CONTRIBUTIONS TO THE EPIDEMIOLOGY OF COCAINE DEPENDENCE: NOVEL ESTIMATES OF TRANSITION PROBABILITIES AMONG SUBGROUPS OF COCAINE INITIATES

By

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ABSTRACT

CONTRIBUTIONS TO THE EPIDEMIOLOGY OF COCAINE DEPENDENCE: NOVEL ESTIMATES OF TRANSITION PROBABILITIES AMONG SUBGROUPS OF COCAINE INITIATES

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Cocaine use is associated with several adverse health consequences such as increased risk of cardiovascular complications, HIV, hepatitis B and C, and higher mortality. Between 2016 and 2018, for example, cocaine-related fatal poisonings in Michigan increased 52.9% (MDHHS, 2019). Trends explicating the incidence of cocaine use and transition to a cocaine use disorder (CUD) for sub-groups of cocaine users might help to inform policy and to tailor a suitable public health response to cocaine-related morbidity and mortality.

Building from pre-clinical animal experiments, clinical research on cocaine has mainly focused on understanding the effect of cocaine on human experiences such as mood state profiles, heart rate, and pharmacokinetic, pharmacodynamics, and other pharmacological parameters studied in labs. However, there has been little research on variations in estimates of cocaine dependence over time. This dissertation fills this gap by estimating a 15-year epidemiological trend in the proportion of the population transitioning from cocaine initiation to dependence within 12 months. The data are from the Online Restricted Data Analysis System of the United States National Survey on Drug Use and Health (RDAS), 2002-2016. The novel discovery from study 1 (Aim1) is that roughly one-in-five (22%) of the powder-then-crack subgroup of initiates developed cocaine dependence within 1-12 months after powder-onset versus a powder-only attack rate of roughly one-in-20 (5%) – a fourfold variation.

Study 2 (Aim 2) accounts for within-person statistical interdependence of cocaine-related side effect problem experience (SEPE) responses during formation of cocaine dependence syndromes through use of Generalized Estimating Equations (GEE) modeling. It provides novel evidence on the occurrence of cocaine-related SEPEs among a crack + powder group contrasted with a powder-only group. The data are the National Surveys on Drug Use and Health 2011-2017, (n~ 55,000/year). I first estimated analysis-weighted incidence proportions for cocaine powder-only users (n=2364) and crack + powder users (n=231). Subsequently, I estimated odds ratios for 21 individual SEPEs reflecting crack/powder-only contrasts, year-by-year with corresponding Taylor series 95% confidence intervals. A fixed effects meta-analysis approach yielded summary estimates for each SEPE. Strong crack-associated excess odds were observed for inability to keep limits; aOR=9.5 (5.9, 15.4) and use despite emotional problems aOR=10.5 (6.7, 16.5). This work provides a novel and broadened view of experiences during early phases of what might become cocaine use disorders. This evidence suggests that treatment modalities for different subgroups of cocaine users might need to be tailored based on the route of administration of the drug.

The third study (Aim 3) shifts focus from the epidemiological rubric of 'Quantity' to the rubric of 'Prevention and Control' (Anthony, 1998). The main aim is to analyze oral cocaine use as a potential adaptation to the Medication Assisted Treatment (MAT) program in a County jail to address the issue of comorbid OUD and CUD. Results show that oral cocaine agonist treatments like coca tea, which have been used for more than 4,000 years in Peru and Bolivia with little evidence of harm might offer a potentially viable treatment modality for CUD. However, larger trials recruiting specific subpopulations of users are needed to build the evidence base for the efficacy of this approach.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

KEY TO ABBREVIATIONS

ACASI	Audio Computer-Assisted Self-Interviewing
CBT	Cognitive Behavioral Therapy
CHCl	Cocaine Hydrochloride or cocaine powder
CI	Confidence Interval
CM	Contingency Management
CUD	Cocaine Use Disorder
DSM	Diagnostic and Statistical Manual
FI	Field Interviewer
MAT	Medication Assisted Treatment
MTF	Monitoring the Future
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NCS	National Comorbidity Survey
NICU	Newly Incident Cocaine Powder Only Use
NICRU	Newly Incident Crack + Powder Only Use
NSDUH	National Survey on Drug Use and Health
OUD	Opioid Use Disorder
SEPE	Side Effect Problems and Experiences
SAMHSA	Substance Abuse and Mental Health Services Administration
US	United States
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Introduction

Cocaine is a powerful stimulant obtained from the coca plant indigenous to South America. In 2015, 0.4% of the US population ages 12 and older initiated cocaine use in the previous year, and this number was higher than in each of the years from 2008 to 2014 (US NSDUH, 2016). Additionally, in 2015, the total number of cocaine-related deaths was the second highest it has been since 1999 (US NSDUH, 2016). These data suggest that cocaine use is an important public health problem in the US, particularly so due to the association between cocaine use and serious cardiovascular problems (Havakuk et al., 2017, Richards, et al., 2016, Schwartz et al., 2010). Despite an apparent uptick in cocaine production and use in recent years (UNODC, 2018), estimated meta-analytic national trends particularly with respect to cocaine dependence proportions for different routes of cocaine administration are not available. This dissertation seeks to fill this gap in the literature and shines a spotlight on side-effect problems and experiences of sub-groups of cocaine users in the 12 months following cocaine onset.

1.2 Specific Aims

This dissertation incorporates three distinct studies pertinent to the natural history and progression of cocaine dependence with focus on two subgroups of newly incident cocaine users: those who use only cocaine powder (henceforth, CHCl-only), and those who initiate with powder, but then progress to using crack in addition to powder (powder-then-crack).

1.2.1 Specific Aim 1 (Manuscript 1)

The main aim of manuscript 1 is to estimate cocaine dependence attack rates (incidence proportions) for subgroups of cocaine initiates observed within 12 months of cocaine onset.

These subgroups consist of 1) those who initiated cocaine hydrochloride or cocaine powder-only use within 12 months of the date of assessment by the NSDUH staff, and 2) a smaller subgroup who initiated crack-cocaine use within the same timeframe, but after onset of CHCl-only use.

1.2.2 Specific Aim 2 (Manuscript 2)

Manuscript 2 offers novel epidemiological evidence on the odds of developing 21 individual cocaine-attributed side effect problems and experiences (SEPEs) within 1-12 months of initiating cocaine use, with hypothesized excess odds for CHCl-then-crack-cocaine users, as contrasted with CHCl-only users. A multivariate vector of interrelated side-effect problems and experiences prompted use of a generalized linear model (GZLM/GEE) approach to estimation.

1.2.3 Specific Aim 3 (Manuscript 3)

Manuscript 3 shifts focus from the epidemiological rubric of quantity and location to the rubric of prevention and control. The main aim of manuscript 3 is to review the evidence base for oral cocaine agonist therapy in general and coca tea in particular as a viable treatment modality and as a potentially useful adaptation to a local county's newly instituted medication assisted treatment program for OUDs in order to better serve inmates with comorbid cocaine-use disorder and opioid use disorder. I also analyze and identify barriers and strengths to initiating, implementing, and expanding an MAT program from the perspective of a local public health department in the US using process mapping as the methodology of choice. This manuscript takes a public health approach oriented toward harm reduction and reintegration of a vulnerable population (jail inmates with a drug use disorder) back into the community.

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

2.1 Background

2.1.1 The Coca Plant

The coca plant is native to South America, and is an integral part of the social, religious and cultural fabric of that society. The practice of chewing coca leaves has existed for more than 4000 years and is still firmly entrenched in cultural traditions (Petersen, 1977). During the Inca period (AD 800-1000), the use of coca was reserved for the royal family and a chosen few selected by them (courtiers and members of the army during battle). The upper echelons of Inca society veneered the cultivation and use of coca. From historical accounts we can infer that culturally coca was used in a way that moderated use. To illustrate, the coca plant occupied center stage in celebrations since the earliest times and is still central to religious practices and ceremonies. Over time, the plant also came to be used for therapeutic, religious, recreational, occupational and economic purposes. With the advent of the Spanish conquistadors, use was no longer limited to nobility. The Church for example, also maintained coca plantations. Shortly, thereafter, it became *de rigeur* to give workers coca as part of their wages.

It is important to understand that traditional coca-use was work-related rather than recreational. Coca leaves were either chewed or used in tea with intent to increase the productivity of laborers. To put things in perspective, a compelling analogy to the consumption of the coca leaf in the Andes is the consumption of coffee in the US.

Cocaine is the key psychoactive ingredient obtained from the coca plant. The purified alkaloid of cocaine was discovered approximately a hundred years ago, introducing new modes of administration of the psychoactive ingredients present in this highly concentrated form.

Access to purified cocaine changed the dynamic of cocaine consumption in the world because it meant that cocaine could now also be snorted, injected, or smoked.

2.1.2 Pharmacology of Cocaine

Cocaine may be extracted from coca leaves (containing approximately 0.6% to 1.8% alkaloidal cocaine) yielding coca paste that contains about 80% cocaine (Carrera, 2004; Fischman & Johanson, 1996). Cocaine in the form of Cocaine hydrochloride (CHCl) has been used as a local anesthetic and is also most widely misused. CHCl may be administered orally, intranasally, or intravenously and is water soluble. When transformed into cocaine freebase or crack, the hydrochloride salt may be smoked (Hatsukami, 1996).

Cocaine concentration in plasma varies based on the route of administration. Intravenous injection and smoking both precipitate rapid absorption (Johanson & Fischman, 1989). A typical single dose of cocaine can yield a relatively high concentration of cocaine, between 500 and 1000 ng/mL (Carrera, 2004). However, the rate of absorption varies. The rate of absorption is slowest via the oral route because cocaine is ionized in the digestive system. However, snorting is also associated with a slower rate of absorption as compared with injection. These two routes yield cocaine concentrations of 100 to 500 ng/mL" (Carrera, 2004).

The probability that an individual might develop cocaine dependence is a function of the mode of administration, as well as the frequency and duration of cocaine use. Prior research shows that much of the drug dose is lost as a result of the heating process when cocaine is smoked (Carrera, 2004, Jones, 1984; 1990). Nevertheless, the effects of the drug are rapid – with approximately 8-10 seconds to a user experienced high. Peak concentrations of the drug occur more rapidly via smoking and this method is also associated with greater behavioral effects that last for a relatively short duration. The fact that the effect is short term (lasting only for 8 to 10

minutes), contributes to the reinforcing nature of the drug (Carrera, 2004). A cocaine high is thus typically followed by feelings of anxiety, depression, and paranoia, which reinforces the need to take the drug again.

The pharmacokinetics (that is, the short half-life, rapid absorption and delivery) and the pharmacodynamics (that is, intense neural stimulation) of cocaine help clarify and understand the effects of the drug. Cocaine is rapidly metabolized in the liver and therefore has a short half-life of approximately 90 minutes (Carrera, 2004). The main cocaine metabolites are benzoylecgonine and ecgonine methylester, both of which are renally excreted. The chemical structure of cocaine and its metabolites is illustrated in Figure 2.1 below.

Figure 2.1. The Chemical Structure of Cocaine and its Metabolites

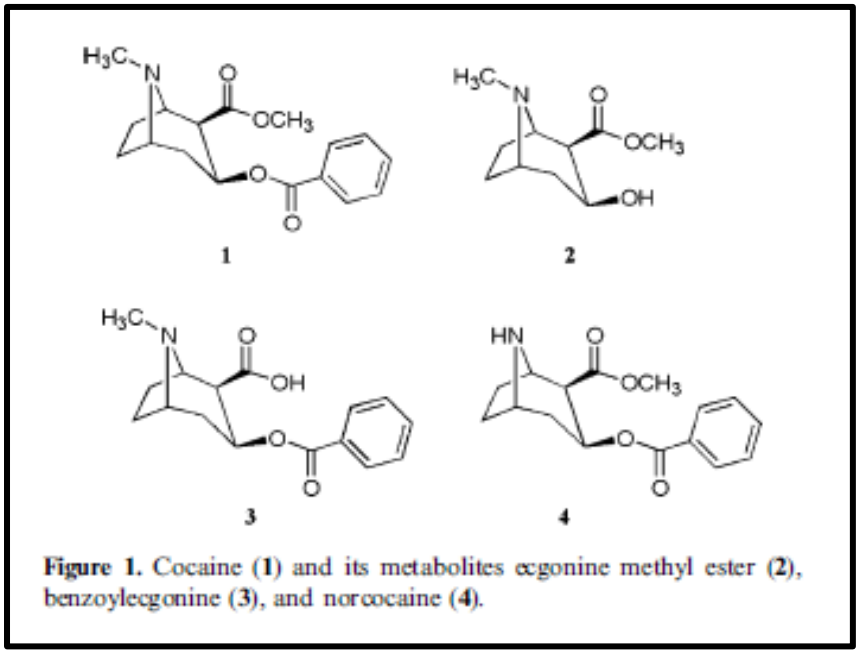


Figure 1. Cocaine (**1**) and its metabolites ecgonine methyl ester (**2**), benzoylecgonine (**3**), and norcocaine (**4**).

Citation: Carrera, M. R. A., Meijler, M. M., & Janda, K. D. (2004). Cocaine pharmacology and current pharmacotherapies for its abuse. *Bioorganic & medicinal chemistry*, *12*(19), 5019-5030.

According to Carrera et al., (2004), when administered intravenously, the "half-life elimination of cocaine varies from 16-90 minutes across different individuals. The rapid clearance of cocaine

results in a subjective 'high' produced by a single intravenous or smoked dose of cocaine, which may last only about 30 minutes" (Carrera, 2004, p.5021). This pharmacokinetic feature of cocaine is central to the reinforcing characteristic of the drug.

With respect to the neuropsychopharmacology of cocaine, cocaine is a schedule II psychomotor stimulant that inhibits the reuptake of monoamines like dopamine, norepinephrine and serotonin (Pomara et al., 2012). To illustrate, Table 2.1 below shows US Drug Enforcement Agency drug classifications. "Reuptake is the main mechanism by which these neurotransmitters are removed from extracellular spaces where they bind to and activate receptors. Therefore, cocaine potentiates neurotransmission of all three monoamines." (Izenwasser in Higgins & Katz (Eds.), 1998). Research also shows that behaviorally, cocaine increases locomotor activity triggered by its inhibition of dopamine uptake (Johanson & Fischman, 1989). There is a strong correlation between the behavioral effects of cocaine and actions at the dopamine transporter. Consequently, the dopamine transporter is sometimes called the cocaine-binding site and is responsible in large measure for the drugs reinforcing effects (Izenwasser, 1998).

Cocaine has also therapeutically be used as an anesthetic (Benowitz, 1993; Carrera, 2004). However, medical complications like hypertension, which arise due to vasoconstriction and CNS stimulation make the drug less tenable for medical use. "The effects of cocaine on the CNS and cerebral blood flow are complex" and the pathways are generally not well understood (Carrera, 2004, p.5021).

Table 2.1. Drug Scheduling by the US Drug Enforcement Agency (USDEA).

	DRUG CLASSIFICATION	DRUGS UNDER EACH CLASSIFICATION
Schedule I	Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse.	Heroin, Lysergic acid diethylamide (LSD), Marijuana (Cannabis), 3,4-methylenedioxymethamphetamine (Ecstasy), Methaqualone, and Peyote
Schedule II	Schedule II drugs, substances, or chemicals are defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are considered dangerous.	Combination products with less than 15 milligrams of hydrocodone per dosage unit (Vicodin), **cocaine**, methamphetamine, methadone, hydromorphone (Dilaudid), meperidine (Demerol), oxycodone (OxyContin), fentanyl, Dexedrine, Adderall, and Ritalin
Schedule III	Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence. Schedule III drugs abuse potential is less than Schedule I and Schedule II drugs but more than Schedule IV.	Products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), ketamine, anabolic steroids, testosterone
Schedule IV	Schedule IV drugs, substances, or chemicals are defined as drugs with a low potential for abuse and low risk of dependence.	Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, Tramadol
Schedule V	Schedule V drugs, substances, or chemicals are defined as drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes.	Cough preparations with less than 200 milligrams of codeine or per 100 milliliters (Robitussin AC), Lomotil, Motofen, Lyrica, Parepectolin

Source: Table reproduced from the United States Drug Enforcement Administration. (no date) Drug Scheduling. URL: https://www.dea.gov/drug-scheduling. Downloaded on April 4, 2019.

2.2 History of Cocaine Use in the United States

The purified form of cocaine has been in use for approximately a hundred years. However, use of coca in its natural form is traceable to prehistoric times. Coca is obtained from the leaf of the coca plant known as *Erythroxylon coca*. Some historians trace chewing of coca leaves to the 6th century A.D based on archeological evidence consisting of supplies of coca leaves in burial grounds (Petersen, 1977). The consumption of coca typically involves chewing the leaves with lime. The purpose of the lime is somewhat open to interpretation as it might be to improve the flavor of the leaves, release cocaine from the leaf, or simply to promote salivation (Petersen, 1977).

Archeological evidence indicates that coca use predates the Inca civilization. Nevertheless, the Incas integrated coca use into the fabric of society such that it had great symbolic and religious significance. Geographically, their empire encompassed what is modern day Peru, Bolivia, Ecuador, and Columbia. Only the highest classes were privileged to use coca. When coca plantations became state monopolies in the 15th century, use of the drug remained quite restricted (Montoya & Chilcoat, 2009). Nevertheless, the privilege of using the drug was sometimes extended to soldiers and workers in public works considered by the ruling elite to be deserving of the honor.

With the decline of the Inca Empire, many of the taboos associated with coca use and cultivation fell into disuse. During this period, coca lost much of its earlier religious significance and social status. Some historians are of the view that after the advent of the Spanish (c.1536), coca use was encouraged and became a means of exploitation of the Indians (Petersen, 1977). It has been asserted by some that the Spanish conquistadors recognized coca's potential to help

them obtain the labor they needed to work in mines where working conditions were less than exemplary (Petersen, 1977).

Cocaine was commonly used in folk remedies as a cure all for headaches, muscle aches, venereal diseases, and stomach ailments from the 16th to the 17th century. In the 18th century, it became the preferred stimulant drink over and above coffee and tea. Nevertheless, coca attracted little European attention until its isolation from the coca plant in 1855 by Albert Niemann of the University of Gottingen (Petersen, 1977).

Several other figures also played a role, and deserve mention in this regard. Dr. Paolo Mantegazza, an Italian neurologist for example, contributed greatly to furthering the psychopharmacology of coca. He noted the physiological and psychological effects engendered by coca. Mantegazza's early exposition on coca was highly influential for physicians such as Sigmund Freud who initially endorsed cocaine uncritically as a miracle drug capable of warding off hunger, fatigue, and sleep. By 1883, there was a growing interest in cocaine in Europe, as well as the US. In medicine, a young ophthalmologist by the name of Karl Koller became the first to be credited with using cocaine as an anesthetic in eye surgeries. Around the same time, William Stewart Halstead, a significant American medical figure started to use cocaine as a "neural block." In the process of his research, Halstead became severely cocaine dependent. Thus, by the turn of the century (1891) several reports of systemic cocaine intoxication and deaths attributable to the drug began to gradually erode the lustre of the drug (Petersen, 1977).

Medically, cocaine was useful primarily as a local anesthetic. However, by the end of the 19th century cocaine was actively being promoted by commercial interests. "Manufacturers of patent medicines, tonics and soft drinks produced a plethora of cocaine-containing products ranging from ointments, nose powders, suppositories, throat lozenges, and sprays to wines and

coca cigarettes" (Petersen, 1977, p.27). Of these, perhaps the most successful advocate was Angelo Mariani, a chemist who dedicated his life to the development and promotion of coca wine acclaimed by such luminaries as Thomas A. Edison, Auguste Rodin, and Jules Verne, among others. The soft drink called 'Coca Cola,' was another coca-containing product which became internationally famous. It contained extracts of the coca leaf as well as other ingredients for flavoring.

Although originally considered safe, acceptance of cocaine declined with a recognition of the undesirable side effects of cocaine and its potential to be a serious health hazard. Given individual variation in dose response to cocaine as well as its toxicity, government regulation of the drug seemed to be warranted to curb the indiscriminate excesses of the patent medicine era (Petersen, 1977).

The 20th century marked the start of a novel trend in the history of cocaine. It was a time when the American Medical Association began to maintain higher standards of medical training and practice including medicines with the potential to induce dependency. Between 1900 and 1920, media-generated fears associated with race-based cocaine crimes resulted in a general decline in the use of cocaine and its products. In 1914, the Federal Harrison Narcotics Act precipitated state laws that prohibited the distribution of cocaine. In essence, it reflected the view that cocaine was a bigger problem than opiates (only 29 states had laws regulating opiates vs. 46 for cocaine). The Pure Food and Drug Act of 1906 also curbed cocaine consumption by restricting "marketing of proprietary remedies containing cocaine" and requiring a list of ingredients on the label (Petersen, 1977, p.30).

The Harrison Act placed severe constraints on the availability of cocaine by requiring all those "involved in the importation, manufacture and distribution of opium, cocaine and their

derivatives" to register with the Internal Revenue Service (Petersen, 1977). Penalties for violation included fines of up to $2000 and up to five years in prison. Subsequent legislation (1922) amended the Act to make the penalty even more stringent ($5,000 fine and 10-year imprisonment) and set a pattern for subsequent state laws pertinent to cocaine.

The Comprehensive Drug Abuse Prevention and Control Act of 1970 replaced earlier federal legislation on drugs. This Act categorized drugs in schedules based on use and potential for misuse. It also required producers and distributors of controlled drugs to register with the government. Additionally, it established import-export limitations on these drugs. As compared to heroin, which was classified as a Schedule 1 drug (with no known medical use) under the new restrictions, cocaine came to be categorized as a Schedule II drug in federal as well as state legislation (with some potential for medical use but also a high potential for abuse).

The above-mentioned federal and state laws markedly changed cocaine use patterns. Widespread use by a swathe of society gave way to use among a "bohemian" set comprising artists, jazz musicians, and actors. Use also continued among affluent drug dealers. Cocaine, thus became a status drug available to an affluent minority.

2.3 Popular Perceptions about Crack during the Crack Epidemic of the '80s

By 1986, a wave of crack-cocaine had swept through the US and women's magazines were describing crack as "the 20th century's most egalitarian phenomenon," given ubiquitous use that transcended political, economic, and racial divisions. This section provides insight into how the US crack epidemic of the '80's was perceived and portrayed in popular writing (as might appear in the 'Ladies Home Journal' or 'Good Housekeeping,' for example) and how these writings shaped popular perceptions about the crack epidemic. It is as much a social commentary

as a historical reflection on prevalent attitudes and prejudices about a drug that took the US by storm.

At a time when powdered cocaine cost approximately $100 for 1 gram, crack houses sold $10-$20 bags of heroin, offering it as a way to minimize the intensity of the crash from crack. Crack itself sold for $10 to $20 a hit (Nelson, 1987). Dealers had found a way to make their product more widely available to a wider audience. During this time, statistics warning against the addictive potential of crack were making headlines. One magazine, for example, published that approximately 10% of all individuals who began to use cocaine recreationally would become drug dependent (Nelson, 1987). Crack users made up an increasingly large percentage of all cocaine users and horror stories about crack-related crimes abounded as did crack sales. Experts speculated that 'cocaine psychosis' characterized by visual, auditory and other sensory hallucinations was responsible for the spiraling number of violent crimes among crack users. Polydrug use among crack users was common and in particular, alcohol, PCP, marijuana, and pills received mention. With an increase in crack availability and use came other kinds of crime. The reinforcing nature of the drug set up a complex relationship between women, crack, and sex for example, wherein female users might engage in sex to obtain more crack.

By 1990, crack was purported to have had a more devastating impact on the sub-group of African-American women than any other illegal drug including heroin (Nelson, 1990). The hype that in general accompanied public information on crack at the height of the epidemic reflected to a large extent the uncertainty and still-nascent knowledge about the drug itself and of the mechanisms underlying the use of the drug. Nevertheless, a positive externality of the media spotlight on crack "facts" was that it extended support to people who became dependent and also

gave them the means (1-800-COCAINE hotline, for example) to connect to treatment facilities and professional organizations providing confidential advice.

2.4 Epidemiology of Cocaine Dependence

Sections 2.4 to 2.5 of this dissertation provide a descriptive review of the epidemiology of cocaine dependence and cocaine use disorders (CUD) categorized under the five main rubrics of epidemiology elucidated in Anthony & Van Etten (1998) and originally adapted from Morris's seven uses of epidemiology (Morris, 1957). These rubrics, with permission from the author are summarized in Table 2.4.

Table 2.2. The Main Rubrics and Research Questions of Epidemiology, as Applied to Clinical Syndromes of Drug Dependence

The Rubrics	General Issues	Research Question Associated with Each Rubric
1. Quantity (Prevalence + Incidence)	How Many?	In the population, how many are becoming new cases of drug dependence? How many already have become drug dependent?
2. Location (Variation)	Where?	In the population, does the frequency or occurrence of drug dependence cases vary from place to place, from time-to-time, or in relation to individual-level characteristics, conditions, or processes?
3.Causes (Etiology)	Why?	In the population, why do some people become drug dependent, while others are spared?
4.Mechanisms	How?	What sequences of circumstances, conditions, and processes lead to the development of drug dependence?
5.Prevention and Control	What Can Be Done?	What can be done to prevent, reduce, or ameliorate the adverse impact of drug dependence?

Source: Adapted from Anthony JC, Van Etten ML. Epidemiology and its rubrics. In: Bellock AS, Hersen M, eds. Comprehensive clinical psychology, first ed. New York: Pergamon, 1998, with permission. URL: https://jpo.wrlc.org/bitstream/handle/11204/3725/Epidemiology%20of%20Drug%20Dependence.pdf?sequence=3

2.4.1 Quantity

The first rubric quantifies the burden of disease. At the population level, this rubric addresses the question – "how many are affected?" It also asks, "How many are becoming

affected?" (Anthony & Van Etten, 1998). The first question pertains to the concept of prevalence or to the likelihood that an individual might become a case at some point or during a defined interval of time. The second question refers to incidence of the condition. Incidence refers to the likelihood that an individual might become a case for the first time. Based on data from the 2014-15 US National Surveys on Drug Use and Health, approximately 5% of the young adult population had used cocaine in the past year. Among males age 12 and older, about 23,000 had ever used cocaine (including crack) in 2016. Recent statistics on lifetime prevalence show a statistically significant increase in US cocaine use among males between 2016 and 2017 (n~24,000 in 2017). Lifetime prevalence was highest among non-Hispanics or Latinos (n~35,000) and lowest among Pacific Islanders (n=111). With respect to other demographic characteristics, most cocaine users age 18 and older were employed full-time and had some college education or an Associates degree.

Crack users aged 12 and older in 2017 followed similar demographic patterns. Three times as many males as females had ever used crack in their lifetime. Lifetime prevalence was highest among the non-Hispanic or Latino sub-groups and lowest among Native Hawaiians and Asians. The majority of crack users age 18 and older in 2017 had some college education and were employed full-time.

The National Comorbidity Survey, a nationally representative sample of the US population, ages 15-64 years in the 1990s, provided epidemiological estimates for developing drug dependence drug-by-drug. The population-averaged estimate for cocaine dependence was 17% (Anthony et al., 1994). This number is not very different from Wagner & Anthony (2002) estimate of about 16% becoming dependent within a decade of initiating cocaine use. Analyses from a sub-sample of lifetime cocaine users (n=2259) from the National Epidemiological Survey

on Alcohol and Related Conditions (NESARC) estimated the cumulative probability of transitioning to cocaine dependence at 20.9% for cocaine users (Lopez-Quintero et al., 2011). Within a narrowed timeframe of 24 months after cocaine onset dependence estimates for cocaine were about 5% (O'Brien & Anthony, 2005).

2.4.2 Location

The second rubric addresses the question – "Does the occurrence of drug dependence cases vary geographically in time, or with respect to individual-level characteristics, conditions, or processes?" (Anthony & Van Etten, 1998).

2.4.2.1 Variation by Geographic Region

The geographic region showing the highest cocaine use is the Northeast. Specifically, past year cocaine use among young adults in the US ranged from 4.2% in the Midwest to 6.1% in the Northeast (US NSDUH, 2016). Past year cocaine use within states varied from 1.8% in Mississippi to 10.5% in New Hampshire (See Figure 1). States like Maine, Massachusetts, and Rhode Island in the Northeast, Arizona, Colorado, and Oregon in the West, and Delaware in the South had the highest rates of cocaine use. States in the South and Midwest had the lowest rates of cocaine use. These included Alabama, Arkansas, Mississippi, Oklahoma, and Virginia, Kansas, Michigan, North Dakota and South Dakota. Additionally, cocaine use was concentrated in large urbanized metros, as opposed to rural areas.

By comparison, past year crack use in 2017 among persons age 12 and older in the US was highest in the south (n=438) and lowest in the west (n=150). Use was most frequent in less-urbanized large metros (United States, 2016).

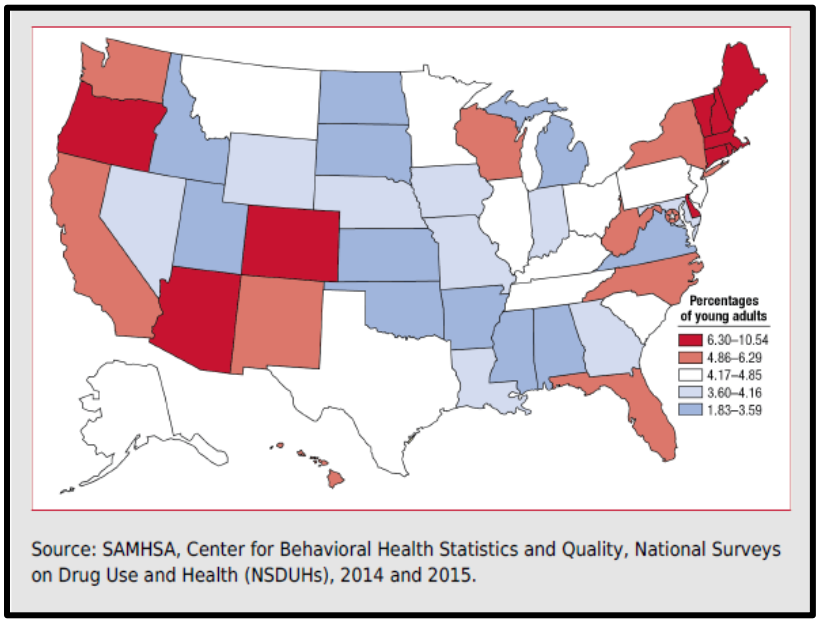
Notwithstanding the fact that Michigan was not among the states with the highest rates of cocaine use, the most recent data out of Michigan indicates that cocaine poisonings are becoming a public health concern in that state. Between 2016 and 2018, the rate of non-fatal drug

poisonings/hospitalizations involving cocaine rose 47%, while fatal drug poisonings involving cocaine rose 53% (MDHHS, 2019). Drug poisonings involving cocaine but not opioids were more likely to occur in adults 45 years and older compared to poisonings involving both cocaine and opioids (MDHHS, 2019).

2.4.2.2. Variation by Socio-demographic Correlates

Prior research indicated that cocaine use is higher among males than females (Chen & Anthony, 2004; John & Wu, 2017; O'Brien & Anthony, 2005; Rouse, 1991; Wagner & Anthony, 2007). However, there is also recent evidence showing the gender gap has narrowed with respect to cocaine use (Kerridge et al., 2019). Among other factors, changes in the norms and values surrounding cocaine use in women, increasing participation of women in the workforce and higher levels of associated work-life stress might potentially be contributing to the change.

Figure 2.2. Past Year Cocaine Use among Young Adults, Ages 18-24 by State. Data from the 2014-2015 National Survey on Drug Use and Health.



Citation: Hughes A, et al. The CBHSQ report: State estimates of past year cocaine use among young adults: 2014 and 2015. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Available at: http://www.samhsa.gov/data. Accessed July 20, 2019.

It is also worth mentioning that rates of CUD have significantly increased only for the oldest subgroup despite the fact that prevalence has significantly increased in all age groups over time, (Kerridge, 2019; Nicholson, 2019). Previously, older adults showed comparatively lower rates of cocaine use and CUD (Degenhardt, 2008, John & Wu, 2017, O' Brien & Anthony, 2005).

Variation in cocaine use by race in studies conducted prior to the 1990s showed that the prevalence of cocaine use for Whites was higher than for African Americans or Hispanics (Rouse, 1991). In contrast, recent research by Leeman et al., (2016) shows that cocaine-only use is higher among Hispanics in comparison to Whites and African Americans though Hispanics have a low risk for crack use (Palamar et al., 2015). Interestingly, in 1993, Lillie-Blanton and colleagues found that the relative odds of cocaine use did not substantively differ for African-Americans or Hispanics as compared with White Americans once neighborhood clustering was taken into account. The literature on differences in the prevalence of CUD by race is more consistent. Investigations using NSDUH and NESARC data report higher rates of CUD among African Americans (Chen & Kandel, 2002; Lopez-Quintero, 2011; Nicholson & Ford, 2019; Sartor, 2014). Identifying variation in CUD by race-ethnicity is thus an important step to tailoring prevention efforts to address cocaine dependence (Sartor, 2014).

With respect to educational levels, the year 1990 marked a transition year in which individuals with lower levels of education used more cocaine than the more educated (Harder & Chilcoat, 2007; Miech et al., 2005). In contrast, Kerridge et al., 2018 reported a significant increase in cocaine use among those with higher education between the years 2001 and 2013.

The discrepancy might be attributed to differences in the data analyzed, that is, findings from the NESARC are not always consistent with those from the NSDUH.

The NSDUH staff measure poverty level as a function of household composition, size and family income. The poverty level is a percentage of the Census Bureau's poverty threshold" (US, 2015, 2019). As of 2017, most cocaine users were at 200% of the poverty level, with the majority able to afford private health insurance (US, 2019). Sociodemographic profiles for past year crack users in 2017 showed an approximately even split among the three federally determined poverty thresholds.

2.4.3 Causes and Mechanisms

This section focuses on potential linkages explaining why some people develop cocaine dependence, while others do not. Specifically, it asks the question "what are the sequences underlying circumstances and processes that lead to the development of drug dependence?" Before exploring the literature on mechanisms of cocaine dependence, it is important to understand that drug dependence is a multi-faceted disorder influenced among other things by development, personality traits, psychiatric conditions, social stress, environmental and genetic factors. The scope of associations researched are reflective of the diversity and complexity characterizing the transition into dependence (Leis, 2017).

Co-occurrence of cocaine dependence with other drug use disorders (DUDs) such as alcohol use disorder and its comorbidity with nicotine dependence, cannabis dependence, and opioid dependence is well established in the literature (Bierut et al., 2008; Cottler, 2008). In addition to DUDs psychiatric disorders such as depression and attention-deficit hyperactivity disorder (ADHD) are more likely to occur in cocaine dependent individuals (Bohnert & Miech, 2010; Falck et al., 2008; Goldstein et al., 2012). Similarly, individuals with CUD have a higher

probability of childhood physical and sexual abuse (Shin, 2010). Grounded in the literature, Figure 2.4.3 is a conceptualization of the key associations underlying the transition to cocaine dependence.

If a sequence of events can be determined such that cocaine dependence occurs downstream from suspected genetic and social factors such as comorbid alcohol and other drug use, depression, anti-social personality disorder, and early use of stimulants like Adderall and Ritalin, then these suspected factors might be considered suspected causal factors, and might potentially explain why some cocaine initiates progress to cocaine dependence while others do not.

For ease of understanding, mechanisms associated with cocaine dependence are broadly classified as follows:

2.4.3.1 Genetic

The notion that genetics contribute to drug seeking and drug using behaviors has been gaining popularity, but it is only recently that researchers have gained some traction methodologically in their attempts to isolate specific receptor genes. The reward mechanism in humans is of key importance in assessing vulnerability to drug dependence. Doperminergic neurons constitute pathways in this mechanism and cocaine results in its stimulation. It has been hypothesized that the dopamine type 2 receptor gene (DRD2) might be involved in vulnerability to drug dependence (Comings, 1996). Research has also shown a high correlation between the frequency of DRD2 variants and multi-drug use. These early studies supported the notion that personality traits were contingent on differences in dopamine receptor variants, which in turn affected impulsive, compulsive, and addictive behaviors in persons.

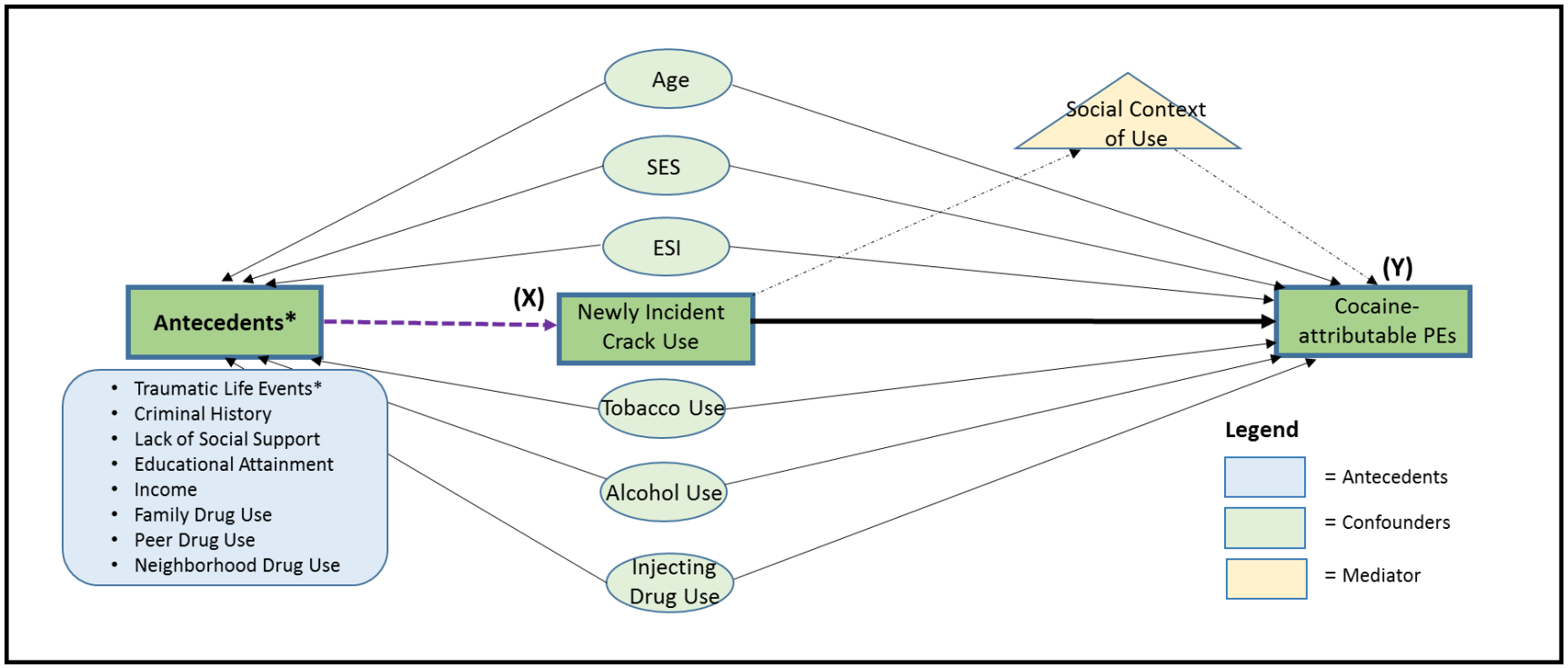
Prior literature has also identified childhood conduct disorders and adult antisocial personality disorder (ASPD) as risk factors for drug dependence (Jaffe, 1988). It has been suggested that the above disorders might also make a person more susceptible to drug use due to shared genetic factors. This line of research concluded that genetic pathways to dependence might be via biological parents with ASPD or via biological parents with alcohol problems who did not have ASPD.

Overall, genetic research has failed to tie a single gene to this spectrum of comorbid disorders. However, this body of research has successfully identified a few major genes and several other genes that modify the serotonin-dopamine balance and are therefore of note.

2.4.3.2 Social

Prior literature indicates that neighborhood disadvantage is related to drug use (Lillie-Blanton et al., 1993). Relative deprivation, poverty and social exclusion have all been cited as risk factors for drug use and dependence. Crack-cocaine for example, is more easily available in high poverty neighborhoods with social disorder (Sterk, 2014). Additionally, norms supportive of use might mediate neighborhood disorder and increased crack-cocaine use. In such neighborhoods, places facilitating use such as crack-houses, abandoned houses, and street corners or parks are more likely to emerge. Patterns of crack use might thus differ based on place and available social networks (Sterk, 2014). The context of crack-cocaine use is also influenced by socio-demographic characteristics like age. For example, older adults who initiate at a later phase in their lives tend to find it harder to support their habit as compared with those who get drawn into the drug world early.

Figure 2.3. A Conceptual Model of Suspected Factors Underlying a Prodromal Cocaine Dependence Syndrome



2.4.3.3 Pharmacological

Recent research on N-acetylcysteine (NAC) has shown its potential as a therapeutic intervention for cocaine dependence with capacity to reduce craving and cocaine-related spending (Echevarria et al., 2017). Preclinical studies indicate that "NAC reverses the disruption of glutamate homeostasis caused by long-term cocaine use, thus restoring function of the cystine-glutamate exchanger in glial cells and reversing the downregulated GLT-1 receptor" (Echevarria, 2017). However, evidence from double-blind placebo trials indicates that NAC only appears to work as an anti-relapse agent in patients who are already abstinent. This research suggests that NAC may be better suited for avoiding relapse in already abstinent subjects.

Despite promising forays into the pathways underlying cocaine dependence, the interrelationships are still not well understood leaving the area of pharmacological interventions wide open to future explorations.

2.4.4 Prevention and Control

The final rubric examines ways in which the adverse impact of cocaine dependence might be reduced or prevented. Characteristics of cocaine dependence include compulsive drug-seeking and use despite severe psychiatric, socio-economic, and legal consequences, as well as chronic relapses (Dakis & O'Brien, 2001, Karila et al., 2008). Further, although cocaine use is widespread in North America, South America, and increasingly Europe as well, there is currently no effective pharmacological treatment for cocaine dependence. Several candidates such as Topiramate, Baclofen, and Vigabatrin (all GABA agents) and others such as Modafinil, Disulfiram, and Methylphenidate (agonist agents) have been extensively investigated and continue to hold promise as a potential treatment for cocaine dependence (Haney et al., 2006, Hart et al., 2007, Higgins et al., 1993, Gossop & Carroll, 2006, Karila et.al, 2008). The

anticocaine vaccine, N-Acetylcysteine, and ondansetron are currently under review. Additionally, medications slated for use in other conditions have also shown some efficacy. Notwithstanding these advances, most of these findings have yet to be corroborated in larger trials with less selective populations. To date, no medication is FDA approved for the treatment of cocaine dependence.

2.4.4.1 GABA Agents

Prior research indicates that cocaine influences neurotransmitter systems like GABA and glutamate. Preclinical studies involving GABA agents such as topiramate, for example, indicate that topiramate reduces cocaine self-administration via a decreased doperminergic response (Kampman et. al., 2004, Karila et al., 2008). The first double-blind randomized clinical trial using topiramate in conjunction with CBT showed significantly lower cocaine use in the treatment group compared with a placebo. Continuous abstinence was maintained by 59% for at least 3 weeks after. Baclofen is another drug that has shown reduced cocaine-seeking behavior as well as cocaine craving in preliminary clinical studies (Brebner et al., 2002, Ling et al, 1998). The first randomized trial with Baclofen indicated reduced cocaine use among heavy cocaine users and the effect was significant (Shoptaw, 2003). Additionally, research has shown that Baclofen has some anxiolytic and anti-depressant effects indicating that the utility of baclofen might extend to addressing psychiatric comorbidity in addition to cocaine dependence. Clinical evidence was also favorable for other GABA agents such as Tiagabine, and Vigabatrin.

2.4.4.2 Dopamine Agents

The hypothesis that blocking dopamine receptors might also block cocaine's action is a plausible one given the direct correlation between the dopaminergic system and cocaine's action and forms the basis for research on dopamine agents. Buproprion is an antidepressant approved

for nicotine dependence but with low clinical efficacy for treating cocaine dependence (Karila et al., 2008). Laboratory studies have shown that second generation neuroleptics such as Risperidone and Aripiprazole can reduce cocaine craving and euphoria. However, this benefit does not trigger in patients without psychiatric comorbidities (Grabowski et al., 2004). Clinical trials with respect to Aripiprazole are currently underway to evaluate its efficacy to address cocaine dependence.

2.4.4.3 Agonist Replacement Therapy

Agonist replacement therapy uses a drug from the same pharmacological family as the drug of abuse to suppress withdrawal and craving. An example is the use of methadone to address heroin dependence (Gorelick, 1998). Disulfiram, methylphenidate, modafinil, d-amphetamine, and oral cocaine are all examples of agonist medications. There is some clinical evidence to indicate that sustained release oral methylphenidate and modafinil might reduce the effects of cocaine withdrawal and thus the need to use cocaine (Karila, 2008). It may be considered a substitute treatment for cocaine dependence akin to buprenorphine for heroin dependence. However, a recent trial showed that modafinil shows efficacy only in the subgroup who do not have alcohol dependence. The high comorbidity between cocaine and alcohol dependence prompted research into disulfiram as a treatment approach, the rationale being that a decrease in alcohol dependence might correlate with a decrease in cocaine use and dependence (Karila et al., 2008, Xi, 2012). Evidence from published trials indicates that disulfiram decreases cocaine use in outpatients who don't have comorbid alcohol dependence. A caveat, however, is that the cocaine and alcohol-disulfiram interaction is associated with severe cardiovascular outcomes (Karila et al., 2008). Other medications that have shown varying degrees of success in

the treatment of cocaine dependence include d-amphetamine and coca leaf chewing (Grabowski, 2004).

2.4.4.4 Vaccine Pharmacotherapy

The basic principle of vaccine pharmacotherapy is getting antibodies to isolate cocaine molecules (Carrera et al., 2004, Karila et al., 2008). Animal studies on cocaine vaccines have shown significantly reduced behavioral effects of cocaine (Kantak et al., 2000). Advantages of this approach include no direct psychoactive effects and better treatment adherence (Kosten & Owens, 2005). A potential disadvantage is the amount of time it can take to achieve the levels of antibodies necessary to treat cocaine dependence.

To date, there is no single medication that has been effective in addressing cocaine dependence fully. However, several promising options exist and research into these treatments is ongoing. Integrating pharmacological and psychosocial treatment to address comorbid psychiatric issues and concurrent dependence is important when implementing pharmacological treatment for cocaine dependence (Karila et al., 2008).

