: Manuscripts 2 & 3

Newly incident users are defined by comparing each individual's year of first use with the year of the survey. Adolescents were required to have started use within the past 24 months, the difference between the value of a calendar year variable (YEAR) and NSDUH's 'year of first use' variable (IRANLYFU) must be less than or equal to 2 years.

IRANLYFU is an imputation revised version of the original 'year of first use' variable (ANALYFU) for more accurate values. ANALYFU asks questions about drugs that people are supposed to take only if they have a prescription from a doctor. It specifies that the survey questions are only interested if the drug was not prescribed for the respondent and that over-the-counter pain relievers should not be included. Supplemental cards are provided to show pictures of different kinds of prescription pain relievers and names of others. ANALYFU is composed of three separate questions:

1. Did you first use any prescription pain reliever that was not prescribed for you or that you took only for the experience or feeling it caused in [CURRENT YEAR - 1] or [CURRENT YEAR]?
2. Did you first use any prescription pain reliever that was not prescribed for you or that you took only for the experience or feeling it caused in [CURRENT YEAR - 2] or [CURRENT YEAR - 1]?
3. In what month in [CURRENT YEAR] did you first use any prescription pain reliever that was not prescribed for you or that you took only for the experience or feeling it caused?

The outcome variable used is a count variable, the 'total number of days used pain reliever in the past 12 months' (ANLYRTOT). This variable was incorporated into the model by removing all of the users who had 'bad data', 'didn't know', 'refused', or did not answer and transforming users who had not used in the past year as a zero value (rather than missing values).

In this way, newly incident EMPPR users who did not use in the past 12 months had a valid outcome value.

For the outcome variable, it was important to differentiate between users whose onset of pain reliever use began in the past 12 months and those who began 13-24 months ago. Because 'persistence' was of interest for the research question, the outcome variable (ANLYRTOT) was shifted down one value for users who began in the past 12 months. For example, if someone used one time in the past year and also started using in the same year, so that 'persistence' was measured, the one 'trial' use was replaced with a zero. This allowed measurement of how many days of pain reliever use happened after a user started.

Lifetime alcohol use and recency of last alcohol use was assessed among all respondents. The alcohol involvement covariate was created out of these two NSDUH variables: IRALCRC and DEPNDALC with 4 possible levels:

1. Never drank in lifetime
2. Drank at least once, but not in past year
3. Drank in past year, no AD (if IRALCRC shows use within the past 12 months)
4. Drank in past year, AD case (if IRALCRC shows use within the past 12 months)

IRALCRC is an alcohol recency variable created from the original 'time since last drank alcoholic beverage' variable (ALCREC). This question defines a "drink" and asks, "How long has it been since you last drank an alcoholic beverage?" After imputation, IRALCRC is composed of four alcohol recency levels:

1. Within the past 30 days
2. More than 30 days ago but within the past 12 months
3. More than 12 months ago
4. Never used alcohol

A drink is explained as a can or bottle of beer, a glass of wine or a wine cooler, a shot of liquor, or a mixed drink with liquor in it. The survey clarifies that there is no interest in times when one took a sip or two from a drink.

Dependence upon alcohol (DEPNDALC) was measured only among respondents reporting six or more days of alcohol use in the past year, with clinical feature criteria based on the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* (30). Dependence was diagnosed when 3 out of 7 criteria were met within the same year. DEPNDALC has four possible responses:

1. Never drank (yet)
2. Drank at least once, but not in past year
3. Drank in past year, but not alcohol dependent
4. Drank in past year, and now alcohol dependent

Beginning with the 2002 NSDUH, missing values for the sex question (QD01) were not allowed so no imputation was required. This variable has the prefix 'IR', which stands for 'Imputation Revised', only for the sake of consistency with data sets from earlier surveys (pre-2002). The sex variable IRSEX has two values, 1: Male and 2: Female.

The NSDUH respondent age variable (AGE2) provides the age for the study sample in years. In modeling, an age-squared variable was created by squaring the age variable.

APPENDIX D

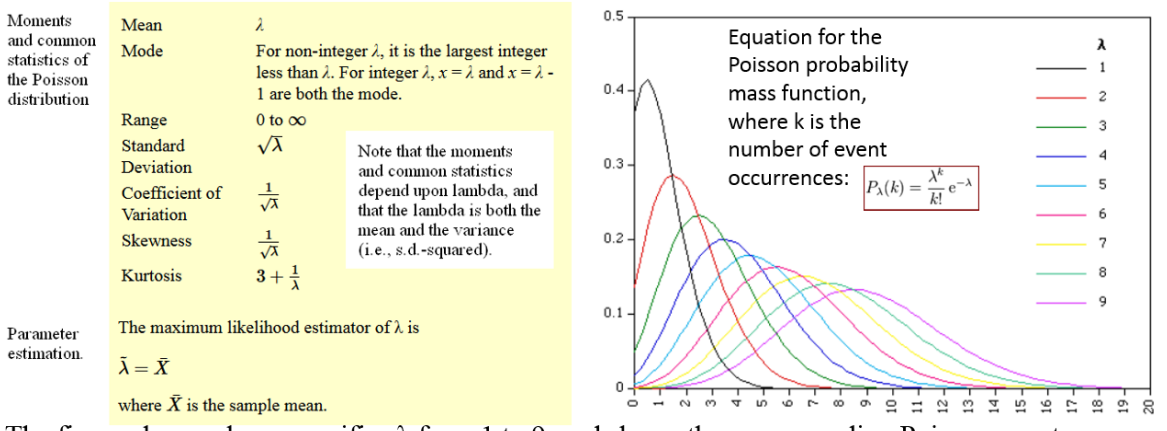
Primer on Zero-inflated Poisson Models: Manuscript 2

Note: This is an extension of an appendix from a manuscript under review by Parker & Anthony, 2016 (112).

Introduction to Poisson distribution for counts of events within or during specified time intervals

As shown in Figure D.1, a Poisson distribution is useful when one is counting the number of events that are occurring within or during a specified time interval. The figure lists the moments and common statistics used to summarize the Poisson distribution, as well as a very interesting feature that for any count of events, k, the expectations for the Poisson mean and the Poisson variance are equal to the parameter called lambda λ.

Figure D.1 The Poisson distribution application for counting the number of events occurring within or during a specified interval of time.



The figure shown above specifies λ from 1 to 9, and shows the corresponding Poisson count distributions. For example when λ = 1 in a Poisson count distribution of events, the expected number of zeroes should be just over 40% of the total. Readers interested in exploring various specifications for λ parameter can use this online Poisson distribution graphing tool: http://keisan.casio.com/exec/system/1180573180 An online tutorial from Penn State University can be found here: https://onlinecourses.science.psu.edu/stat414/book/export/html/54

Figure D.1 also shows the equation for the Poisson probability mass function, as typically is learned in the first or second course on the theory of probability and statistics. The inset with λ varying from 1 to 9 for a fixed value of k (the total number of events) shows the shapes of the Poisson distribution under these alternative specifications. In the figure, one can see that when λ = 1, the expected number of zeroes in the Poisson distribution is just over 40%. At λ = 2, that expected number is just below 15%. And so on.

The figure provides 'hot URL links' to web resources that can be used to learn more about the standard Poisson distribution, and to specify non-integer values of λ, which might be of interest to some readers.

When there is one and only one count process that generates counts of events as time passes, and one wishes to estimate the effects of suspected determinants of the process, it is possible to make use of a generalized linear model (GZLM) with a standard Poisson distribution link function specified in place of the identity link function used to fit a general linear model (GLM) to Gaussian (normally distributed) distributions of response variables. Sometimes, there can be more than one count process in play, and in this instance, the observed Poisson distribution no longer satisfies the defining characteristics mentioned in Figure D.1 (namely, with λ as both mean and variance).