2.4.4.5 Approaches to Harm Reduction

Historically, treatment approaches to addressing the issue of drug dependence in the US has focused on eliminating drug use. More recently, interventions focused on minimizing drug use associated harms for individuals and communities have received attention in the US and elsewhere (Voon, 2018). The UNODC (2008) states that prevention, treatment, and harm reduction are complementary strategies. The main objective of strategies that focus on harm reduction is to mitigate negative effects of drug dependence by minimizing the risk of contracting infectious diseases, overdosing etc. Harm minimization also addresses issues that

affect the quality of life such as family, social, and legal problems. Strategies might vary based on the drug and the needs of the individual who consumes the drug (Ritter & Cameron, 2006).

Harm minimization strategies reduce drug harms by modifying drug use behaviors pertaining to drug acquisition, use and withdrawal. The UNODC (2008) categorizes harms into three types enumerated below.

- **Drug acquisition harms** are associated with exposure to high-risk criminal behavior.
- **Drug use harms** pertain to the amount of the drug, frequency of use, and mode of administration. The pharmacology of drugs differs and impacts an individual's health in different ways. In the case of cocaine for example, the mode of administration is associated influences the nature of physical problems experienced by the user. Injection drug use (IDU) may lead to abscesses and problems with veins with an increased risk for HIV and other infectious diseases as a result of needle sharing and sharing drug paraphernalia. Cocaine-associated morbidity and mortality is high and may be affected by factors such as drug dose, purity, frequency, duration, mode of administration, and polydrug use.
- **Drug withdrawal harms** refer to the experience of stopping drug use or reducing it, both of which might affect the social and professional functioning.

General Harm Reduction Strategies include components such as educating the public about risks and harms associated with drug use, brief interventions and counseling, and interventions that help reduce injury and violence. Specific to the sub-population of injecting drug users, harm reduction might encompass **low-threshold pharmacological interventions** (opioid antagonist drugs). Drug substitution can help switch users from illegal drugs to drugs prescribed by a health professional with intent to minimize medical problems and the risk of overdose. Additionally, drug substitution reduces crime by lowering the urgency to acquire the

drug. When health professionals maintain contact with a user, the likelihood of treatment adherence increases and health professionals are better able to prevent drug relapse.

Needle exchange programs typically promote the safe disposal of injecting paraphernalia while also raising awareness of the risks of infectious disease associated with injecting drug use. Strategies include providing instructions about how to safely inject, provision of sterile syringes and information on safe injection drug use practices that include how to disinfect and safely dispose of syringes, needles, and other equipment.

Emphasizing alternative routes of administration over injection routes can also help reduce the initiation of IDU among new users. Routine wound care and maintenance, HIV testing and counseling, and controlling sexually transmitted diseases are other components of harm reduction programs focused on injection drug use. Harm reduction strategies may differ by sex based on social, political and cultural factors. For example, sex workers and HIV-positive females who are breastfeeding require specific attention.

Finally, **social assistance for marginalized** sub-populations that are drug dependent can include vaccination programs against hepatitis, medication, emergency kits with Naloxone for overdoses, and well-trained peer outreach workers who have the ability to connect with drug dependent individuals who are in need of assistance (Radcliffe et al., 2016).

2.5 Significance

The 2016 United Nations General Assembly Special Section on Drugs (UNGASS, 2016) recognized drug dependence as a "complex multifactorial health disorder characterized by chronic and relapsing nature that is preventable and treatable rather than a result of moral failure or criminal behavior." Historically, strategies to address drug use disorders have been constrained on account of the stigma surrounding dialogue and response to drug use. The

UNGASS (2016) guidance embodies "a radical shift from criminal justice to public health" (Volkow et al., 2017). Philosophically, this dissertation takes a public health approach to the complex problem of drug dependence in keeping with the guidance provided by the UNGASS.

Prior research has mainly focused on the effect of cocaine on human experiences. However, there has been no research on variations in cocaine dependence over the course of the last decade. This dissertation fills this gap by estimating a 15-year epidemiological trend in the proportion of the population transitioning from cocaine initiation to dependence within 12 months. Epidemiological estimates such as these can be especially useful when educating patients, professionals, and the public about potential hazards that are faced soon after drug use starts.

The second aim provides novel evidence on the estimated differences in the occurrence of cocaine-related side effect problem experiences (SEPE) among sub-groups of cocaine users – a crack + powder group contrasted with a powder only group. This evidence suggests that treatment modalities for different subgroups of cocaine users might need to be tailored based on the route of administration of the drug.

The third aim shifts focus from the rubric of quantity to the rubric of prevention and control with an investigation into community public health measures to address comorbid cocaine use among justice-involved individuals at a county jail.

Collectively, this dissertation makes a valuable contribution to the existing literature on cocaine dependence by shedding new light on national trends in cocaine incidence and highlighting with current data the observed differences in the risk of developing cocaine-related side-effect problems and experiences among sub-groups of cocaine users stratified based on

route of administration. These are facets of cocaine dependence that have previously not received adequate attention.

CHAPTER 3: MATERIALS AND METHOD

3.1 The Population under Study and Sample Design

The population of interest for the National Surveys on Drug Use and Health (NSDUH) consists of non-institutionalized individuals ages 12 and older in the US. The survey is cross-sectional, and is administered annually to civilian residents encompassing residents of households and individuals in non-institutionalized group quarters that include college dormitories, boarding houses and shelters (United States, 2019). Exclusions include homeless individuals, individuals not in shelters, active military personnel, and institutionalized individuals in correctional and long term care facilities and mental institutions (United States, 2015; 2019). A description of the sample design for the NSDUH closely follows the description provided in the NSDUH methodological resource from 2014 and 2019 as enumerated below.

Every year, independent, multi-stage probability samples are collected by NSDUH staff from each state and the District of Columbia. The state is therefore the first level of stratification. Equal-sized state sampling regions (SSRs) are determined from within each state. Next, census tracts are selected within each SSR, census block groups within each census tract, and area segments, which are a collection of census blocks within census block groups. Dwelling units are then selected within each area segment and as a final step, two individuals from each dwelling unit are selected for the interview (United States, 2019).

As compared with earlier surveys, the 2014-2017 sample design made the sample sizes proportional to the state population sizes with intent to improve precision of estimates (United States, 2015). Prior to the 2014 redesign, the eight largest states had a target sample size of 3,600, while the rest had target sizes of 900 each (United States, 2015). The sampling frame for

2014-2017 was based on population projections from the 2010 census as well as data from the 2006 to 2010 American Community Surveys (ACS). In contrast, the sampling frame for the 2005-2013 surveys were from the 2000 census (United States, 2015; 2019).

3.2 Participation Levels

From the 2002 NSDUH through the most recently conducted survey respondents have been given a $30 incentive for survey participation (United States, 2018). As compared with prior surveys, this incentive increased survey response rates and reduced the need to select more households. Recently, however, NSDUH response rates have declined, and number of selected households has increased. Between 2014 and 2018, this need was offset by selecting fewer youths in the age-group 12 to 17 years, thus requiring fewer selected households per interview (United States, 2019). In a two-stage survey like the NSDUH, three types of response rates might be calculated. These include i) the household response rate, ii) the response rate of the individual selected via the screener, and iii) an unconditional response rate representing the number of interviews in the second stage divided by the number of persons eligible to be interviewed if all households had been successfully screened (Czajka & Beyler, 2016). The unconditional response rate is estimated as the product of the first two response rates. To illustrate, if 88% of sample households were screened and 70% of the selected respondents were interviewed, then the unconditional response rate would be (88x70)/100=62% (Czajka, & Beyler, 2016). NSDUH response rates (conditional as well as unconditional) as reported by Czajka & Beyler (2016) are reproduced in table 3.1. The table illustrates participation levels for the NSDUH in the range 60%-75% for the years 2002 to 2014. For 2017, the response rate was 50.4%.

It is an established fact that surveys asking about drug use might be particularly vulnerable to nonresponse bias defined by Gfroerer et al (1997) as "the nonresponse rate multiplied by the difference in the characteristic of interest among respondents and non-respondents" (Gfroerer, Lesser, & Parsley, 1997). Nevertheless, a study comparing 1990 census data with NSDUH non-respondents reported that high drug use rates in populations and low response rates do not necessarily correlate (Gfroerer, Lesser, & Parsley, 1997). In that study, high income older adults had low response rates as well as low rates of drug use suggesting thereby, that "many of the potential sources of bias could cancel each other in estimates of overall prevalence" (Gfoerer, Lesser, & Parsley, 1997).

Table 3.1: Response Rates for the National Surveys on Drug Use and Health, 1999 to 2014.

Survey Year	Screening	Conditional Interview	Unconditional Interview
1999	**90.1**	74.2	66.8
2000	**93.0**	78.0	72.6
2001	**91.8**	76.8	70.5
2002	**90.8**	84.5	76.8
2003	**91.0**	83.0	75.6
2004	**91.3**	82.7	75.4
2005	**91.3**	81.5	74.4
2006	**90.2**	79.7	71.9
2007	**88.8**	79.0	70.2
2008	**88.8**	79.3	70.4
2009	**88.6**	80.2	71.0
2010	**88.3**	79.8	70.4
2011	**87.0**	79.2	68.9
2012	**86.2**	77.9	67.1
2013	**84.4**	76.4	64.5
2014	**82.6**	74.1	61.2

Source: Year 1999 response rates obtained from Gfroerer et al. (2002), available at: http://media.samhsa.gov/data/NHSDA/redesigningNHSDA.pdf [January 2016]. Year 2000-2012 response rates obtained from multiple annual issues of the NSDUH Data Collection Final Report, available by choosing individual years from http://media.samhsa.gov/data/Methodological_Reports.aspx [January 2016]. Year 2013-2014 response rates obtained from Center for Behavioral Health Statistics and Quality (2014, 2015).

3.3 Assessments

Field Interviewers (FI) with the NSDUH conduct in-person interviews designed to increase respondents' willingness to talk about sensitive issues like drug use and mental health. The confidentiality of respondents is emphasized via computer assisted interviewing techniques (CAI) that maintain anonymity of subjects because they do not collect respondent names with the data (United States, 2017).

Letters are sent in advance of the FI visit to sampled addresses. The FI typically speaks with an adult resident of the household (18 years of age or older), who serves as the screening respondent (United States, 2017). The FI then records basic demographic data about the respondent via a hand-held computer. Based on a pre-programmed selection algorithm and the composition of the household, the computer selects between zero and two individuals for the interview. The selection process usually yields adequate sample sizes for specified population age-groups (United States, 2017)

English as well as Spanish versions of the NSDUH interview are available and have the same content. In areas that are predominantly Spanish-speaking, the initial letters are mailed with a Spanish version. If no English speakers are available, a certified Spanish-speaking FI visits the address. If the sampled person speaks neither English nor Spanish, then the interview is not conducted. The survey does not get translated into languages other than English and Spanish.

The FI conducts the interview, which is about an hour long in the respondent's home. The interview has 2 components - computer assisted personal interviewing (CAPI), as well as audio computer assisted self-interview techniques (ACASI) (United States, 2017). For CAPI, the interviewer reads out questions to the respondent and enters the answers into a computer. For the ACASI portion, however, the respondent self reads or listens to the questions on headphones

and inputs responses into the computer without revealing responses to the interviewer. The drug use module is self-reported and includes alcohol, tobacco, marijuana, cocaine, crack-cocaine and other stimulants, heroin, hallucinogens, and inhalants. The module on mental health typically follows the drug use questions. Demographic data on household income, education, school enrollment, household composition and health insurance among others are administered in CAPI mode.

3.4 Statistical Analyses

The three manuscripts within this dissertation provide a detailed description of the respective analytical approaches taken, however, a few preliminary statements pertinent to the NSDUH sampling approach, which affect statistical analyses carried out with these data deserve mention.

First, the multi-stage sampling approach of the NSDUH mentioned earlier imposes certain constraints on the confidence intervals – namely, the standard formulae for variances and confidence interval estimation do not necessarily hold. The key reason for this is that persons sampled within a census block are likely to be more similar to one another than persons drawn at random from a national registry. The research approach taken in this dissertation is adapted to address these interdependent observations.

Second, in probability sampling surveys of this type, the sample selection probability might vary. We can conceptualize this source of variation via an example. Consider a dwelling unit that consists of only one individual who is eligible to participate in the survey. The probability of selecting that individual is 100%. Now consider the scenario where there are two potentially eligible participants. The probability of selecting one of these at random is 50%. Finally, consider a situation where there are three potentially eligible individuals. Now the

probability of selection is 33.3%. Fundamental principles of survey statistics indicate that valid estimations of summary statistics on data such as this requires the application of analysis weights using the inverse of selection probabilities.

A final consideration for the NSDUH is the use of a post-stratification adjustment factor to compensate for non-response participation levels not under the control of the researcher. The key advantage of such a post-stratification adjustment factor is that it might make survey estimates more credible than they would otherwise be. To illustrate, suppose females sampled are more likely to participate than males and after application of survey weights we obtain a female-male ratio of 55 to 45. Based on census figures, the ratio should look more like 51 to 49. We can in effect make a correction to the analysis weights via a post-stratification adjustment factor that brings the skewed ratio into alignment with the appropriate census value. All estimates produced for this dissertation project use the appropriate analysis weights, and take into account the inverse of selection probabilities as well as a post-stratification adjustment factor using US Census Bureau tables as the standard.

The next chapter provides a 15-year trend analysis of the transition from cocaine initiation to dependence. As a note for readers, the material presented in this chapter has been accepted for publication in the journal, *Drug & Alcohol Dependence*.

CHAPTER 4 - COCAINE DEPENDENCE: "SIDE-EFFECT" AND SYNDROME FORMATION WITHIN 1-12 MONTHS AFTER FIRST COCAINE USE (Manuscript 1 – In Press, *Drug & Alcohol Dependence*, February 2020)

Abstract

Background: This project offers new epidemiological estimates for DSM-IV cocaine dependence among sub-groups of newly incident cocaine users in the United States (US), including estimated attack rates for 21 dependence-related cocaine side effect problems and experiences occurring <12 months after onset.

Method: In 2002-2016, US National Surveys on Drug Use and Health (NSDUH) sampled, recruited, and assessed cocaine experiences of non-institutionalized civilians. Unweighted estimates for year-pairs (2002-3 to 2015-16) are from 3488 cocaine powder-only initiates and 275 powder-then-crack initiates (all evaluated <12 months after onset). Analysis-weighted attack rate estimates are incidence proportions with 95% confidence intervals (CI), summarized via meta-analysis.

Results: Evaluated <12 months after onset, meta-analysis summaries show 5% of powder-only initiates developed cocaine dependence (95% CI = 4%, 6%) versus 22% of powder-then-crack initiates (95% CI = 17%, 29%). For several cocaine side effect problems and experiences (e.g., 'loss of control' indicators) there is a statistically robust crack-associated excess risk.

Conclusions: Three interpretations of observed crack-associated excess risk are especially cogent and deserving of continued inquiry: (1) Powder-then-crack initiates start with heightened dependence risk susceptibilities (i.e., pre-dating onset); (2) Powder-using initiates become cocaine dependent and then start using crack; (3) The cocaine delivery variant of 'crack-smoking' is more toxic than powder insufflation. For powder-then-crack initiates, the cocaine

dependence risk (22%) is modestly lower but statistically undifferentiable from a recently estimated risk of heroin dependence <12 months after heroin onset (30%). Clinicians can use these side effect estimates in an evidence-based diagnostic workup when patients disclose new onsets of cocaine use.

Keywords: Cocaine dependence; Incidence; Random effects meta-analysis; Crack-cocaine; Cocaine powder; National Survey on Drug Use and Health; NSDUH.

4.1 Introduction

In the United States (US), on each day an estimated 3000 individuals start using cocaine hydrochloride powder (Lipari et al., 2017). For some powder-only initiates, cocaine-using repertoires quickly expand. Corresponding daily estimates are: (1) about 240 showing a powder-then-crack sequence; (2) 50-135 experiencing cocaine dependence (CD); (3) about 25-35 injecting cocaine. Whereas some estimates have suggested an end to crack epidemics in the US, recent international reports show emerging crack use in other countries. In some areas of North America and Europe, overall cocaine use has been increasing (Bisch et al., 2019; European Monitoring Centre for Drugs and Drug Addiction 2019; Parker & Anthony, 2014; United Nations, 2019).

This short communication explores crack-associated toxicity. It presents the first published estimates of cocaine dependence attack rates (AR) as incidence proportions for two subgroups of cocaine initiates evaluated within 12 months after onset: (1) a larger subgroup that starts with powder (mainly nasal insufflation) but never has used crack, and (2) a smaller powder-then-crack subgroup, with all crack onsets occurring *after* powder onset. Precursor and prodromal experiences for CD syndrome formation also merit attention. Accordingly, the paper shows estimated attack rates for dependence-related cocaine side effect problems and experiences (SEPE), all occurring <12 months after cocaine onset. [Appendix Table B1 explains SEPE and identification of newly incident users.]

The study's hypothesized expectation is one of crack-associated excess risk, not only for CD syndromes, but also for cocaine SEPE. This expectation is from an evidence base that includes commentaries and estimates published before 1990 (e.g., Fischman, 1988; Strang & Edwards, 1989; Washton, Gold, & Pottash, 1986), as well as later field surveys and patient-

oriented investigations (e.g., Benowitz, 1993; Chen & Anthony, 2004; Gossop, 1994; Hatsukami & Fischman, 1996; Lopez-Quintero et al., 2011; O'Brien & Anthony, 2005; Reboussin & Anthony, 2006). Contributions by Strang and Edwards (1989) and by Hatsukami and Fischman (1996) make clear that 'crack' (cocaine base) denotes a cocaine delivery variant, but *per se* is not a 'different' drug.

This cocaine study's research approach is matched with that of recent work on newly incident heroin users (Rivera et al., 2016). Alignment of approach facilitates direct comparison of published heroin dependence risk estimates with this study's new subgroup estimates for cocaine dependence. Notably, the cocaine dependence estimates (22%) produced here are not significantly different from published heroin estimates (30%) at a 5% significance level.

4.2. Materials and Method

4.2.1. Study Population and Design

Each year, 2002-2016, National Surveys on Drug Use and Health (NSDUH) staff members followed institutional review board-approved protocols to sample, recruit, and assess non-institutionalized US civilian residents, age 12-years-and-older. They drew multi-stage area probability population samples of dwelling unit residents. Across stages, sampling covered states, sub-state areas, and non-institutional dwelling units (including homeless shelters, college dormitories, and other group quarters, plus households), as well as dwelling unit rosters. Each year's sample included >50,000 individuals, with participation levels >70% (United States, 2017).

NSDUH staff prepared public release Restricted-use Data Analysis System (RDAS) year-pair datasets for analysis-weighted estimation via online cross-tabulations (i.e., 2002-3, 2004-5, …, 2015-16). RDAS datasets include standardized variables identifying lifetime ever-

users, past-year users, and past-year initiates. Michigan State University's institutional review board reviewed RDAS study plans, judging them as 'not human subject research.'

4.2.2 Survey Assessments

NSDUH assessments involved audio computer-assisted self-interviews (ACASI) with standardized multi-item modules on drug and health topics. Drug-specific ACASI modules identified cocaine initiates (any form) with onsets <12 months before assessment, differentiating powder-only versus powder-then-crack subgroups. (NSDUH technical staff confirmed absence of crack-only and crack-then-powder users in these samples).

ACASI items ask about 21 side effect problems and experiences with cocaine as used in any form, without asking what was caused by powder and what was caused by crack. Responses identified cocaine dependence cases based on the Diagnostic and Statistical Manual, Fourth Edition, DSM-IV (American Psychiatric Association, 1994). Table 4.2 shows wording of items and Appendix B1-B3 shows other case ascertainment details.

4.2.3 Statistical Analyses

RDAS online analysis software produced seven year-pair attack rate (AR) estimates for each cocaine subgroup. AR numerators are analysis-weighted numbers of initiates becoming DSM-IV cocaine dependence cases between onset and assessment; denominators are analysis-weighted new initiates. Variance and 95% confidence interval (CI) approximations are from Taylor series to account for NSDUH design effects. Table 4.1 shows unweighted effective sample sizes based on back-calculation methods (Vsevolozhskaya & Anthony, 2014): n=194-590 powder-only initiates; n=9-96 powder-then-crack initiates.

Table 4.1: Effective Sample Size by Year-Pair for Newly Incident Users of Cocaine Hydrochloride 'Powder-Only' and 'Powder-only' + Crack-Cocaine. Data from the Restricted Data Analysis System Online, NSDUH (2002-2016).

Year-Pairs	Effective n of Newly Incident 'Powder-only' Users	Effective n of Newly Incident 'Powder-only' Users + Crack
2002-03	590	96
2004-05	637	58
2006-07	651	32
2008-09	429	34
2010-11	428	26
2012-13	194	20
2015-16	559	9

Notes: 1. The year-pair 2014-15 is omitted from this table to be consistent with Figures 1 and 2. For the year-pair 2014-15, the number of 'Powder-only' users = 532. The number of 'Powder-only' + Crack =NTS (Numbers too small).
2. The effective sample size calculation is based on a back-calculation method specified in detail elsewhere (See Vsevolozhskaya & Anthony, 2014 https: www.ncbi.nlm.nih.gov/pubmed/25175545).

Table 4.2. ACASI Coverage of Cocaine Problems and Experiences in the United States National Surveys on Drug Use and Health, 2002-2017.

PEs	Items as worded in the ACASI module	Tolerance [a.]	Withdrawal [b.]	Impaired Control [c.]	Activities [d.]	Time Spent [e.]	Contd. Use [f.]
PE1	Wanted to/tried to cut down/stop using cocaine during the past 12 months			X			
PE2	Spent a month or more getting over the effects of cocaine used in the past 12 months					X	
PE3	Tried to set limits on how much cocaine used or how often used during the past 12 months			X			
PE4	Not able to keep limits or used more than intended in the past 12 months			X			
PE5	Needed more cocaine to get the same effect as before in the past 12 months	X					
PE6	Same amount of cocaine had less effect during the past 12 months	X					
PE7	Spent a lot of time (month or more) getting/using cocaine during the past 12 months					X	
PE8	Was not able to cut down/stop using cocaine every time during the past 12 months			X			
PE9	Was not able to cut down/stop using at least one time in the past 12 months			X			
PE10	When cut down on cocaine, felt blue during the past 12 months						
PE11	Experienced 2+ cocaine withdrawal symptoms during the past 12 months or had 2+ withdrawal symptoms at the same time		X				
PE12	Cocaine caused problems with emotions/nerves or mental health in the past 12 months		X				
PE13	Continued to use cocaine despite emotional problems						X

Table 4.2 (cont'd)

PEs	Items as worded in the ACASI module	Tolerance [a.]	Withdrawal [b.]	Impaired Control [c.]	Activities [d.]	Time Spent [e.]	Continued Use [f.]
PE14	Physical problems caused or worsened by cocaine in the past 12 months		X				
PE15	Continued to use cocaine despite physical problems						X
PE16	Spent less time engaged in important activities because of cocaine use				X		
PE17	Cocaine caused serious problems at home /school/work in the past 12 months (Serious problems defined as neglecting their children, missing work or school, doing a poor job at work or school, and losing a job or dropping out of school).				X		
PE18	Cocaine caused you to engage in dangerous activities in the past 12 months			X			
PE19	Using cocaine caused problems with the law during the past 12 months			X			
PE20	Using cocaine caused problems with family/friends during the past 12 months			X			
PE21	Continued to use cocaine despite problems with family/friends						X

Notes: The DSM-IV case definition for Cocaine Dependence is based on the concept of syndromic 'running together' of at least three of the six criteria listed in columns of this table. ACASI items that 'tap' each criterion's subject matter are indicated with an 'X' in the corresponding columns. Some of the indicated items are combined in an computerized algorithm and do not by themselves indicate fulfillment of the criterion. The Cocaine Dependence case definition also states that three of the criteria must be fulfilled during a 12 month interval (i.e., a 'clustering' of the criteria as described in Hasin et al., 2006).

[a.] **Tolerance:** "A need for markedly increased amounts of substance to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of substance."

[b.] **Withdrawal:** "The characteristic withdrawal syndrome from the substance or same substance (or a closely related) is taken to relieve or avoid withdrawal symptoms."

[c.] **Impaired Control:** "Persistent desire or one or more unsuccessful efforts to cut down or control use. Using in larger amounts or over a longer period than the person intended."

[d.] **Activities:** "Important social, occupational, or recreational activities given up or reduced because of use."

[e.] **Time Spent:** "A great deal of time spent in activities necessary to obtain, to use or to recover from the effects of use."

[f.] **Continued Use:** "Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by use."

Citation for the 6 criteria: Hasin, D., Hatzenbuehler, M. L., Keyes, K., & Ogburn, E. 2006. Substance use disorders: diagnostic and statistical manual of mental disorders, (DSM-IV) and International Classification of Diseases, (ICD-10). *Addiction*, *101*, 59-75

Meta-analysis summary estimates are from Stata MP Version 15 software (StataCorp LLC), with 'fixed effects' (FE) estimators unless chi-square tests of heterogeneity were significant at alpha=0.05. Heterogeneity, when detected, prompted use of the 'random effects' (RE) estimator because RE models typically produce more conservative estimates via wider confidence intervals (Harris et al., 2013). Appendix B3 provides technical details on the differences between these estimators.

The term 'heterogeneity' here specifically references between year study variability on account of NSDUH post-stratification adjustments in analysis weights (2002-2016) as well as time varying sources of variation such as the opioids crisis. The meta-analysis summary estimate obtained from combining each year-pair-specific estimate is preferable to pooling all years of individual level data together because this approach takes into account the variability between each NSDUH year-pair under study.

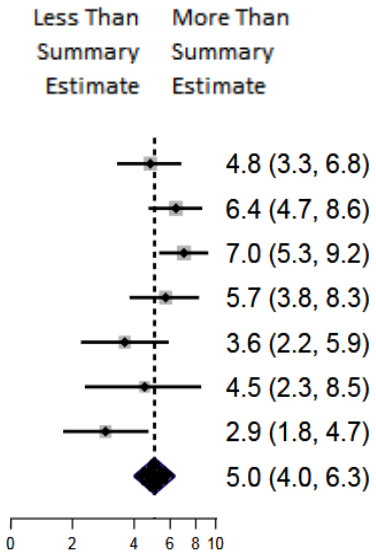
4.3 Results

Figure 4.1 in two panels presents estimated cocaine dependence attack rates (AR). Heterogeneity test statistics with a p-value <0.05 indicated the need to use the DerSimonian & Laird (1986) random effects approach to estimate the meta-analysis summary (MAS). For cocaine powder-only initiates (Panel A), the MAS AR estimate shows an estimated 5% becoming CD cases within 1-12 months after powder onset (95% CI = 4.0%, 6.3%). For powder-then-crack initiates (Panel B), the corresponding random effects MAS AR estimate is 22% (95% CI = 16.7%, 29.4%). Year-pair-specific AR estimates are shown in columns to the right. Footnotes provide additional methodological details of note.

Figure 4.1. Random Effects Meta-Analysis Summary Estimates of Cocaine Dependence among Sub-groups of Cocaine Users. Data from the United States National Surveys on Drug Use and Health (2002-03 to 2015-16).

Panel A. Powder-Only Users Who Have Never Used Crack

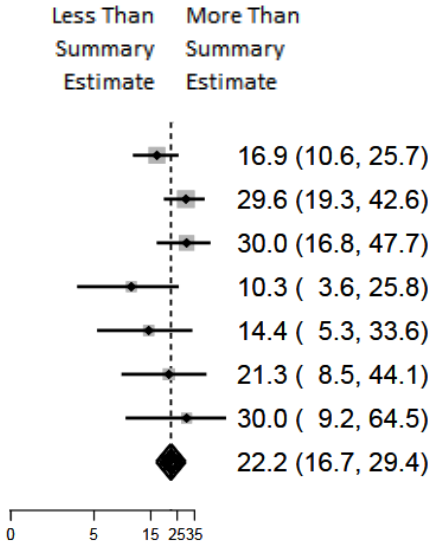
Survey Year	Newly Incident Powder-Only Users [a] No.('000)[b]	Estimated Proportion (%) Who Had Developed Cocaine Dependence (95% CI)
2002-03	904	4.8 (3.3, 6.8)
2004-05	851	6.4 (4.7, 8.6)
2006-07	855	7.0 (5.3, 9.2)
2008-09	648	5.7 (3.8, 8.3)
2010-11	628	3.6 (2.2, 5.9)
2012-13	597	4.5 (2.3, 8.5)
2015-16	1017	2.9 (1.8, 4.7)
Meta-analysis Summary Estimate		**5.0 (4.0, 6.3)**



[a] Excludes all individuals who had tried crack-cocaine even once. [b] Projected number in thousands each year in the US.

Panel B. Powder-Only Users Who Then Started Crack-Cocaine Use.

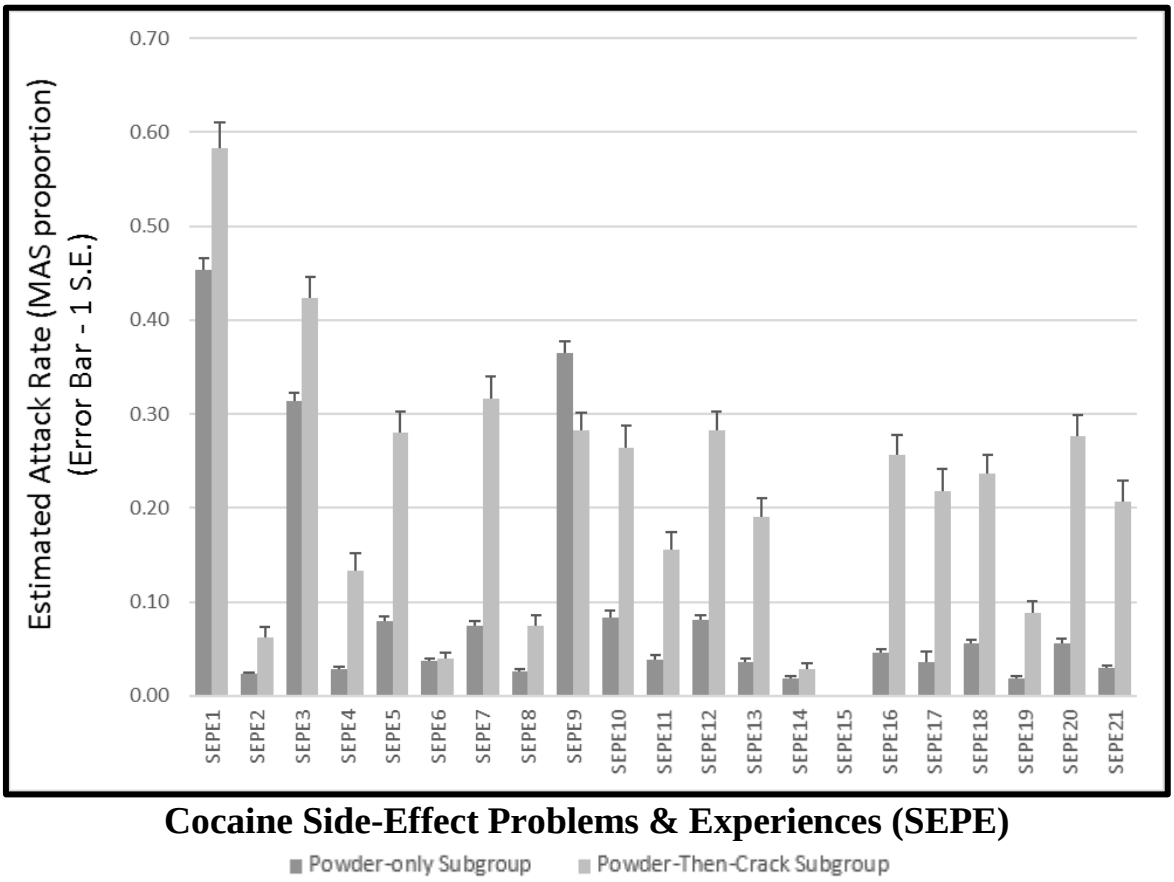
Survey Year	Newly Incident Powder + Crack Users [a] No. ('000)[b]	Estimated Proportion (%) Who Had Developed Cocaine Dependence (95% CI)
2002-03	113	16.9 (10.6, 25.7)
2004-05	84	29.6 (19.3, 42.6)
2006-07	95	30.0 (16.8, 47.7)
2008-09	38	10.3 (3.6, 25.8)
2010-11	30	14.4 (5.3, 33.6)
2012-13	24	21.3 (8.5, 44.1)
2015-16	16	30.0 (9.2, 64.5)
Meta-analysis Summary Estimate		**22.2 (16.7, 29.4)**



[a] Includes individuals who used crack-cocaine for the first time during the same 12 month interval as first use of cocaine powder. In this sample, all crack users had tried cocaine powder prior to first crack use. [b] Projected number in thousands each year in the US.

Figure 4.2 is a histogram that shows 21 cocaine SEPE on the x-axis. Y-axis estimates are MAS attack rates for each SEPE, with error bars. The most and least frequent SEPE were the same in both subgroups. Most frequent was 'wanting or trying to cut down or stop using cocaine,' with a powder-only attack rate of 45.4% (95% CI=43.1%, 47.9%) versus a larger ($p<0.05$) powder-then-crack AR of 58.3% (95% CI=53.0%, 64.2%). The least frequent SEPE was 'continuing to use despite physical problems caused or worsened by cocaine,' with powder-only AR of 1.9% (95% CI=1.6%, 2.4%) not appreciably different from the powder-then-crack AR (2.8%; 95% CI=1.6%, 5.2%) and $p>0.05$.

Figure 4.2. Estimated Meta-Analysis Attack Rates for Cocaine Side Effect Problems and Experiences within 12 Months after Onset of Cocaine Use (Powder-Only Subgroup; Powder-Then-Crack Subgroup). Data from the Restricted Data Analysis System of United States National Surveys on Drug Use and Health (NSDUH RDAS), 2002-2017.



Note: Table 4.2 identifies each SEPE.

All other SEPE showed crack-associated excess risk with one exception ('not able to stop using cocaine at least one time'). Figure 4.3 below provides forest plots of all SEPE estimates.

Figure 4.3. Meta-analysis Forest Plots Illustrating Cocaine Side Effect Problems and Experiences among Sub-groups of Newly Incident Cocaine Users in the United States. Data from the Restricted Data Analysis System of the National Surveys on Drug Use and Health (NSDUH, RDAS), 2002-2017.

Powder-Only Sub-group vs. Powder-Then-Crack Sub-group

PE 1=Wanted to/tried to cut down/stop using cocaine during the past 12 months.

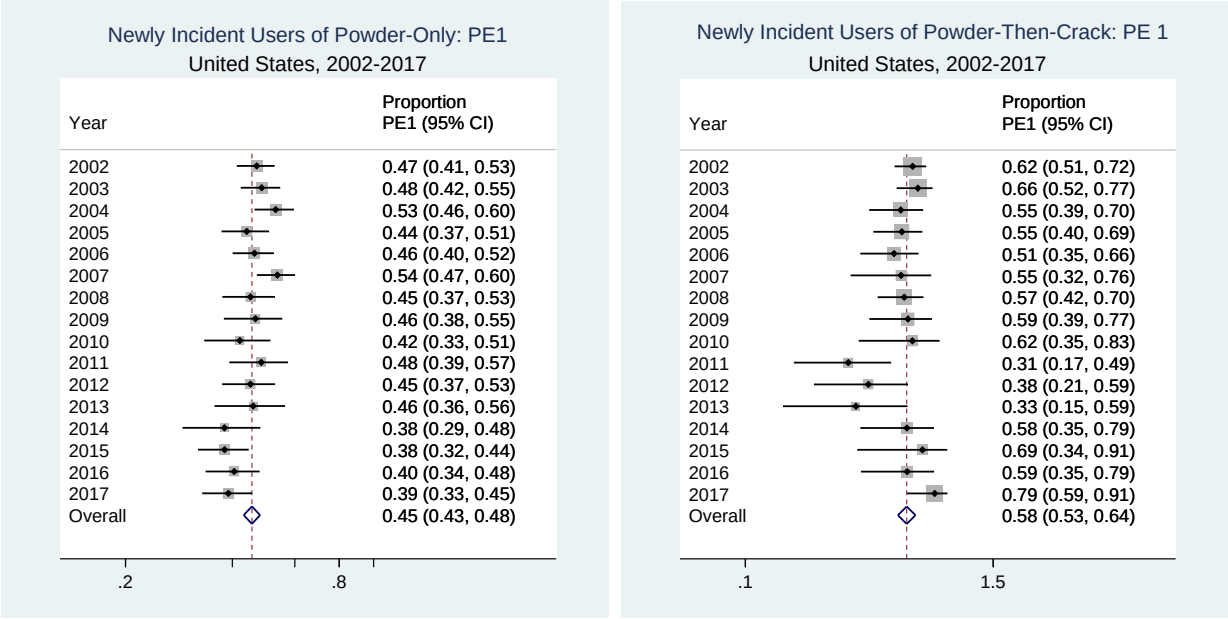
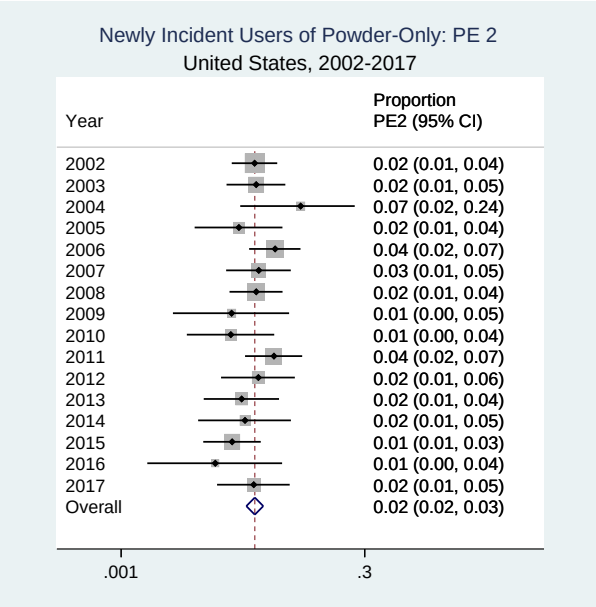
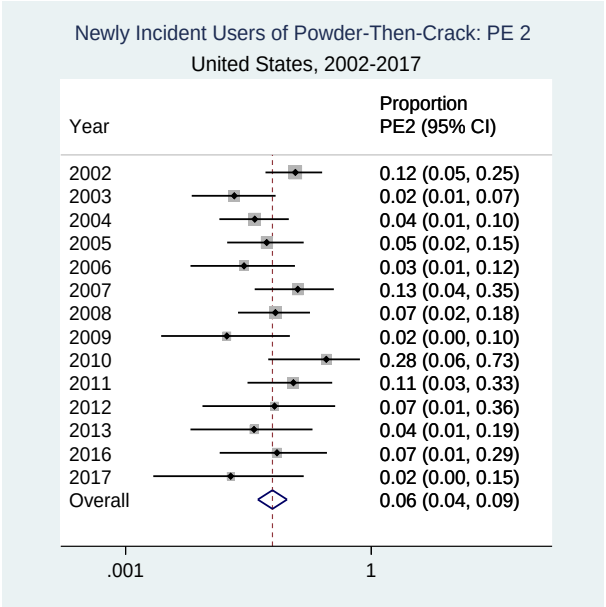


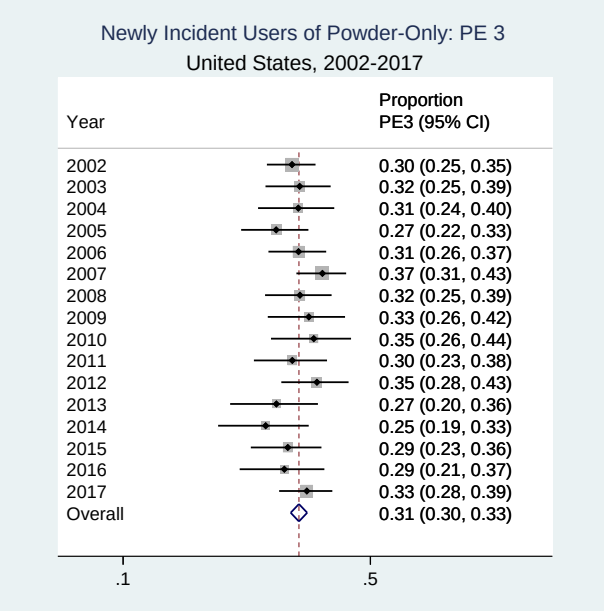
Figure 4.3 (cont'd)

PE 2=Spent a month or more getting over the effects of cocaine used in the past 12 months.





PE 3=Tried to set limits on how much cocaine used or how often used during the past 12 months.



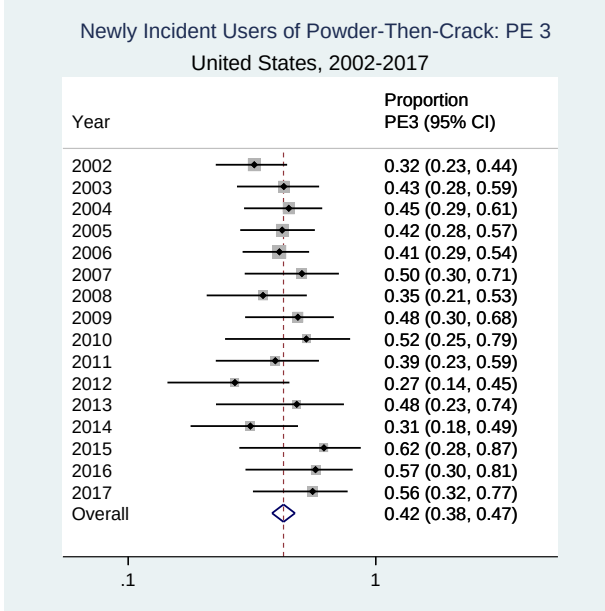
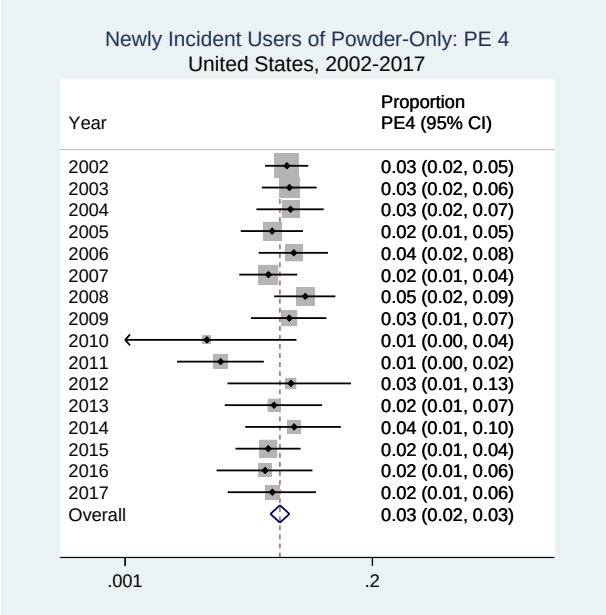
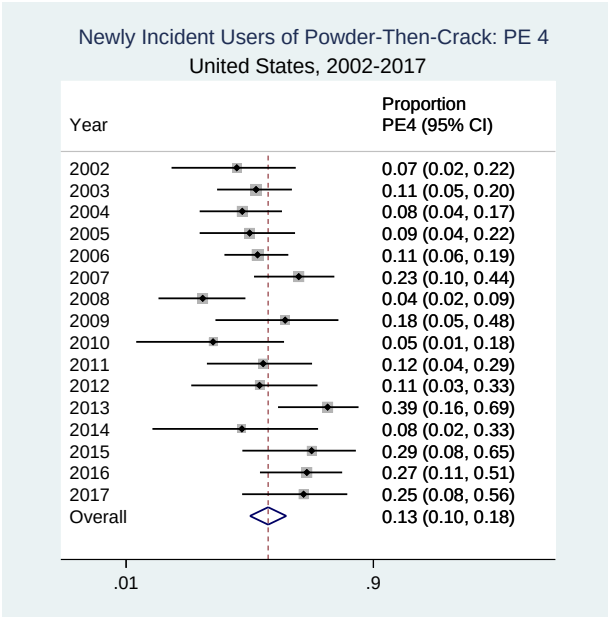


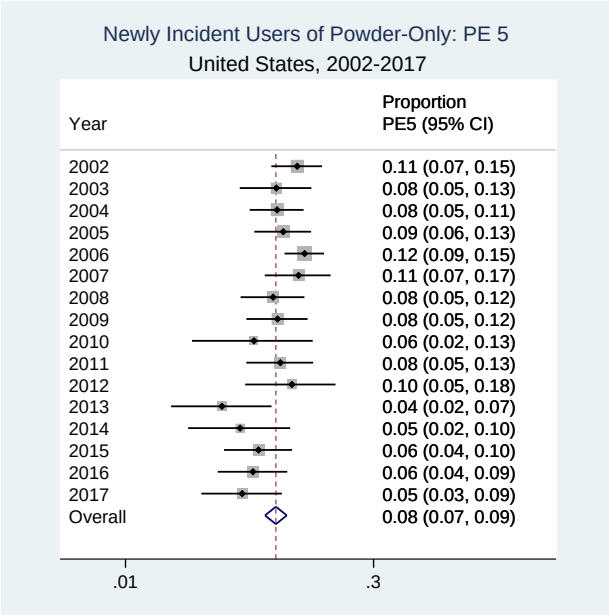
Figure 4.3 (cont'd)

PE 4=Not able to keep limits or used more than intended in the past 12 months.





PE 5=Needed more cocaine to get the same effect as before in the past 12 months.



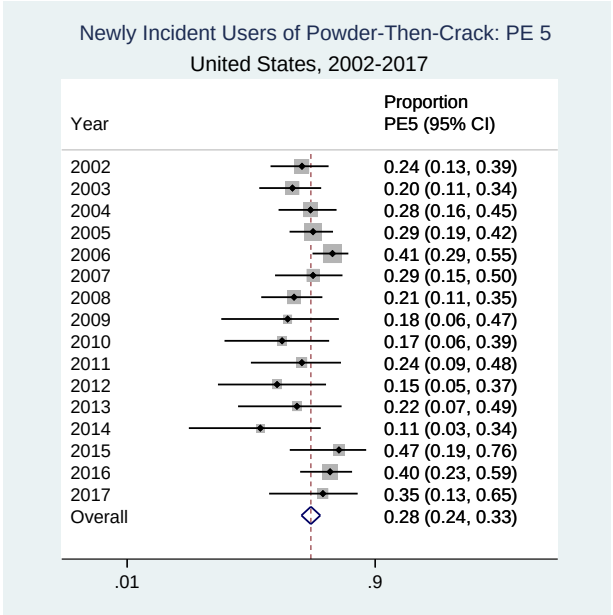
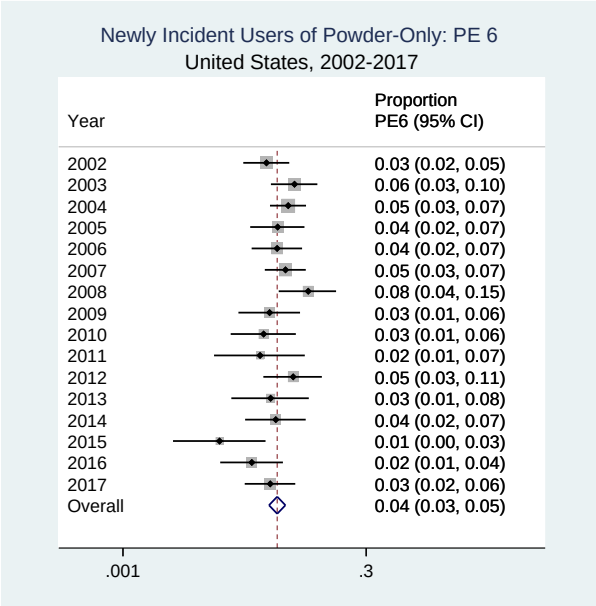
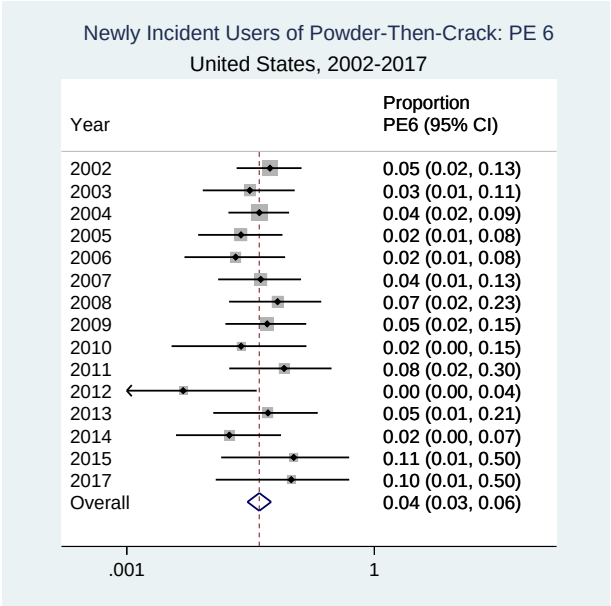


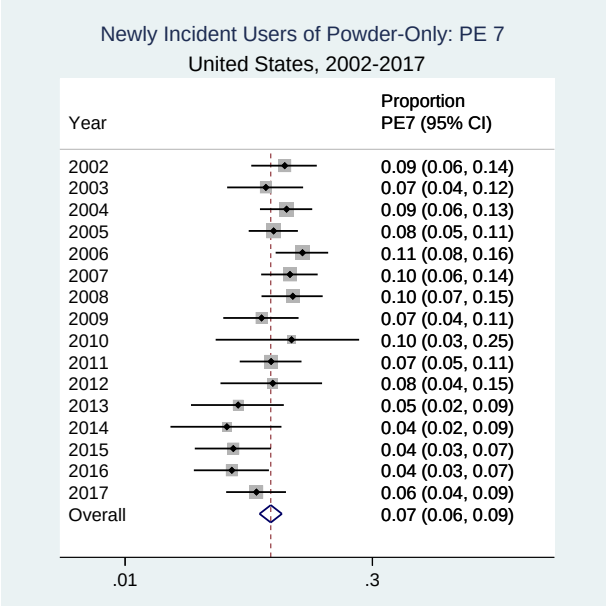
Figure 4.3 (cont'd)

PE 6=Same amount of cocaine had less effect during the past 12 months.





PE 7=Spent a lot of time (month or more) getting/using cocaine during the past 12 months.



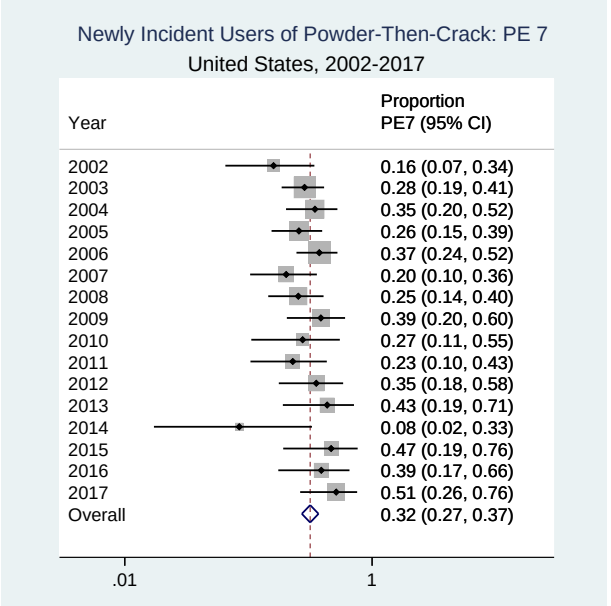
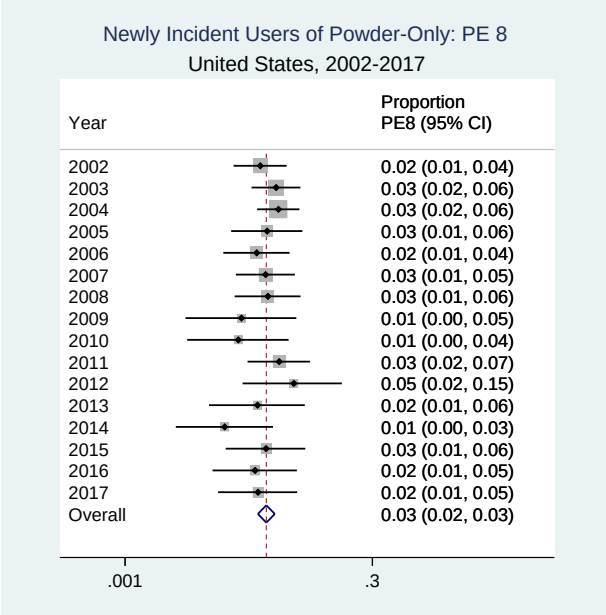
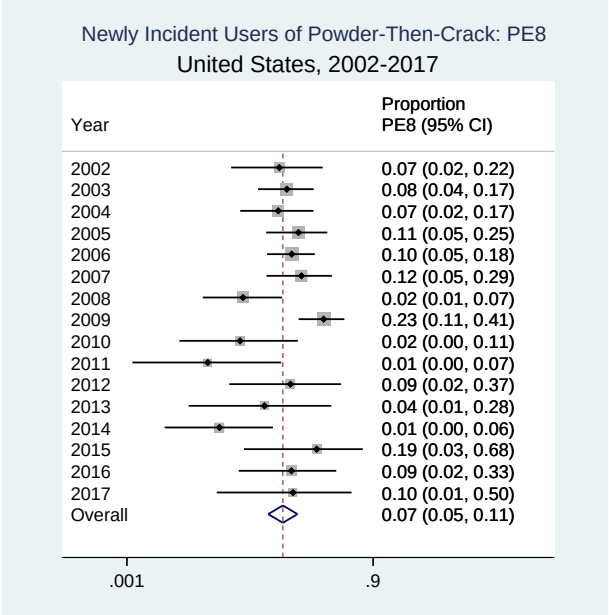


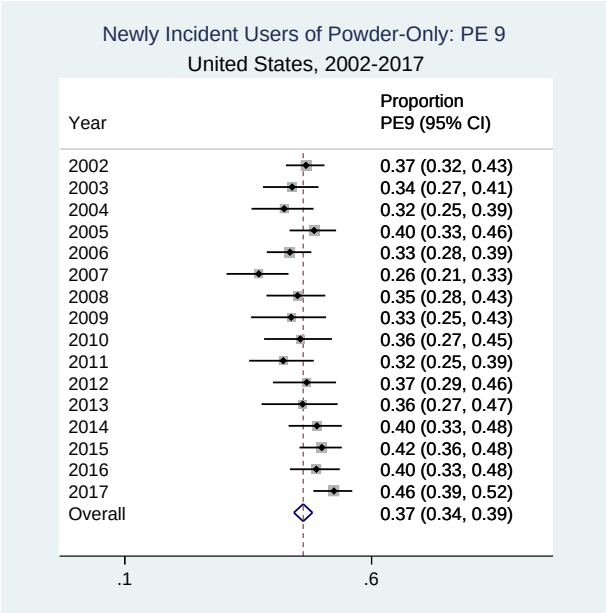
Figure 4.3 (cont'd)

PE 8=Was not able to cut down/stop using cocaine every time during the past 12 months.





PE 9=Was not able to cut down/stop using at least one time in the past 12 months.



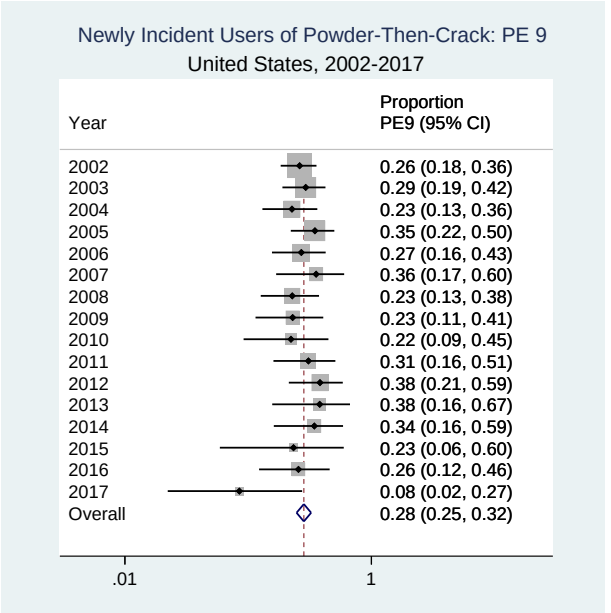
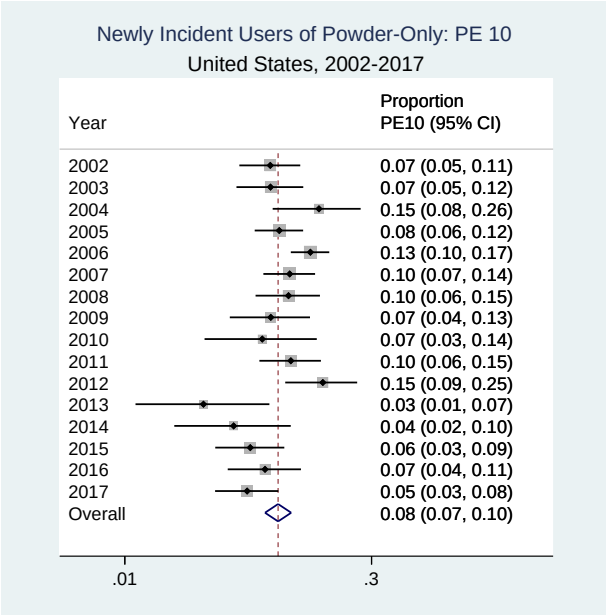
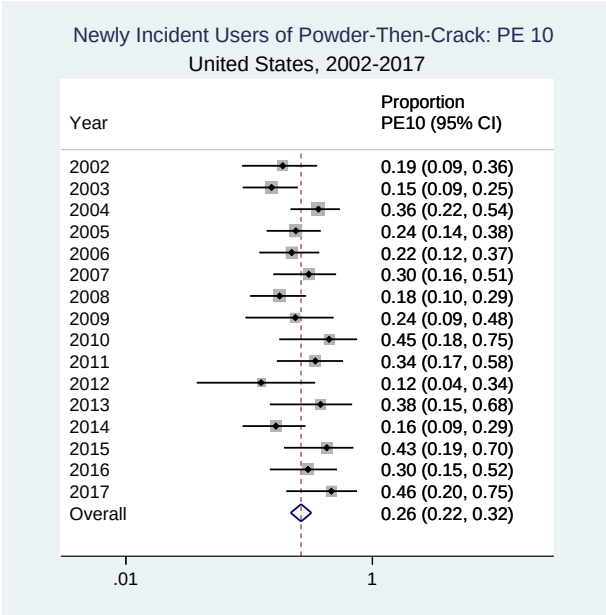


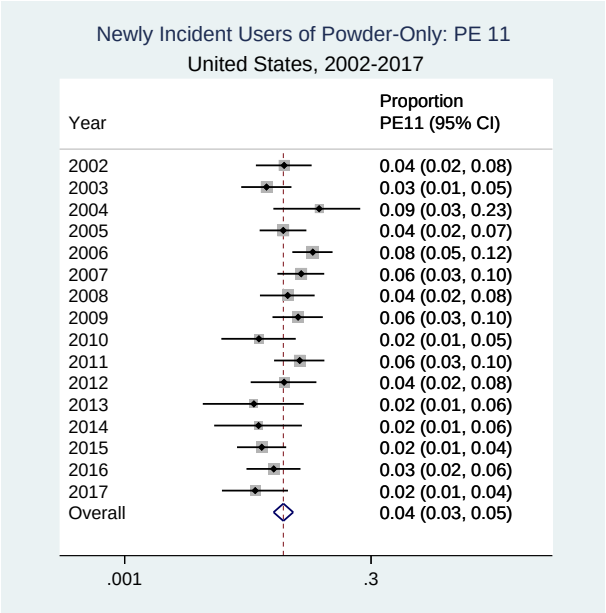
Figure 4.3 (cont'd)

PE 10=When cut down on cocaine, felt blue during the past 12 months.





PE 11=Experienced 2+ cocaine withdrawal symptoms during the past 12 months or had 2+ withdrawal symptoms at the same time.



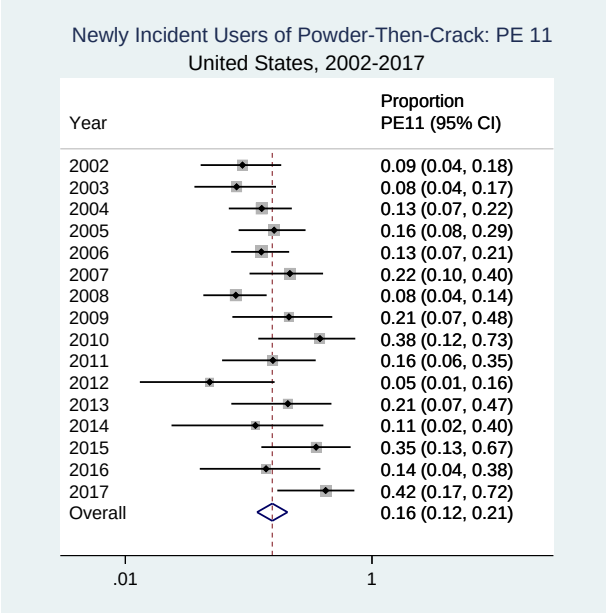
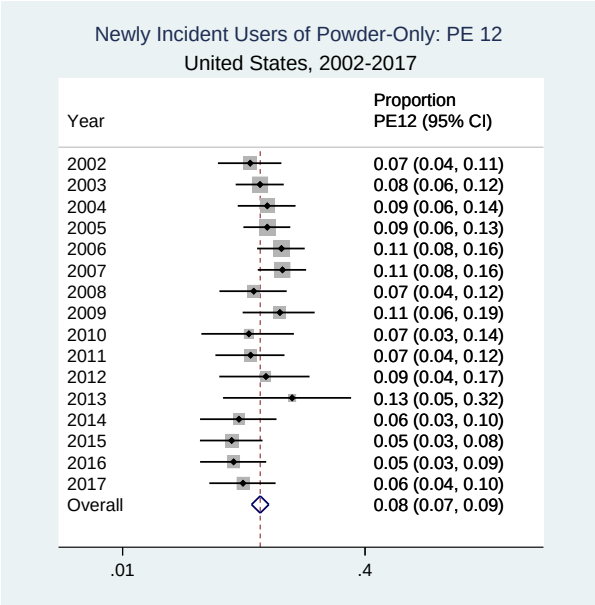
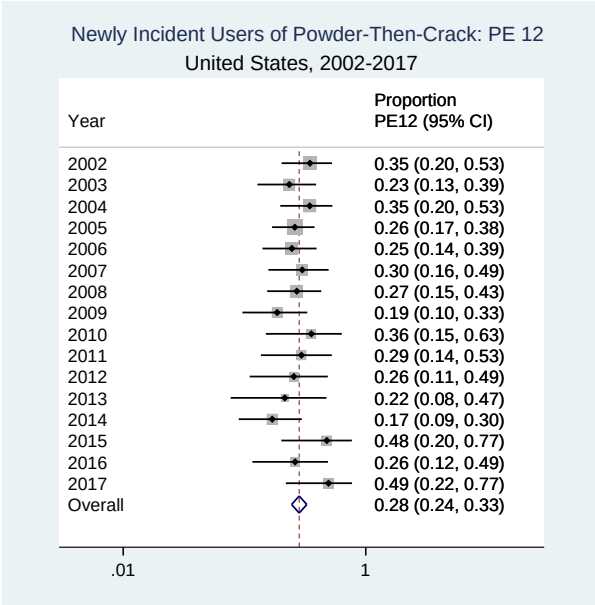


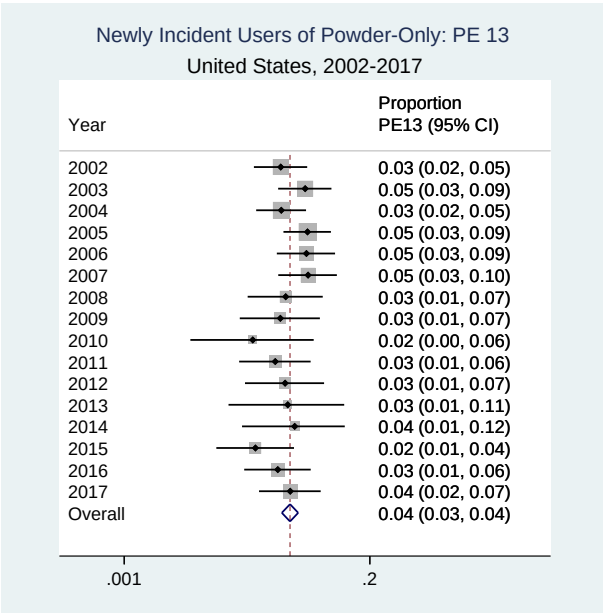
Figure 4.3 (cont'd)

PE 12=Cocaine caused problems with emotions/nerves or mental health in the past 12 months.





PE 13=Continued to use cocaine despite emotional problems.



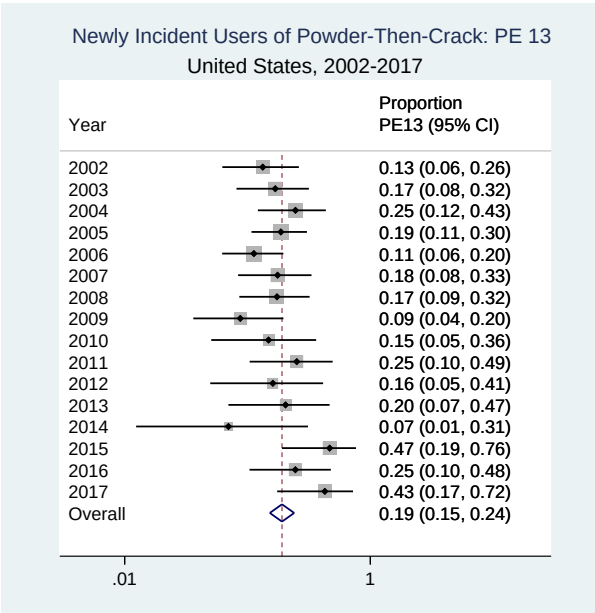
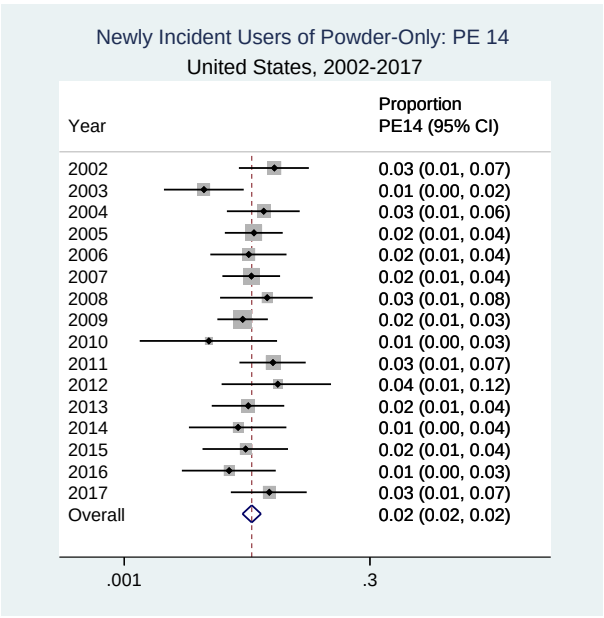
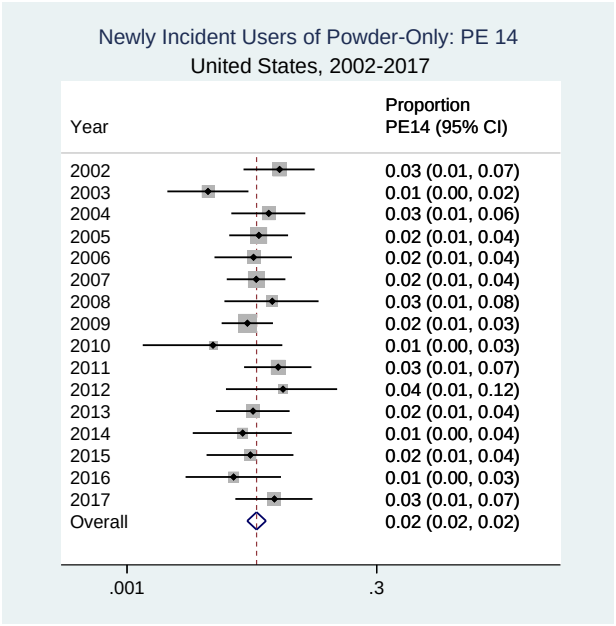


Figure 4.3 (cont'd)

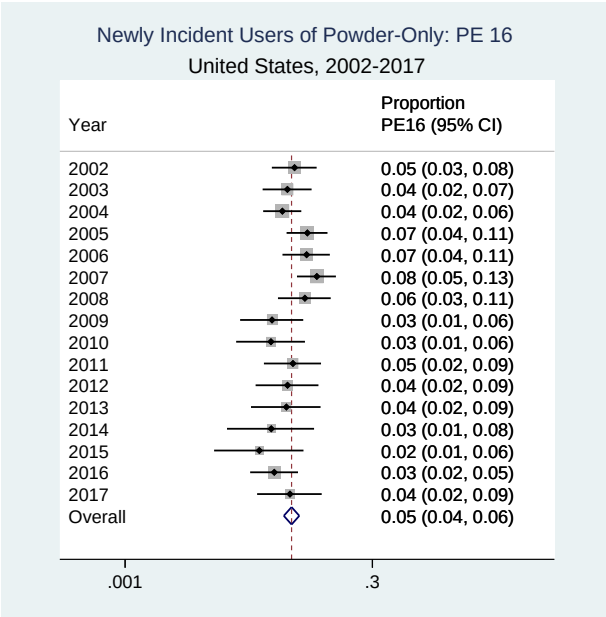
PE 14=Physical problems caused or worsened by cocaine in the past 12 months.





NOTE: PE 15=Continued to use cocaine despite physical problems. PE15 had no observations 2008-2017 for the powder-then-crack-group.

PE 16=Spent less time engaged in important activities because of cocaine use.



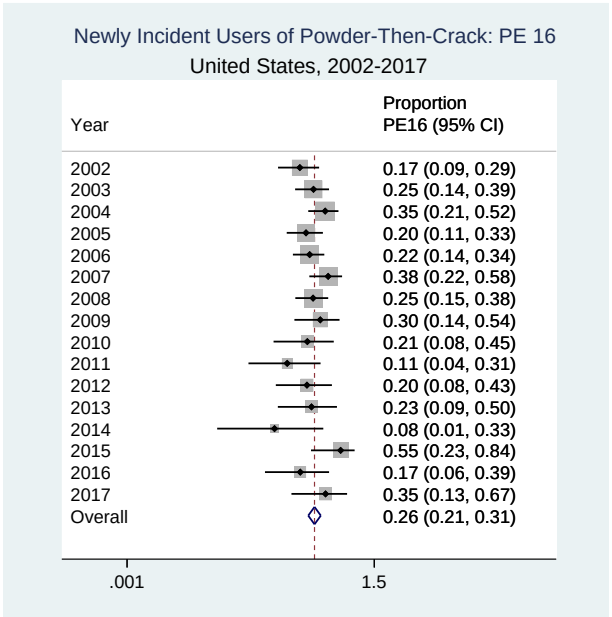
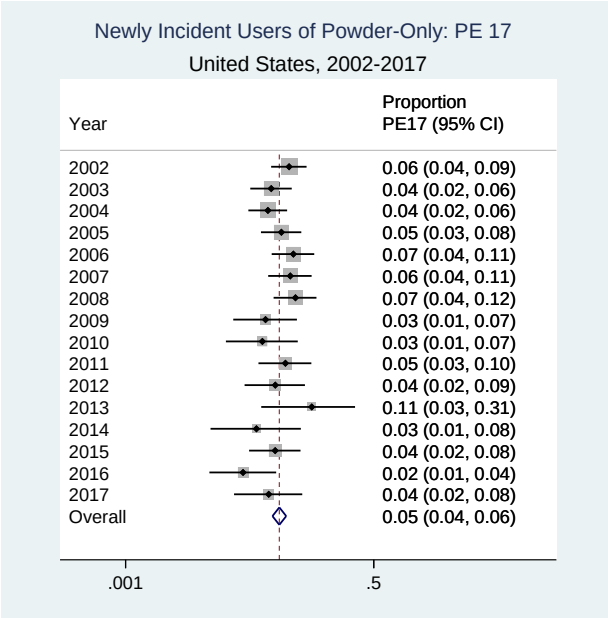
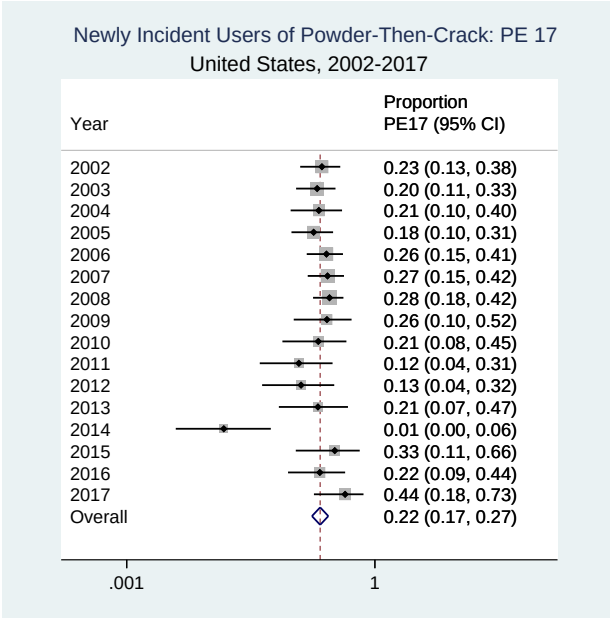


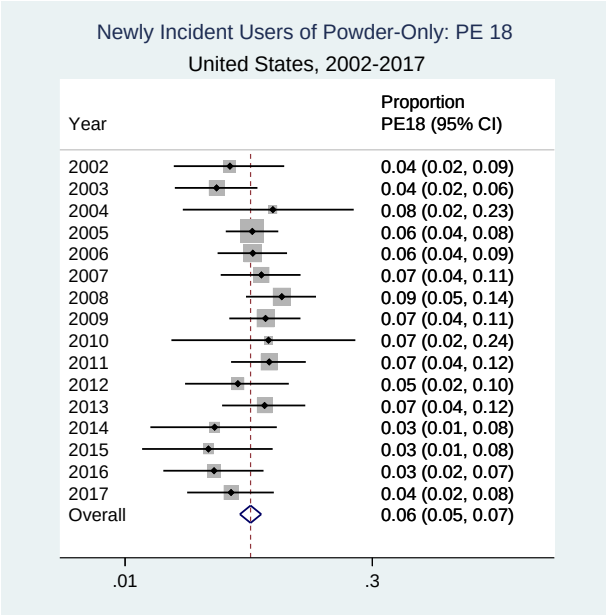
Figure 4.3 (cont'd)

PE 17=Cocaine caused serious problems at home/school /work in the past 12 months (Serious problems defined as neglecting their children, missing work or school, doing a poor job at work or school, and losing a job or dropping out of school).





PE 18=Cocaine caused you to engage in dangerous activities in the past 12 months.



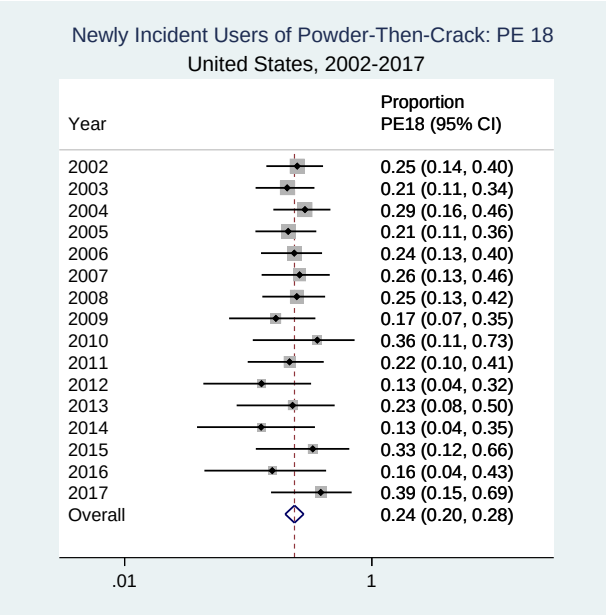
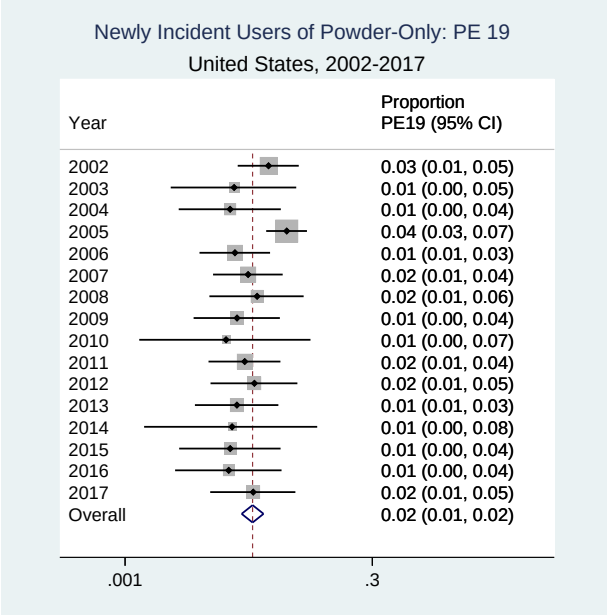
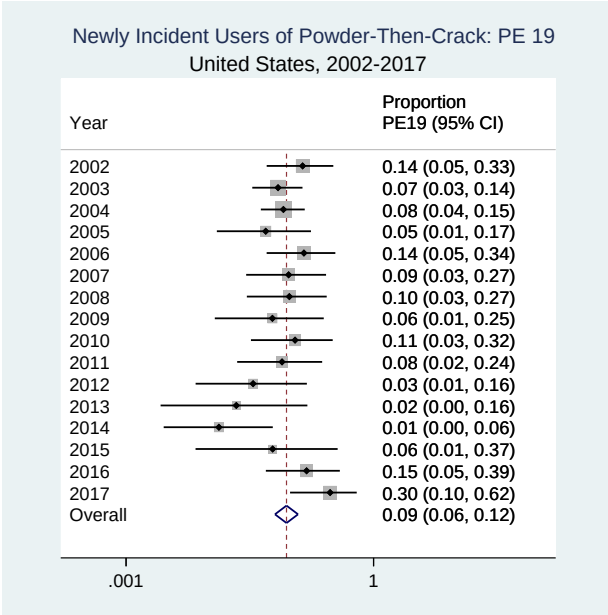


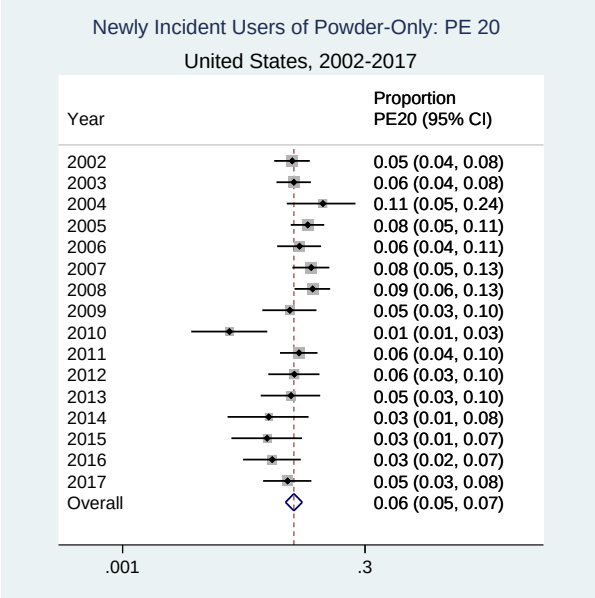
Figure 4.3 (cont'd)

PE 19=Using cocaine caused problems with the law during the past 12 months.





PE 20=Using cocaine caused problems with family/friends during the past 12 months.



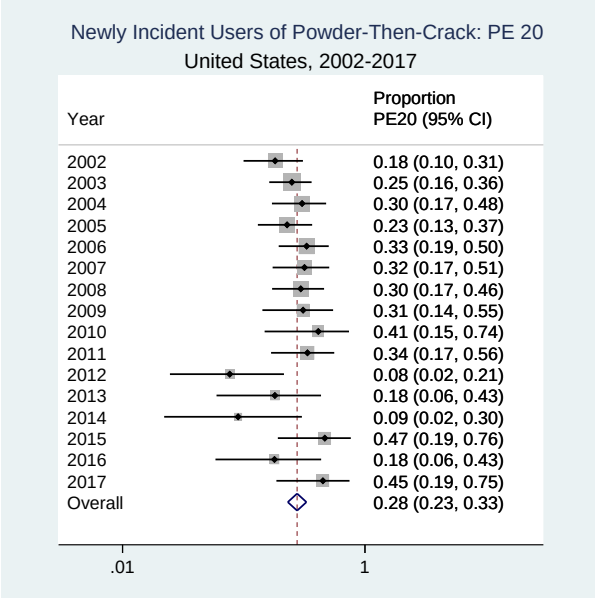
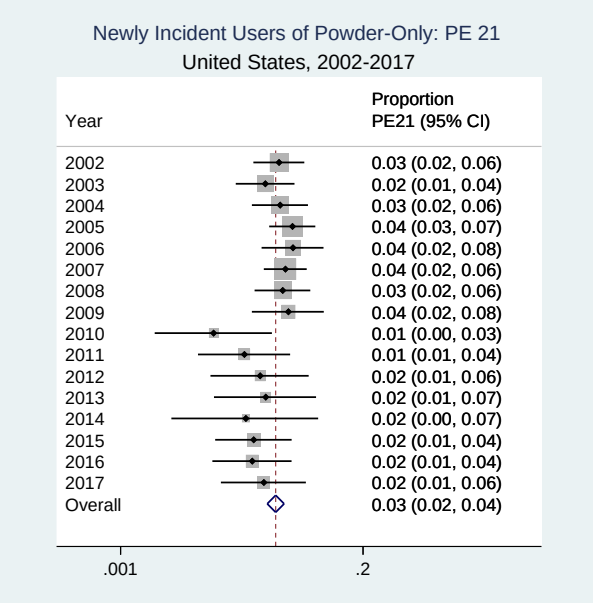
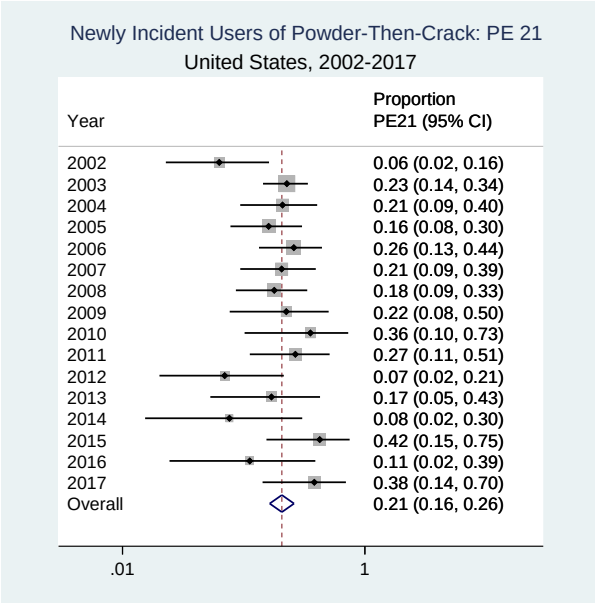


Figure 4.3 (cont'd)

PE 21=Continued to use cocaine despite problems with family/friends.





4.4 Discussion

This study's main novel discovery is that roughly one-in-five (22%) of the powder-then-crack subgroup of initiates developed cocaine dependence within 1-12 months after powder-onset versus a powder-only attack rate of roughly one-in-20 (5%) – a fourfold variation (22% divided by 5%). Trends in dependence for the powder-only subgroup show individual year-pair AR estimates greater than the MAS AR until 2008-09 and less than the MAS AR thereafter. However, the powder-then-crack subgroup shows a steady increase in the dependence AR from the year 2008-09 onward. An unexpected finding was a dramatic reduction in size of the powder-then-crack subgroup from 2002 through 2016, reflecting continuation of a dynamic epidemiological process of US crack epidemic decline noted by Parker & Anthony (2014). The size of the powder-only subgroup is more stable.

This study's cocaine SEPE estimates can be regarded as preliminary in that they offer an initial glimpse of specific domains of potential crack-associated excess risk (e.g., problems with wanting to or trying to cut down or stop using cocaine, and other 'loss of control' manifestations). However, this study's approach does not yet account for within-person statistical interdependence of SEPE responses during formation of cocaine dependence syndromes. Work underway involves Generalized Estimating Equations (GEE) modeling, which addresses this complexity (Chandra & Anthony, in preparation).

When crack-associated excess risk is observed and confirmed in a study of this type, three exceptionally cogent alternative interpretations deserve attention. First, newly incident cocaine users showing powder-then-crack sequences may start with heightened dependence risk susceptibilities (i.e., pre-dating onset). Second, some powder-only users might become cocaine dependent fairly quickly after cocaine onset, and then start using crack in a manifestation of pre-crack cocaine dependence processes. Third, something else about crack use or crack users might be responsible for the observed elevated risk seen in the powder-then-crack subgroup, including a possible excess toxicity of the cocaine delivery variant of 'crack-smoking,' relative to powder insufflation, as suggested long ago (Washton, Gold, & Pottash, 1986). Intranasal cocaine gradually increases blood concentration over 30-45 minutes and has a half-life of 73 minutes. By comparison, crack-cocaine peaks blood concentration in 1.1 minutes, with a half-life of 58 minutes, resulting in greater cardiovascular and subjective effects (Oliveira et al., 2018). It is due to these differences that crack-cocaine has a greater abuse liability and risk of dependence than intranasal cocaine (Hatsukami & Fischman, 1996). These several interpretations may explain how and why this short communication is presenting preliminary estimates as a building block for future investigations. These estimates provide a rationale for continued inquiry.

As for antecedent attributes of crack users, observers of the current US 'opioid crises' have notes that prior use of non-cocaine drugs (including opioids) might heighten dependence susceptibilities manifest in subsequent crack onset. Social conditions such as proximity to drug markets and crack using peers can increase availability or reduce cost, thereby playing roles in how rapidly a cocaine dependence process gets underway. It also is possible that crack onset is a signal of more active cocaine seeking once cocaine powder use has started, as is the possibility that a street dealer first selling cocaine powder might introduce powder users to crack (Wagner & Anthony, 2002a; 2002b).

Interpretations of this type deserve continued study, and there are some new investigations that will become possible with re-opening of extramural scientist access to NSDUH restricted datasets (e.f., disclosure of calendar dates of survey assessments relative to months of first use). In addition, the subject-as-own-control epidemiological case-crossover approach can be used to localize risk of starting to use crack month-by-month after onset of cocaine powder use, as in work described by O'Brien and colleagues (2012).

In addition to limitations already mentioned, this preliminary investigation's sample faces a shortcoming that is somewhat akin to left-truncation problems in follow-up research, as can occur when drug users truly are in the study population and should be included in the sample, but are missed for reasons such as flaws in survey sampling frames or differential non-participation. A process akin to follow-up study left-censoring also is possible, as can occur when a newly incident drug user is included in the sample, but there is a thwarted or terminated assessment – i.e., an event of cocaine dependence onset has occurred but is not observed. In addition, even though NSDUH assessments are set up for focus on the most recent 12 months in

the participant's life, errors due to recall or reporting problems might occur, particularly among new initiates who are polydrug users, as explained by Lopez-Quintero & Anthony (2015).

NSDUH 'frequency of use' variables were deliberately omitted as control variables for these estimates on crack-associated excess risk in order to avoid two forms of estimation bias. First, as time passes, 'frequency of use' is positioned on potential mediational pathways linking 'crack use' with whether dependence syndromes form. Second, 'frequency of use' can be influenced by syndrome formation, with dependence driving up frequency; a result is called 'collider bias.' Either way, there is model mis-specification when frequency is controlled (Lederer et al., 2019). Elsewhere, Vsevolozhskaya and Anthony (2016) suggest starting with unconditional risk estimates (as in this study) followed by appropriate methods when initial estimates show need for more attention (e.g., functional analysis).

4.5 Conclusions

The main estimates from this study suggest fairly rapid development of cocaine dependence for roughly 1-in-5 newly incident powder-then-crack users (20%) versus roughly 1-in-20 for newly incident powder-only users (5%), and indicate many cocaine side effects that seem to form more quickly with the powder-then-crack sequence. These novel estimates complement published US estimates for cocaine dependence treatment caseloads, which imply roughly 50 new crack-cocaine dependence cases per day and roughly 135 new powder-only cocaine dependence cases per day (Lipari et al., 2017). For comparison, Rivera and colleagues (2018) used essentially the same research approach and estimated 140 heroin dependence cases per day in the midst of the current US opioids crises. They found that almost 1-in-3 newly incident heroin users developed heroin dependence within 1-12 months after heroin onset (30%).

We currently lack definitive evidence to explain why powder-then-crack initiates might have excess risk for cocaine side effects and for becoming a cocaine dependence case within 1-12 months after cocaine onset. A subsiding crack epidemic may mean we never will understand this excess risk. Even so, epidemiological estimates of this type can be especially useful when the public health goal is to educate school children or their parents, professionals, and the general public about potential hazards faced soon after cocaine onset.

CHAPTER 5 – HETEROGENEITY IN RISK OF COCAINE 'SIDE EFFECT' EXPERIENCES FOR COCAINE POWDER USERS WHO THEN START USING CRACK-COCAINE. UNITED STATES EPIDEMIOLOGICAL EVIDENCE ON NEWLY INCIDENT USERS OBSERVED WITHIN 12 MONTHS AFTER COCAINE ONSET (2011-2017).
(Manuscript 2)

Abstract

Aims:

In this chapter novel epidemiological evidence on the odds of developing 21 individual cocaine-attributed side effect problems and experiences (SEPEs) within 1-12 months of initiating cocaine use are presented with hypothesized excess odds for crack-cocaine users, most with co-incident cocaine powder (CHCl) use, as contrasted with cocaine powder-only users.

Methods:

The study population encompasses United States community residents age 12 years and older, 2011-17, ascertained within nationally representative probability samples recruited for the National Surveys on Drug Use and Health (n~ 55,000/year). I first estimated analysis-weighted incidence proportions for cocaine powder-only users (n=2364) and crack + powder users (n=231). Subsequently, I estimated odds ratios for 21 individual SEPEs reflecting crack/powder-only contrasts, year-by-year with corresponding Taylor series 95% confidence intervals. A fixed effects meta-analysis approach yielded summary estimates for each SEPE.

Results:

Results indicate excess odds of several cocaine SEPEs for crack smokers, relative to experiences of 'powder only' users ($p<0.05$), with no appreciable attenuation of the estimates after covariate adjustments or in sensitivity analyses. Strong crack-associated excess odds were observed for inability to keep limits; aOR=9.5 (5.9, 15.4), use despite emotional problems aOR=10.5 (6.7, 16.5) and continued use despite problems with friends and family aOR=11.2 (6.7, 18.6).

Conclusions:

This work provides a novel and broadened view of experiences during early phases of what might become cocaine use disorders. Several early emerging targets for possible preventive interventions by clinicians seeing patients in the early months after first cocaine use are identified.

Keywords: Crack cocaine, Cocaine Hydrochloride, Incidence, Drug Dependence, Drug Use Disorders, Meta-Analysis

5.1. Introduction

The main aim is to study crack-associated excess odds of 21 side effect problems and experiences (SEPEs) among newly incident cocaine users in the United States (US) during the first 1-12 months following cocaine onset. What is novel about this work is a tight focus on drug experiences within a short time interval after drug initiation, which addresses the issue of recall bias in earlier works on cocaine dependence that examined lifetime histories or the interval from 1-24 months after first cocaine use. This approach also brings the time-window of interest into alignment with decisions made to focus NSDUH drug dependence assessments on the 12 months prior to the assessment date. The resulting estimates display what happens during the first months after cocaine use starts.