For example, there might be a process that generates an excess of zeroes relative to the expected number based on the standard Poisson distribution. Figure D.1's value of about 40% zeroes when $\lambda = 1$ might instead be shifted upward such that the observed number of zeroes is 60% of the event total, relative to the expectation based on the standard Poisson distribution.
As outlined below, there are alternatives to the standard GZLM with a Poisson link function when the observed count distribution has an excess of zeroes.

What is a Zero-inflated Poisson regression model?
The zero-inflated Poisson (ZIP) regression model has been developed as a way to study determinants of two separable processes that give rise to excess zeroes, as gauged against the standard Poisson model expectations. These ZIP regression models are fit to response distributions of count data with an excess of zeroes. The ZIP regression model has two parts: (1) A logit model is generated for predicting the excess zeroes; (2) a Poisson regression model is generated to predict non-zero event counts. Then, the two parts are combined.

Why are the excess zeroes so important?
The excess zeroes are separately modeled using a ZIP model when the underlying theory specifies the possibility of at least two processes for generating count response distribution. In effect, the ZIP model allows the observed zeroes to come from a mixture of two classes. Professor German Rodriguez of Princeton University provides an exceptionally clear description of the mixture of two classes in his lecture notes on the use of ZIP models when there is over-dispersion (excess zeroes) in the observed count distribution, as appears to be the case in research on the publication track records of biochemist PhDs, some observed to publish nothing during the time interval under study, and with over-dispersion and an excess of zeroes when the response distribution is examined:

> The zero-inflated Poisson model postulates that there are two latent classes of people. The "always zero", which in our example would be individuals who never publish, and the rest, or "not always zero", for whom the number of publications has a Poisson distribution with a mean and variance… [λ] > 0. The model combines a logit model that predicts which of the two latent classes a person belongs, with a Poisson model that predicts the outcome for those in the second latent class. In this model there are two kinds of zeroes: some are structural zeroes from the always zero class, and some are random zeroes from the other class (http://data.princeton.edu/wws509/notes/c4a.pdf, last accessed 8 March 2016).

Why not just use simpler methods?
A standard Poisson model would be a simpler method than the two-part multivariate ZIP regression model. The same can be said for the negative binomial regression model. These alternatives might promise simpler-to-interpret results as compared to the ZIP model. Nonetheless, the resulting slope coefficients do not have the same interpretation, even if over-dispersion (excess zeroes) can be ignored.
Both the standard Poisson model and the NBM yield slope coefficients that have the typical unconditional 'rise over run' interpretation of a regression slope estimate. That is, they convey the estimated increase in the count Y-variable for each unit increase in the explanatory X-variable.

The slope coefficients from the two-part multivariate ZIP model do not have this interpretation at all. The first part of the ZIP model evaluates what might be determining membership in the latent classes as described above (i.e., being in the 'structural zero' class versus being in the 'random zero' class); for this reason, this part of the ZIP model often is call the 'ZIP inflate' model. The second part of the ZIP model yields coefficients that have a conditional interpretation. That is, conditional on 'not being in the structural zero class', and with an allowance for 'random zeroes' in the response distribution, the 'ZIP count' model's slope conveys the estimated increase in the Y-variable for each unit increase in the explanatory X-variable.

What happens if two separate models used instead?
It might be suggested that we should fit a logistic model to binary response data with Y=0 when the count is zero and with Y=1 when the count is greater than zero. Then, deal with the excess zeroes by fitting a separate Poisson model to the observed non-zero counts.

The logistic regression solution quite clearly involves a 'simpler method' as compared to the two-part multivariate ZIP model, but it will yield an incorrect solution because it fails to distinguish between the two classes of zeroes. It will be based on too few individuals with an observed count greater than zero. It fails to take into account the presence of the second class of 'random zeroes' (i.e., those who just happened to be observed as zeroes during the time interval under study).

The Poisson regression for Y>0 counts also is simpler, but it also will yield an incorrect solution. Why? Because it has no zero values whatsoever. This situation occasionally will be observed when $\lambda > 4$, as illustrated in Figure D.1, but not when $\lambda < 5$.

A similarly incorrect solution also would be found if we were to estimate rates of use by deriving a simple mean from the Y>0 part of the count distribution. The denominator for that rate (d1) will consist of users with Y>0, which makes d1 a smaller number than the corresponding ZIP model's denominator (d2). Why? Because d2 includes those users who have observed zero counts, as well as users with Y>0.

What do you mean by two processes?
Empirical example (adapted from: http://www.ats.ucla.edu/stat/stata/dae/zip.htm, last accessed 8 March 2016). The common example to explain ZIP models considers people who go to a park in groups. Of interest is predicting how many fish each group has caught by the time they leave the park (response variable = number of fish). There is also information available on whether the

group brought a camper with them. Looking at the data, there is clear evidence of an excess of zero fish caught, so predicting the excess number of zeroes is of interest. We know there are two ways for people to be observed with zero caught fish:

1. Those groups who did not fish at all, and
2. Those groups who fished, but who had bad luck fishing.

Substantive example
Consider a set of ambulatory care patients scheduled for evening outpatient surgery. After surgery, the prescriber dispenses one tramadol tablet to be taken by mouth as soon as the anesthetic's effect on pain subsides, and gives a written prescription for a two week supply of a sustained release opioid pain-reliever (SROPR) with oral and written instructions to take no more than one SROPR tablet each day. They are told to switch to an over-the-counter pain compound such as ibuprofen once pain subsides. We are interested in the number of days patients used the prescribed SROPR post-surgery. There are two ways the number of days would be observed to be zeroes in these patients:

1. Class 1, those who do not fill the prescription (such that observed Y = 0 for them), and
2. Class 2, those who fill the prescription, but whose use of the tablets follows the standard Poisson distribution for any given observed estimate of λ (including some who fill the prescription and receive the tablets, but who take none of them such that observed Y = 0 for them).

Numerical example
Drawing from the above substantive example, we have simulated a dataset by generating a standard Poisson distribution to depict count response distributions observed in a set of hypothetical outpatient post-surgery patients, where the response is the rate of tablet use (i.e., the number of days the sustained release opioid pain reliever (SROPR) has been used during the two weeks prescription interval post-surgery). We start with a standard Poisson distribution and we add some zeroes to the dataset because we are trying to show the material importance of the inflation of zeroes (by virtue of being in Class 1), and how alternative approaches might be misleading.

One hypothesis might be that males and females are different in relation to the use of SROPR post-surgery. To create the simulation, we add inflated zeroes, but not so much as to create a male-female imbalance in these inflated zeroes, and we set up the simulation so that females in a susceptible-to-persistence class would have higher rates than the males in that class.

In the two-part univariate response model approach, we turn to the logistic regression model to evaluate the degree to which the male-female ratio is the same irrespective of whether Y=0 or Y>1, and we turn to the standard Poisson model to estimate male-female differences in the count of days of tablet use, given that Y>0.

In the two-part multivariate response model approach (ZIP model), we use the latent class approach to discriminate 'structural zeroes' (e.g., as might be conceptualized for those who did not fill the prescription) from 'random zeroes' (e.g., as might be conceptualized for those who filled the prescription but then took no tablets), and we use the standard Poisson approach,

conditional on not being in the 'structural zeroes' latent class, in order to estimate male-female differences in the count of days of tablet use (allowing some observed 'random' zeroes).

First, based on our specification for the simulated dataset, we observe 31.5% of patients with zeroes in the outcome variable (# of days used SROPR in the two week interval under study). Values 0-3 account for 92.7% of the patients. As shown in Table D.1, we also can see that there is overdispersion, with variance larger than mean, by design because we added zeroes to the standard Poisson distributions we had generated to begin.

Table D.1 Moments and common statistics for number of days of tablet use post-surgery (simulated dataset based on standard Poisson distribution with excess zeroes by design).