The guiding framework underlying contrasts of newly incident users of crack-cocaine with co-incident cocaine hydrochloride use versus individuals who used only cocaine hydrochloride powder (CHCl) is the assumption that drug effects are determined as a function of routes of administration (RoA), and other variables (Benowitz, 1993; Gossop et al., 1994). Working within this framework, my work builds from a research line on crack-cocaine that started in the 1980s (Washton et al., 1984; Anthony & Petronis, 1989; Hatsukami & Fischman, 1996). Subsequent studies disclosed that a minority of users move from first occasion of cocaine use to become newly incident cases of cocaine dependence within a 24 month timeframe, (Anthony et al., 1994; Vsevolozhskaya & Anthony, 2016; Wagner & Anthony, 2002a; Wagner & Anthony, 2002b) and that crack use might accelerate the process (Chen & Anthony, 2004; Reboussin & Anthony, 2006). The two prior studies examining crack and powder contrasts emphasized crack-associated excess risk of four clinical features: (1) salience of cocaine experiences within the drug user's behavioral repertoire, (2) emotional problems said to be

caused by cocaine (e.g., mood problems), (3) subjectively felt tolerance, and (4) an inability to cut down. These findings now are a decade old. In the interim, no one has examined dependence among sub-groups of cocaine users with nationally representative data. This study addresses this omission.

International, as well as US audiences might find these estimates to be useful. In the US, cocaine powder incidence and cocaine-related overdose events are increasing in the wake of the opioids epidemic (McCall et al., 2017; Palamar et al., 2014, 2015; Parker and Anthony, 2014). In other parts of the world, cocaine production and use is steadily increasing (Paim Kessler et al., 2012; United Nations, 2016). Given this backdrop, an epidemiological examination of subgroups of cocaine users is both relevant and timely to develop appropriate treatment modalities for each user subgroup.

5.2. Materials and Method

5.2.1. Study Population and Design

The study population for this investigation consists of non-institutionalized civilian residents of the United States, age 12-years-and-older, as sampled and recruited for the US National Surveys on Drug Use and Health from 2011 through 2017. Each year, NSDUH field operations involved drawing a new nationally representative probability sample with more than 55,000 participants, recruited and assessed using Institutional Review Board-approved protocols (United States, 2015).

The NSDUH research design is cross-sectional, with participation levels generally ranging upward from 70% (United States, 2015). Standardized assessment modules administered to all participants are via a confidential self-report audio computer-assisted self-interview (ACASI) intended to promote completeness and accuracy of self-report.

5.2.2 Study Sample

The ACASI cocaine module included items on the month and year of first crack-cocaine and CHCl powder use, from which I identified newly incident users of these cocaine formulations (i.e., when first use occurred during the 1-12-month interval just prior to the assessment date). Each year's nationally representative sample in NSDUH Public Use Files (PUF) included 321 to 419 newly incident cocaine users, with an aggregate sample of 2,595 newly incident users: 2,364 CHCl powder users with no use of crack-cocaine, plus 231 newly incident crack-users (most co-incident with CHCl use). Figure 4.1 is a flowchart illustrating how the study sample was derived. NSDUH analysis weights take probabilities of sample selection into account, as well as post-stratification adjustment to US Census distributions as formulated for the 2011-2017 public use datasets.

5.2.3 Multivariate Response Variable

Key response variables under study were specified as elements in a multivariate vector of interdependent cocaine-attributable PEs, measured as binary responses (the presence of each individual PE was coded "1" with "0" denoting its absence). Elicited via standardized items in the ACASI cocaine dependence module (See Appendix Table 1 for a complete list of 21 cocaine PEs), the PE assessment focuses strictly on the 12-month interval prior to assessment (i.e., all events experienced after onset of first cocaine use) and maps onto the DSM-IV criteria.

5.2.4 Covariates

Covariates under study were: (a) time-invariant characteristics unlikely to be influenced by onset of cocaine use (e.g., male sex, age at assessment, and race-ethnicity), as well as (b) time-varying characteristics which might influence cocaine use such as antecedent alcohol, tobacco, and cannabis use (ever used alcohol/cigarettes/marijuana), and injecting drug use all

measured via NSDUH standardized items. Additionally, in an exploratory model, I estimate the risk of cocaine dependence controlling for socioeconomic status. Socioeconomic status was assessed as incomes at or below the federal poverty threshold and coded "1" for incomes at or below the threshold versus "0" for incomes above this threshold. Drug history variables were dropped in this exploratory model given that between 98% and 100% of cocaine users had a prior history of using alcohol, cigarettes, and marijuana.

5.2.5 Statistical Analyses

The NSDUH multivariate vector of interdependent binary "cocaine SEPE" response variables motivated choice of a multivariate regression approach known as the generalized linear model with generalized estimating equations (GZLM/GEE). The use of product terms and a logit link function within the GZLM/GEE framework yielded odds ratio estimates for the crack-associated excess odds of each SEPE. These ORs approximate 'relative risks' for relatively rare SEPEs (i.e., those affecting <10% of users).

The preliminary model was a 'common slope' specification with a single slope estimate of the degree to which crack users might experience excess odds. However, the 'common slope' OR estimate was untenable due to a qualitative variation in SEPE-specific slope estimates (i.e. one SEPE was inversely associated with crack use). Hence, for this chapter, I focus mainly on the SEPE-specific slope estimates as outlined in model 3 of Table 2.

Stata 15 with its *subpop* and *lincom* commands was used for estimation (StataCorp, 2017). The 95% confidence intervals (CI) were generated using the delta method (Taylor series linearization). I did not 'pool' the data across years, because this is an approach that increases analysis complexities described elsewhere (Hicks, 1994; Podesta, 2002; Stimson, 1985) and because it does not account for the year-by-year heterogeneity in the NSDUH data. I therefore

derived a set of study estimates for each year 2011, 2012, 2013,.., 2017. I then produced SEPE-specific fixed effect meta-analysis summary estimates across all the years under consideration. A DerSimonian-Laird 'random effects' approach was adopted to accommodate potential between-year variations where the heterogeneity statistic was significant (StataCorp, 2017).

5.3. Results

Table 1 provides a weighted sample description comparing the demographic characteristics of newly incident crack and powder-only users. Most newly incident CHCl-only users self-identified as Non-Hispanic White (For each year, values ranged between 61.8% and 81.6%). Just over half of CHCl-only users were males (values between 53.3% and 58.7%), and roughly 14%-20% were age 12-17 years. For crack, the corresponding value ranges were 60.9% and 86.4% Non-Hispanic White, with roughly 5.0%-22.5% age 12-17 years. Socioeconomic status of CHCl-only and crack users as measured by the Federal poverty threshold level did not vary appreciably with exception of the year 2017. Prior use of gateway drugs such as alcohol, tobacco, and marijuana was somewhat more common among crack users versus CHCl-only users. Finally, injecting drug use occurred very infrequently among both newly incident crack and CHCl-only initiates.

The main study estimates are presented in Table 2 with the meta-analysis summary estimates (aOR) and 95% confidence intervals below each summary estimate. The aOR estimates take NSDUH analysis weights into account, and were from the multivariate GZLM/GEE regression models with covariates. Four models are presented in Table 2. Model 1 presents a meta-analysis summary estimate of crack-associated odds with no statistical adjustment for covariates. Model 2 shows meta-analysis summary estimates for each SEPE controlling for age, race-ethnicity and sex. Model 3 is the most comprehensive model presenting

adjusted odds ratio estimates from a multivariate GZLM/GEE model controlling for age, race-ethnicity, sex, and prior drug history. Finally, Model 4 is an exploratory model controlling age, race, sex and SES only.

Looking at model 3 estimates, the summary meta-analysis estimate of 1.3 for SEPE1 signifies no excess odds of the 'cut down' SEPE for newly incident crack users versus 'powder only' users, which is contrary to the general expectation of excess crack-associated odds for this particular problem-experience. In contrast, SEPE2 ('spent a lot of time getting over the effects') was seen more often among crack users aOR = 2.5, (95% CI = 1.6, 4.0). The summary aOR for SEPE3, setting limits on one's cocaine use are null (Table 2, row 4). In contrast, with respect to difficulty or inability faced when trying to set limits on cocaine use (SEPE4), the year-specific and meta-analysis summary estimates generally suggest strong crack-associated excess odds. The summary aOR is large and statistically robust at 9.5 (95% CI = 5.9, 15.4).

Crack users were more likely to experience subjectively felt tolerance with respect to needing more drug to get the desired effect (SEPE5). I also see a crack association with the odds of sensing that the same amount of drug produced less effect (SEPE6, OR = 2.1 (95% CI = 1.3, 3.6).

The reader's attention should be drawn to SEPE7 and SEPE16, which pertain to the behavioral repertoire of users, including increased salience of cocaine use as well as a complementary reduction in salience of activities that might function as non-drug reinforcers within the repertoire. Here, 'salience' of drug use encompasses spending 'a lot of time' getting or using cocaine. In contrast, 'reduced salience' is seen when users acknowledge that cocaine use had caused reduced time allocations to important activities such as going to school, work, or spending time with family or friends. The moderately strong meta-analysis summary odds ratio

estimates for ‘salience’ of cocaine use and for ‘reduced salience’ of non-drug activities are 6.0 and 7.4, respectively.

As for emotional disturbances seen in prior crack research, SEPE10, SEPE12, and SEPE13 deserve attention. PE10 refers to ‘feeling blue’ upon stopping cocaine use, whereas SEPE12 refers to emotional problems caused by cocaine use, and SEPE13 signifies continuing to use despite emotional problems. New crack users + CHCl users were more likely to experience all of these problem-experiences, with all OR point estimates greater than 4.5 and $p < 0.05$.

Summarizing across the 21 problem-experiences represented by PE1 through PE21 in Table 2, we see 17 summary meta-analysis estimates consistent with the expectation of crack-associated excess odds of these problems or experiences early in the months after first cocaine use. The strongest meta-analysis summary aOR estimate is 11.2 (95% CI = 6.7, 18.6), seen in relation to ‘continuing to use despite family problems.’ Other OR estimates are statistically significant at $p<0.05$, but with associations that are less strong. For 4 of the 21 problem-experiences under study we can see no excess crack-associated odds, and for one problem-experience, we see an inverse point estimate (aOR = 0.8; 95% CI = 0.6, 1.1). That is, the odds of not being able to cut down or stop using at least once within 1-12 months after onset of cocaine use actually might be lower among crack-cocaine users as compared with cocaine powder-only users though this effect is statistically insignificant.

5.4. Discussion and Conclusion

The main findings of this study may be summarized succinctly. The experiences of newly-incident crack users studied very soon after onset provide an indication that crack use with co-incident CHCl use is a signal for excess odds of 17 of the cocaine problems and experiences under study. These results are consistent with prior comparisons of crack versus CHCl-only new

initiates (Chen & Anthony, 2004; Reboussin & Anthony, 2006) with respect to 'salience' of cocaine use and emotional problems associated with use. I extend these earlier results with the finding of concurrently reduced salience of non-drug activities that otherwise might have functioned as alternative reinforcers within that repertoire (SEPE16). Second, with previously unexamined NSDUH mood questions, there is novel evidence of a crack-associated excess occurrence of 'feeling blue' when cutting down on cocaine use (SEPE10). Finally, results showed strong evidence for continued use despite problems with family and friends (SEPE20).

Diverging from prior work, I did not find a consistent pattern of crack associations with an inability to cut down. One can speculate that this is a side effect problem experience that requires more elapsed time since first use of cocaine.

Before additional discussion of these results, several of the more important study limitations merit attention. First, self-report data of this type though valid reflections of drug user experiences are potentially subject to shared methods co-variation or common method variance bias (Del Boca et al., 2003; Podsakoff et al., 2003). Second, the cross-sectional design is an approximation of what might be found in a future more confirmatory longitudinal study. Nevertheless, the cross-sectional approach has strengths in that it does not face problems such as sample attrition and measurement reactivity, and it is sharply focused on newly incident users to constrain problems as described elsewhere by Anthony (2010).

A third limitation of note involves unmeasured confounding. For example, it is possible that crack users start out with a greater predisposition to experience cocaine problems as compared with powder only users (Chen & Anthony, 2003). It is also possible that the norms, practices, and circumstances of use might influence drug effects (Waldorf et al, 1991). Statistical adjustments in this chapter helped control for race-ethnicity, age, sex, prior tobacco

use, and injecting drug use, as well as socioeconomic status. The large-sample nation-wide NSDUH does not, however, assess peer norms and other context variables discussed in that prior ethnographic work with smaller and more local samples.

Notwithstanding these limitations, the study findings are timely in relation to recently observed increases in overall cocaine powder incidence among adolescents ages 12-17 and young adults ages 18-25 years in the US, and internationally (Lipari et al, 2017, United Nations, 2016). This work provides a novel view of cocaine experiences during early phases of what might become cocaine use disorders. Noted herein are several early emerging targets for possible preventive interventions by clinicians seeing patients in the early months after first cocaine use.

Table 5.1: Weighted Demographic Characteristics of Newly Incident Cocaine Users. Data from the United States National Surveys on Drug Use and Health, NSDUH (2011-2017)

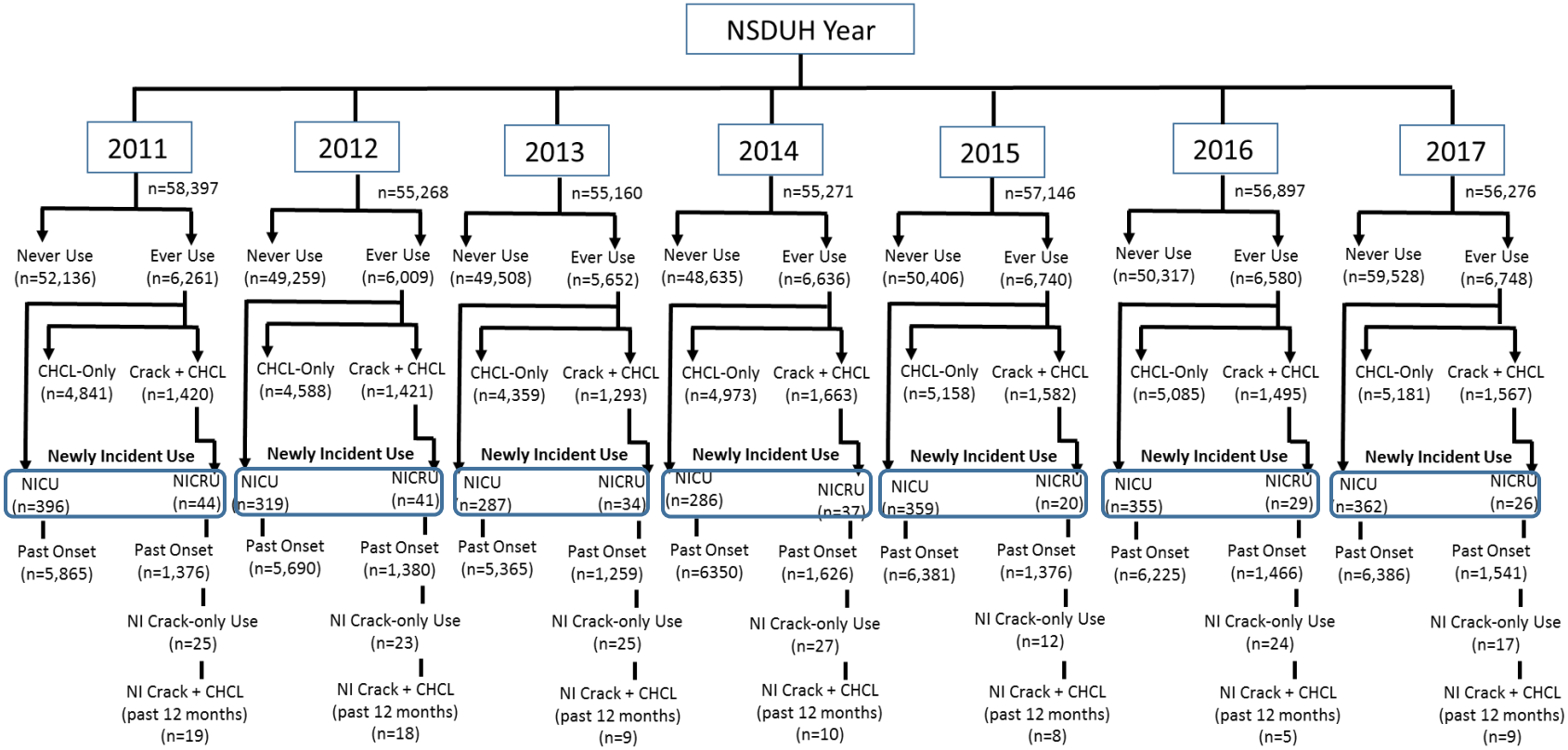
Panel A: Weighted Characteristics of Newly Incident Cocaine Powder-Only Users.

Years	2011		2012		2013		2014		2015		2016		2017	
Variables	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Sex (Male)	217	54.7 (48.8, 61.1)	173	54.1 (44.4, 63.5)	169	58.7 (49.5, 67.3)	159	55.7 (48.2, 62.9)	195	55.5 (48.1, 62.5)	202	57.0 (50.4, 63.4)	193	53.3 (45.1, 61.4)
Age (12-17 years)	87	21.9 (17.0, 27.6)	65	20.3 (15.6, 25.8)	41	14.2 (10.3, 19.2)	46	15.9 (11.1, 22.2)	41	11.8 (8.8, 15.5)	39	10.9 (7.6, 15.5)	36	9.9 (7.5, 13.0)
Race (NH White)	249	62.9 (55.3, 69.9)	209	65.5 (56.1, 73.9)	234	81.6 (75.2, 86.7)	177	61.8 (51.7, 71.0)	233	66.5 (59.1, 73.2)	250	70.5 (64.2, 76.1)	235	65.0 (59.4, 70.3)
SES (% in Poverty)	101	25.4 (19.3, 32.6)	59	18.5 (13.9, 24.2)	109	37.7 (29.0, 47.4)	70	24.5 (18.9, 31.4)	87	24.8 (20.5, 29.7)	77	21.7 (16.6, 27.9)	98	27.1 (22.6, 32.0)
Ever Use Tobacco	368	92.9 (84.9, 96.8)	310	97.2 (93.1, 98.9)	275	95.8 (92.5, 97.7)	256	90.2 (85.3, 93.6)	321	91.3 (85.3, 95.9)	321	90.3 (85.2, 93.8)	312	86.2 (79.8, 90.9)
Ever Use Alcohol	394	99.4 (98.0, 99.8)	312	98.1 (94.9, 99.3)	287	99.9 (99.0, 99.9)	281	98.3 (95.4, 99.4)	348	99.2 (97.4, 99.8)	355	100.0 (na)	362	100.0 (na)
Ever Use Marijuana	394	98.6 (96.0, 99.5)	311	97.5 (93.9, 99.0)	286	99.6 (98.1, 99.9)	273	95.3 (91.6, 97.5)	343	97.8 (91.1, 99.5)	349	98.2 (93.5, 99.5)	353	97.7 (94.5, 99.0)
Injecting Drug Use (Yes)	3	1.0 (0.4, 2.9)	9	2.8 (1.4, 5.8)	0	0 (na)	1	0.3 (.06, 1.4)	5	1.3 (0.5, 3.4)	0	0 (na)	2	0.4 (0.1, 1.8)
Newly Incident Powder-Only Users		396		319		287		286		359		355		362

Panel B: Weighted Characteristics of Newly Incident Crack + Powder-only Users.

Years	2011		2012		2013		2014		2015		2016		2017	
Variables	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Sex (Male)	25	57.5 (37.1, 75.6)	26	62.7 (42.4, 79.4)	21	61.9 (35.5, 82.8)	19	47.6 (29.2, 66.8)	12	60.0 (31.3, 83.2)	13	44.9 (27.9, 63.2)	15	57.9 (28.5, 82.6)
Age (12-17 years)	10	22.5 (11.6, 39.1)	7	15.8 (5.6, 37.3)	4	12.2 (4.4, 29.3)	3	8.8 (3.1, 22.7)	1	0.6 (0.1, 5.0)	2	7.5 (2.6, 19.5)	1	4.4 (1.3, 13.7)
Race (NH White)	36	81.8 (62.9, 92.2)	29	69.9 (51.2, 83.7)	29	86.4 (61.3, 96.3)	28	74.7 (50.0, 89.7)	14	68.0 (42.6, 85.8)	23	79.4 (54.3, 92.6)	16	60.9 (34.0, 82.6)
SES (% in Poverty)	11	25.8 (12.2, 46.6)	9	21.4 (11.1, 37.4)	7	21.0 (7.2, 47.5)	11	29.4 (13.3, 53.0)	3	15.0 (4.9, 37.6)	8	26.5 (9.9, 54.2)	10	38.5 (22.1, 57.9)
Ever Use Tobacco	44	100.0 (na)	41	100.0 (na)	33	98.4 (88.8, 99.8)	37	100.0 (na)	19	98.9 (90.4, 99.9)	24	83.9 (37.9, 97.8)	26	99.7 (97.2, 99.9)
Ever Use Alcohol	44	100.0 (na)	40	99.0 (92.1, 99.9)	34	99.9 (99.2, 99.9)	37	100.0 (na)	20	100.0 (na)	29	100.0 (na)	26	100.0 (na)
Ever Use Marijuana	43	98.7 (90.4, 99.8)	41	100.0 (na)	33	97.2 (81.2, 99.6)	37	99.1 (93.0, 99.9)	20	100.0 (na)	29	100.0 (na)	24	92.9 (61.5, 99.1)
Injecting Drug Use	11	25.6 (10.0, 51.4)	9	22.3 (9.1, 45.3)	1	3.1 (0.6, 13.9)	2	6.1 (1.1, 27.4)	1	1.1 (0.1, 9.4)	6	21.1 (6.9, 49.2)	2	8.0 (1.0, 41.3)
Newly Incident Crack Users		44		41		34		37		20		29		26
All Newly Incident Cocaine Users		419		360		321		323		379		384		388

Figure 5.1: Flowchart Illustrating Cocaine Prevalence & Incidence by Year & Route of Administration. Data from the National Surveys on Drug Use & Health, NSDUH (2011-2017)



Notes:

[1] NICU=Newly Incident Cocaine Powder Only Use; NICRU=Newly Incident Crack-Cocaine Use with Possible Past Use of Cocaine Powder. [2] Newly Incident Use is defined as first use the the 12 months preceding interview date. [3] NI Crack + CHCL refers to use of both Crack and Cocaine Powder in the past 12 months.

Table 5.2: Estimated Meta-Analysis Summary of Year-Specific Odds Ratio Estimates from Generalized Linear Models/Generalized Estimating Equations (GZLM/GEE).

	Cocaine Side Effect Problems & Experiences Assessed in the NSDUH ACASI Assessment	Model 1: Estimated Meta-Analysis Summary of Year-Specific Odds Ratio Estimates from the Crude GZLM/GEE Model, Before Statistical Adjustments (95% CI)†	Model 2: Estimated Meta-Analysis Summary of Year-Specific Odds Ratio Estimates from the GZLM/GEE Multivariate Response Model, with Statistical Adjustments for Age, Sex, and Race-ethnicity (95% CI) ††	Model 3: Estimated Meta-Analysis Summary of Year-Specific Odds Ratio Estimates from the GZLM/GEE Multivariate Response Model, with Statistical Adjustments for Age, Sex, Race-ethnicity, and Drug History (95% CI) †††	Model 4: Estimated Meta-Analysis Summary of Year-Specific Odds Ratio Estimates from the GZLM/GEE Multivariate Response Model, with Statistical Adjustments for Age, Sex, Race-ethnicity, and SES (95% CI) ††††
	Powder + Crack vs. Powder Only	2.5	-	-	-
		(2.1, 3.0)	-	-	-
SEPE1	Wanted/Tried to Cut Down Use		1.4	1.3	1.4
			(1.0, 2.0)	(1.0, 1.8)	(1.0, 1.8)
SEPE2	Spent a Lot of Time Getting Over the Effects		2.5	2.5	2.5
			(1.6, 4.0)	(1.6, 4.0)	(1.6, 4.0)
SEPE3	Tried to Set Limits on Use		1.8	1.8	1.8
			(1.3, 2.3)	(1.3, 2.4)	(1.3, 2.3)
SEPE4	Not Able to Keep Limits		9.8	9.5	9.8
			(6.1, 15.6)	(5.9, 15.4)	(6.1, 15.6)
SEPE5	Needed More Cocaine, Same Effect		4.3	4.2	4.3
			(3.0, 6.1)	(2.9, 6.1)	(3.0, 6.1)
SEPE6	Same Amount, Less Effect		2.1	2.1	2.0
			(1.2, 3.4)	(1.3, 3.6)	(1.2, 3.4)

Table 5.2 (cont'd)

	Cocaine SEPE's Contd.	Model 1	Model 2	Model 3	Model 4
SEPE7	Spent a Lot of Time Getting/Using		6.0	6.0	6.1
			(4.3, 8.5)	(4.2, 8.5)	(4.3, 8.6)
SEPE8	Not Able to Cut Down/Stop Using Every Time		2.6	2.5	2.6
			(1.3, 5.2)	(1.3, 5.0)	(1.3, 5.2)
SEPE9	Not Able to Cut Down/Stop One Time		0.8	0.8	0.8
			(0.6, 1.1)	(0.6, 1.1)	(0.6, 1.1)
SEPE10	Felt Blue When Cut Down		4.5	4.5	4.5
			(2.9, 6.9)	(3.1, 6.5)	(3.1, 6.4)
SEPE11	Experienced 2+ Withdrawal Symptoms		6.0	6.0	6.0
			(3.8, 9.5)	(3.8, 9.3)	(3.9, 9.3)
SEPE12	Emotional Problems		5.5	5.4	5.5
			(3.9, 7.8)	(3.8, 7.7)	(3.9, 7.8)
SEPE13	Continued Use Despite Emotional Problems		10.8	10.5	10.8
			(6.9, 16.8)	(6.7, 16.5)	(6.9, 16.8)
SEPE14	Physical Problems		2.7	2.6	2.8
			(1.7, 4.5)	(1.6, 4.2)	(1.7, 4.4)
SEPE15	Used Despite Physical Problems		NTS [d]	NTS [d]	NTS [d]
			na	(na)	(na)
SEPE16	Reduced Salience of Non-Drug Acts		7.6	7.4	7.6
			(4.9, 11.7)	(4.9, 11.2)	(5.0, 11.4)
SEPE17	Serious Problems at Home/Work/School		7.3	7.0	7.3
			(4.3, 12.2)	(4.6, 10.8)	(4.8, 11.1)
SEPE18	Engaged in Dangerous Activities		5.2	5.2	5.3
			(3.6, 7.7)	(3.5, 7.7)	(3.6, 7.7)
SEPE19	Problems with the Law		7.7	7.4	7.8
			(4.2, 14.4)	(3.9, 13.9)	(4.2, 14.4)
SEPE20	Problems with Family/Friends		6.2	6.3	6.3
			(4.1, 9.4)	(4.2, 9.3)	(4.3, 9.2)
SEPE21	Used Despite Problems with Family/Friends		11.3	11.2	11.3
			(6.9, 18.6)	(6.7, 18.6)	(6.9, 18.6)

Table 5.2 (cont'd)

	Covariate Controls		Model 1		Model 2		Model 3		Model 4
	Age (12-17 year)				1.1		1.1		1.1
					(1.0, 1.2)		(1.0, 1.3)		(1.0, 1.2)
	Sex (Male)				1.0		1.1		1.1
					(1.0, 1.1)		(1.0, 1.2)		(1.0, 1.2)
	Race (NH White)				0.8		0.8		0.8
					(0.7, 1.0)		(0.7, 0.9)		(0.7, 0.9)
	SES (% at Federal Poverty Level or below)						-		1.0
							-		(0.9, 1.1)
	Ever Use Alcohol						1.4		
							(0.9, 2.1)		
	Ever Use Tobacco						1.1		
							(0.9, 1.2)		
	Ever Use Marijuana						1.0		
							(0.8, 1.3)		
	Injecting Drug Use						1.2		
							(0.9, 1.6)		

Notes: † Meta-Analysis Summary Estimate derived from year-specific GZLM/GEE odds ratio (OR) estimates reported in Appendix Table C3(Aggregate unweighted n across all years of the downloaded NSDUH PUF datasets, after subgroup stratification n = 2,364 powder-only users, n = 231 powder-then-crack users). There are no control covariates in this crude unadjusted model.

†† Meta-Analysis Summary Estimate derived from year-specific GZLM/GEE odds ratio (OR) estimates reported in Appendix Table C3 (Aggregate unweighted n across all years of the downloaded NSDUH PUF datasets, after subgroup stratification n = 2,364 powder-only users, n = 231 powder-then-crack users). Covariate terms in this multivariate response model were for the age group (12-17 years =1), sex (male=1), and ethnic self-identification (Non-Hispanic White=1 vs. all other US Census race-ethnicity categories).

††† Same as above, but with additional covariate terms to reflect drug history including (a) history of drinking alcoholic beverages, (b) history of smoking tobacco, (c) history of cannabis use and (d) history of injecting drug use.

†††† This was an exploratory model due to the possibility that covariate adjustment for SES at the time of assessment is subject to influence by exposure to crack versus powder-only, and also is subject to influence by cocaine problems and experiences of the type under study here, with a resulting bias (e.g., 'collider bias' of the type that is created in epidemiological analyses when the covariate is subject to influence by both (a) the exposures under study, and (b) the outcomes under study, as explained recently in Lederer et al., 2019). SES was coded as at or below the federal poverty threshold vs. those above that threshold.

CHAPTER 6: COCAINE USE IN THE COMMUNITY: ADAPTING A MEDICATION-ASSISTED TREATMENT APPROACH FOR COMORBID CUD AND OUD AMONG JUSTICE-INVOLVED INDIVIDUALS IN A COUNTY JAIL
(Manuscript 3)

Abstract

Background: Rates of incarceration in US jails and prisons have risen over the past four decades. The risk of overdose related deaths are also much higher among individuals recently released from jail. State and local public health departments in conjunction with community healthcare workers and healthcare systems are integral to the prevention and response associated with drug use disorders and drug related morbidity and mortality in the criminal justice system.

Materials & Method: I used process-mapping as a tool to illustrate the flow of justice-involved individuals through the jail system in a mid-western County in the US. I then synthesized best practices in medication assisted treatment for cocaine use disorder and examined the use of coca tea as a potential adaptation to the County's MAT program to address the issue of comorbid OUD and CUD.

Results: Process mapping indicated that until 2019, access to MAT was restricted to those entering the criminal justice system who were already on methadone. This presented a significant barrier to making MAT more widely available for justice-involved individuals. Aggregated socio-demographic data from the County jail showed that about 6% of inmates had lifetime opioid use. The majority of inmates were male (~81%), White (~53%) and single (~75%) with comorbid alcohol, cannabis, cocaine or benzodiazepine use.

Conclusions: While there is currently no FDA approved pharmacological treatment for CUD, oral cocaine agonist treatments like coca tea, which have been used for more than 4,000 years in Peru and Bolivia with no evidence of harm might offer a potentially viable treatment modality

for comorbid OUD and CUD. However, larger trials recruiting specific subpopulations of users are needed to build the evidence base for the efficacy of this approach.

Keywords: Cocaine Use Disorder, Medication Assisted Treatment, MAT, jail

6.1 Introduction

As compared with the previous chapters in this dissertation, this chapter is oriented more toward epidemiology's function to improve public health. In this chapter I review how a local health department might respond to cocaine problems in the community, with attention to how the recently adopted approach to medication assisted treatment (MAT) for opioid use disorder (OUD) might be adapted to address cocaine dependence problems of the type I am studying in Aims 1 and 2 of this dissertation. Specifically, I focus on a sub-population of justice-involved individuals initiating MAT in the County jail, who might benefit from an expanded treatment approach to address their comorbid cocaine use disorder (CUD).

Briefly, the chapter is organized as follows. First, I quantify the public health burden associated with drug use disorders in the criminal justice system in the US and at the local level. Second, I create a process map that furthers understanding of how inmates in the county jail progress through the justice system with intent to identify potential opportunities and barriers to MAT. Next, I synthesize the literature on agonist medications as a treatment modality for CUD and examine whether oral cocaine use in diluted form might be adapted to address comorbid CUD in a local setting. Finally, I identify the challenges associated with expanding the jail MAT program to include MAT for CUD. This chapter will address Epidemiology's 5th rubric, "Prevention & Control."

6.2 Public Health Burden in Correctional Facilities

State and local public health departments in conjunction with community healthcare workers and healthcare systems play a critical role in the prevention and response efforts associated with drug use disorders. Over the course of the last four decades, US incarceration rates have quadrupled and drug-related overdose mortality on account of opioid and other drug

use including cocaine and methamphetamine concurrently with opioids has been increasing (CDC, 2015, Dumont et al., 2012, Joudrey, 2019, Karisa et al., 2019, Maxwell, 2020, Rudd, 2016, Travis et al., 2014). According to the National Inmate Survey (2007-2009), approximately two-thirds of sentenced jail inmates met the DSM-IV criteria of drug dependence as compared with 5% of the general population aged 18 and older (Bronson et al., 2017). In 2016, up to 20% of the people housed in US prisons met the criteria for opioid use disorder with approximately 2.3 million in the criminal justice system (Joudrey, 2019, Fazel et al., 2006, Lo & Stephens, 2000, Wagner & Rabuy, 2016, Winkelman et al., 2018; Zeng, 2018).

Similar trends have been observed at the local level. In this chapter, I focus on a mid-western County with a relatively large inmate population as compared to other counties in the State. Between 2014 and 2018 the number of individuals incarcerated ranged from 9,500 to 10,000. The average daily population in the county jail is about 600 inmates with approximately 30 individuals entering or leaving the facility on any given day. Between 2006 and 2016 opioid related deaths in the county increased more than eight-fold.

These national and local trends are of concern from a public health perspective because prior research shows that incarcerated populations in the US experience significant health problems that funnel back into the broader community (Dolan et al., 2016, Douglas et al., 2009, Fazel & Baillargeon, 2011, Lazarus et al., 2018, Kinner & Young, 2018). These threats include, but are not restricted to interrupted provision of care for behavioral health conditions, issues in the treatment of drug use disorders, infectious diseases such as HIV and Hepatitis C, as well as difficulty accessing treatment for chronic health conditions such as diabetes, Chronic Obstructive Pulmonary Disease, and liver disease (Ndeffo-Mbah et al., 2018). Justice involved individuals are more likely to experience neurological disorders and higher levels of stress, anxiety, sleep

deprivation and depression than other individuals in the population (Binswanger et al., 2009, Fazel & Danesh, 2002, Freudenberg et al., 2005, Heidari et al., 2014, Massoglia et al., 2008, Richie, 2001, Rutherford and Duggan, 2009, Vaughn et al, 2014). Being in jail is also associated with lower self-efficacy, stigma, and loss of social ties (Schnittker, 2007). These multiple interacting comorbidities significantly and negatively impact the overall ecology of health in jail systems (Trotter et al., 2018). As a first step to promoting the health of justice-involved individuals at the local level, I created a process map of a County jail in a Mid-western US state as described in detail in the following section.

6.3 A Process Map of MAT in a County Jail.

The County Health Department is the organizational unit responsible for jail medical services and is also a public entity federally qualified health center (FQHC) with a network of community health centers (CHCs) delivering primary care. The CHCs are in the beginning stages of increasing the County's capacity to provide SUD services including MAT. Additionally, the health department has close partnerships with Community Mental Health (CMH) to provide outpatient SUD services in the county jail and works directly with the jail, as well as specialty courts to provide case management. Having these diverse functions under one umbrella presents significant opportunities to improve access to MAT for justice-involved individuals.

Figure 6.1 illustrates a process map I developed in 2019 to assess the flow of inmates in the County jail and to identify potential opportunities as well as existing barriers to implementation of a jail-based MAT program. At the time the map was created, the only medication-assisted treatment (MAT) available to inmates was methadone and access to MAT was restricted to those already on methadone upon entering the system. Subsequently, adjustments were made to the process in order to enable initiation of MAT for inmates.

The process map showed that all inmates in the County jail were being administered a behavioral/physical assessment upon entry. The deputy on call assigned a score between 1 and 6 to every inmate based on their physical appearance and response to behavioral questions about drug use coded as 1= admit to the cell; 2-5 = refer to jail medical and 6=immediate transfer to ICU. Inmates had the option to self-identify a drug problem and get evaluated by a nurse. Some inmates got triaged to CATS (the jail substance use provider service) after nurse evaluation. Occasionally, an inmate might suppress their drug use information, go into withdrawal and then get seen by jail medical staff.

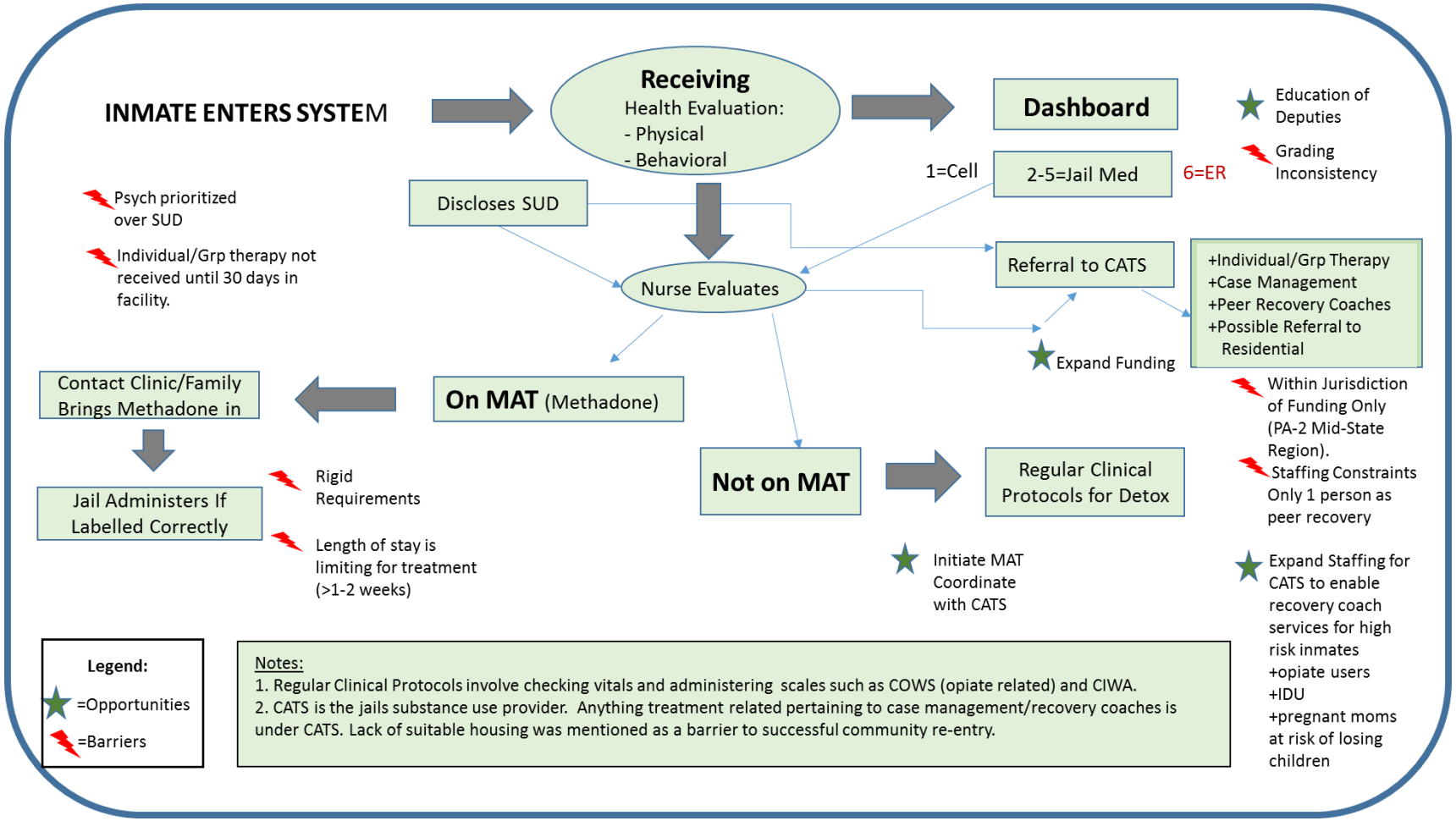
Notably, individuals already on methadone treatment were administered their medications contingent on family members delivering those medications to the jail. If an individual was not already on methadone when they were admitted, the jail did not initiate MAT. Inmates not on methadone, but with a drug use disorder went through established clinical protocols for detox.

To summarize, the process map helped identify the following challenges: 1) The need to continue educating deputies in the Sheriff's office about MAT and the concept of drug dependence as a disease rather than a moral failing such that jail staff could better understand and empathize with the stigma of drug dependence. 2) The need to make MAT accessible to a wider subset of inmates. 3) The need to expand staffing for CATS to provide services to inmates upon release with respect to continuation of MAT and reintegration into the community once they had initiated MAT in the jail. It also underscored a lack of consistency in how inmates were receiving referrals to CATS. The deputies did not have a medical background or medical training, but were nevertheless the first point of contact for all inmates.

Under recently adopted MAT protocols, per County policy all inmates are currently offered clinical services and supports pertinent to MAT (SAMHSA, 2019). The protocol defines MAT as "the use of medication in combination with behavioral health services to provide an individualized approach to the treatment of substance use disorders." A treatment plan is outlined for each person served that enumerates mutually acceptable short term goals that are acceptable to the individual as well as to the MAT Program and specifies which services are to be provided and by when. Individuals are identified for MAT through multiple channels such as receiving, CATS appointments, health assessments that include the Clinical Opiate Withdrawal Scale (COWS) and the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) and internal staff referrals via the Electronic Health Record (EHR) system (SAMHSA, 2019, National Commission on Correctional Healthcare, 2018).

Under the new program, a Community Health Center (CHC) designated as part of the health department's network of Federally Qualified Health Centers will serve as an integrated primary health care/SUD recovery home and point of contact providing comprehensive care to individuals at all stages of substance abuse and recovery including those on MAT (National Commission, 2018). It will also serve as a repository for patients referred from emergency departments /hospitals as well as jail-based SUD programs who are looking to transition back into the community. At the local level, the CHC is thus an important component of the SUD recovery "ecosystem" in the County because it extends SUD treatment to those underserved in the current treatment network.

Figure 6.1. A Process Map Illustrating Medication Assisted Treatment (MAT) in a County Jail, 2019-2020.



Preliminary research on inmates in the County jail has shown that more than half of the inmates with drug use disorders have comorbid mental health conditions as well. Additionally, a majority of those with OUD have recently used other drugs such as alcohol, cannabis, and cocaine. These preliminary data underscore the need to expand the scope of MAT to address CUD and other drug use among inmates. With this background, the following section is a review of the current status of pharmacological treatments for CUD.

6.4 Synthesis of Oral Agonists as a Treatment Modality for CUD.

Previous trials on cocaine use disorder have been inconclusive due to protocol and medication non-adherence, inconsistent findings, and large dropout rates prohibiting definitive conclusions. Indeed, the search for an effective pharmacotherapeutic treatment for CUD has been somewhat elusive with over 100 agents tested in over 66 placebo-controlled trials, yet not enough positive data to support an FDA recommendation (Alexander, 2001, Brady, 2019, Buccholz & Saxon, 2019, Fiscella et al., 2018).

Continued consideration of agonist medications for CUD is based on preclinical and clinical evidence for their efficacy (Gorelick, 1998, Grabowski, 2004, Karila, 2008, Xi, 2012). As a body of evidence on efficacy gradually accumulates, concerns about safety and distribution of the drug become increasingly relevant. Negus and Henningfield (2015) define treatment efficacy as "reductions in drug-taking behavior, as well as reallocation of behavior toward healthy alternative activities" (Negus & Henningfield, 2015, p.1). Pharmacotherapy can foster this change in several ways. One way is by using an antagonist agent that inhibits the drug from getting to the brain. Naltrexone, which is an approved medication to treat OUD is an example of an antagonist medication with good safety and efficacy under certain conditions. However, the use of Naloxone has been limited by issues of compliance, and antagonist agents have not yet

yielded a viable treatment for CUD (Negus & Henningfield, 2015). An alternative approach is that of 'agonist' medications. These are defined as drugs that share certain molecular, biochemical and physiologic effects with the drug of abuse but typically have different pharmacokinetic characteristics such as bioavailability, onset and duration of action. Agonist medications compete for receptors or produce cross-tolerance to the drug at those receptors b) functioning as effective reinforcers, ensuring their compliance and c) alleviating symptoms of withdrawal that contribute to relapse (Negus & Henningfield, 2015). It should be noted that slow drug onset and a longer duration of action can reduce the frequency of treatment necessary. Examples of agonist medications successfully deployed include methadone for OUD and nicotine for tobacco dependence (Fiscella et al., 2018).

Agonist medications to address drug use disorders are an example of medications to manage a disease rather than cure it. The primary end points in pre-clinical and clinical trials of medications to address cocaine dependence, focus on a reduction in cocaine seeking and use during medication maintenance (Negus & Henningfield, 2015). However, cocaine use might persist despite use of agonists and their eventual acceptance depends on their efficacy to reduce consumption, but also their ability to retain participation in treatment (Negus & Henningfield, 2015). Among the candidates under consideration as potential agonists, amphetamines have shown promise. However, amphetamine itself is a drug of great concern in the US. Risk perceptions play a crucial role in assessing the cost-benefit tradeoff of a drug, which in turn may govern eventual approval or disapproval of a drug. Ultimately, the benefits (therapeutic effectiveness) need to outweigh the costs (side-effects, potential for diversion) associated with the medication. Because the way cocaine acts in the brain is complex, it makes finding a single pharmacotherapeutic treatment for cocaine dependence extremely challenging. Distinct from the

treatment of OUD, therefore, effective agonists for CUD would need to be directed to multiple molecular targets (Kampman, 2019, Shorter et al., 2015).

With no FDA approved pharmacological treatment for CUD, psychosocial treatment is currently the accepted standard treatment (Dutra et al., 2008, De Crescenzo et al., 2018, Vocci & Montoya, 2009). In the short term, several psychosocial treatments have proven effective for CUD including individual and group drug counseling (intensive outpatient therapy), cognitive behavioral therapy (CBT), motivational interviewing and contingency management (CM) (Kampman, 2019). In the contingency management approach, patients receive incentives to achieve predetermined therapeutic goals. CM is particularly effective at promoting initial abstinence from cocaine (Higgins et al., 1994, Higgins et al., 2000, Silverman et al., 1996, Rawson et al., 2002). CM is based on the behavioral notion that rewards are reinforcing (Kampman, 2019). A behavior that is rewarded is therefore more likely to be repeated. Psychosocial treatments like CM for CUD do not work across the board. Many patients do not respond to these treatments. Additionally, the treatments have a high dropout rate and many do not achieve abstinence for any length of time.