Variable	Patients	Mean	Variance	Minimum	Maximum
Count of days	2184	**1.41**	**2.31**	0	14

Inspection of Table D.2 shows what might be inferred with the two-part univariate response model approach with logistic regression of the binary response variable coded as 1 for counts of 0 and as 0 for counts>0, and then with a Poisson modeling of those with count>0. That is, the initial logit model for having count>0 (coded 0) versus count=0 (coded 1) detects what we built into the simulated dataset, but it ignores the existence of the not-susceptible-to-persistence class of inflated zeroes, leaving the impression of a male excess (logit slope coefficient = 0.98 would exponentiate to OR = 2.7 at $p<0.0001$).

All observed zeroes have been removed from the estimation of rate rates in the Part 2: Poisson modeling of counts>0, leaving the impression of a modest female excess rate ratio (logit RR = -0.37 for males, exponentiated as 0.7, meaning the male rate is 70% of the size of the female rate.

In contrast, given the way we constructed the dataset with zero inflation, the appropriate zero-inflated Poisson inflate equation shows no male-female imbalance in the not-susceptible-to-persistence class ($p = 0.558$) and a stronger male-female contrast of rate ratios, given membership in the susceptible-to-persistence class.

Table D.2 Comparison of estimates from two-part univariate response model approach versus two-equation multivariate response model (ZIP) Approach (simulated dataset based on standard Poisson distribution, with excess zeroes by design).

Model	Covariate	Coefficient[a]	[95% Confidence Interval]		p-value
Part 1: Logit	Male	0.98	0.79	1.16	$2.2*10^{-24}$
Part 2: Poisson	Male	-0.37	-0.45	-0.30	$2.5*10^{-22}$
ZIP inflate	Male	0.20	-0.48	0.89	0.558
ZIP count	Male	-0.65	-0.75	-0.55	$7.3*10^{-34}$

a = Slope estimates are on the natural log scale; have not been exponentiated.

A more detailed explanation of the two-equation multivariate response ZIP model results might be of help to some readers. Fitting this model to the same simulated dataset used to fit the two-part logistic+Poisson equations, the ZIP modeling leads to different interpretations and inferences because the meaning of the slope estimates in the ZIP model differs from the meaning

of the slope estimates in the logistic+Poisson equations. By design, we did not add enough extra female excess zeroes to create a male-female imbalance in the latent class of 'structural zeroes'. In consequence, the first part of the multivariate response ZIP model, labelled 'ZIP Inflate', shows no male-female difference in the odds of being a member of the 'structural zero' class relative to membership in Class 2 (β = 0.20; p = 0.558).

Nevertheless, the second part of the multivariate response ZIP model, labelled 'ZIP count', shows a much more substantial male-female difference in the rate of tablet use when we take the 'random zeroes' into account, as compared to the much-attenuated estimate derived from the two-part univariate response approach, which took the possibility of the random zeroes (count=0) out of the analysis picture via stratification on count=0 versus count>1. The estimated standard Poisson β = -0.65 when the possibility of random zeroes is allowed in the ZIP Count model, whereas the estimated standard Poisson slope is much smaller when the possibility of random zeroes is not allowed by virtue of stratification on observed Y>0 (β = -0.37).

Whereas a reader focused strictly on p-values and issues of statistical significance might point to the fact that both slopes have p < 0.001, anyone interested in estimation of substantively important rate ratios will notice that the 95% CI for the β = -0.37 estimate do not overlap with the 95% CI for the β = -0.65 estimate. Gauged as a departure from the null value of 0.0, the ZIP Count approach yields a female excess that is almost double the size of the female excess inferred from the slope estimate of the Y>0 stratified approach. (Some readers might prefer to have the β estimates on the log scale converted to risk ratios, RR, and to see the comparison as a positive departure from an RR = 1.0. This can be achieved by taking the absolute value of the β, and exponentiating the $|\beta|$ for the comparison. Accordingly, exp($|\beta|$) from the ZIP count model is exp(0.65) = 1.9, or almost RR = 2.0, with females having almost double the tablet use rate seen for males (i.e., 190%). In contrast, the corresponding exp($|\beta|$) from the Y>0 stratified approach is exp(0.37) = 1.4 (i.e., 140%), with non-overlapping 95% CI.