CBT focuses on reducing craving. Patients are taught to recognize situations that trigger drug craving and to avoid these situations when possible. Patients are also taught coping skills to address cocaine craving. Cocaine dependent patients on CBT often continue to show improvement even after therapy is completed (Llosa, 1994) suggesting that a combination oral agonist in conjunction with CBT might have better success than either treatment alone. The following section reviews the evidence on oral cocaine as a treatment modality for CUD and examines whether it might be adapted across cultural boundaries to meet a growing US public health need.

6.5 Oral Cocaine Treatment as an Adaptation to a Local MAT Program

Oral cocaine agonist treatment in South America has been efficacious in the treatment of CUD and has a low potential for harm. Prior research indicates that oral cocaine use does not lead to drug dependence, behavioral disorders or intoxication (Carroll, 1977, Kantak, 1975, Llosa, 2010, Llosa, 1994, Rush, 1999, Siegel, 1986, Walsh, 2000). However, legal restrictions on the coca plant, which contains cocaine alkaloid, currently prohibit its use and distribution in the US (Llosa, 2010).

Geographically, coca leaf cultivation is permitted mainly in Peru and Bolivia (Montoya & Chilcoat, 1996). Research has shown that coca leaves typically contain between 0.25% and 2.25% of alkaloids. In addition to the cocaine alkaloid, coca leaves have also been found to contain calcium, iron, phosphorous and other trace elements (Jenkins, 1996, Martin, 1970). Traditionally, coca leaves have been either chewed or imbibed as a tea known as 'mate de coca.' The leaves are mixed with 'Illipta' (a substance made from seeds) prior to being chewed. 'Illipta' increases intestinal absorption and helps with the release of cocaine from the coca leaves (Carrol, 1977, Llosa & Chang, 2007). Similarly, infusing the leaves in hot water facilitates the release of cocaine.

Culturally, in the Andean region, it is not unusual for a person to chew 30-50 grams of fresh coca leaves daily with no adverse side effects (Siegel, 1986). Oral cocaine is mainly absorbed in the intestine and has a bioavailability ranging between 20% and 30%, which is much lower than that of other routes of administration (Vereby & Gold, 1988). The effects of oral cocaine are twice as long-lasting as effects via nasal insufflation, and five to 10 times as long lasting as the effects via smoking. Additionally, oral cocaine has a slow absorption rate, which gives it therapeutic advantages as compared with other routes of administration such as nasal

insufflation or smoking. It has been surmised that the slower absorption rate is related to the negligable rate of drug dependence via the oral route (Llosa, 2010).

Llosa & Llosa (2005) describe two methods by which physicians might use oral cocaine to treat CUD. They call these 1) 'cocalization' and 2) 'cocainization.' The first involves extracting cocaine alkaloid by chewing coca leaves, drinking coca tea, or eating foods containing cocaine powder. Due to legal and political restrictions on the coca tree and its by-products, 'cocalization' though legal in Peru is currently not a viable treatment modality in the US. The 'cocainization' method involves administration of cocaine alkaloid in gelatin capsules as agonist therapy and has been tested previously in the US to assess physiological and behavioral responses in subjects (Filmore et al., 2002, Llosa, 2010, Rush et al., 1999, Walsh et al., 2000). These studies produced evidence indicating that oral consumption of cocaine alkaloid (CHCl) when taken in doses similar to what users in the Andean region typically consume (~50-300 mg divided into three daily doses) is efficacious for individuals with a history of cocaine use and may be administered safely under controlled conditions. Appendix Table D1 serves as a proof of concept for the oral cocaine treatment methods developed by Llosa et al. It summarizes results from n=127 patients in multiple clinical trials held between 1989 and 2006. Llosa (2010) indicates that under cocainization therapy, gelatin capsules or tablets containing cocaine alkaloid may be mixed with another substance such that cocaine is only released in the intestine. This reduces the potential for diversion of these gelatin capsules.

It should be noted that patients treated with oral cocaine agonist therapy typically show positive benzoylecgonine urine levels between 30,000 and 100,000 ng/mL. When a patient relapses, levels normally exceed that range (Llosa, 2010). Thus, in the case of oral cocaine treatment, the presence of the cocaine metabolite, benzoylecgonine in urine is a measure of

treatment compliance rather than a measure of abstinence from the drug. The levels of metabolites in urine screens may vary based on the method of oral cocaine treatment adopted.

The low potential for dependence associated with the use of oral cocaine to treat CUD as demonstrated in prior research, as well as a preliminary body of evidence suggesting its efficacy in controlling CUD, particularly when combined with a psychosocial treatment such as CBT suggests that oral cocaine use as agonist treatment for CUD might be a potentially viable treatment modality for some users (Dutra et al., 2008, De Crescenzo et al., 2018, Llosa, 1994, Vocci & Montoya, 2009). Further research expanding the size of the trials and identifying specific subgroups of users is, however, recommended to boost the initial building blocks of evidence in a cultural context that is different from that of the US.

6.5 Barriers & Challenges to MAT for CUD

Going forward, concerns regarding safety and tolerability in promising medications for CUD need to receive attention. Identifying partial agonists that are also long acting would make this treatment strategy more practical and useful for clinics. CUD is a heterogenous disorder which might potentially be affecting pharmacotherapeutic results (Kampman, 2019). Identifying subgroups of patients and medications that are geared specifically to those subgroups may eventually help us to develop effective medications for CUD (Kampman, 2019).

Among the challenges underlying the development of psychosocial treatments for CUD is finding innovative ways to apply them. For example, finding novel ways to reward abstinence can be challenging. Additionally, establishing a continuum of care from jail to community is challenging, but essential to facilitate program retention and promote recovery.

Finally, at the practitioner level, educating deputies and members of the community about oral agonists for CUD, gaining community trust and acceptance for a novel treatment approach,

finding sustainable funding to institute and keep the program ongoing and facilitating cross-sector communication and resource sharing to ensure successful re-integration of justice involved individuals into the community are all key challenges that would need to be overcome if this significant public health issue is to be addressed in a holistic way.

CHAPTER 7: SUMMARY AND CONCLUSIONS

7.1 Summary of Findings

The first study in this dissertation analyzed crack-associated toxicity in the US between 2002 and 2016. It presented first published estimates of cocaine dependence attack rates (AR) as incidence proportions for two subgroups of cocaine initiates evaluated within 12 months after onset – 1) a larger subgroup that starts with powder but has never used crack, and 2) a smaller powder-then-crack subgroup with all crack onsets occurring after powder onset. For cocaine powder-only initiates, the meta-analysis AR estimate showed an estimated 5% becoming cocaine dependence cases within 1-12 months after powder onset (95% CI = 4.0%, 6.3%). For powder-then-crack initiates, the corresponding meta-analysis AR estimate was 22% (95% CI = 16.7%, 29.4%). Thus, this study's main novel discovery is that roughly one-in-five crack initiates developed cocaine dependence within 1-12 months versus roughly one-in-twenty for powder-only - is a fourfold variation. For several cocaine side effect problems and experiences there is a statistically robust crack-associated excess risk.

Study 2 built on the preliminary evidence presented in study 1 by taking a multivariate GEE approach to estimating crack-associated excess odds of developing a prodromal cocaine dependence syndrome, thereby addressing the interdependence of within subject SEPEs. I first estimated analysis-weighted incidence proportions for cocaine powder-only users (n=2364) and crack + powder users (n=231). Subsequently, I estimated odds ratios for 21 individual SEPEs reflecting crack/powder-only contrasts, year-by-year with corresponding Taylor series 95% confidence intervals. A fixed effects meta-analysis approach yielded summary estimates for each SEPE. Results indicated excess odds of 17 cocaine SEPEs for crack smokers, relative to

experiences of 'powder only' users ($p<0.05$), with no appreciable attenuation of the estimates after covariate adjustments for age, race, sex and drug history. Strong crack-associated excess odds were observed for inability to keep limits; aOR=9.5 (5.9, 15.4), use despite emotional problems aOR=10.5 (6.7, 16.5) and continued use despite problems with friends and family aOR=11.2 (6.7, 18.6). These results highlighted a need to differentiate among sub groups of cocaine initiates in order to develop appropriate treatment modalities for both groups.

Study 3 was oriented toward epidemiology's rubric of prevention and control. The main aim was to show how a local public health department might response to cocaine use in the community. Local public health departments in conjunction with community healthcare workers and healthcare systems play a critical role in the prevention and control of drug use disorders and drug related morbidity and mortality. I illustrated via process-mapping, the flow of justice-involved individuals through the jail system in the County and synthesized evidence on the use of oral cocaine agonist treatments 'cocalization' and 'cocainization' as a potential adaptation to the County's MAT program to address the issue of comorbid OUD and CUD.

Results indicated that oral cocaine has a low potential for dependence. A preliminary body of evidence suggests its efficacy in controlling CUD, particularly when combined with a psychosocial treatment such as CBT. Oral cocaine use as agonist treatment for CUD might therefore be a potentially viable treatment modality for some users (Dutra et al., 2008, De Crescenzo et al., 2018, Llosa, 1994, Vocci & Montoya, 2009). Further research expanding the size of the trials and identifying specific subgroups of users is, however, recommended to boost these initial building blocks of evidence in a cultural context that is different from that of S. America.

7.2 Strengths and Limitations

The three studies that constitute this dissertation are subject to certain limitations. First, because the studies are cross-sectional in design, they are perhaps less rigorous than longitudinal studies might be. However, taken collectively, they do serve as preliminary evidence that can help guide future longitudinal studies and clinical trials on the subject.

Second, participation levels for the NSDUH have been declining over time. Between 2002 and 2016, NSDUH response rates went down from approximately 72% in 2002 to ~53% in 2016 (Czajka & Beyler, 2016). Given the sensitive subject matter of drug use surveys, this is not surprising in and of itself. However, if the non-response is related to drug use in the sample, then the high non-response rates would affect the results presented in these studies due to selection bias. Another limitation with respect to the study sample is that the NSDUH does not include homeless individuals or transient populations living in shelters, resulting in potential underestimation of the occurrence of cocaine related side effect problems and experiences studied here.

Third, because the key response variables under study are self-reported, they are subject to all of the constraints pertinent to self-report surveys including potential recall bias. In this dissertation, these reporting errors are reduced by limiting the timeframe of recall to 12 months prior to the interview date.

Counterbalancing the above mentioned limitations are some study strengths worthy of mention. First, the NSDUH has large study samples from year to year which improve the precision and validity of the studies herein. Second, analysis conducted year-by-year reduces sources of between year heterogeneity as compared to pooled analysis. Third, the interviews, made use of computer-assisted personal interviews (CAPI) and audio computer assisted self-

interviews (ACASI) for data collection. Interviewers conducted a personal interview via the CAPI method to obtain background information and determine the date of administration of the survey. Subsequently, inmates directly entered responses into a computer using a touchscreen and synchronized audio instructions delivered via headphones (Bronson et al., 2017). During the ACASI portion of the interview, respondents recorded their responses privately. ACASI administration, thus helped to elicit more candid responses on sensitive behaviors by protecting confidentiality of responses. They also helped eliminate literacy issues, promoting greater accuracy in survey self-report. Thus, the overall extent of underreporting of behaviors was considerably reduced (Bronson, 2017).

7.3 Public Health Implications and Next Steps

The results of this dissertation's studies have several public health implications. First, there appears to be a need to screen for newly incident cocaine use and early manifestations of CUD. One way for clinicians to do this is by examining clustering of cocaine-related side effect problems and experiences in subgroups of cocaine users. This approach, in turn might help reduce onset of CUD.

Second, higher odds of several cocaine-related SEPEs in powder-then-crack versus powder only users suggests that treatment modalities for different subgroups of cocaine users might need to be tailored based on the route of administration of the drug.

Third, provision of MAT is a first step in helping inmates navigate their drug use disorders. However, multiple drug comorbidities among justice-involved individuals need to be addressed with a multipronged strategy which involves establishing a continuum of care from jail to community in addition to providing MAT for comorbid drug use. Adequate treatment of drug use disorders in jail involve provision of wraparound services and continuity of care upon

release. These services might include housing support, psychosocial support, and scheduling assistance provided by recovery coaches to help with program compliance and retention. Throughout this process it is critically important for the community in question to accept the notion that drug dependence is a disease rather than a moral failing. This acceptance would greatly help address stigma associated with drug use and dependence and might need to be achieved via training videos, public service announcements and community education events. Additionally, high level cross-sector support is required before meaningful engagement with harm reduction approaches like MAT can occur.

Future research will focus on investigating the covariation of 21 cocaine-related side-effect problems and experiences among newly incident cocaine users over the duration of cocaine use, wherein duration is defined as elapsed time from the month of cocaine onset to the quarter of assessment for each individual within 12 months after onset. This research will provide fine-grained estimates of a prodromal cocaine syndrome of potential use to clinicians in making early diagnoses of cocaine dependence.

Given the high rates of drug comorbidities (opioids and cocaine) observed, next steps might also involve a comparative analysis of male-female differences in newly incident opioid and cocaine use.

Additionally, future directions might include analysis of baseline community data pre-MAT with data in the months following institution of the MAT in the County jail to assess program efficacy, rates of recidivism, and psychosocial outcomes in individuals on MAT.

APPENDICES

Appendix A

IRB Determination

MICHIGAN STATE
UNIVERSITY

DETERMINED NOT "HUMAN SUBJECTS"
Revised Common Rule

February 22, 2019

To: Madhur Chandra

Re: **MSU Study ID:** STUDY00002209
Principal Investigator: Madhur Chandra
Determination Date: 2/22/2019

Title: CONTRIBUTIONS TO THE EPIDEMIOLOGY OF COCAINE DEPENDENCE: NOVEL ESTIMATES OF TRANSITION PROBABILITIES AMONG SUBGROUPS OF COCAINE INITIATES

The activity described in this submission was determined not to involve "human subjects" as defined by the Common Rule as codified in the U.S. Department of Health and Human Services (DHHS) regulations for the protection of human research subjects.

Definition of Human Subject
For DHHS, "*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens." [45 CFR 46.102(e)(1)]

Determination
This study will use publicly available deidentified data from the Substance Abuse and Mental Health Services Administration for the United States National Surveys on Drug Use and Health (2002-2017).

Hence, the activity does not involve human subjects.

Therefore, the federal regulations for the protection of human subjects would not apply to this activity and Michigan State University (MSU) Institutional Review Board (IRB) approval is not needed to proceed. However, please note that while MSU IRB approval is not required, other federal, state, or local regulations or requirements or ethical or professional standards may still be applicable based on the activity.

Modifications: If any of the activities described in this submission change, please contact the IRB office as the activity may involve human subject research and require IRB approval. For example, this determination is not applicable to activities that may

Office of Regulatory Affairs
Human Research Protection Program

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be regulated by U.S. Food & Drug Administration (FDA), such as those involving drugs, medical devices, human food additives, color additives, electronic products, or any other test articles regulated by the FDA.

Modifications to Funding: **Changes in funding may alter this determination.** For example, MSU IRB review and approval is required if MSU receives an award through a grant, contract, or cooperative agreement directly from a federal agency, even where all non-exempt research involving human subjects are carried out by employees or agents of another institution. In addition, the new funding source may have additional or different requirements.

For More Information: See HRPP Manual Section 4-3, Determination of Human Subject Research (available at hrpp.msu.edu).

Contact Information: If we can be of further assistance or if you have questions, please contact us at 517-355-2180 or via email at IRB@msu.edu. Please visit hrpp.msu.edu to access the HRPP Manual, templates, etc.

Appendix B

Manuscript 1

Table B1. NSDUH DSM-IV Dependence Criteria (American Psychiatric Association, 1994).

DSM-IV requires 3 or more of the following 7 dependence criteria as applied to the pattern of cocaine experiences (cocaine in any form).	
(1)	During the past 12 months, was there a month or more when you spent a lot of your time getting or using cocaine? (1=Yes; 2=No).
Salience	During the past 12 months, was there a month or more when you spent a lot of your time getting over the effects of the cocaine you used? (1=Yes; 2=No).
(2)	During the past 12 months, did you try to set limits on how often or how much cocaine you would use? (1=Yes; 2=No).
Keeping Limits	Were you able to keep to the limits you set, or did you often use cocaine more than you intended to? (1=usually kept to the limits set; 2=Often used more than intended).
(3)	During the past 12 months, did you need to use more cocaine than you used to in order to get the effect you wanted? (1=Yes; 2=No).
Tolerance	During the past 12 months, did you notice that using the same amount of cocaine had less effect on you than it used to? (1=Yes; 2=No).
(4)	During the past 12 months, did you want to or try to cut down or stop using cocaine? (1=Yes; 2=No).
Cut Down	During the past 12 months, were you able to cut down or stop using cocaine every time you wanted to or tried to? (1=Yes; 2=No).
(5)	Did you continue to use cocaine even though you thought it was causing you to have problems with your emotions, nerves, or mental health? (1=Yes; 2=No).
Continued Use Despite Problems	Did you continue to use cocaine even though you thought it was causing you to have physical problems? (1=Yes; 2=No).
(6)	This question is about important activities such as working, going to school, taking care of children, doing fun things such as hobbies and sports, and spending time with friends and family. During the past 12 months, did using cocaine cause you to give up or spend less time doing these types of important activities? (1=Yes; 2=No).
Reduced Activity	During the past 12 months, have you felt kind of blue or down when you cut down or stopped using cocaine? (1=Yes; 2=No).
(7)	Please look at the symptoms listed below. During the past 12 months, did you have 2 or more of these symptoms that lasted for more than a day after you cut back or stopped using cocaine? • Feeling tired or exhausted • Having bad dreams • Having trouble sleeping or sleeping more than you normally do • Feeling hungry more often • Feeling either very slowed down or like you couldn't sit still
Withdrawal	

B2: A Technical Note on Signs vs. Symptoms of Dependence and Identification of Newly Incident Cocaine Users

1. Cocaine Side Effect Problems and Experiences

The Oxford English Dictionary (http://www.oed.com) distinguishes between a 'sign' of an underlying pathological process in medicine or pathology *vs* a 'symptom' as follows:

[In Medicine, a sign is defined as:] An indication of the presence or course of a disease or injury; *spec.* an abnormality detected by physical (or, in later use, radiological or laboratory) examination of a patient which is regarded as an objective indicator of a particular disease or pathological condition (as opposed to a subjective indicator; ….

[A symptom is defined as:] A (bodily or mental) phenomenon, circumstance, or change of condition arising from and accompanying a disease or affection, and constituting an indication or evidence of it; a characteristic sign *of* some particular disease. Esp., in modern use, a subjective indication, perceptible to the patient, as opposed to an objective one or sign….

The NSDUH audio computer assisted self interview (ACASI) assessment includes a cocaine module that is administered to any participant who describes the experience of using cocaine, in any form, during the 12 months preceding the date of the ACASI assessment session. The cocaine module asks a set of survey items about cocaine problems and experiences that might or might not qualify as 'symptoms' of cocaine dependence, as defined in the OED and in medicine and psychiatry generally.

To illustrate, as shown in this work, quite a few newly incident cocaine users in the NSDUH samples acknowledge 'wanting to or trying to cut down or stop cocaine use,' as experienced within the first 12 months after initiation of cocaine use. Nevertheless, simply wanting to or trying to cut down or stop cocaine use does not qualify as a 'symptom' of cocaine

dependence or cocaine use disorder as these conditions have been defined in any of the DSM editions or in the ICD classifications or glossaries. When the cocaine dependence syndrome has formed, not being able to cut down or stop might be experienced as a symptom manifestation of the syndrome, but successful stopping or cutting down every time the user wants or tries to do so does not qualify as a cocaine dependence 'symptom' *per se*. (In actuality, the capacity to be successful when trying to cut down or stop might be taken as an indication that the user has not developed cocaine dependence.)

Another illustration involves 'spending a lot of time getting, using, or getting over the effects' of a drug, and the participants who say that they have had to spend a lot of time getting cocaine during the first 12 months after cocaine onset. A new initiate, particularly one in the early adolescent years, might have to spend a lot of time getting a second chance to try cocaine, after trying it for a first time, but it would be hard to claim that cocaine dependence had formed after a single occasion of using cocaine.

These two illustrations help convey why this study refers to cocaine problems and experiences. A clinician-reviewer of our work suggested that we add the phrase 'side effect' and we have taken that recommendation seriously. In this paper, we refer to cocaine 'side effect problems and experiences' (SEPE). The result is a way of talking about what can be seen to occur within 12 months or other shorter intervals after onset of drug use, without drawing any inference about an underlying pathological process that might or might not be leading up to the formation of a drug dependence syndrome or other drug use disorder. Here, we note that the first OED definition for 'side effect' is "a secondary, unintended, and typically undesirable effect of an action, situation, etc," and the list of problems and experiences covered in the NSDUH modules seem to fall well within those boundary conditions.

2. Identification of Newly Incident Cocaine Users

In the online NSDUH Restricted Data Analysis System (RDAS), past-year initiation designates individuals whose date of first use of each drug has occurred within a 12-month interval before the date of the NSDUH audio computer assisted self interview (ACASI) assessment. Therefore, past year initiates are 'newly incident' users, all with onset within that 12-month interval.

The reference period in RDAS is based on a calendar approach that is used during the ACASI session. To illustrate, if a participant completes the ACASI assessment on December 1, 2016, then 12 months prior to that date would be the interval starting on December 1, 2015.

The focus on newly incident users constrains problems of memory (recall) and reporting that can become more prominent as time passes from the first occasion of drug use. According to technical support staff, the NSDUH samples for the RDAS datasets from 2002 through 2016 included no past year initiates with crack use in the same month as cocaine powder use, and all of the past year initiates started as cocaine powder-only users. When crack-smoking occurred among these past year initiates, it occurred in a month after onset of cocaine powder use.

Adapted from:

United States (2017). Center for Behavioral Health Statistics and Quality. *2016 National Survey on Drug Use and Health: Methodological summary and definitions*. Retrieved from https://www.samhsa.gov/data/ on 15th March, 2019.

United States (2016). *2016 National Survey on Drug Use and Health: Codebook, Appendix F.* Retrieved from https://datafiles.samhsa.gov/info/nsduh-rdas-codebooks-nid17216 on 15th March, 2019.

B3: A Technical Note on the Differences between Fixed and Random Meta-Analysis

Meta-analysis estimates in this short communication were produced using Stata's 'metan' suite of commands. The 'metan' command in Stata permits the meta-analysis of studies that have two groups. The effect measure might be a difference between proportions if the data are binary, or a standardized difference in means if the data are continuous. Either fixed or random effects models can be fitted for both binary as well as continuous data. Mantel-Haenszel fixed effects models are the default in Stata's 'metan' command. These models are preferable to inverse variance fixed effects methods because they are robust when data are sparse. DerSimonian & Laird (1986) developed an approach to perform random effects meta-analysis. The DerSimonian & Laird method incorporates an estimate of between study variation τ^2 into both the study weights and the standard error of the estimate of the common effect. Where there is excess variability (or heterogeneity) between study results, random effects models typically "produce more conservative estimates of the significance of the treatment effect (i.e. a wider confidence interval) than fixed effects models" (Harris et al., 2013).

Appendix C

Manuscript 2

Table C1: Unweighted Characteristics of Newly Incident Crack-Cocaine vs. Powder Only Users. Data from the Unites States National Surveys on Drug Use and Health (2011-2017).

Panel A: Cocaine Powder Only Users

Years	2011		2012		2013		2014		2015		2016		2017	
Variables	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Sex (Male)	218	55.1 (50.1, 59.8)	175	54.9 (49.3, 60.2)	154	55.1 (49.3, 60.7)	149	52.1 (46.3, 57.8)	191	53.2 (48.0, 58.3)	190	53.5 (48.3, 58.7)	194	53.6 (48.4, 58.7)
Age (12-17 years)	111	28.0 (23.8, 32.7)	80	25.1 (20.6, 30.1)	60	23.0 (18.5, 28.2)	58	20.3 (16.0, 25.3)	63	17.5 (14.0, 21.8)	62	17.5 (13.1, 21.8)	66	18.2 (14.6, 22.6)
Race (NH White)	258	65.2 (60.3, 69.7)	220	68.9 (63.7, 73.8)	199	71.4 (65.9, 76.4)	187	65.4 (59.7, 70.7)	231	64.3 (59.3, 69.1)	233	65.6 (60.5, 70.4)	235	64.9 (59.9, 69.7)
SES (% in Poverty)	104	26.3 (22.2, 30.8)	72	22.6 (18.3, 27.5)	78	27.5 (22.7, 33.0)	81	28.3 (23.4, 33.8)	89	24.8 (20.5, 29.7)	84	23.7 (19.5, 28.4)	95	26.2 (22.0, 31.1)
Ever Use Tobacco	379	95.7 (93.2, 97.3)	305	95.6 (92.7, 97.4)	264	95.1 (91.9, 97.1)	262	91.6 (87.9, 94.3)	332	92.5 (89.3, 94.8)	320	90.1 (86.6, 92.8)	320	88.4 (84.7, 91.3)
Ever Use Alcohol	390	98.5 (96.7, 99.3)	313	98.1 (95.9, 99.2)	276	99.7 (97.6, 99.9)	281	98.3 (95.9, 99.3)	354	98.6 (96.7, 99.4)	355	100.0 (N/A)	362	100.0 (N/A)
Ever Use Marijuana	388	98.0 (96.0, 99.0)	311	97.5 (95.1, 98.7)		99.3 (97.3, 99.8)	278	97.2 (94.5, 98.6)	353	98.3 (96.3, 99.2)	352	99.1 (97.4, 99.7)	355	98.1 (96.0, 99.1)
Injecting Drug Use (Yes)	4	1.0 (.04, 2.7)	5	1.6 (0.7, 3.7)	0	0	2	0.7 (0.2, 2.8)	5	1.4 (0.6, 3.3)	0	0	3	0.8 (0.3, 2.5)
Total Powder-Only Users		396		319		287		286		359		355		362

Panel B: Users of Crack-Cocaine

Years	2011		2012		2013		2014		2015		2016		2017	
Variables	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Sex (Male)	26	59.1(44.2, 72.5)	23	56.1 (40.8, 70.3)	15	44.1 (28.6, 60.9)	19	51.4 (35.6, 66.8)	12	60.0 (38.0, 78.6)	11	37.9 (22.4, 56.4)	12	46.2 (28.4, 65.0)
Age (12-17 years)	13	29.5 (18.0, 44.5)	7	17.1 (8.4, 31.7)	9	26.5 (14.4, 43.6)	8	21.6 (11.2, 37.6)	1	5.0 (0.7, 28.3)	4	13.8 (5.3, 31.5)	6	23.1 (10.8, 42.8)
Race (NH White)	35	79.6 (65.1, 89.0)	28	68.3 (52.7, 80.6)	25	73.5 (56.4, 85.6)	25	67.6 (51.1, 80.6)	11	55.0 (33.6, 74.7)	23	79.3 (60.9, 90.4)	18	69.2 (49.4, 83.8)
SES (% in Poverty)	13	29.5 (18.0, 44.5)	12	29.5 (18.0, 44.5)	7	20.6 (10.1, 37.3)	11	29.4 (13.3, 53.0)	3	15.0 (4.9, 37.6)	7	24.1 (12.0, 42.7)	10	38.5 (22.1, 57.9)
Ever Use Tobacco	44	100.0 (na)	41	100.0 (na)	32	94.1 (79.3, 98.5)	37	100.0 (na)	19	95.0 (71.8, 99.3)	27	93.1 (76.2, 98.3)	25	96.2 (77.2, 99.5)
Ever Use Alcohol	44	100.0 (na)	40	97.6 (84.6, 99.7)	33	97.1 (81.8, 99.6)	37	100.0 (na)	20	100.0 (na)	29	100.0 (na)	26	100.0 (na)
Ever Use Marijuana	43	97.7 (85.5, 99.7)	41	100.0 (na)	32	94.1 (79.3, 98.5)	36	97.3 (83.1, 99.6)	20	100.0 (na)	29	100.0 (na)	24	92.3 (73.9, 98.1)
Injecting Drug Use	7	15.9 (7.8, 29.8)	7	17.1 (8.4, 31.7)	7	5.8 (1.5, 20.7)	2	5.4 (1.4, 19.2)	1	5.0 (0.7, 28.3)	6	20.7 (9.6, 39.0)	3	11.5 (3.8, 30.3)
Total Crack Users		44		41		34		37		20		29		26
All Newly Incident Cocaine Users		440		360		321		323		379		384		388

Table C2: Unweighted Proportions of Side Effect Problems & Experiences by Cocaine Subgroup. A Comparison of Newly Incident Crack Cocaine and Cocaine Powder Only Users in the United States (2011-2017).

Panel A. Cocaine Powder Only Users

	Cocaine Side Effect Problems & Experiences																				
Year	**PE1**	**PE2**	**PE3**	**PE4**	**PE5**	**PE6**	**PE7**	**PE8**	**PE9**	**PE10**	**PE11**	**PE12**	**PE13**	**PE14**	**PE15**	**PE16**	**PE17**	**PE18**	**PE19**	**PE20**	**PE21**	**n**
2011	**0.46**	0.03	**0.31**	0.02	0.08	0.02	0.07	0.03	**0.34**	0.07	0.05	0.07	0.02	0.02	0.01	0.04	0.04	0.06	0.02	0.06	0.01	6240
	(.41, .51)	(.02, .05)	(.27, .36)	(.01, .04)	(.05, 11)	(.01, .04)	(.05, .10)	(.02, .05)	(.30, .39)	(.05, .11)	(.03, .07)	(.05, .10)	(.01, .04)	(.01, .05)	(.001, .02)	(.02, .07)	(.02, .06)	(.04, .09)	(.01, .04)	(.04, .09)	(.01, .03)	
2012	**0.43**	0.03	**0.33**	0.01	0.08	0.03	0.06	0.02	**0.40**	0.10	0.04	0.07	0.02	0.03	0.003	0.04	0.04	0.04	0.01	0.06	0.02	5991
	(.37, .49)	(.02, .06)	(.28, .39)	(.004, .03)	(.05, 11)	(.02, .06)	(.04, .09)	(.01, .04)	(.35, .46)	(.07, .14)	(.02, .07)	(.04, .10)	(.01, .05)	(.02, .06)	.0005, .02	(.02, .07)	(.02, .06)	(.03, .07)	(.005, .03)	(.04, .09)	(.01, .04)	
2013	**0.43**	0.03	**0.30**	0.03	0.05	0.04	0.06	0.02	**0.35**	0.04	0.02	0.06	0.01	0.03	na	0.04	0.05	0.07	0.02	0.05	0.01	5642
	(.38, .49)	(.02, .06)	(.25, .35)	(.01, .05)	(.03, .09)	(.02, .07)	(.04, .10)	(.01, .05)	(.30, .41)	(.02, .07)	(.01, .05)	(.04, .10)	(.01, .04)	(.01, .06)	na	(.02, .07)	(.03, .08)	(.04, .11)	(.01, .04)	(.03,.08)	(.01, .05)	
2014	**0.34**	0.02	**0.26**	0.02	0.05	0.03	0.05	0.02	**0.42**	0.04	0.03	0.04	0.02	0.02	0.004	0.03	0.02	0.04	0.004	0.03	0.01	6624
	(.29, .40)	(.01, .05)	(.21, .31)	(.01, .05)	(.03, .08)	(.02, .06)	(.03, .08)	(.01, .04)	(.37, .48)	(.03, .08)	(.01, .05)	(.03, .08)	(.01, .04)	(.01, .04)	(.001, .03)	(.01, .05)	(.01, .04)	(.02, .07)	.001, .025	(.02, .06)	(.002, .03)	
2015	**0.38**	0.02	**0.28**	0.03	0.07	0.01	0.05	0.02	**0.39**	0.06	0.03	0.05	0.02	0.02	0.01	0.02	0.04	0.03	0.01	0.02	0.02	6732
	(.33, .43)	(.01, .04)	(.24, .33)	(.01, .05)	(.05, .10)	(.01, .03)	(.03, .08)	(.01, .04)	(.34, .44)	(.04, .09)	(.02, .06)	(.03, .08)	(.01, .04)	(.01, .04)	(.001, .02)	(.01, .04)	(.03, .07)	(.02, .06)	(.004, .03)	(.02, .05)	(.01, .04)	
2016	**0.42**	0.01	**0.29**	0.02	0.06	0.03	0.05	0.02	**0.40**	0.08	0.04	0.07	0.03	0.01	0.002	0.03	0.02	0.03	0.01	0.03	0.02	6574
	(.37, .47)	(.001, .02)	(.24, .34)	(.01, .04)	(.04, .09)	(.02, .06)	(.03, .08)	(.01, .04)	(.35, .46)	(.06, .11)	(.02, .06)	(.04, .10)	(.01, .05)	(.01, .03)	.0004, .02	(.01, .05)	(.01, .04)	(.02, .06)	(.003, .03)	(.02, .06)	(.01, .04)	
2017	**0.40**	0.03	**0.32**	0.02	0.05	0.05	0.07	0.02	**0.43**	0.07	0.03	0.07	0.03	0.02	0.003	0.04	0.02	0.05	0.02	0.05	0.02	6739
	(.35, .45)	(.02, .05)	(.27, .37)	(.01, .04)	(.03, .08)	(.03, .08)	(.05, .10)	(.01, .05)	(.38, .48)	(.04, .10)	(.01, .05)	(.04, .10)	(.01, .05)	(.01, .05)	.0003, .02	(.02, .06)	(.01, .05)	(.03, .08)	(.01, .04)	(.03,.08)	(.01, .04)	

Panel B. Users of Crack-Cocaine

Year	**PE1**	**PE2**	**PE3**	**PE4**	**PE5**	**PE6**	**PE7**	**PE8**	**PE9**	**PE10**	**PE11**	**PE12**	**PE13**	**PE14**	**PE15**	**PE16**	**PE17**	**PE18**	**PE19**	**PE20**	**PE21**	**n**
2011	**0.39**	0.07	**0.46**	0.14	0.18	0.07	**0.25**	0.02	**0.30**	**0.25**	0.18	**0.25**	0.21	0.05	na	0.14	0.16	**0.25**	0.07	**0.30**	0.21	1420
	(.26, .54)	(.02, .19)	(.31, .60)	(.06, .27)	(.09, .32)	(.02, .19)	(14, .40)	(.003, .15)	(.18, .45)	(.14, .40)	(.09, .32)	(.14, .40)	(.11, .35)	(.01, .17)	na	(.06, .27)	(.07, .30)	(.14, .40)	(.02, .19)	(.18, .45)	(.11, .34)	
2012	**0.39**	0.02	**0.27**	0.07	0.15	0.02	**0.27**	0.05	**0.39**	0.12	0.07	0.20	0.1	0.05	na	0.17	0.12	0.12	0.05	0.10	0.07	1421
	(.26, .55)	(.003, .15)	(.16, .42)	(.02, .20)	(.07, .29)	(.003, .15)	(16, .42)	(.01, .18)	(.26, .55)	(.05, .26)	(.02, .20)	(.10, .34)	(.04, .23)	(.01, .18)	na	(.08, .32)	(.05, .26)	(.05, .26)	(.01, .18)	(.04, .23)	(.02, .20)	
2013	**0.47**	0.09	**0.47**	0.21	0.21	0.06	**0.29**	0.06	**0.32**	**0.26**	0.18	0.24	0.18	0.03	na	0.24	0.21	0.21	0.06	0.21	0.15	1293
	(.31, .64)	(.03, .24)	(.31, .64)	(.10, .37)	(.10, .37)	(.01, .21)	(.17, .47)	(.02, .21)	(.19, .50)	(.14, .44)	(.08, .34)	(.12, 41)	(.08, .34)	(.004, .18)	na	(.12, .40)	(.10, .37)	(.10, .37)	(.02, .21)	(.10, .37)	(.06, .31)	
2014	**0.49**	na	**0.38**	0.11	0.16	0.05	0.14	0.05	**0.35**	0.16	0.14	0.19	0.11	0.03	na	0.11	0.08	0.16	0.05	0.19	0.11	1663
	(.33, .64)	na	(.24, .54)	(.04, .26)	(.07, .32)	(.01, .19)	(.06, .29)	(.01, .19)	(.22, .52)	(.08, .32)	(.06, .29)	(.09, .35)	(.04, .26)	(.004, .17)	na	(.04, .26)	(.03, .22)	(.08, .32)	(.01, .19)	(.09, .35)	(.04, .26)	
2015	**0.70**	na	**0.55**	0.15	**0.30**	0.15	**0.30**	0.05	**0.25**	**0.30**	0.20	**0.35**	**0.30**	na	na	**0.35**	0.20	**0.25**	0.05	**0.30**	**0.25**	1582
	(.47, .86)	na	(.34, .75)	(.05, .38)	(.14, .53)	(.05, .38)	(.14, .53)	(.01, .28)	(.11, ,48)	(.14, .53)	(.08, .43)	(.18, .57)	(.14, .53)	na	na	(.18, .57)	(.08, .43)	(.11, .48)	(.01, .28)	(.14, .53)	(.11, .48)	
2016	**0.52**	0.07	**0.52**	0.24	**0.28**	na	**0.28**	0.07	**0.38**	0.24	0.10	**0.28**	0.17	0.14	0.03	0.17	0.24	0.14	0.10	0.17	0.10	1495
	(.34, .69)	(.02, .24)	(.34, .69)	(.12, .43)	(.14, .46)	na	(.14, .46)	(.02, .24)	(.22, .56)	(.12, .43)	(.03, .28)	(.14, .46)	(.07, .35)	(.05, .32)	(.01, .21)	(.07, .35)	(.12, .43)	(.05, .32)	(.03, .28)	(.07, .35)	(.03, .28)	
2017	**0.58**	0.04	**0.39**	0.23	**0.31**	0.04	**0.39**	0.04	**0.27**	**0.31**	**0.27**	**0.35**	**0.31**	na	na	**0.27**	**0.35**	**0.31**	0.23	**0.27**	0.23	1567
	(.38, .75)	(.01, .23)	(.22, .58)	(.11, .43)	(.16, .51)	(.01, .23)	(.22, .58)	(.01, .23)	(.13, ,47)	(.16, .51)	(.13, .47)	(.19, .54)	(.16, .51)	na	na	(.13, .47)	(.19, .54)	(.16, .51)	(.11, .43)	(.13, .47)	(.11, .43)	

Notes: Side-Effect Problems & Experiences where the proportion equals or exceeds 25% of the study sample are highlighted in gray.

Table C3. Unweighted, Unadjusted Odds Ratio Estimates Contrasting Newly Incident Crack-Cocaine Users with Crack + Cocaine Powder Only Users. Data are from the United States National Surveys on Drug Use and Health, 2011-2017.

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Crack-Cocaine vs. CHCl	**2.5**	2.4	1.6	2.8	2.2	3.9	2.9	3.6
	(2.1, 3.0)	(1.6, 3.8)	(1.1, 2.4)	(1.8, 4.4)	(1.4, 3.6)	(2.1, 7.1)	(1.8, 4.7)	(2.1, 5.9)

Table C4: Unweighted, Covariate-Adjusted Odds Ratio Estimates (Adjusted for Age, Race, Sex) for Problems & Experiences of Newly Incident Crack-Cocaine Users in Contrast with Cocaine Powder Only Users. Data are from the United States National Surveys on Drug Use and Health, 2011-2017.

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE1: Wanted/Tried to Cut Down Use	**1.4**	0.8	0.8	1.2	1.9	3.7	1.5	2.1
	(1.0, 2.0)	(0.4,1.5)	(0.4,1.7)	(0.6,2.3)	(0.9,3.8)	(1.4,9.9)	(0.7,3.2)	(0.9,4.7)
PE2: Spent a Lot of Time Getting Over the Effects	**2.5**	2.6	0.8	3.2	1.9	3.7	13.1	1.5
	(1.6, 4.0)	(0.7,9.5)	(0.1,6.7)	(0.8,12.5)	(0.9,3.8)	(1.4,9.9)	(1.8,96.3)	(0.2,13.1)
PE3: Tried to Set Limits on Use	**1.8**	2.0	0.7	2.1	1.7	3.1	2.7	1.3
	(1.3, 2.3)	(1.,3.8)	(0.4,1.6)	(1.,4.3)	(0.8,3.6)	(1.2,7.6)	(1.3,5.8)	(0.6,3.)
PE4: Not Able to Keep Limits	**9.8**	10.5	6.0	9.8	5.5	6.6	15.9	14.8
	(6.1, 15.6)	(3.2,34.)	(1.3,27.8)	(3.2,30.2)	(1.5,20.3)	(1.6,27.1)	(5.1,49.6)	(4.6,47.8)
PE5: Needed More Cocaine, Same Effect	**4.3**	3.0	2.1	4.5	3.7	5.5	5.8	8.8
	(3.0, 6.1)	(1.3,6.9)	(0.8,5.5)	(1.7,11.8)	(1.3,10.2)	(2.,15.5)	(2.3,14.6)	(3.4,23.1)
PE6: Same Amount, Less Effect	**2.1**	4.9	0.7	1.5	1.7	12.1	1.5	0.8
	(1.2, 3.4)	(1.2,19.9)	(0.1,5.9)	(0.3,7.1)	(0.4,8.1)	(2.6,55.3)	(0.7,3.2)	(0.1,6.5)
PE7: Spent a Lot of Time Getting/Using	**6.0**	4.8	6.2	6.3	3.2	7.8	7.2	8.3
	(4.3, 8.5)	(2.2,10.6)	(2.7,14.5)	(2.6,15.3)	(1.1,9.4)	(2.7,22.7)	(2.8,18.5)	(3.5,19.9)
PE8: Not Able to Cut Down/Stop Using Every Time	**2.6**	0.8	3.1	2.7	4.0	2.6	3.7	1.7
	(1.3, 5.2)	(0.1,6.3)	(0.6,16.7)	(0.5,14.6)	(0.7,21.9)	(0.3,22.1)	(0.7,18.8)	(,)
PE9: Not Able to Cut Down/Stop One Time	**0.8**	0.9	1.0	0.9	0.8	0.5	0.9	0.5
	(0.6, 1.1)	(0.4,1.7)	(0.5,1.9)	(0.4,1.9)	(0.4,1.5)	(0.2,1.5)	(0.4,2.)	(0.2,1.2)
PE10: Felt Blue When Cut Down	**4.5**	4.5	1.3	8.6	4.3	6.6	3.7	6.4
	(2.9, 6.9)	(2.,9.7)	(0.5,3.5)	(3.3,22.5)	(1.5,12.3)	(2.3,19.3)	(1.5,9.5)	(2.5,16.5)
PE11: Experienced 2+ Withdrawal Symptoms	**6.0**	5.1	2.1	9.5	6.1	7.6	3.0	14.1
	(3.8, 9.5)	(2.1,12.4)	(0.6,8.)	(2.9,31.4)	(1.8,20.2)	(2.1,27.2)	(0.8,11.5)	(4.7,42.2)
PE12: Emotional Problems	**5.5**	5.0	3.4	4.6	5.2	9.8	5.5	7.7
	(3.9, 7.8)	(2.3,11.1)	(1.4,8.5)	(1.8,11.7)	(1.9,14.2)	(3.5,27.3)	(2.2,13.9)	(3.1,19.)
PE13: Continued Use Despite Emotional Problems	**10.8**	11.3	4.6	14.3	6.7	20.8	8.0	15.3
	(6.9, 16.8)	(4.2,30.3)	(1.3,16.6)	(3.9,53.1)	(1.7,25.8)	(6.2,69.8)	(2.5,26.1)	(5.4,43.2)
PE14: Physical Problems	**2.7**	2.1	1.7	1.0	1.6	3.7	11.2	2.1
	(1.7, 4.5)	(0.5,9.8)	(0.3,8.2)	(0.1,8.4)	(0.2,12.8)	(1.4,9.9)	(2.9,44.2)	(0.9,4.7)
PE15: Used Despite Physical Problems	**NTS**	NTS [d]	NTS [d]	NTS [d]	NTS [d]	NTS [d]	NTS [d]	NTS [d]
	na	na	na	na	na	na	na	na
PE16: Reduced Salience of Non-Drug Acts	**7.6**	4.1	5.5	8.1	4.7	26.1	8.0	9.7
	(4.9, 11.7)	(1.5,11.1)	(2.,15.2)	(3.,22.2)	(1.3,16.8)	(7.9,85.6)	(2.5,26.)	(3.4,27.3)
PE17: Serious Problems at Home/Work/School	**7.3**	5.3	3.7	5.2	4.9	5.5	15.9	23.0
	(4.3, 12.2)	(2.,13.8)	(1.2,11.3)	(1.9,13.9)	(1.1,20.9)	(1.7,18.5)	(5.1,49.7)	(7.9,67.3)

(Table C4 cont'd)

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE18: Engaged in Dangerous Activities	**5.2**	5.3	3.1	3.5	5.2	9.3	4.6	8.8
	(3.6, 7.7)	(2.4,11.6)	(1.,9.3)	(1.3,8.9)	(1.8,15.1)	(2.9,29.7)	(1.4,15.4)	(3.3,23.5)
PE19: Problems with the Law	**7.7**	4.9	3.9	3.3	16.2	4.6	13.6	17.4
	(4.2, 14.4)	(1.2,19.6)	(0.7,21.8)	(0.6,18.)	(1.5,178.9)	(0.5,42.9)	(2.6,71.)	(5.1,59.1)
PE20: Problems with Family/Friends	**6.2**	7.3	1.8	4.8	7.0	14.4	6.5	7.3
	(4.1, 9.4)	(3.4,15.8)	(0.6,5.8)	(1.8,12.9)	(2.5,20.)	(4.6,45.2)	(2.1,20.5)	(2.7,20.)
PE21: Used Despite Problems with Family/Friends	**11.3**	20.5	3.9	7.6	16.9	16.2	6.7	14.8
	(6.9, 18.6)	(6.6,63.8)	(0.9,16.5)	(2.2,26.4)	(3.,95.6)	(4.6,57.4)	(1.6,28.6)	(4.5,48.5)
Age (12-17 years)	**1.1**	1.1	1.2	1.0	1.3	1.1	1.0	1.1
	(1.0, 1.2)	(0.8,1.4)	(0.9,1.5)	(0.7,1.5)	(1.,1.8)	(0.8,1.4)	(0.8,1.4)	(0.9,1.5)
Male	**1.0**	1.0	1.2	0.9	1.1	1.0	1.1	1.1
	(1.0, 1.1)	(0.8,1.2)	(1.,1.5)	(0.7,1.2)	(0.8,1.4)	(0.8,1.3)	(0.8,1.3)	(0.8,1.3)
NH White	**0.8**	0.7	1.1	0.8	0.9	0.8	0.9	0.8
	(0.7, 1.0)	(0.5,0.8)	(0.8,1.3)	(0.6,1.1)	(0.7,1.2)	(0.6,1.0)	(0.7,1.1)	(0.6,1.)

Notes: [a] Odds ratio estimates are from unweighted GZLM/GEE regression models. [b] Covariates included age, race-ethnicity, sex. [c] MAS=Meta-analytic Summary Estimates using Fixed Effects approach. [d] NTS=Numbers too small. Newly Incident Cocaine Powder Only users (n): 2011 =396; 2012=319; 2013=287; 2014=286; 2015=359; 2016=355; 2017=362. Newly incident crack users (n): 2011 =44; 2012=41; 2013=34; 2014=37; 2015=20; 2016=29; 2017=26.

Table C5: Unweighted, Covariate-Adjusted Odds Ratio Estimates (Adjusted for Age, Race, Sex, & Drug history) Contrasting Problems & Experiences of Newly Incident Crack-Cocaine Users with Crack + Cocaine Powder Only Users. Data are from the United States National Surveys on Drug Use and Health, 2011-2017.

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE1: Wanted/Tried to Cut Down Use	**1.3**	0.9	0.8	1.1	1.9	3.8	1.6	1.8
	(1.0, 1.8)	(0.5, 1.8)	(0.4, 1.6)	(0.6, 2.2)	(0.9, 3.8)	(1.4, 10.7)	(0.7, 3.7)	(0.8, 4.0)
PE2: Spent a Lot of Time Getting Over the Effects	**2.5**	2.9	0.8	3.0	1.9	3.8	14.2	1.2
	(1.6, 4.0)	(0.8, 10.7)	(0.1, 6.2)	(0.7, 12.0)	(0.9, 3.8)	(1.4, 10.7)	(1.9, 105.2)	(0.2, 9.7)
PE3: Tried to Set Limits on Use	**1.8**	2.3	0.7	2.0	1.7	3.1	2.9	1.1
	(1.3, 2.4)	(1.2, 4.5)	(0.3, 1.5)	(1.0, 4.1)	(0.8, 3.6)	(1.3, 7.8)	(1.3, 6.4)	(0.5, 2.5)
PE4: Not Able to Keep Limits	**9.5**	11.8	5.5	9.4	5.5	6.8	17.1	11.9
	(5.9, 15.4)	(3.6, 39.0)	(1.2, 25.4)	(2.9, 30.8)	(1.5, 20.2)	(1.7, 27.6)	(5.3, 55.0)	(3.3, 42.7)
PE5: Needed More Cocaine, Same Effect	**4.2**	3.3	2.0	4.2	3.6	5.6	6.2	7.2
	(2.9, 6.1)	(1.4, 7.8)	(0.7, 5.1)	(1.6, 11.6)	(1.3, 10.2)	(2.0, 15.8)	(2.4, 16.1)	(2.6, 20.1)
PE6: Same Amount, Less Effect	**2.1**	5.5	0.7	1.4	1.7	12.3	1.6	0.6
	(1.3, 3.6)	(1.3, 22.5)	(0.1, 5.5)	(0.3, 6.8)	(0.4, 8.0)	(2.6, 59.4)	(0.7, 3.7)	(0.1, 4.7)
PE7: Spent a Lot of Time Getting/Using	**6.0**	5.5	5.8	6.1	3.2	8.0	7.7	6.8
	(4.2, 8.5)	(2.4, 12.3)	(2.5, 13.7)	(2.4, 15.2)	(1.1, 9.3)	(2.8, 23.1)	(3.0, 20.1)	(6.8, 16.8)
PE8: Not Able to Cut Down/Stop Using Every Time	**2.5**	1.0	2.9	2.6	4.0	2.6	4.0	1.4
	(1.3, 5.0)	(0.1, 7.0)	(0.5, 15.1)	(0.5, 14.1)	(0.7, 21.8)	(0.3, 22.4)	(0.8, 20.9)	(0.2, 10.8)
PE9: Not Able to Cut Down/Stop One Time	**0.8**	1.0	0.9	0.8	0.7	0.5	1.0	0.4
	(0.6, 1.1)	(0.5, 2.0)	(0.5, 1.8)	(0.4, 1.9)	(0.4, 1.5)	(0.2, 1.5)	(0.5, 2.2)	0.1, 1.1)
PE10: Felt Blue When Cut Down	**4.5**	5.0	1.2	8.2	4.3	6.8	4.0	5.2
	(3.1, 6.5)	(2.3, 11.1)	(0.4, 3.4)	(3.1, 21.6)	(1.5, 12.2)	(2.3, 19.7)	(1.5, 10.7)	(1.9, 13.9)
PE11: Experienced 2+ Withdrawal Symptoms	**6.0**	5.7	2.0	9.0	6.0	7.8	3.3	11.4
	(3.8, 9.3)	(2.3, 14.1)	(0.5, 7.8)	(2.8, 29.7)	(1.8, 20.1)	(2.2, 27.7)	(0.8, 12.8)	(3.6, 35.6)
PE12: Emotional Problems	**5.4**	5.7	3.2	4.4	5.2	10.0	5.9	6.2
	(3.8, 7.7)	(2.6, 12.6)	(1.3, 7.9)	(1.8, 11.1)	(1.9, 14.1)	(3.6, 28.0)	(2.2, 15.9)	(2.4, 16.3)
PE13: Continued Use Despite Emotional Problems	**10.5**	12.7	4.3	13.7	6.6	21.2	8.7	12.4
	(6.7, 16.5)	(4.8, 34.0)	(1.2, 14.7)	(3.6, 52.1)	(1.7, 25.7)	(6.3, 71.3)	(2.5, 29.6)	(4.1, 37.3)
PE14: Physical Problems	**2.6**	2.4	1.6	0.9	1.6	3.8	12.1	1.8
	(1.6, 4.2)	(0.5, 11.0)	(0.3, 7.7)	(0.1, 7.6)	(0.2, 12.6)	(1.4, 10.7)	(3.0, 48.5)	(0.8, 4.0)
PE15: Used Despite Physical Problems	**NTS [d]**	NTS [d]	NTS [d]	NTS [d]	NTS [d]	NTS d	NTS [d]	NTS [d]
	na	na	na	na	na	na	na	na
PE16: Reduced Salience of Non-Drug Acts	**7.4**	4.6	5.1	7.7	4.7	26.7	8.7	7.8
	(4.9, 11.2)	(1.7, 12.6)	(1.9, 14.2)	(2.8, 21.3)	(1.3, 16.7)	(8.1, 87.6)	(2.6, 29.4)	(2.6, 23.0)
PE17: Serious Problems at Home/Work/School	**7.0**	5.9	3.5	4.9	4.8	5.6	17.1	18.7
	(4.6, 10.8)	(2.3, 15.6)	(1.1, 10.6)	(1.7, 14.1)	(1.1, 20.8)	(1.7, 19.0)	(5.2, 56.7)	(6.1, 56.9)

(Table C5 cont'd)

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE18: Engaged in Dangerous Activities	**5.2**	5.9	2.9	3.3	5.2	9.5	4.9	7.2
	(3.5, 7.7)	(2.7, 13.3)	(1.0, 8.6)	(1.2, 9.1)	(1.8, 15.0)	(3.0, 30.2)	(1.4, 17.2)	(2.6, 20.0)
PE19: Problems with the Law	**7.4**	5.5	3.6	3.1	16.1	4.6	14.6	13.9
	(3.9, 13.9)	(1.4, 22.0)	(0.6, 21.0)	(0.6, 17.2)	(1.5, 178.0)	(0.5, 43.7)	(2.7, 79.9)	(3.9, 48.9)
PE20: Problems with Family/Friends	**6.3**	8.2	1.7	4.6	7.0	14.7	7.0	5.9
	(4.2, 9.3)	(3.8, 18.1)	(0.5, 5.6)	(1.7, 12.5)	(2.5, 19.8)	(4.7, 46.0)	(2.1, 23.1)	(2.1, 16.9)
PE21: Used Despite Problems with Family/Friends	**11.2**	23.2	3.7	7.2	16.8	16.5	7.2	11.9
	(6.7, 18.6)	(7.5, 71.3)	(0.8, 16.1)	(2.0, 26.5)	(3.0, 95.1)	(4.7, 58.4)	(1.7, 31.8)	(3.4, 41.2)
Age (12-17 years)	**1.1**	1.0	1.2	1.3	1.3	1.1	1.0	1.1
	(1.0, 1.3)	(0.8, 1.3)	(0.9, 1.6)	(0.8, 1.9)	(1.0, 1,8)	(0.8, 1.4)	(0.8, 1.3)	(0.8, 1.4)
Male	**1.1**	1.0	1.2	0.8	1.1	1.0	1.1	1.1
	(1.0, 1.2)	(0.8, 1.2)	(1.0, 1.5)	(0.6, 1.2)	(0.8, 1.4)	(0.8, 1.3)	(0.9, 1.3)	(0.9, 1.3)
NH White	**0.8**	0.7	1.1	0.6	0.9	0.8	0.9	0.8
	(0.7, 0.9)	(0.5, 0.8)	(0.8, 1.3)	(0.4, 1.0)	(0.7, 1.2)	(0.6, 1.0)	(0.7, 1.1)	(0.6, 1.0)
Ever Used Alcohol	**1.4**	0.7	2.4	0.9	1.4	1.0	na	na
	(0.9, 2.1)	(0.2, 2.3)	(1.2, 4.9)	(0.2, 4.8)	(0.4, 6.0)	(0.5, 2.1)	na	na
Ever Used Tobacco	**1.1**	1.1	1.2	2.3	1.1	1.1	0.8	1.3
	(0.9, 1.2)	(0.7, 1.8)	(0.8, 1.9)	(1.2, 4.8)	(0.7, 1.8)	(0.7, 1.7)	(0.6, 1.0)	(0.9, 1.8)
Ever Used Marijuana	**1.0**	1.4	0.9	1.2	1.0	1.5	1.1	0.7
	(0.8, 1.3)	(0.5, 4.1)	(0.5, 1.5)	(0.4, 3.3)	(0.4, 2.8)	(0.8, 2.7)	(0.7, 1.7)	(0.4, 1.3)
Injecting Drug Use (Yes)	**1.2**	0.4	1.5	2.6	0.9	0.5	0.7	4.1
	(0.9, 1.6)	(0.2, 1.2)	(0.8, 3.1)	(1.4, 4.7)	(0., 2.4)	(0.2, 1.2)	(0.3, 1.6)	

Notes: [a] Odds ratio estimates are from unweighted GZLM/GEE regression models. [b] Covariates included age, race-ethnicity, sex, and drug history. [c] MAS=Meta-analytic Summary Estimates using an Inverse Variance Fixed Effects approach. [d] NTS=Numbers too small. Newly Incident Cocaine Powder Only users (n): 2011 =396; 2012=319; 2013=287; 2014=286; 2015=359; 2016=355; 2017=362. Newly incident crack users (n): 2011 =44; 2012=41; 2013=34; 2014=37; 2015=20; 2016=29; 2017=26.

Table C6: Unweighted, Covariate-Adjusted Odds Ratio Estimates (Adjusted for Age, Race, Sex, and SES), Contrasting Problems & Experiences of Newly Incident Crack-Cocaine Users with Crack + Cocaine Powder Only Users. Data are from the United States National Surveys on Drug Use and Health, 2011-2017.

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE1: Wanted/Tried to Cut Down Use	**1.4**	0.8	0.9	1.2	1.9	3.7	1.5	2.1
	(1.0, 1.8)	(0.40, 1.5)	(0.4, 1.7)	(0.6, 2.3)	(0.9, 3.8)	(1.4, 10.0)	(0.7, 3.2)	(1.0, 4.8)
PE2: Spent a Lot of Time Getting Over the Effects	**2.5**	2.6	0.8	3.2	1.9	3.7	13.1	1.5
	(1.6, 4.0)	(0.7, 9.5)	(0.1, 6.8)	(0.8, 12.5)	(0.9, 3.8)	(1.4, 10.0)	(1.8, 96.8)	(0.2, 1.1)
PE3: Tried to Set Limits on Use	**1.8**	2.0	0.8	2.1	1.7	3.1	2.7	1.4
	(1.3, 2.3)	(1.0, 3.8)	(0.4, 1.6)	(1.0, 4.3)	(0.8, 3.6)	(1.2, 7.7)	(1.2, 5.7)	(0.6, 3.1)
PE4: Not Able to Keep Limits	**9.8**	10.4	6.0	9.8	5.5	6.7	15.8	15.0
	(6.1, 15.6)	(3.2, 33.9)	(1.3, 28.0)	(3.2, 30.2)	(1.5, 20.2)	(1.6, 27.3)	(5.1, 49.5)	(4.7, 48.3)
PE5: Needed More Cocaine, Same Effect	**4.3**	3.0	2.1	4.5	3.7	5.5	5.8	8.9
	(3.0, 6.1)	(1.3, 6.9)	(0.8, 5.6)	(1.7, 11.8)	(1.3, 10.2)	(2.0, 15.6)	(2.3, 14.6)	(3.4, 23.3)
PE6: Same Amount, Less Effect	**2.0**	4.9	0.7	1.5	1.7	12.1	1.5	0.8
	(1.2, 3.4)	(1.2, 19.8)	(0.1, 6.0)	(0.3, 7.1)	(0.4, 8.1)	(2.6, 55.7)	(0.7, 3.2)	(0.1, 6.5)
PE7: Spent a Lot of Time Getting/Using	**6.1**	4.8	6.3	6.3	3.2	7.9	7.1	8.4
	(4.3, 8.6)	(2.2, 10.6)	(2.8, 14.7)	(2.6, 15.2)	(1.1, 9.4)	(2.7, 22.8)	(2.8, 18.5)	(3.5, 20.2)
PE8: Not Able to Cut Down/Stop Using Every Time	**2.6**	0.8	3.1	2.7	4.0	2.6	3.7	1.7
	(1.3, 5.2)	(0.1, 6.3)	(0.6, 16.8)	(0.5, 14.5)	(0.7, 21.8)	(0.3, 22.2)	(0.7, 18.9)	(0.2, 15.0)
PE9: Not Able to Cut Down/Stop One Time	**0.8**	0.9	1.0	0.9	0.7	0.5	0.9	0.5
	(0.6, 1.1)	(0.4, 1.7)	(0.5, 1.9)	(0.4, 1.9)	(0.4, 1.5)	(0.2, 1.5)	(0.4, 2.0)	(0.2, 1.2)
PE10: Felt Blue When Cut Down	**4.5**	4.5	1.3	8.6	4.3	6.7	3.7	6.5
	(3.1, 6.4)	(2.0, 9.7)	(0.5, 3.5)	(3.3, 22.5)	(1.5, 12.3)	(2.3, 19.4)	(1.5, 9.5)	(2.5, 16.6)
PE11: Experienced 2+ Withdrawal Symptoms	**6.0**	5.0	2.1	9.5	6.1	7.7	3.0	14.3
	(3.9, 9.3)	(2.1, 12.2)	(0.6, 8.0)	(2.9, 31.3)	(1.8, 20.1)	(2.1, 27.4)	(0.8, 11.5)	(4.8, 42.6)
PE12: Emotional Problems	**5.5**	5.0	3.5	4.6	5.2	9.9	5.5	7.7
	(3.9, 7.8)	(2.3, 11.0)	(1.4, 8.6)	(1.8, 11.6)	(1.9, 14.2)	(3.5, 27.5)	(2.2, 13.8)	(3.1, 19.2)
PE13: Continued Use Despite Emotional Problems	**10.8**	11.3	4.6	14.3	6.7	20.9	8.0	15.5
	(6.9, 16.8)	(4.2, 30.1)	(1.3, 16.8)	(3.9, 53.0)	(1.7, 25.8)	(6.2, 70.1)	(2.5, 26.1)	(5.5, 43.6)
PE14: Physical Problems	**2.8**	2.1	1.7	1.0	1.6	3.7	11.2	2.1
	(1.7, 4.4)	(0.5, 9.8)	(0.4, 8.2)	(0.1, 8.4)	(0.2, 12.9)	(1.4, 10.0)	(2.8, 44.3)	(1.0, 4.8)
PE15: Used Despite Physical Problems	**NTS [d]**	NTS [d]	NTS [d]	NTS d	NTS [d]	NTS [d]	NTS [d]	NTS [d]
	na	na	na	na	na	na	na	na
PE16: Reduced Salience of Non-Drug Acts	**7.6**	4.1	5.5	8.1	4.7	26.2	8.0	9.8
	(5.0, 11.4)	(1.5, 11.0)	(2.0, 15.3)	(2.9, 22,2)	(1.3, 16.8)	(8.0, 86.0)	(2.5, 26.1)	(3.5, 27.5)
PE17: Serious Problems at Home/Work/School	**7.3**	5.3	3.7	5.2	4.9	5.6	15.8	23.3
	(4.8, 11.1)	(2.0, 13.7)	(1.2, 11.4)	(1.9, 13.9)	(1.1, 20.8)	(1.7, 18.6)	(5.1, 49.6)	(8.0, 68.0)

(Table C6, cont'd)

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE18: Engaged in Dangerous Activities	**5.3**	5.3	3.1	3.5	5.2	9.3	4.6	8.9
	(3.6, 7.7)	(2.4, 11.6)	(1.1, 9.4)	(1.3, 8.9)	(1.8, 15.1)	(2.9, 29.8)	(1.4, 15.4)	(3.4, 23.7)
PE19: Problems with the Law	**7.8**	4.9	3.9	3.3	16.1	4.6	13.5	17.6
	(4.2, 14.4)	(1.2, 19.4)	(0.7, 22.0)	(0.6, 18.0)	(1.5, 177.4)	(0.5, 43.1)	(2.6, 71.3)	(5.2, 59.5)
PE20: Problems with Family/Friends	**6.3**	7.3	1.8	4.8	7.0	14.5	6.5	7.4
	(4.3, 9.2)	(3.4, 15.7)	(0.6, 5.8)	(1.8, 12.9)	(2.5, 19.9)	(4.6, 45.4)	(2.1, 20.5)	(2.7, 20.1)
PE21: Used Despite Problems with Family/Friends	**11.3**	20.4	4.0	7.6	16.9	16.2	6.7	15.0
	(6.9, 18.6)	(6.6, 63.5)	(0.9, 16.6)	(2.2, 26.4)	(3.0, 95.0)	(4.6, 57.7)	(1.6, 28.7)	(4.6, 48.9)
Age (12-17 years)	**1.1**	1.1	1.2	1.0	1.3	1.1	1.0	1.1
	(1.0, 1.2)	(0.8, 1.4)	(0.9, 1.5)	(0.7, 1.5)	(1.0, 1.8)	(0.8, 1.4)	(0.8, 1.4)	(0.9, 1.5)
Male	**1.1**	1.0	1.2	0.9	1.1	1.0	1.1	1.1
	(1.0, 1.2)	(0.8, 1.2)	(1.0, 1.5)	(0.7, 1.2)	(0.8, 1.4)	(0.8 1.3)	(0.9, 1.3)	(0.9, 1.3)
NH White	**0.8**	0.7	1.0	0.8	1.0	0.8	0.9	0.8
	(0.7, 0.9)	(0.5, 0.8)	(0.8, 1.3)	(0.6, 1.1)	(0.8, 1.2)	(0.6, 1.0)	(0.7, 1.1)	(0.6, 1.0)
SES	**1.0**	1.0	0.9	1.0	1.1	1.0	1.1	0.9
	(0.9, 1.1)	(0.8, 1.3)	(0.7, 1.2)	(0.7, 1.3)	(0.8, 1.4)	(0.8 1.4)	(0.9, 1.4)	(0.7, 1.2)

Notes: [a] Odds ratio estimates are from unweighted GZLM/GEE regression models. [b] Covariates included age, race-ethnicity, sex, and ses. [c] MAS=Meta-analytic summary estimates using a fixed effects approach. [d] NTS=Numbers too small. Newly Incident Cocaine Powder Only users (n): 2011 =396; 2012=319; 2013=287; 2014=286; 2015=359; 2016=355; 2017=362. Newly incident crack users (n): 2011 =44; 2012=41; 2013=34; 2014=37; 2015=20; 2016=29; 2017=26.

Table C7: Weighted, Crude, Unadjusted Odds Ratio Estimates Contrasting Newly Incident Crack-Cocaine Users with Crack + Cocaine Powder Only Users. Data are from the United States National Surveys on Drug Use and Health, 2011-2017.

Year	**MAS Estimates** [c]	2011	2012	2013	2014	2015	2016	2017
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Crack-Cocaine vs. Powder Only	**2.8**	2.4	1.6	2.9	1.7	6.2	3.4	5.3
	(1.9, 4.0)	(1.4, 4.0)	(1.0, 2.5)	(1.5, 5.5)	(1.0, 2.9)	(2.6, 14.7)	(1.8, 6.6)	(2.7, 10.2)

Note: DerSimonian & Laird Random Effects Meta-analysis was used for the weighted model because variation in estimate due to heterogeneity I^2=62.4% ($p<0.01$)

Table C8: Weighted, Covariate-Adjusted (Age, Race, Sex) Odds Ratio Estimates for Problems & Experiences of Newly Incident Crack-Cocaine Users in Contrast with Crack + Cocaine Powder Only Users. Data are from the United States National Surveys on Drug Use and Health, 2011-2017.

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE1: Wanted/Tried to Cut Down Use	**1.6**	0.5	0.8	0.6	2.4	3.6	2.1	6.0
	(0.8, 3.2)	(0.2,1.3)	(0.3,1.8)	(0.2,1.9)	(0.9,6.2)	(1.,12.8)	(0.8,5.5)	(2.2,16.3)
PE2: Spent a Lot of Time Getting Over the Effects	**2.9**	3.8	2.8	2.2	2.4	3.6	8.4	0.8
	(1.6, 5.1)	(0.9,16.2)	(0.3,24.4)	(0.3,16.6)	(0.9,6.2)	(1.,12.8)	(0.9,74.9)	(0.1,8.4)
PE3: Tried to Set Limits on Use	**1.9**	1.7	0.7	2.4	1.4	3.9	3.4	2.5
	(1.2, 3.0)	(0.7,3.9)	(0.3,1.6)	(0.8,7.9)	(0.5,3.7)	(1.2,13.)	(1.3,9.)	(0.9,7.)
PE4: Not Able to Keep Limits	**12.4**	19.5	3.5	25.6	2.4	18.8	18.3	13.7
	(6.6, 23.4)	(4.5,85.1)	(0.6,21.9)	(5.3,124.2)	(0.4,15.)	(3.3,107.7)	(4.8,70.4)	(2.9,65.1)
PE5: Needed More Cocaine, Same Effect	**5.7**	3.8	1.6	7.1	2.6	13.1	11.1	10.1
	(3.1, 10.3)	(1.2,12.5)	(0.5,5.5)	(1.8,27.6)	(0.6,11.1)	(3.5,48.9)	(3.8,32.4)	(2.8,36.6)
PE6: Same Amount, Less Effect	**1.6**	3.8	0.1	1.6	0.5	12.2	2.1	3.2
	(0.6, 4.4)	(0.6,24.3)	(0.,0.7)	(0.3,9.7)	(0.1,2.9)	(1.6,95.2)	(0.8,5.5)	(0.4,27.3)
PE7: Spent a Lot of Time Getting/Using	**9.2**	4.1	6.6	15.3	2.2	18.7	14.4	16.1
	(5.3, 15.9)	(1.5,11.5)	(2.2,20.1)	(4.1,57.2)	(0.4,12.7)	(4.9,70.7)	(4.7,43.8)	(5.3,49.)
PE8: Not Able to Cut Down/Stop Using Every Time	**2.2**	0.3	2.0	2.1	1.4	8.8	5.2	4.7
	(1.0, 5.0)	(0.,2.3)	(0.2,15.5)	(0.2,22.)	(0.2,8.3)	(0.9,83.7)	(0.8,32.8)	(0.5,45.5)
PE9: Not Able to Cut Down/Stop One Time	**0.6**	1.1	1.0	1.1	0.8	0.4	0.5	0.1
	(0.3, 1.1)	(0.4,2.6)	(0.4,2.5)	(0.3,3.7)	(0.3,2.2)	(0.1,1.6)	(0.2,1.4)	(0.,0.3)
PE10: Felt Blue When Cut Down	**6.3**	5.4	0.8	19.9	4.3	12.4	5.9	15.0
	(2.9, 13.4)	(1.8,15.8)	(0.2,3.)	(4.5,87.3)	(1.,18.1)	(3.2,48.2)	(1.9,18.6)	(4.5,50.1)
PE11: Experienced 2+ Withdrawal Symptoms	**7.3**	3.4	1.2	12.8	5.8	22.1	5.0	34.1
	(3.0, 17.6)	(1.1,10.9)	(0.3,5.2)	(2.4,67.3)	(1.,32.9)	(4.7,104.)	(1.,24.2)	(8.9,129.9)
PE12: Emotional Problems	**6.0**	6.2	3.5	1.8	3.4	16.4	6.3	14.5
	(3.5, 10.5)	(2.,18.7)	(1.1,11.2)	(0.4,8.7)	(0.8,14.2)	(4.4,61.4)	(2.,20.2)	(4.3,49.)
PE13: Continued Use Despite Emotional Problems	**11.5**	14.1	5.8	7.2	1.9	50.3	11.8	19.6
	(5.8, 23.1))	(3.7,53.6)	(1.3,26.1)	(1.2,41.8)	(0.3,12.2)	(11.5,220.4)	(3.2,43.1)	(5.3,73.)
PE14: Physical Problems	**1.0**	0.5	1.0	0.0	0.2	3.6	2.9	6.0
	(0.3, 3.4)	(0.1,2.5)	(0.1,7.4)	(0.,0.3)	(0.,1.4)	(1.,12.8)	(0.6,14.8)	(2.2,16.3)
PE15: Used Despite Physical Problems	**NTS [d]**	NTS [d]	NTS [d]	NTS [d]	NTS [d]	NTS [d]	NTS [d]	NTS [d]
	(na)	(na)	(na)	(na)	(na)	(na)	(na)	(na)

(Table C8, cont'd)

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE16: Reduced Salience of Non-Drug Acts	**7.7**	2.8	5.8	7.0	2.9	54.6	6.4	11.5
	(3.7, 16.0)	(0.8,10.8)	(1.6,20.6)	(1.7,28.9)	(0.4,19.8)	(13.,228.7)	(1.5,26.9)	(2.8,46.8)
PE17: Serious Problems at Home/Work/School	**4.7**	2.6	3.3	2.2	0.6	10.9	14.6	20.4
	(1.9, 11.5)	(0.7,9.5)	(0.9,12.8)	(0.4,12.4)	(0.1,3.3)	(2.3,51.2)	(3.6,58.3)	(5.,82.7)
PE18: Engaged in Dangerous Activities	**5.4**	3.9	3.0	4.0	4.2	15.3	5.4	13.8
	(3.3, 9.0)	(1.4,10.9)	(0.8,11.2)	(1.1,15.3)	(1.,18.6)	(3.1,75.2)	(1.2,23.7)	(3.7,51.2)
PE19: Problems with the Law	**5.5**	5.9	1.8	1.6	1.2	5.6	16.8	21.0
	(2.4, 12.7)	(1.4,24.4)	(0.3,11.7)	(0.2,15.8)	(0.1,13.6)	(0.6,57.3)	(2.8,102.6)	(4.4,100.2)
PE20: Problems with Family/Friends	**6.5**	8.3	1.4	3.9	3.2	28.1	6.4	15.8
	(3.1, 13.5)	(2.9,23.8)	(0.4,5.2)	(0.9,16.2)	(0.7,15.1)	(6.9,114.9)	(1.6,25.7)	(4.4,56.5)
PE21: Used Despite Problems with Family/Friends	**13.1**	26.7	3.5	8.2	5.4	39.1	7.1	25.9
	(6.5, 26.2)	(6.3,113.6)	(0.7,18.3)	(1.6,42.5)	(0.6,45.5)	(8.6,178.5)	(1.3,38.7)	(5.9,113.8)
Age (12-17 years)	**1.1**	1.3	1.0	0.8	1.2	0.9	1.1	1.2
	(1.0, 1.3)	(0.9,1.7)	(0.7,1.4)	(0.5,1.5)	(0.9,1.8)	(0.6,1.3)	(0.8,1.6)	(0.9,1.7)
Male	**1.1**	1.0	1.0	1.3	1.0	1.0	1.1	1.2
	(1.0, 1.2)	(0.8,1.3)	(0.7,1.3)	(0.9,2.)	(0.8,1.4)	(0.8,1.4)	(0.8,1.5)	(0.8,1.7)
NH White	**0.9**	0.6	1.0	0.8	1.0	1.0	0.9	0.8
	(0.7, 1.0)	(0.4,0.8)	(0.7,1.4)	(0.4,1.3)	(0.8,1.4)	(0.7,1.4)	(0.6,1.2)	(0.5,1.1)

Notes: [a] Odds ratio estimates are from unweighted GZLM/GEE regression models. [b] Covariates included age, race-ethnicity, and sex. [c] MAS=Meta-analytic Summary Estimates using a Fixed Effects approach. [d] NTS=Numbers too small. Newly Incident Cocaine Powder Only users (n): 2011 =396; 2012=319; 2013=287; 2014=286; 2015=359; 2016=355; 2017=362. Newly incident crack users (n): 2011 =44; 2012=41; 2013=34; 2014=37; 2015=20; 2016=29; 2017=26.

Table C9: Weighted, Covariate-Adjusted (Age, Race, Sex, & Drug History) Odds Ratio Estimates for Problems & Experiences of Newly Incident Crack-Cocaine Users in Contrast with Crack + Cocaine Powder Only Users. Data are from the United States National Surveys on Drug Use and Health, 2011-2017.

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE1: Wanted/Tried to Cut Down Use	**1.4**	0.5	0.6	0.6	2.3	3.5	2.5	4.1
	(0.7, 2.9)	(0.2, 1.3)	(0.2, 1.5)	(0.2, 1.8)	(0.9, 6.2)	(1.0, 12.4)	(0.8, 7.8)	(1.5, 11.4)
PE2: Spent a Lot of Time Getting Over the Effects	**2.8**	3.7	2.1	2.2	2.3	3.5	9.4	0.3
	(1.6, 5.0)	(0.8, 16.8)	(0.2, 22.0)	(0.3, 15.9)	(0.9, 6.2)	(1.0, 12.4)	(1.0, 84.2)	(>0.0, 7.4)
PE3: Tried to Set Limits on Use	**1.8**	1.6	0.5	2.5	1.4	3.8	4.0	1.7
	(1.1, 3.1)	(0.6, 4.4)	(0.2, 1.4)	(0.8, 8.2)	(0.5, 3.8)	(1.1, 12.5)	(1.5, 10.5)	(0.6, 5.1)
PE4: Not Able to Keep Limits	**11.1**	18.9	2.7	26.1	2.4	18.2	20.6	8.2
	(5.4, 22.9)	(3.9, 91.7)	(0.4, 16.8)	(5.1, 133.6)	(0.4, 15.1)	(3.2, 103.8)	(5.0, 85.6)	(1.0, 68.8)
PE5: Needed More Cocaine, Same Effect	**5.1**	3.7	1.3	7.1	2.5	12.8	12.7	6.5
	(2.7, 9.8)	(1.3, 10.4)	(0.4, 4.4)	(1.9, 27.2)	(0.6, 11.1)	(3.5, 47.2)	(4.1, 38.9)	(1.4 29.3)
PE6: Same Amount, Less Effect	**1.5**	3.7	0.1	1.6	0.5	11.7	2.5	1.5
	(0.5, 4.2)	(0.5, 26.3)	(>0.0, 0.7)	(0.3, 9.2)	(0.1, 2.8)	(1.5, 93.3)	(0.8, 7.8)	(0.1, 43.2)
PE7: Spent a Lot of Time Getting/Using	**8.6**	4.0	5.3	15.6	2.2	18.2	16.4	11.0
	(4.9, 14.9)	(1.2, 12.8)	(1.9, 15.2)	(4.0, 60.7)	(0.4, 12.7)	(4.9, 68.3)	(5.3, 50.8)	(3.3, 36.8)
PE8: Not Able to Cut Down/Stop Using Every Time	**1.9**	0.3	1.5	2.1	1.4	8.5	5.7	2.3
	(0.8, 4.4)	(.04, 2.2)	(0.2, 10.2)	(0.2, 21.7)	(0.2, 8.3)	(0.9, 81.0)	(0.9, 38.9)	(0.1, 68.1)
PE9: Not Able to Cut Down/Stop One Time	**0.7**	1.0	0.8	1.1	0.8	0.4	0.6	0.0
	(0.4, 1.1)	(0.4, 2.9)	(0.3, 2.0)	(0.3, 3.8)	(0.3, 2.2)	(0.1, 1.6)	(0.2, 1.6)	(>0.0, 0.4)
PE10: Felt Blue When Cut Down	**5.9**	5.2	0.6	20.3	4.3	12.0	6.7	10.1
	(2.9, 12.4)	(1.9, 14.2)	(0.1, 2.8)	(4.5, 92.6)	(1.0, 18.1)	(3.1, 46.5)	(2.0, 22.0)	(2.7, 38.3)
PE11: Experienced 2+ Withdrawal Symptoms	**6.7**	3.3	0.9	12.9	5.7	21.5	5.6	22.6
	(2.9, 15.7)	(0.9, 12.3)	(0.2, 4.7)	(2.5, 67.3)	(1.0, 32.9)	(4.6, 100.2)	(1.1, 29.3)	(5.1, 98.9)
PE12: Emotional Problems	**5.3**	6.0	2.8	1.8	3.3	15.9	7.1	9.9
	(3.2, 9.1)	(2.1, 17.0)	(1.0, 7.8)	(0.4, 8.7)	(0.8, 14.2)	(4.3, 59.3)	(2.0, 25.3)	(2.6, 37.1)
PE13: Continued Use Despite Emotional Problems	**10.2**	13.6	4.5	7.2	1.9	49.0	13.2	13.1
	(5.0, 20.7)	(3.9, 47.9)	(1.2, 16.4)	(1.3, 42.1)	(0.3, 12.1)	(11.3, 212.9)	(3.3, 53.3)	(3.1, 56.1)
PE14: Physical Problems	**0.8**	0.5	0.8	0.0	0.2	3.5	3.3	4.1
	(0.2, 2.9)	(0.1, 2.5)	(0.1, 6.3)	(>0.0, 0.2)	(>0.0, 1.4)	(1.0, 12.4)	(0.6, 16.7)	(1.5, 11.4)
PE15: Used Despite Physical Problems	**NTS**	NTS	NTS	NTS	NTS	NTS	NTS	NTS
	na	na	na	na	na	na	na	na
PE16: Reduced Salience of Non-Drug Acts	**7.2**	2.8	4.6	7.1	2.9	53.2	7.1	7.4
	(3.4, 15.2)	(0.6, 12.1)	(1.2, 17.2)	(1.8, 28.7)	(0.4, 19.8)	(12.8, 221.5)	(1.6, 32.7)	(1.5, 37.4)

(Table C9, cont'd)

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE17: Serious Problems at Home/Work/School	**4.2**	2.6	2.5	2.2	0.6	10.6	16.3	13.7
	(1.8, 10.1)	(0.6, 10.7)	(0.7, 9.8)	(0.4, 12.5)	(0.1, 3.2)	(2.3, 49.5)	(3.7, 72.0)	(3.0, 61.6)
PE18: Engaged in Dangerous Activities	**4.9**	3.8	2.3	4.0	4.2	14.8	6.0	9.0
	(2.9, 8.3)	(1.2, 12.3)	(0.6, 8.6)	(1.1, 15.2)	(1.0, 18.5)	(3.0, 72.6)	(1.3, 28.7)	(2.0, 40.8)
PE19: Problems with the Law	**4.7**	5.7	1.3	1.6	1.2	5.4	18.8	13.0
	(2.1, 10.6)	(1.3, 25.7)	(0.2, 10.1)	(0.2, 14.6)	(0.1, 13.5)	(0.5, 56.3)	(2.9, 123.9)	(2.1, 80.8)
PE20: Problems with Family/Friends	**6.1**	8.1	1.0	3.9	3.1	27.3	7.1	10.7
	(3.0, 12.5)	(3.0, 21.8)	(0.2, 4.8)	(1.0, 15.9)	(0.7, 15.0)	(6.7, 110.9)	(1.6, 31.3)	(2.6, 43.3)
PE21: Used Despite Problems with Family/Friends	**12.3**	25.8	2.6	8.3	5.4	38.1	7.9	16.9
	(6.2, 24.5)	(6.5, 102.2)	(0.4, 16.5)	(1.6, 42.6)	(0.6, 45.2)	(8.4, 172.1)	(1.4, 46.0)	(3.3, 87.2)
Age (12-17 years)	**1.1**	1.2	1.1	1.1	1.3	0.9	1.0	1.2
	(0.9, 1.3)	(0.9, 1.7)	(0.8, 1.5)	(0.6, 2.1)	(0.9, 1.8)	(0.6, 1.3)	(0.7, 1.5)	(0.9, 1.7)
Male	**1.0**	1.0	1.0	1.0	1.0	1.0	1.1	1.1
	(0.9, 1.2)	(0.8, 1.3)	(0.7, 1.3)	(0.6, 1.8)	(0.7, 1.4)	(0.7, 1.4)	(0.8, 1.4)	(0.8, 1.6)
NH White	**0.8**	0.6	0.9	0.7	1.0	1.0	0.9	0.7
	(0.7, 1.0)	(0.4, 0.8)	(0.7, 1.3)	(0.4, 1.2)	(0.8, 1.4)	(0.7, 1.4)	(0.6, 1.2)	(0.5, 1.1)
Ever Used Alcohol	**1.7**	0.6	4.2	8.5	1.4	1.4	1.0	1.0
	(0.8, 3.4)	(0.2, 2.4)	(1.1, 15.6)	(0.5, 153.0)	(0.2, 8.4)	(0.6, 3.3)	na	na
Ever Used Tobacco	**1.0**	1.0	0.9	2.9	1.2	1.6	0.9	1.2
	(0.9, 1.3)	(0.7, 1.4)	(0.5, 1.4)	(0.9, 9.3)	(0.7, 2.0)	(0.8, 3.3)	(0.6, 1.2)	(0.8, 1.7)
Ever Used Marijuana	**1.0**	0.5	0.8	1.9	1.0	0.8	1.2	0.8
	(0.8, 1.2)	(0.1, 2.2)	(0.5, 1.3)	(0.6, 6.4)	(0.4, 2.8)	(0.4, 1.7)	(0.9, 1.7)	(0.5, 1.4)
Injection Drug Use	**1.4**	1.1	2.6	2.2	0.8	0.8	0.5	19.5
	(0.8, 2.5)	(0.4, 3.5)	(1.1, 6.2)	(0.9, 5.6)	(0.3, 2.0)	(0.4, 1.8)	(0.1, 1.8)	(1.9, 199.7)

Notes: [a] Odds ratio estimates are from unweighted GZLM/GEE regression models. [b] Covariates included age, race-ethnicity, sex, and drug history. [c] MAS=Meta-analytic Summary Estimates using a Fixed Effects approach. [d] NTS=Numbers too small. Newly Incident Cocaine Powder Only users (n): 2011 =396; 2012=319; 2013=287; 2014=286; 2015=359; 2016=355; 2017=362. Newly incident crack users (n): 2011 =44; 2012=41; 2013=34; 2014=37; 2015=20; 2016=29; 2017=26.

Table C10: Weighted, Covariate-Adjusted (Age, Race, Sex, & SES) Odds Ratio Estimates for Problems & Experiences of Newly Incident Crack-Cocaine Users in Contrast with Crack + Powder Only Users in the Unites States. Data are from the National Surveys on Drug Use & Health (2011-2017).

Year	**MAS Estimates [c]**	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE1: Wanted/Tried to Cut Down Use	**1.6**	0.5	0.8	0.6	2.3	3.6	2.1	6.1
	(0.8, 3.1)	(0.2,1.2)	(0.3,1.8)	(0.2,1.9)	(0.9,6.1)	(1.0,12.6)	(0.8,5.5)	(2.2,16.9)
PE2: Spent a Lot of Time Getting Over the Effects	**2.8**	7.4	3.6	3.8	na	na	4.0	0.1
	(0.8, 9.5)	(2.2,24.7)	(0.5,27.4)	(0.5,30.3)	na	na	(0.4,39.2)	(0.0,1.7)
PE3: Tried to Set Limits on Use	**1.3**	3.2	0.9	4.2	0.6	1.1	1.6	0.4
	(0.7, 2.3)	(1.6,6.6)	(0.3,3.0)	(0.9,19.3)	(0.2,1.7)	(0.6,1.9)	(0.5,5.4)	(0.1,1.4)
PE4: Not Able to Keep Limits	**7.0**	38.2	4.6	44.7	1.0	5.1	8.6	2.3
	(2.6, 18.8)	(6.7,218.3)	(0.6,36.1)	(6.4,311.9)	(0.2,6.7)	(1.1,24.0)	(1.7,43.1)	(0.4,12.5)
PE5: Needed More Cocaine, Same Effect	**3.8**	7.4	2.2	12.2	1.1	3.6	5.2	1.7
	(2.1, 6.9)	(1.6,35.5)	(0.5,10.3)	(3.4,43.8)	(0.2,5.5)	(1.3,10.2)	(1.5,17.5)	(0.4,7.5)
PE6: Same Amount, Less Effect	**1.0**	7.5	0.1	2.8	0.2	3.3	na	0.5
	(0.3, 3.8)	(0.9,61.1)	(0.0,1.2)	(0.4,17.6)	(0.0,1.6)	(0.3,32.0)	na	(0.1,4.9)
PE7: Spent a Lot of Time Getting/Using	**5.8**	8.0	8.7	26.6	1.0	5.1	6.7	2.7
	(3.1, 10.6)	(2.5,25.8)	(2.2,33.8)	(4.8,149.1)	(0.2,5.9)	(1.8,14.8)	(2.1,21.8)	(0.7,10.6)
PE8: Not Able to Cut Down/Stop Using Every Time	**1.5**	0.6	2.6	3.7	0.6	2.4	2.4	0.8
	(0.7, 3.3)	(0.1,4.9)	(0.4,15.9)	(0.4,36.3)	(0.1,4.5)	(0.3,18.8)	(0.4,15.9)	(0.1,8.0)
PE9: Not Able to Cut Down/Stop One Time	**0.4**	2.1	1.4	1.8	0.3	0.1	0.2	0.0
	(0.1, 1.4)	(0.5,8.7)	(0.4,5.1)	(0.2,13.8)	(0.0,2.3)	(0.0,1.4)	(0.0,1.4)	(0.0,0.1)
PE10: Felt Blue When Cut Down	**3.6**	10.4	1.0	34.8	1.8	3.4	2.8	2.5
	(1.7, 7.8)	(2.2,49.4)	(0.3,3.6)	(5.7,210.8)	(0.4,8.4)	(1.1,10.5)	(0.7,10.7)	(0.6,10.5)
PE11: Experienced 2+ Withdrawal Symptoms	**5.2**	6.6	1.6	22.2	2.5	6.1	2.4	5.7
	(2.7, 10.0)	(1.6,27.3)	(0.3,7.8)	(5.5,89.2)	(0.4,15.4)	(1.6,23.1)	(0.4,15.2)	(1.4,23.9)
PE12: Emotional Problems	**3.7**	12.1	4.6	3.1	1.4	4.5	3.0	2.4
	(2.3, 6.1)	(2.7,53.6)	(1.4,15.0)	(0.8,11.3)	(0.3,6.7)	(1.6,12.7)	(0.7,12.4)	(0.7,9.0)
PE13: Continued Use Despite Emotional Problems	**7.1**	27.5	7.6	12.5	0.8	13.9	5.5	3.3
	(3.4, 15.0)	(4.8,156.7)	(1.7,34.4)	(2.4,66.1)	(0.1,6.1)	(4.1,47.3)	(1.2,25.8)	(0.8,13.7)
PE14: Physical Problems	**0.5**	1.0	1.4	0.0	0.1	na	1.4	1.0
	(0.1, 1.9)	(0.2,5.7)	(0.2,12.1)	(0.0,1.0)	(0.0,0.7)	na	(0.2,9.8)	(0.0,0.0)
PE15: Used Despite Physical Problems	**NTS**	NTS	NTS	NTS	NTS	NTS	NTS	NTS
	na	na	na	na	na	na	na	na
PE16: Reduced Salience of Non-Drug Acts	**5.7**	5.6	7.6	12.2	1.2	15.0	3.0	1.9
	(2.9, 11.4)	(1.1,28.6)	(2.0,29.9)	(3.2,47.1)	(0.2,8.9)	(5.4,42.1)	(0.5,17.1)	(0.4,8.9)

(Table C10, cont'd)

Year	**MAS Estimates** [c]	2011	2012	2013	2014	2015	2016	2017
Side Effect Problems & Experiences (PEs)	**aOR[a] (95% CI)**	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)	aOR(95% CI)
PE17: Serious Problems at Home/Work/School	**3.1**	5.1	4.3	3.7	0.2	3.0	6.8	3.4
	(1.6, 6.2)	(1.1,25.2)	(0.8,22.7)	(0.9,16.)	(0.0,1.7)	(0.8,11.9)	(1.3,36.0)	(0.8,15.3)
PE18: Engaged in Dangerous Activities	**4.1**	7.6	3.9	7.0	1.8	4.2	2.5	2.3
	(2.3, 7.2)	(2.1,28.5)	(0.8,20.1)	(2.0,23.8)	(0.3,9.8)	(1.0,18.1)	(0.4,15.3)	(0.5,10.0)
PE19: Problems with the Law	**4.0**	11.5	2.3	2.8	0.5	1.5	7.9	3.5
	(1.9, 8.5)	(2.8,47.3)	(0.3,19.5)	(0.3,30.2)	(0.0,6.7)	(0.1,19.9)	(1.0,61.4)	(0.6,19.1)
PE20: Problems with Family/Friends	**4.4**	16.3	1.8	6.8	1.3	7.7	3.0	2.6
	(2.3, 8.3)	(3.8,70.2)	(0.4,8.1)	(2.0,23.2)	(0.2,7.7)	(2.5,24.4)	(0.5,16.5)	(0.7,10.3)
PE21: Used Despite Problems with Family/Friends	**8.0**	52.1	4.5	14.3	2.3	10.8	3.3	4.3
	(3.9, 16.4)	(8.1,333.6)	(0.7,27.4)	(3.3,61.9)	(0.2,21.6)	(3.0,39.2)	(0.6,19.9)	(0.9,20.8)
Age (12-17 years)	**1.1**	1.3	1.0	0.9	1.2	0.9	1.1	1.2
	(0.9, 1.3)	(0.9,1.7)	(0.7,1.4)	(0.5,1.5)	(0.9,1.8)	(0.6,1.3)	(0.8,1.5)	(0.9,1.7)
Male	**1.1**	1.0	1.0	1.3	1.0	1.0	1.1	1.2
	(1.0, 1.2)	(0.8,1.3)	(0.7,1.3)	(0.9,2.0)	(0.8,1.4)	(0.7,1.4)	(0.8,1.5)	(0.8,1.7)
Non-Hispanic White	**0.9**	0.6	1.0	0.8	1.1	1.0	0.9	0.8
	(0.7, 1.0)	(0.4,0.8)	(0.7,1.3)	(0.5,1.3)	(0.8,1.4)	(0.7,1.4)	(0.6,1.2)	(0.5,1.1)
SES (At or below Federal Poverty Threshold)	**1.0**	0.9	0.8	1.6	1.1	1.1	1.1	1.0
	(0.9, 1.2)	(0.6,1.3)	(0.6,1.1)	(1.0,2.5)	(0.8,1.5)	(0.8,1.6)	(0.8,1.5)	(0.7,1.4)

Notes: [a] Odds ratio estimates are from weighted GZLM/GEE regression models. [b] Covariates included age, race-ethnicity, sex, drug history and ses. [c] MAS=Meta-analytic Summary Estimates using a Random Effects approach. [d] NTS=Numbers too small. [e] Newly Incident Cocaine Powder Only users (n): 2011 =396; 2012=319; 2013=287; 2014=286; 2015=359; 2016=355; 2017=362. Newly incident crack users (n): 2011 =44; 2012=41; 2013=34; 2014=37; 2015=20; 2016=29; 2017=26.