From this simulated example, contrived to show that the two-part univariate response approach might be simpler to conceptualize than the latent class-based ZIP modeling approach, we have illustrated that incorrect inferences can be drawn when there is a theoretical basis for specifying two processes that generate zero values for count distributions with over-dispersion and excess zeroes. The ZIP approach is more complex, but it correctly recovered the data structure we built into the simulation [i.e., with an excess of female zeroes large enough to show over-representation of females among those using zero tablets (count = 0), and with a relatively weak female excess rate when count > 0)].

We note that unless the theory guides one to specify two zero-generating processes (such as not filling a prescription versus filling it but using no tablets) there are two simpler models that might be tried – namely, the standard Poisson model and a NB model. Either or both of these models can tolerate some degree of over-dispersion, and might produce simpler estimates that require no latent class conceptualization.

Table D.3 Comparison of estimates from standard Poisson and negative binomial models versus ZIP count modeling (simulated dataset based on standard Poisson distribution, with excess female zero inflation).

Model	Covariate	Coefficient	[95% Confidence Interval]		p-value
Standard Poisson	Male	-0.67	-0.75	-0.60	$1.2*10^{-69}$
Negative Binomial	Male	-0.67	-0.76	-0.59	$1.4*10^{-53}$
ZIP count	Male	-0.65	-0.75	-0.55	$7.3*10^{-34}$
ZIP inflate	Male	0.20	-0.48	0.89	0.558

As it happens, our simulated dataset makes it possible for us to illustrate this point. Depicted in Table D.3 are regression slope estimates derived by using the standard Poisson and the negative binomial approaches to the simulated data with excess zeroes. As shown, together with the just-reported ZIP Count model estimates, all three modeling approaches yield β point estimates and overlapping 95% CI that are not appreciably different from one another, with β = -0.67 from both simpler models, and with β = -0.65 from the ZIP Count model, given that the ZIP Inflate modeling showed no female-male differences of note. That is, if the ZIP Inflate model had shown a female-male difference with respect to the latent classes, the interpretation of the ZIP Count model's slope estimate is different. The ZIP Count slope estimate is one that is conditional on <u>not</u> being a member of the structural zeroes latent class. This is not the case for the simpler models, which do not condition on latent class membership.

Our simulated dataset was set up with no female-male structure with respect to the structural zero class, such that the conditioning turns out to be immaterial. This fact about the simulated dataset makes interpretation of the resulting β a bit easier, and helps explain the comparability of the three β estimates.

Is there a way to compare the fit of the different models and to proceed accordingly?
In some situations, a statistical test known as the Vuong test that can be used to see whether the ZIP model fits the data better than the standard Poisson. In this example of our simulated dataset, the Vuong test shows that the ZIP model fits the data better and is favored ($p < 0.001$). As such, we have created one of those circumstances in which the three models yield slope estimates that do not differ appreciably, and that have more or less the same interpretations. Nonetheless, the Vuong test favors the more complex ZIP model with its allowance for a structural zeroes class and a standard Poisson distribution that has 'random zeroes' in addition to non-zero counts as responses.

Is there a zero-inflated negative binomial model?
There is a zero-inflated negative binomial model. Methodologists disagree about which is to be preferred, but ultimately the choice is based on grounds of theory specification and approach specification, in advance of any modeling whatsoever. Once the theory and approach have been specified in advance, the estimation steps of an analysis plan can be carried out according to those specifications. Then, and only then, in a post-estimation exploratory data analysis step, alternative specifications can be tried without compromising the original findings. The findings would be compromised if the analyst specified the theory, and then searched for a statistical model that would produce findings in conformity with the theory in a kind of fishing expedition

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