Figure C1. Metal-Analysis Forest Plot Estimates (Unweighted) Illustrating Crude Odds Ratios from a GZLM/GEE Model Contrasting Newly Incident Crack Users and Powder-Only Users in the United States, 2011-2017.

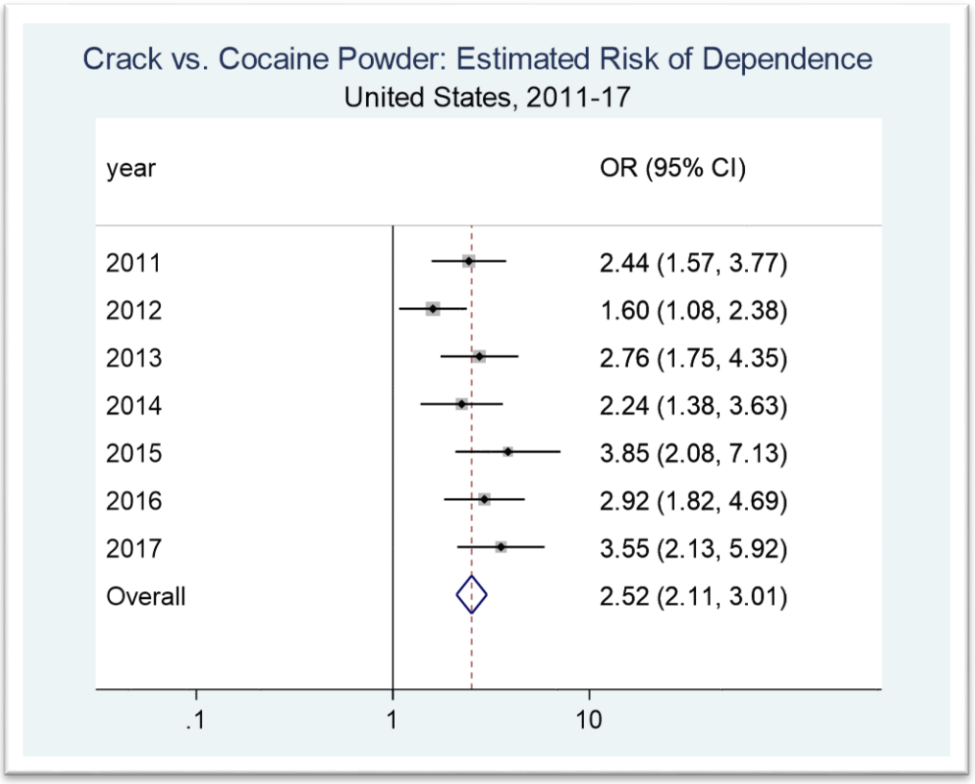
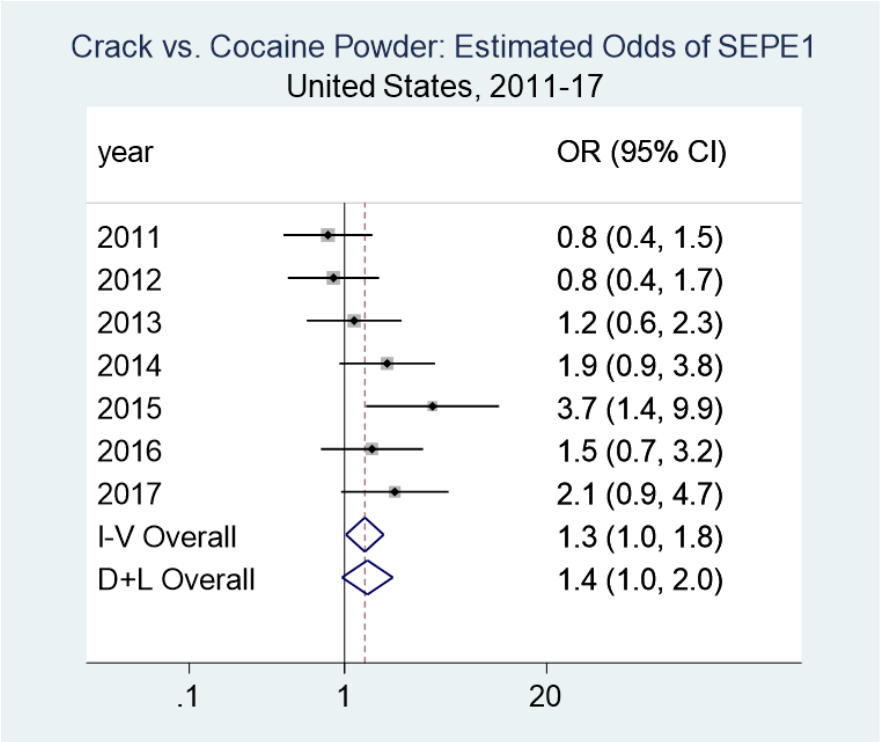
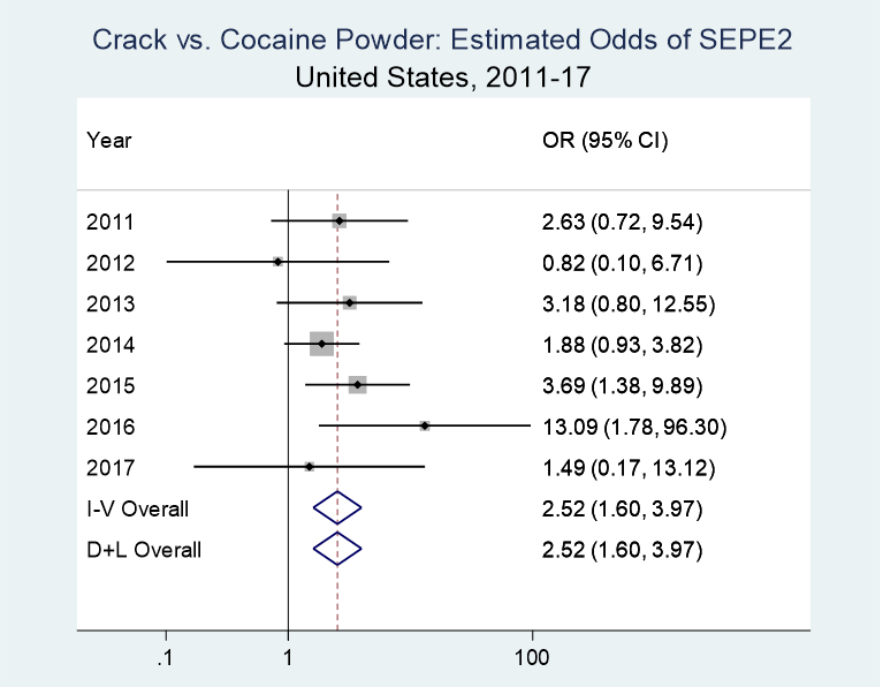


Figure C2. Meta-Analysis Forest Plot Estimates with Unweighted Covariate-Adjusted (Age, Sex, Race-Ethnicity) Odds Ratios from a GZLM/GEE Model, Illustrating Cocaine Side Effect Problems & Experiences Among Newly Incident Crack Users as Contrasted with Powder Only Users. Data from the United States, National Surveys on Drug Use & Health, 2011-2017.





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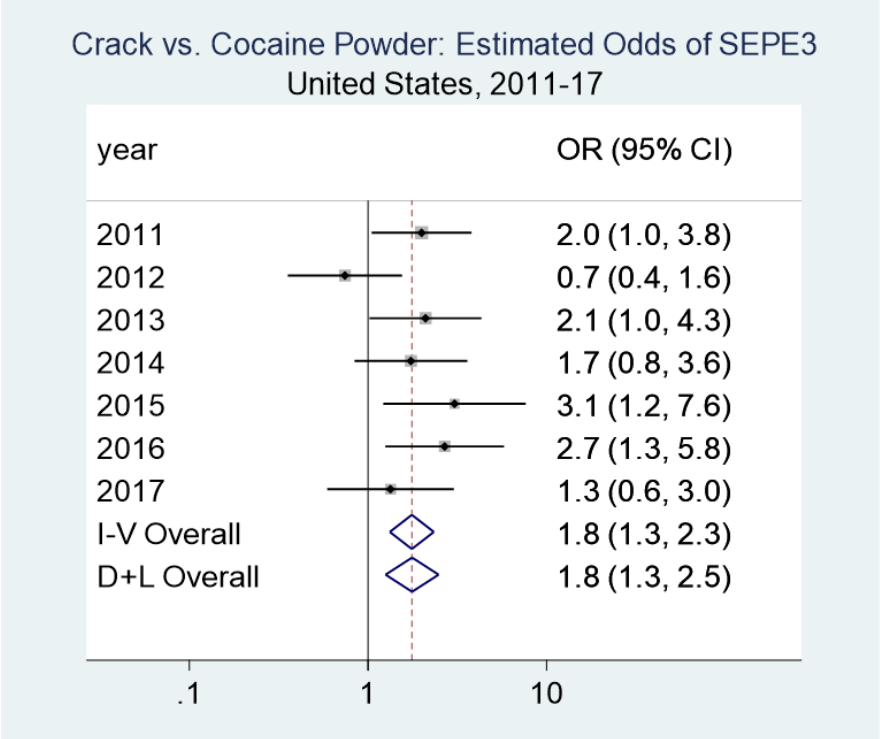

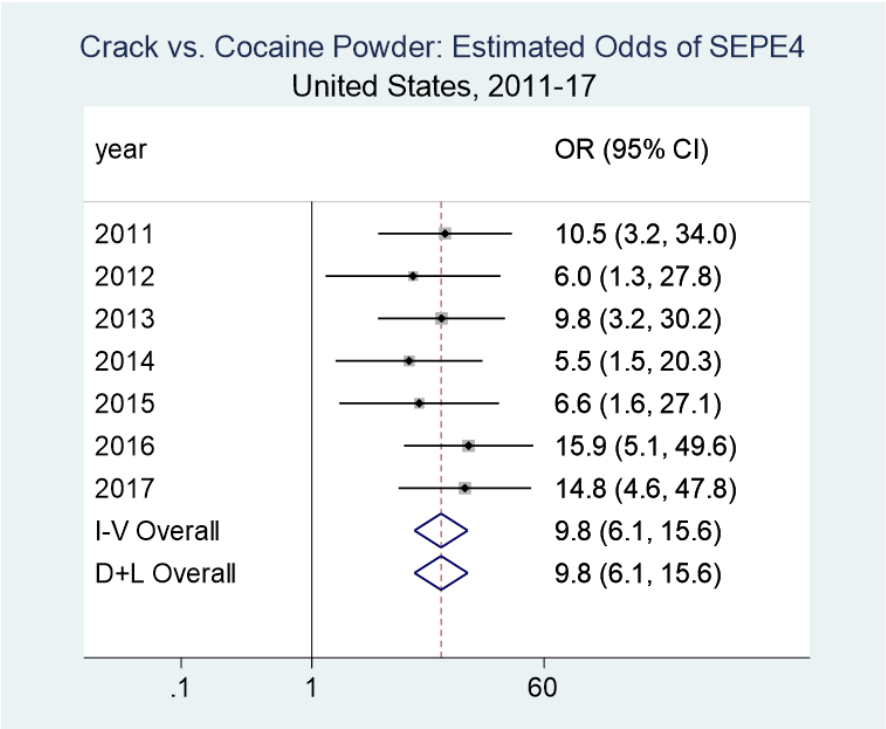

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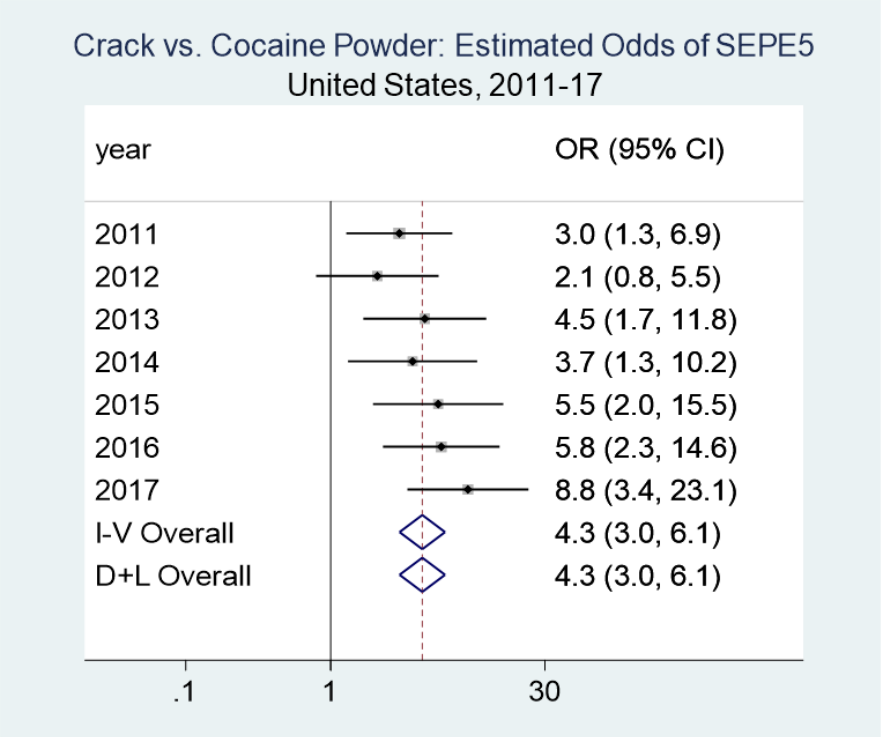

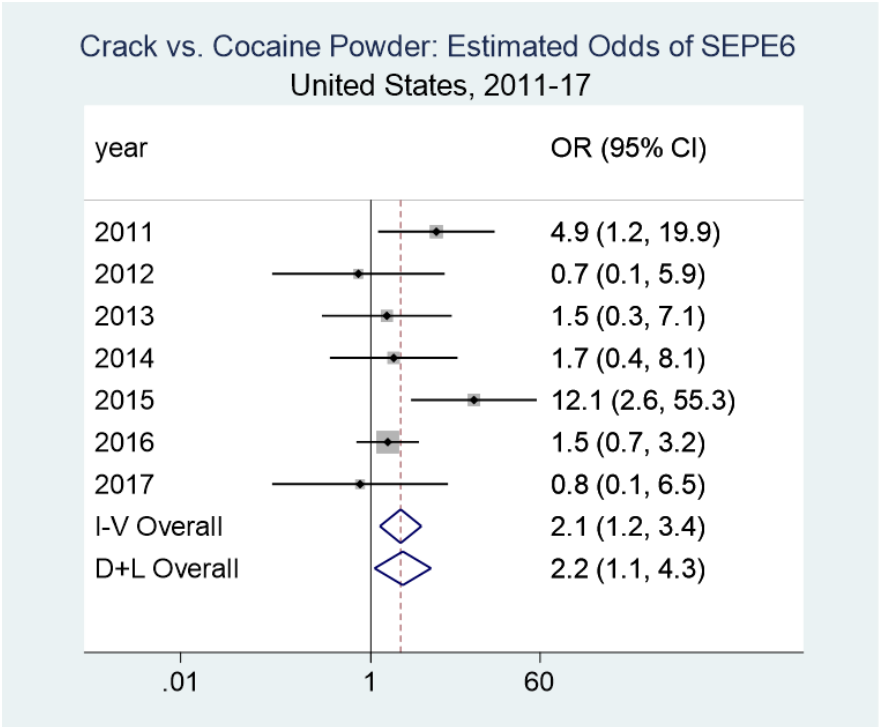

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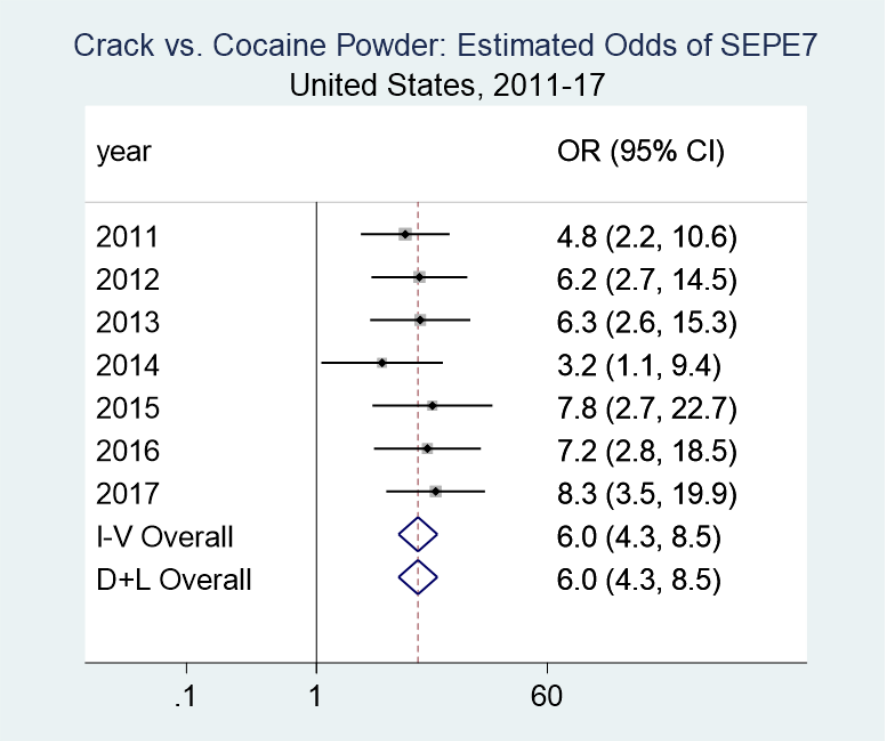

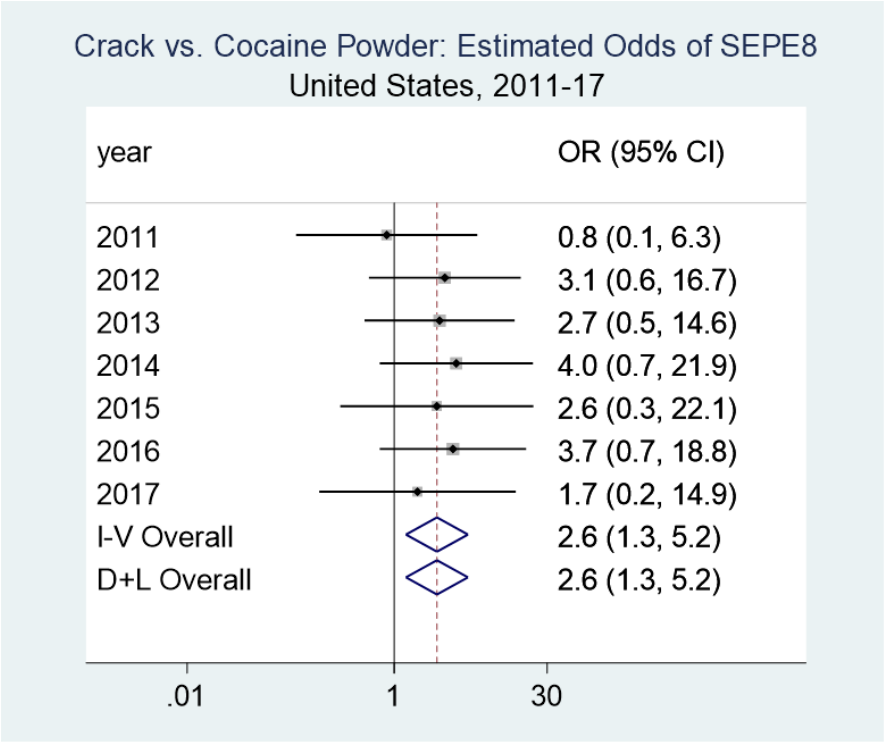

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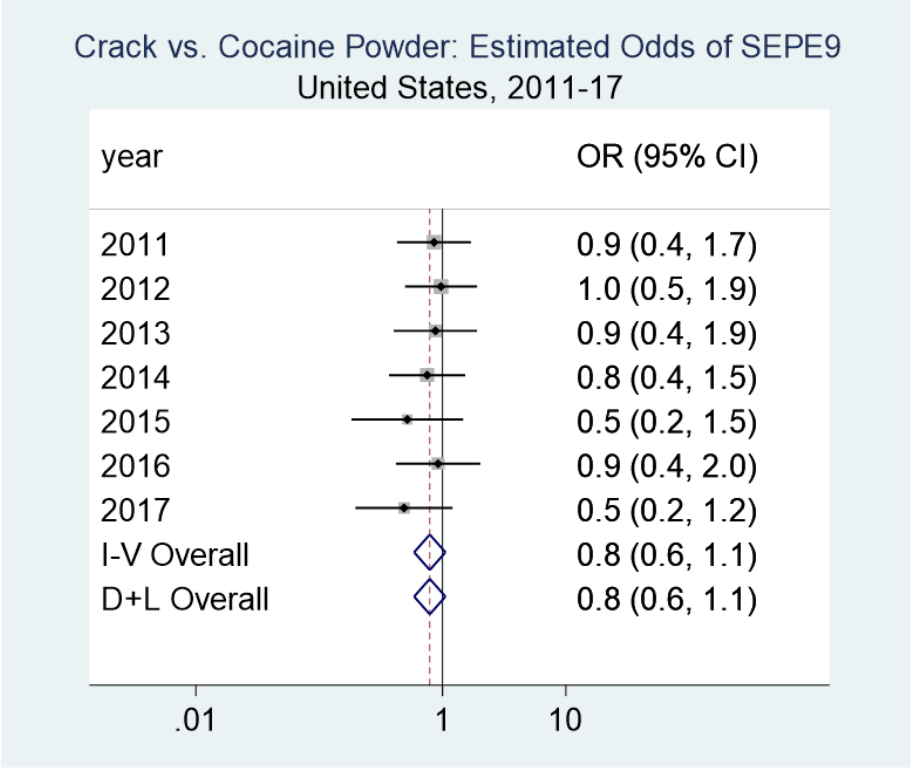

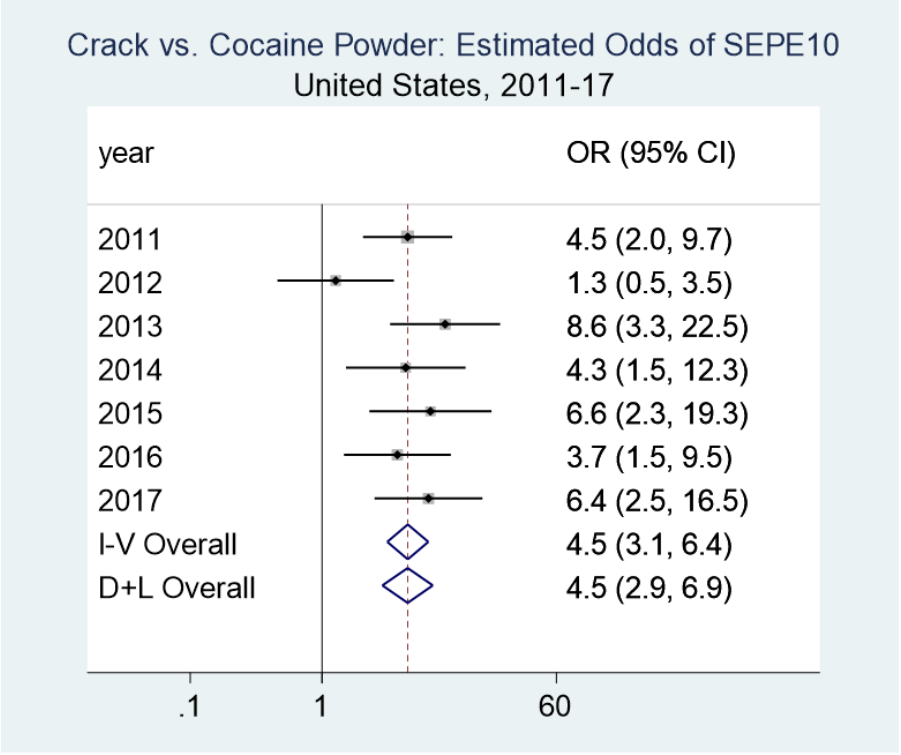

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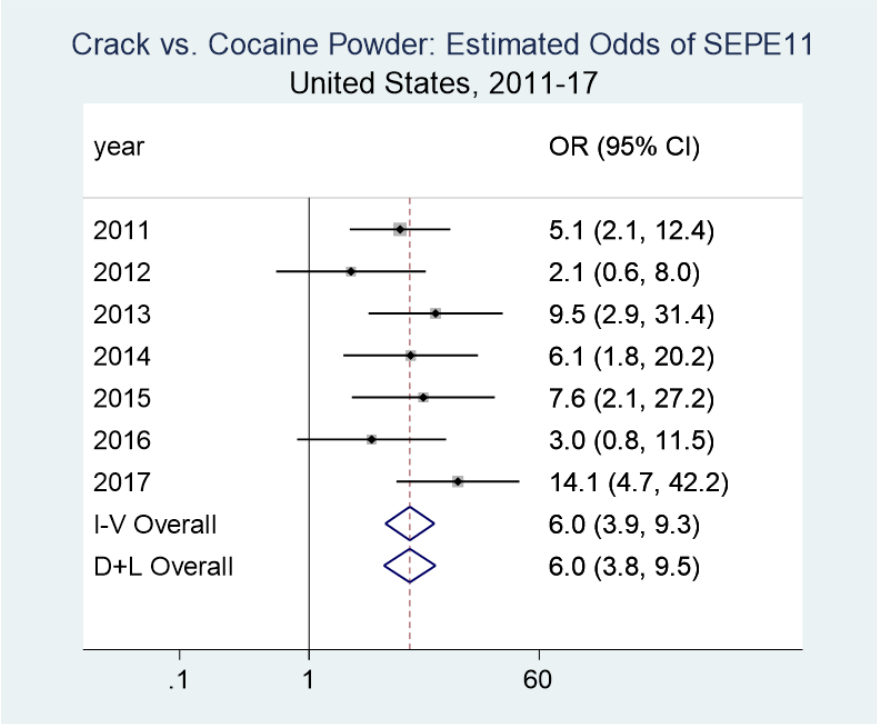

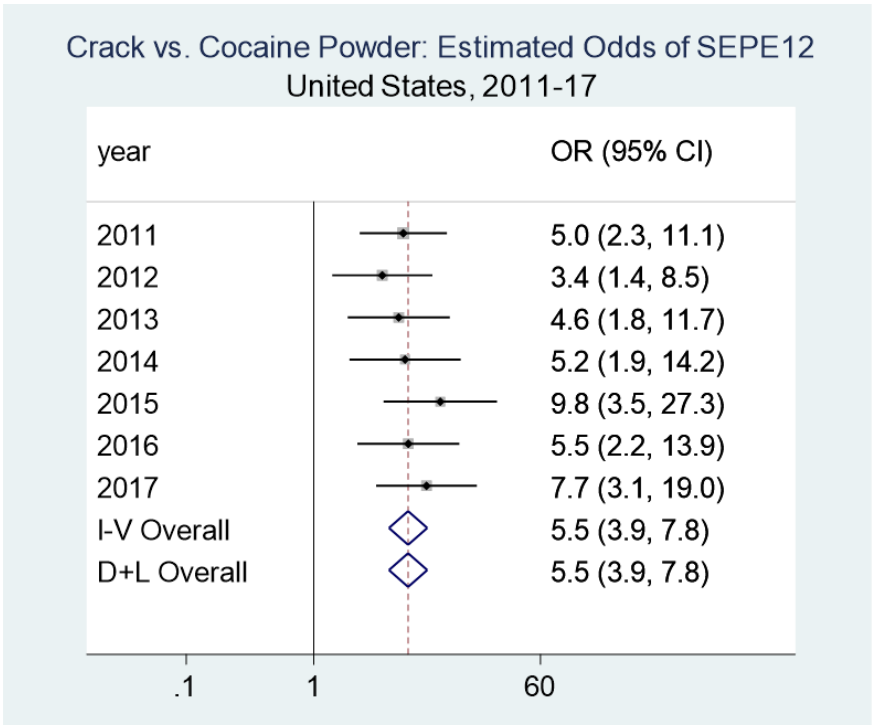

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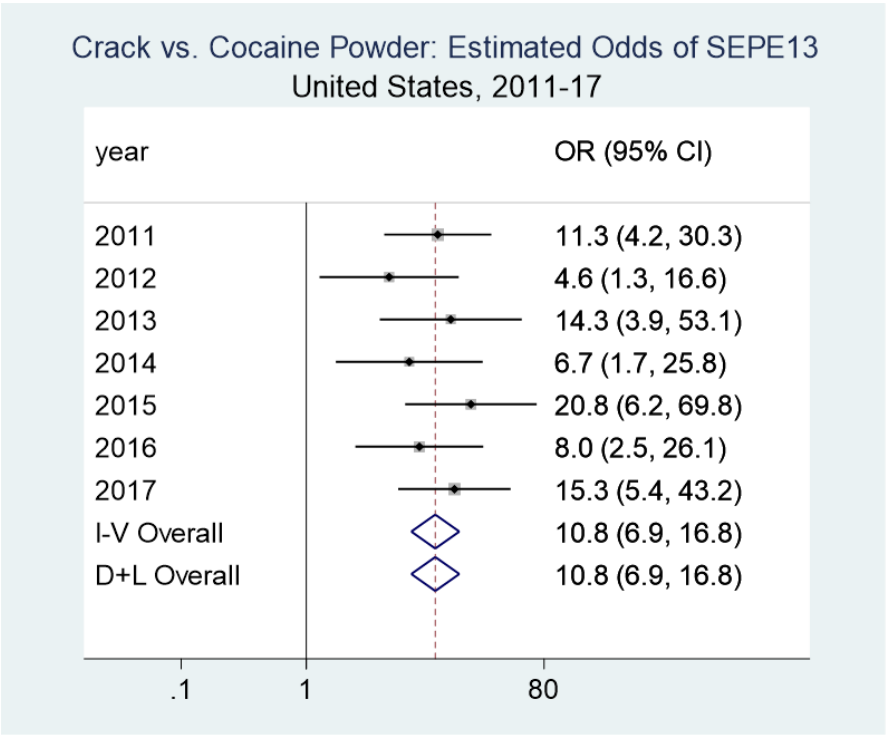

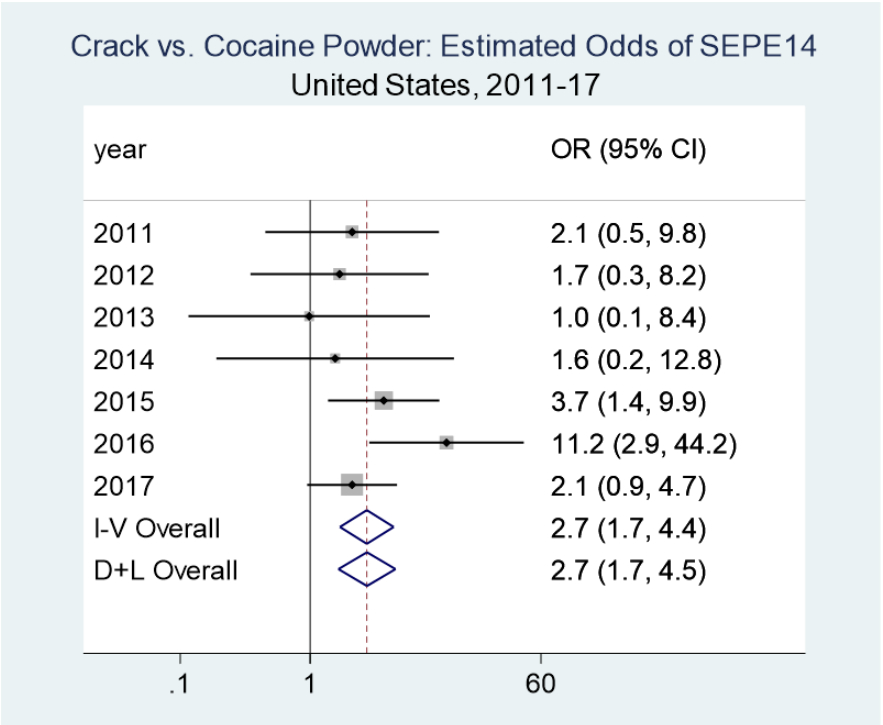

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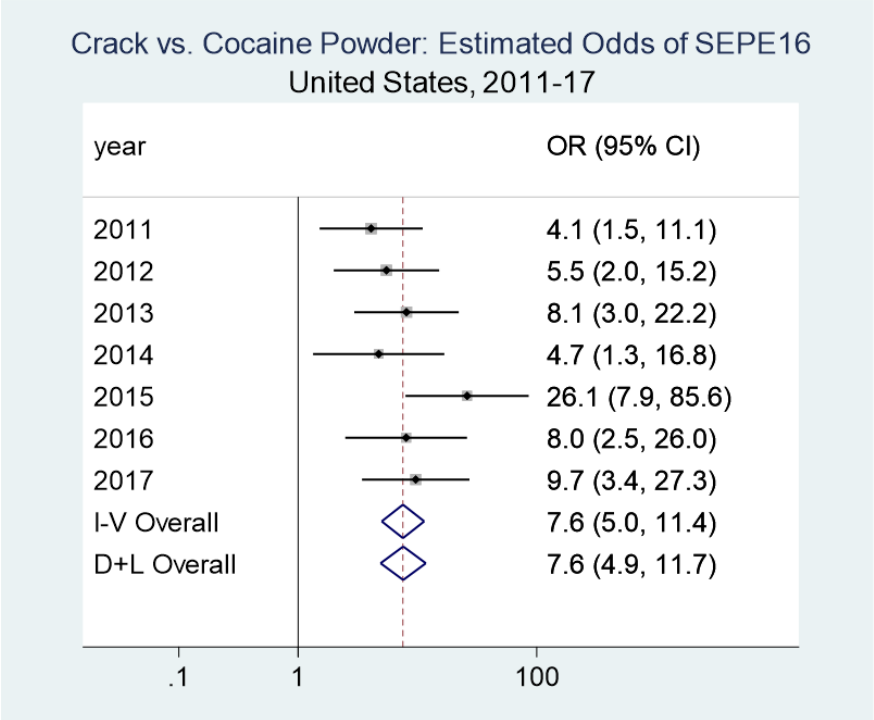

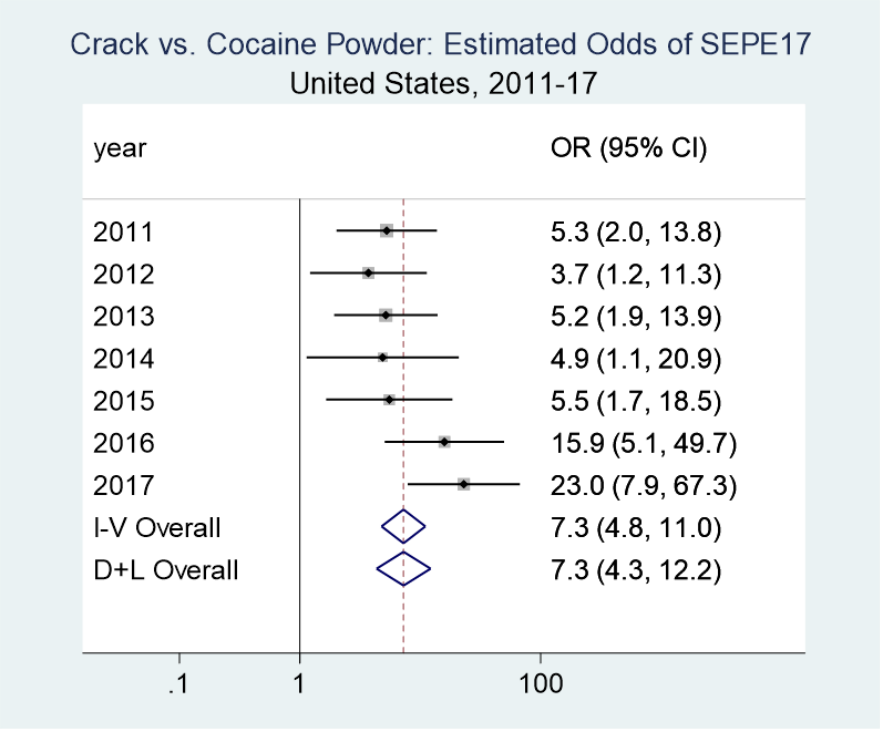

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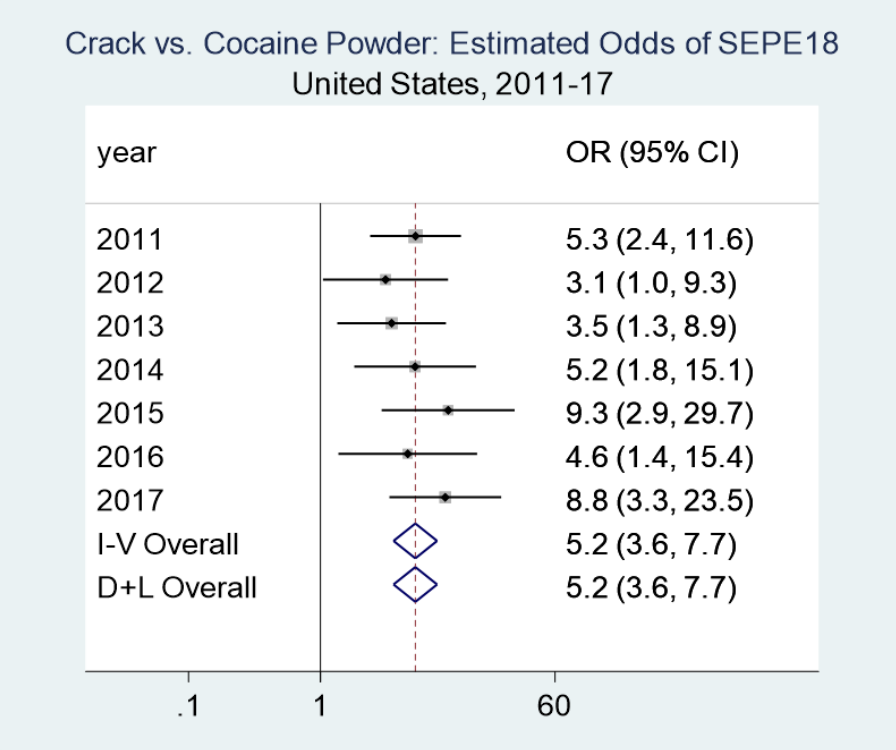

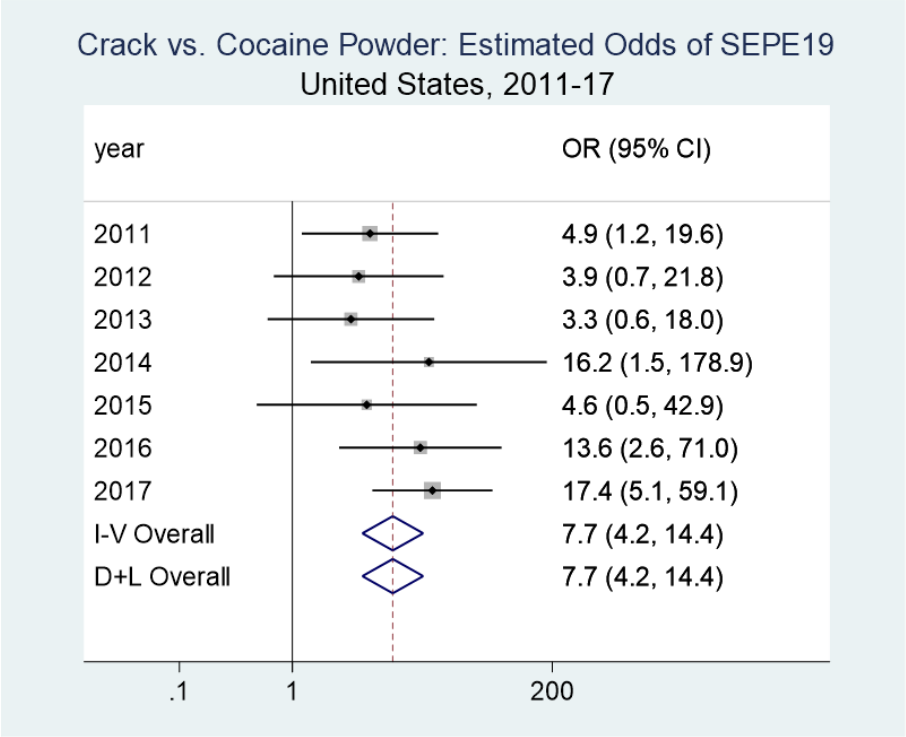

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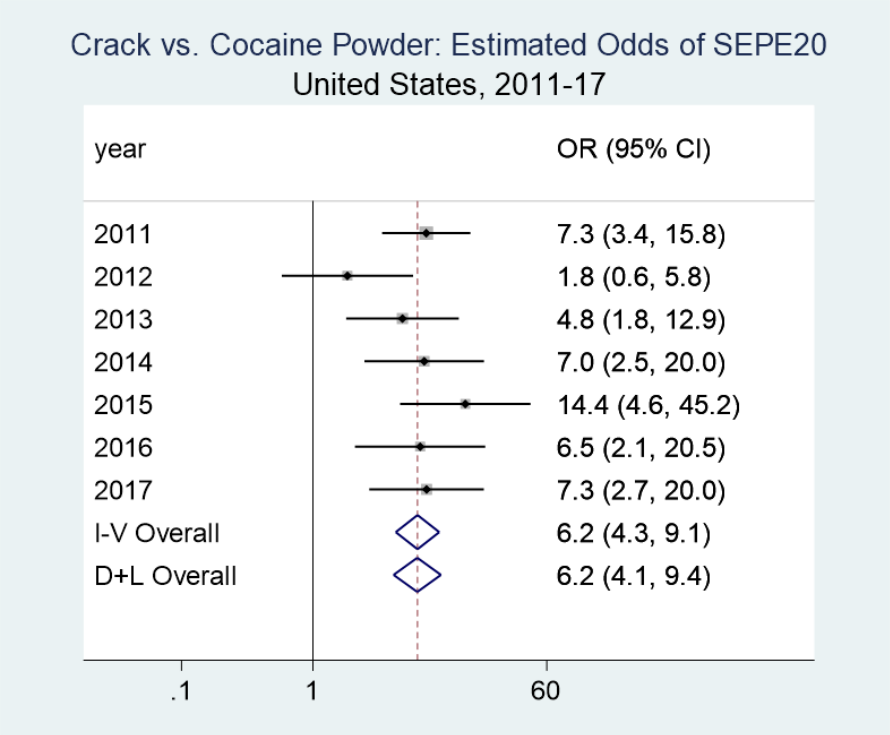


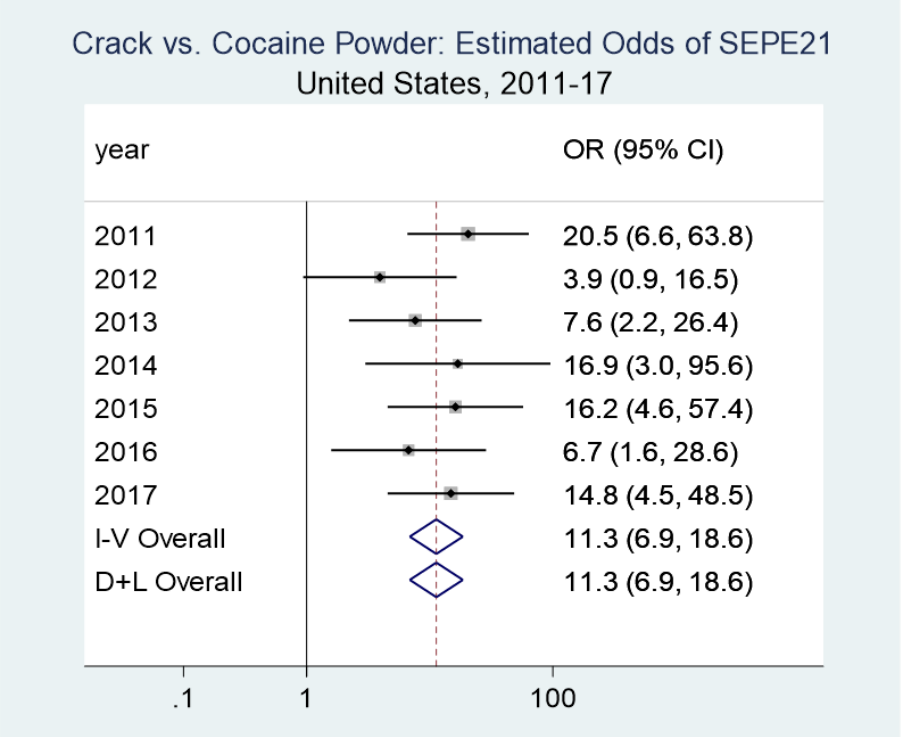
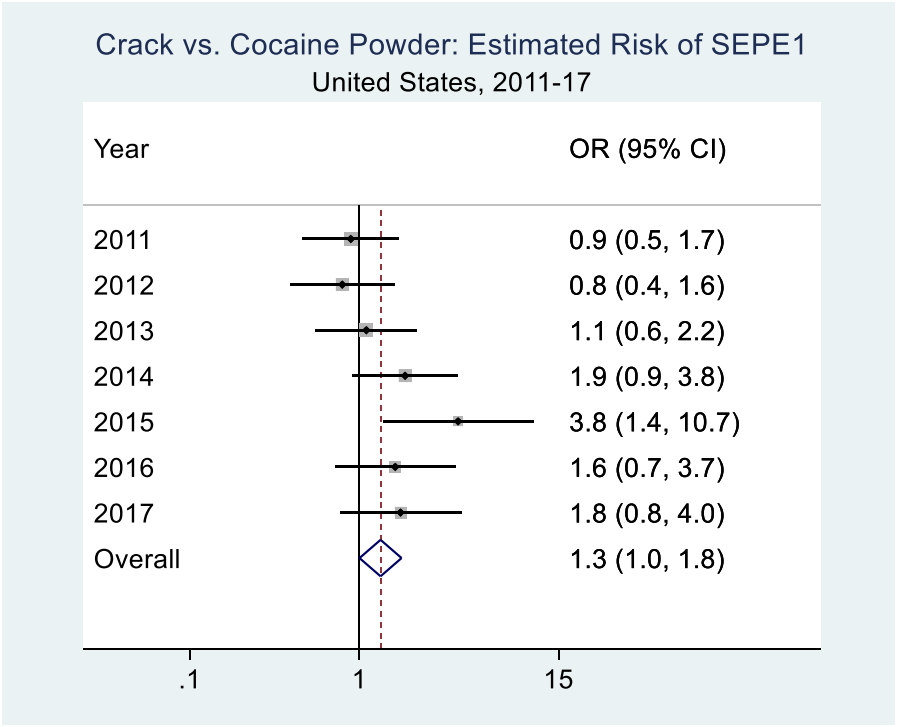
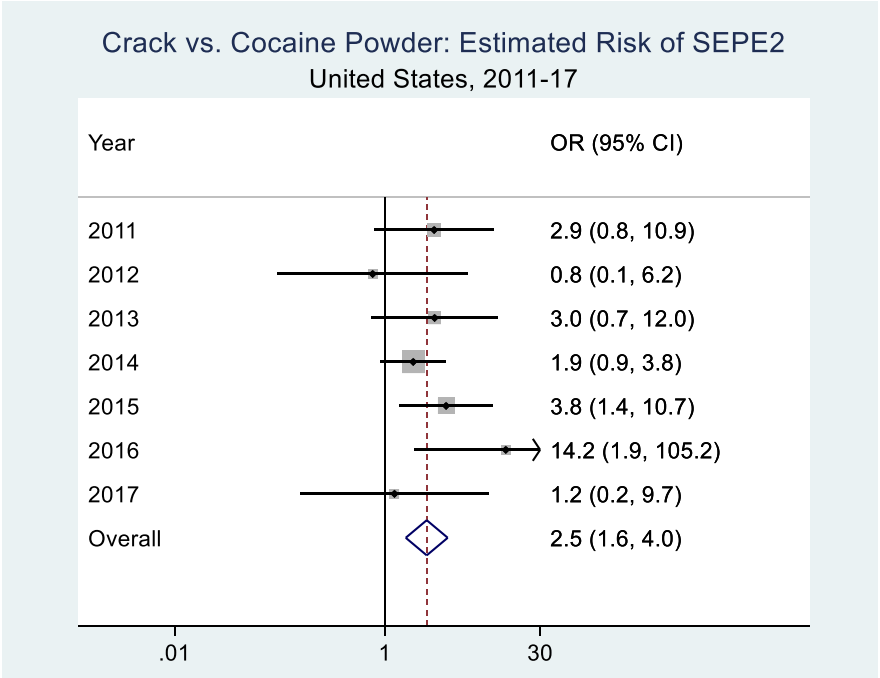


Figure C3. Meta-Analysis Forest Plot Estimates with Unweighted Covariate-Adjusted (Age, Sex, Race-Ethnicity & Drug History) Odds Ratios from a GZLM/GEE Model, Illustrating Cocaine Side Effect Problems & Experiences Among Newly Incident Crack Users as Contrasted with Powder Only Users. Data from the United States, National Surveys on Drug Use & Health, 2011-2017.





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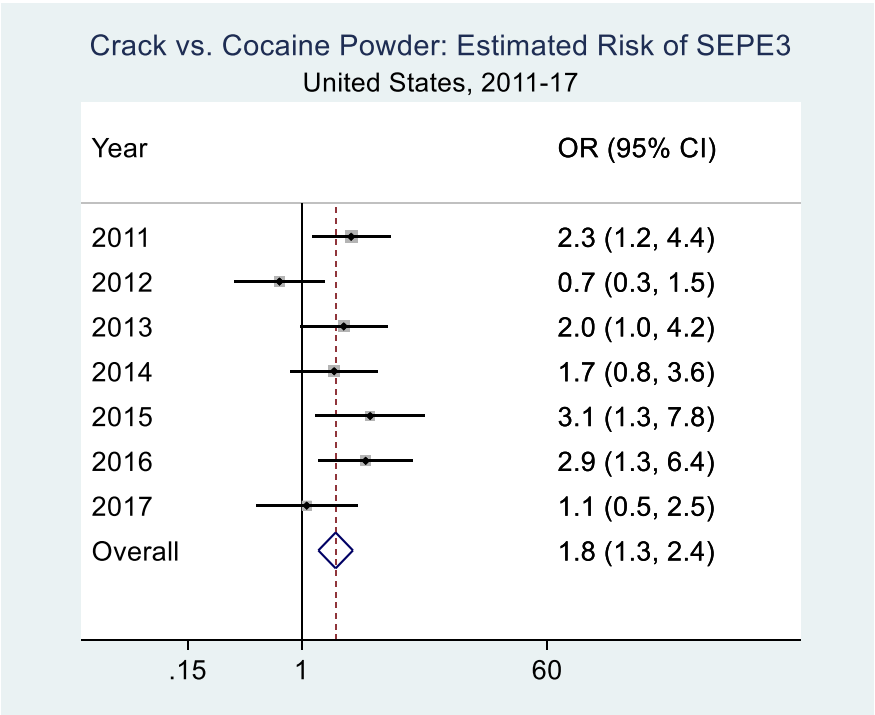

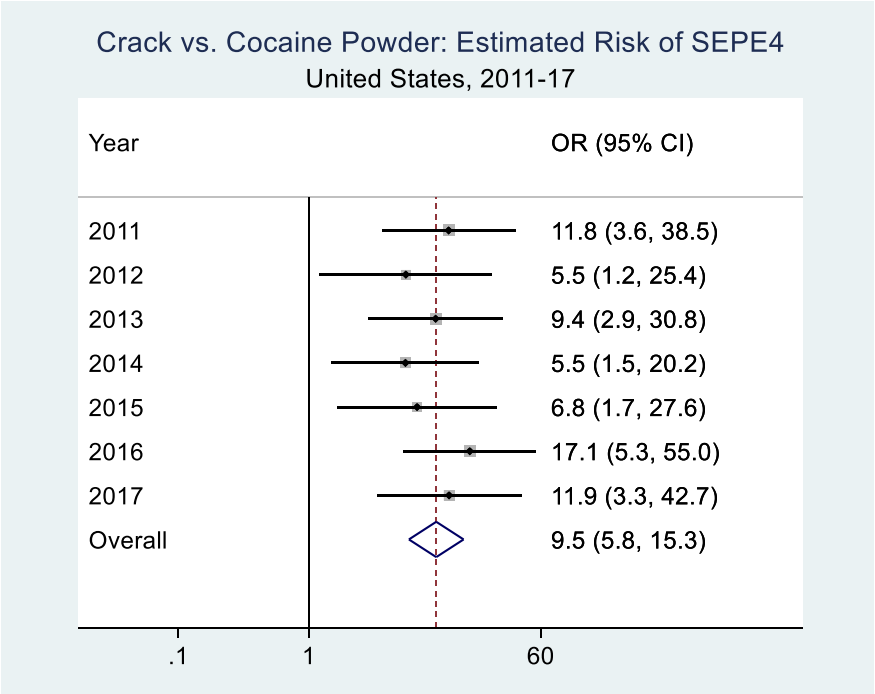

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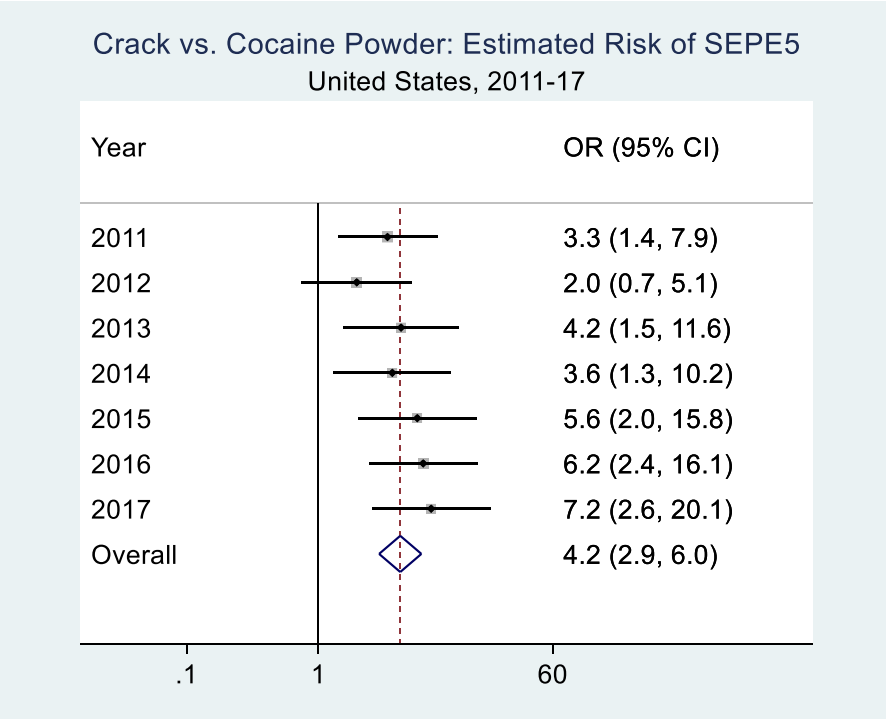

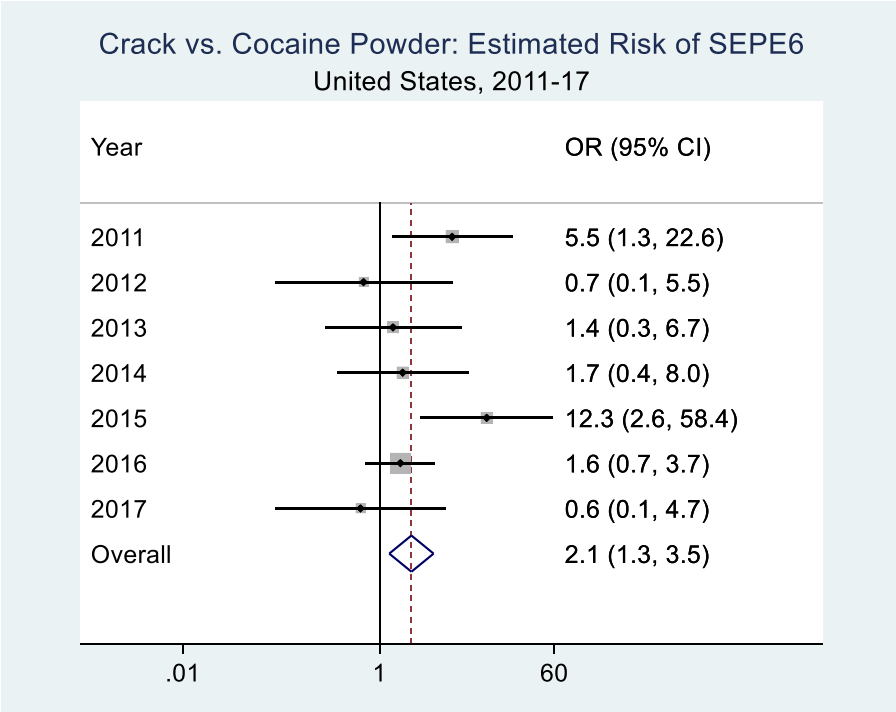

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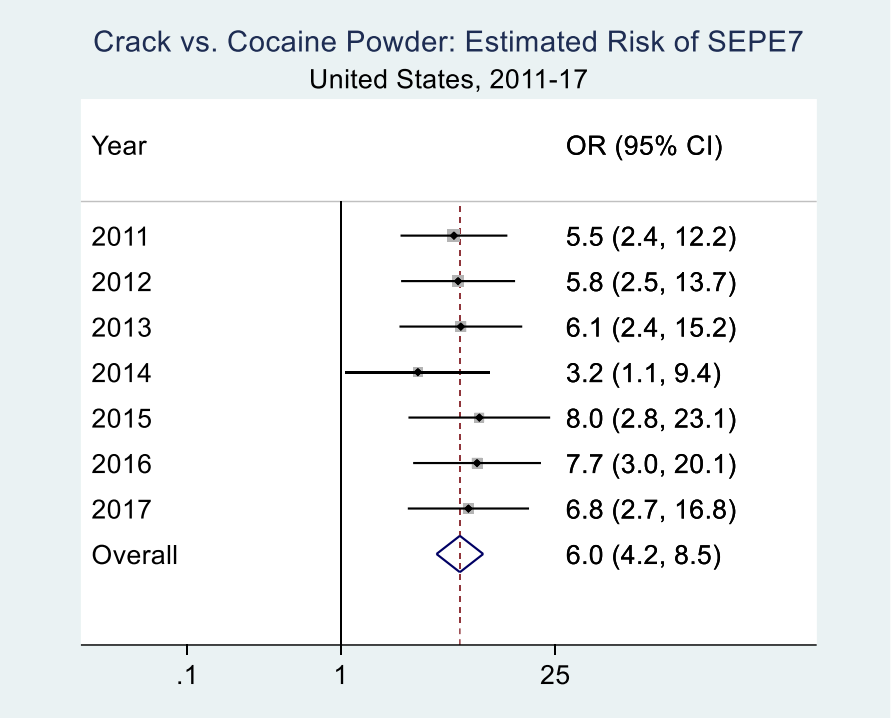

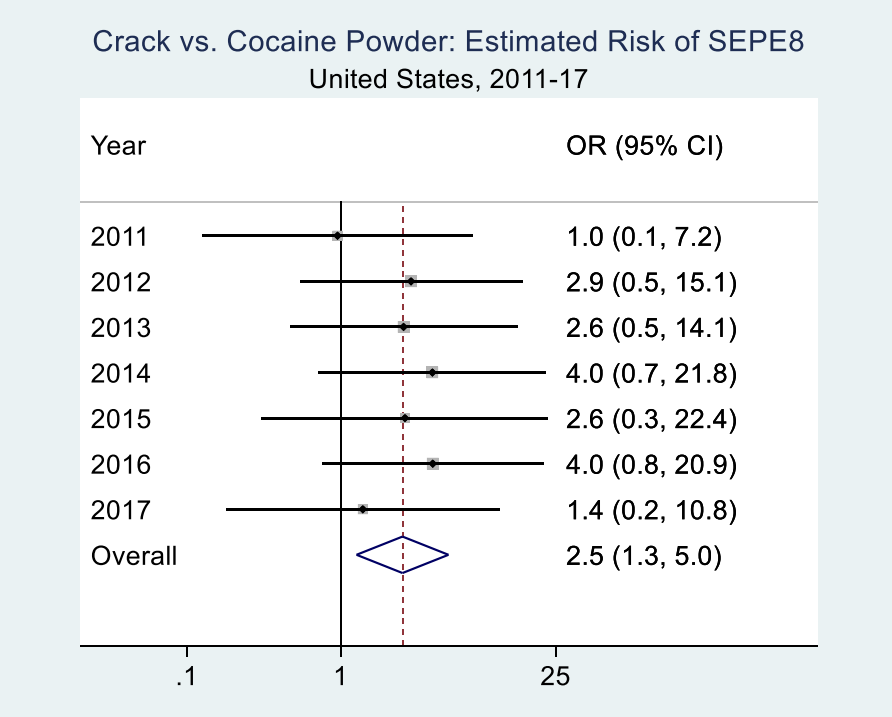

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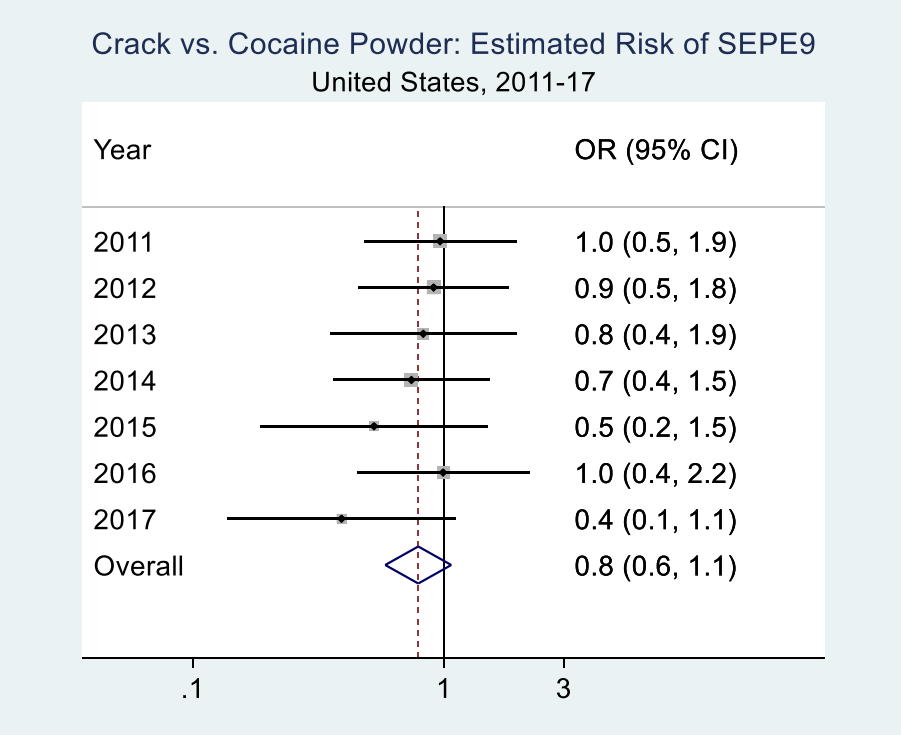

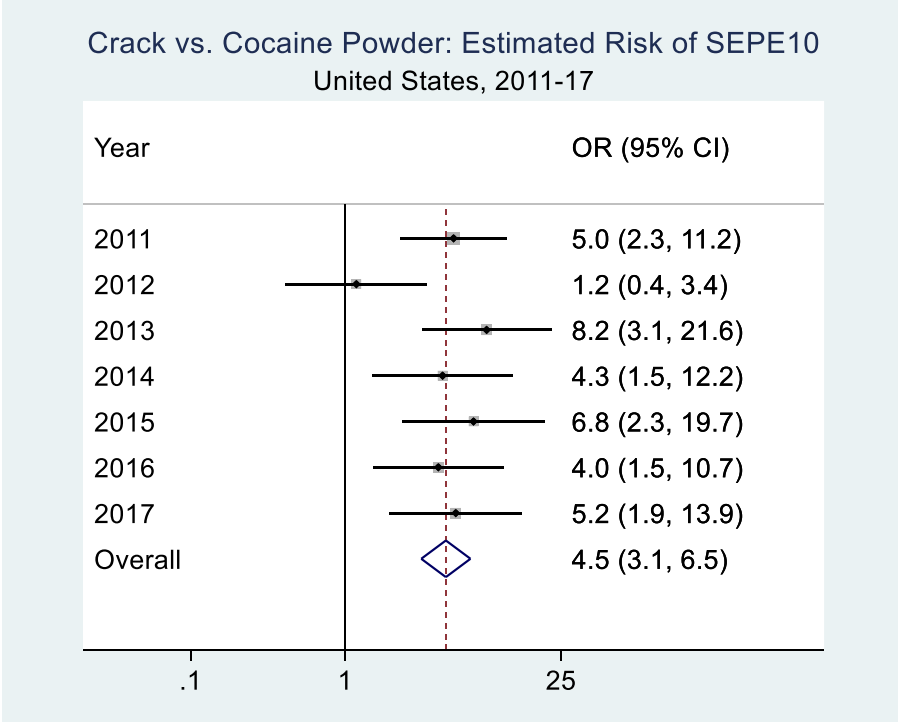

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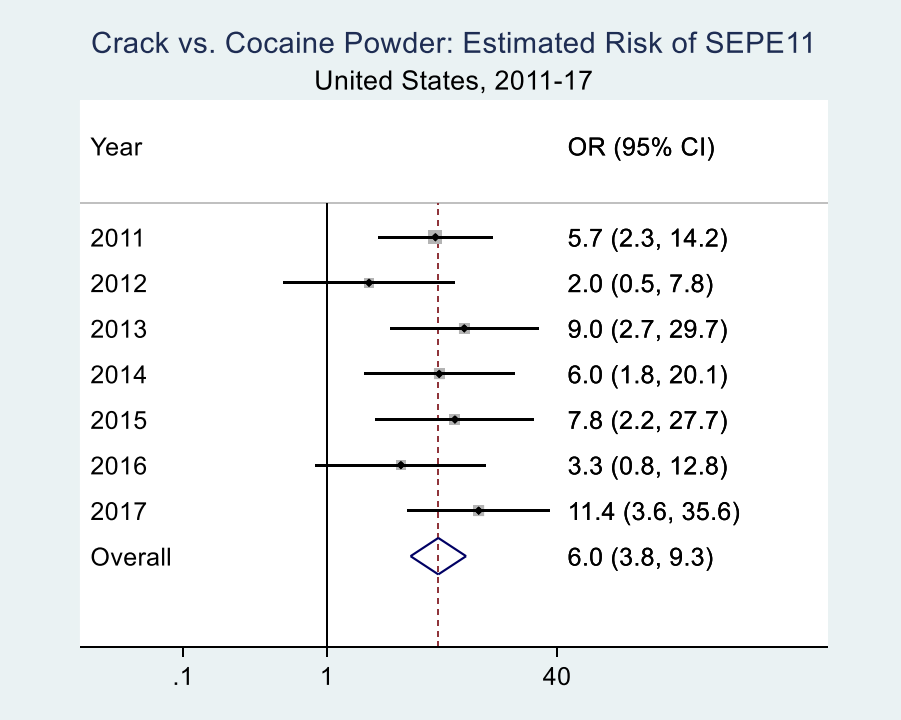

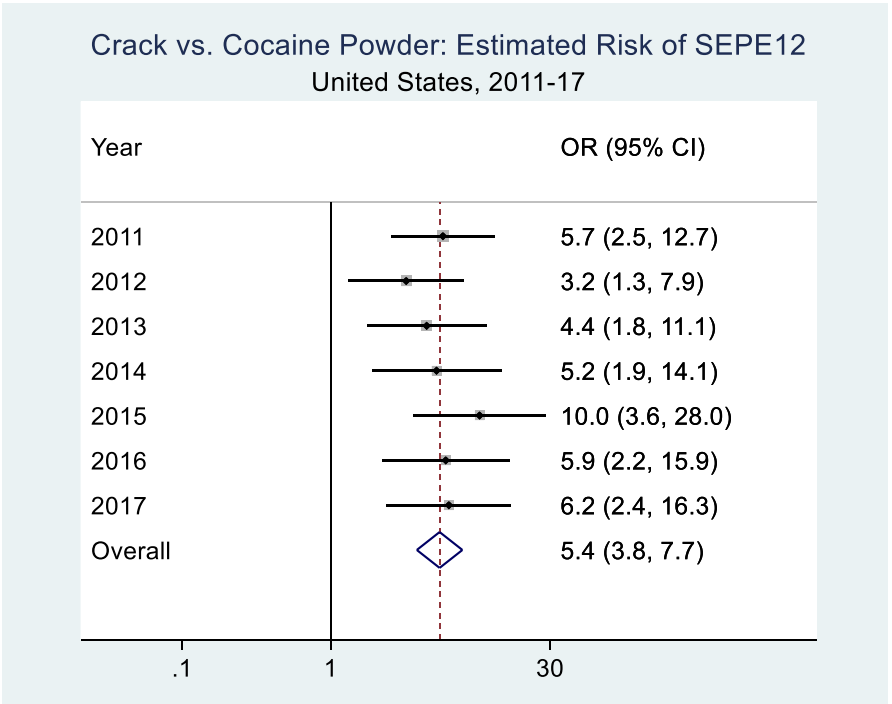

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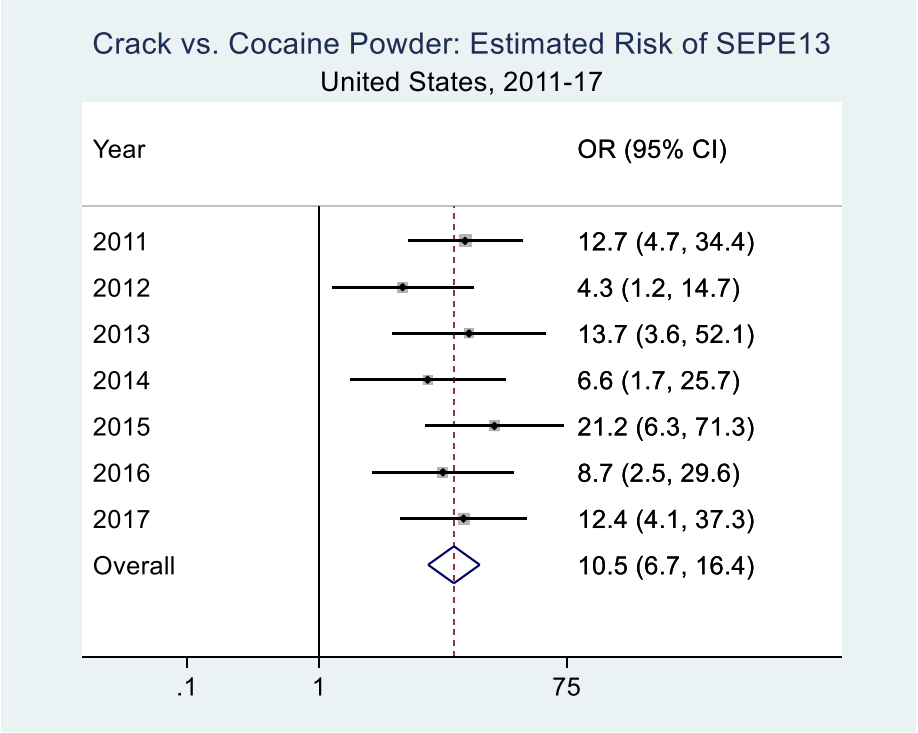

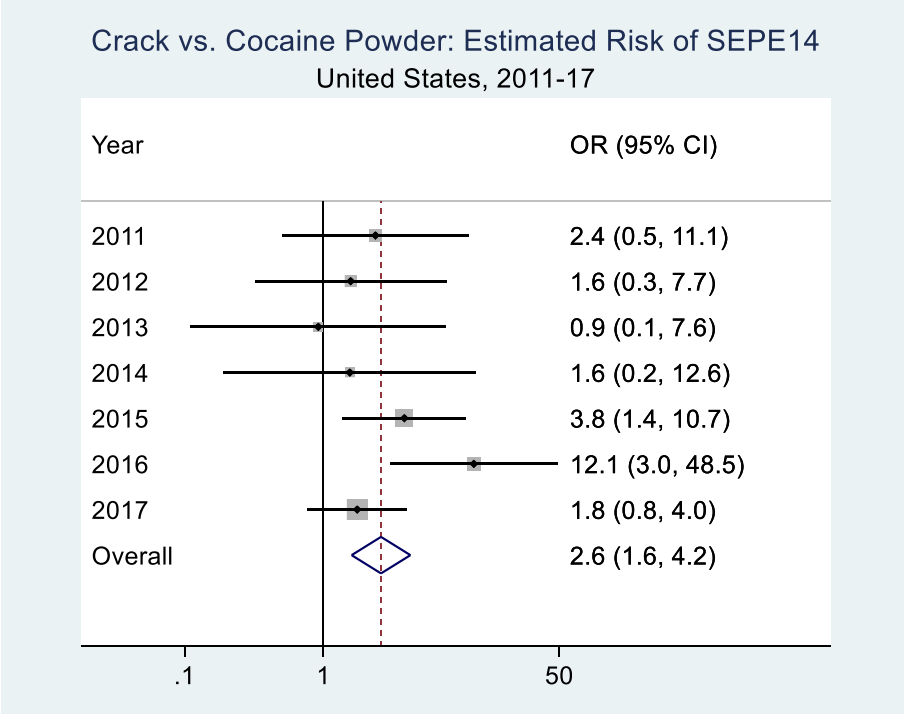

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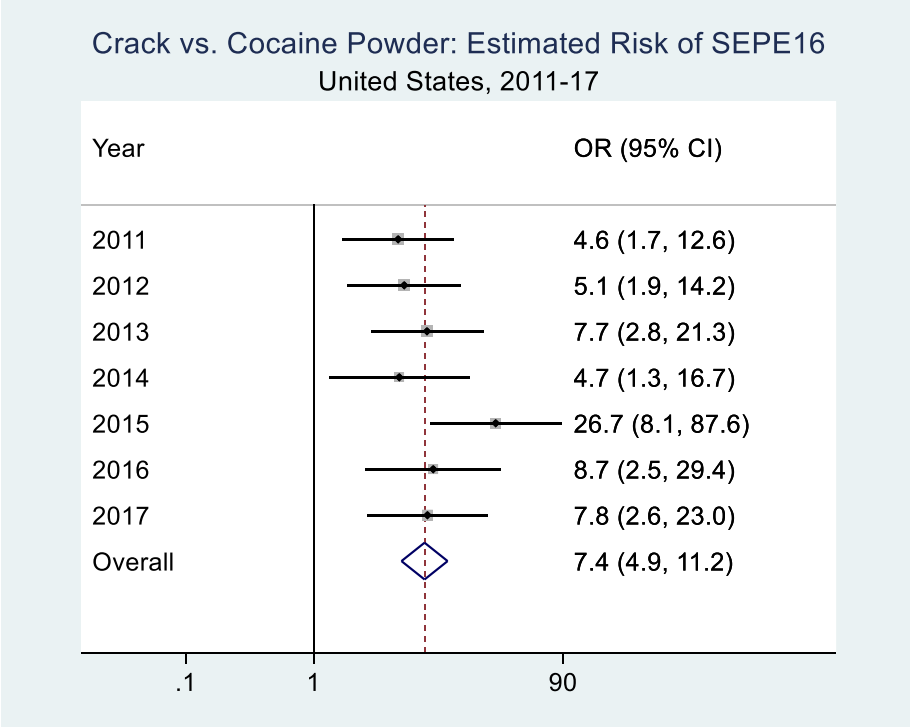

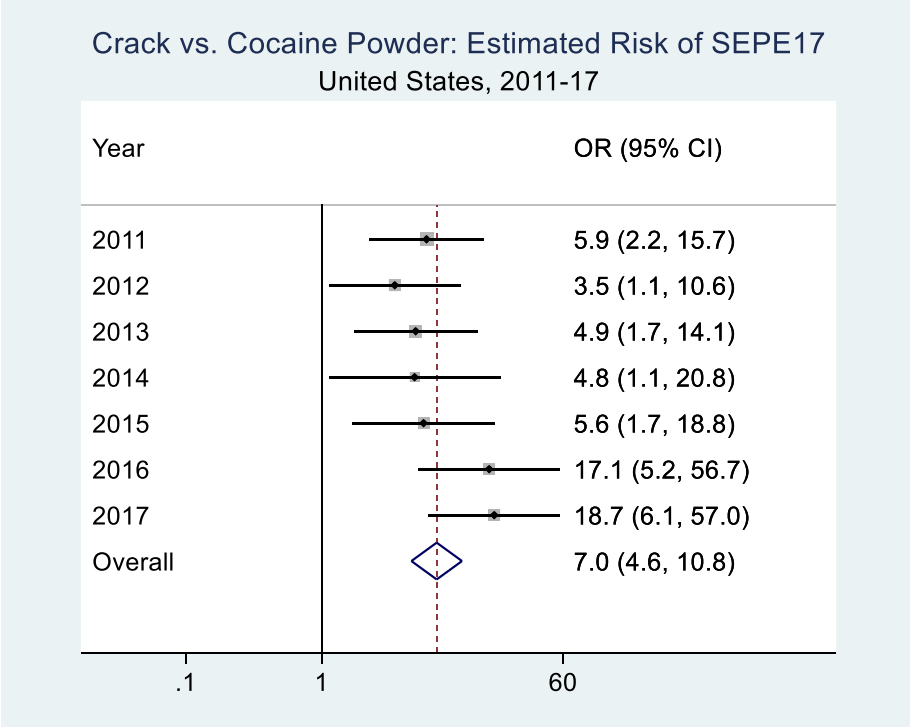

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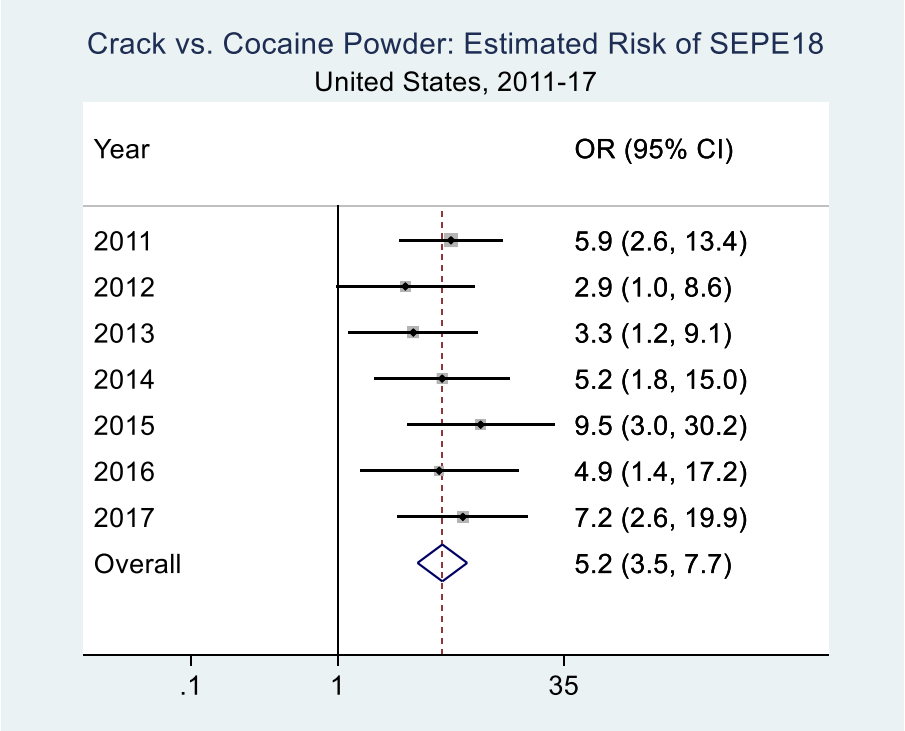

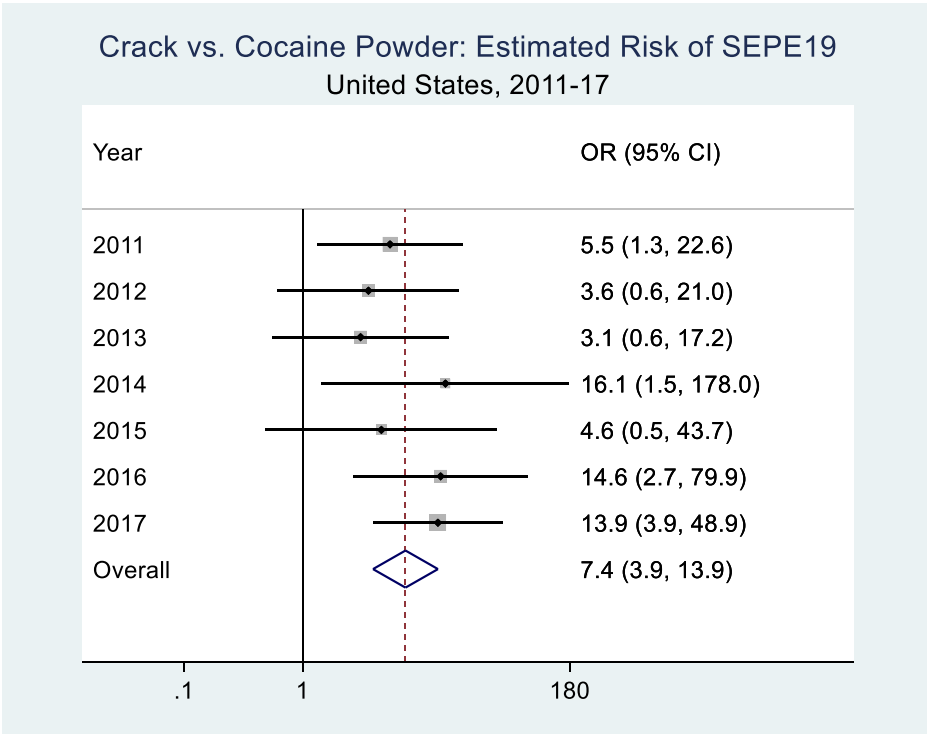

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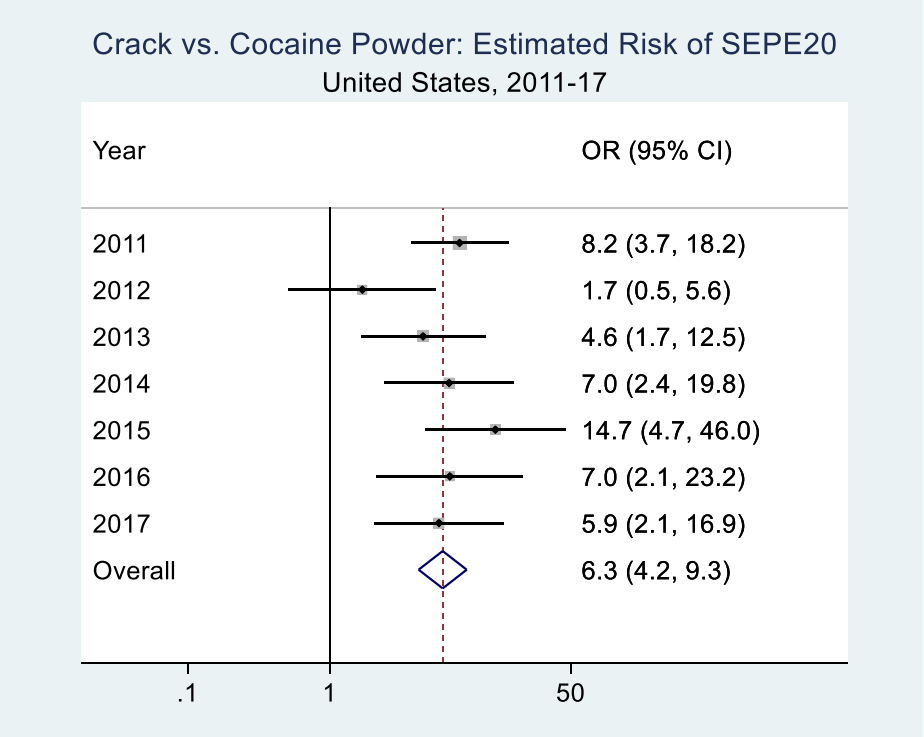

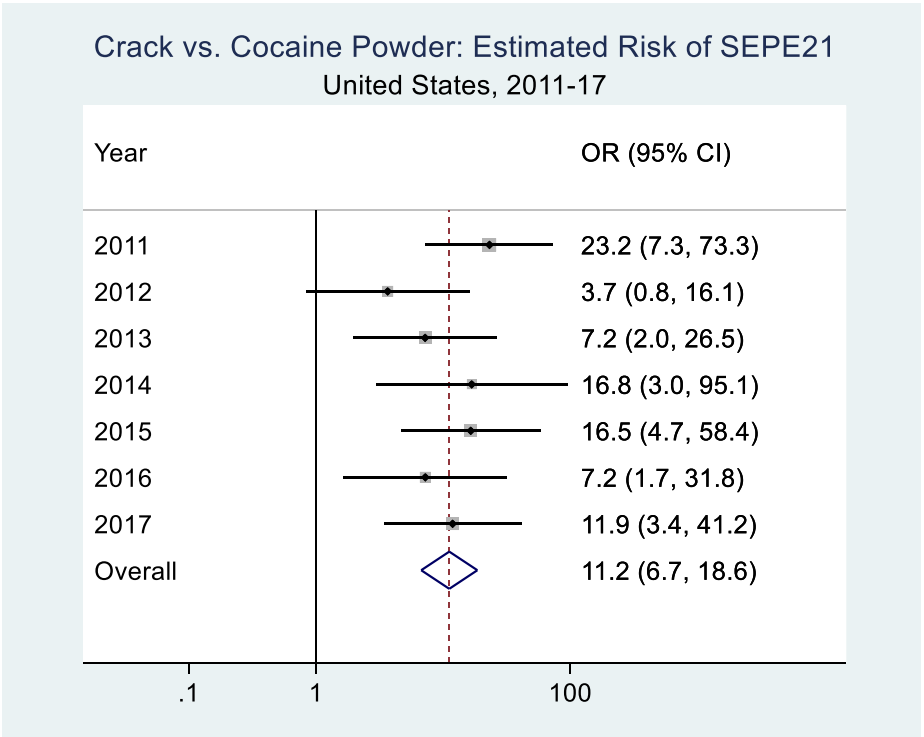

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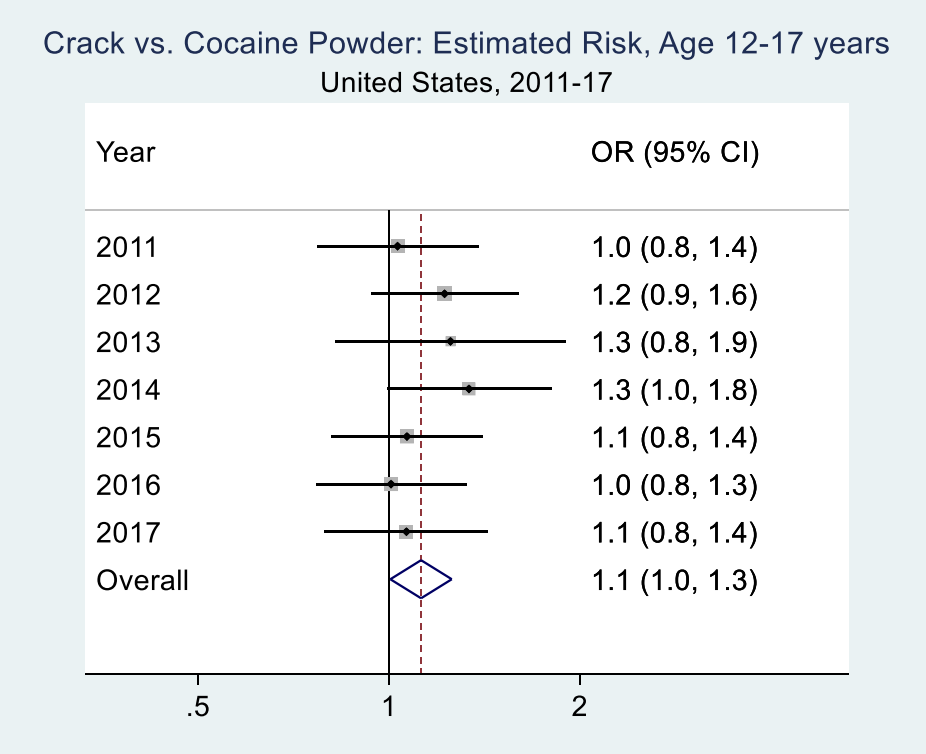

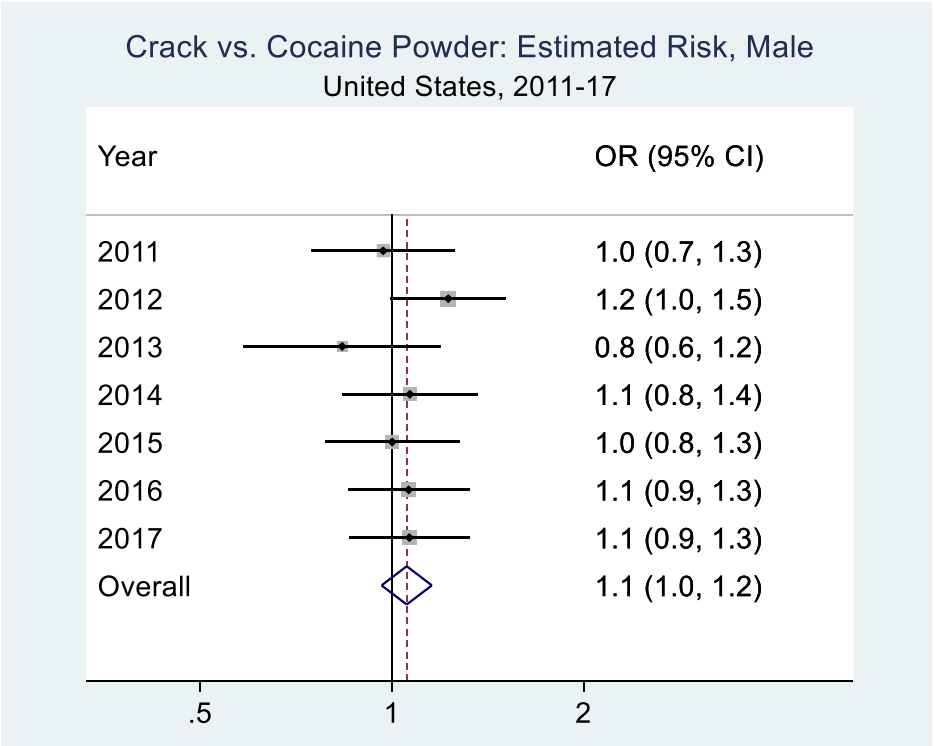

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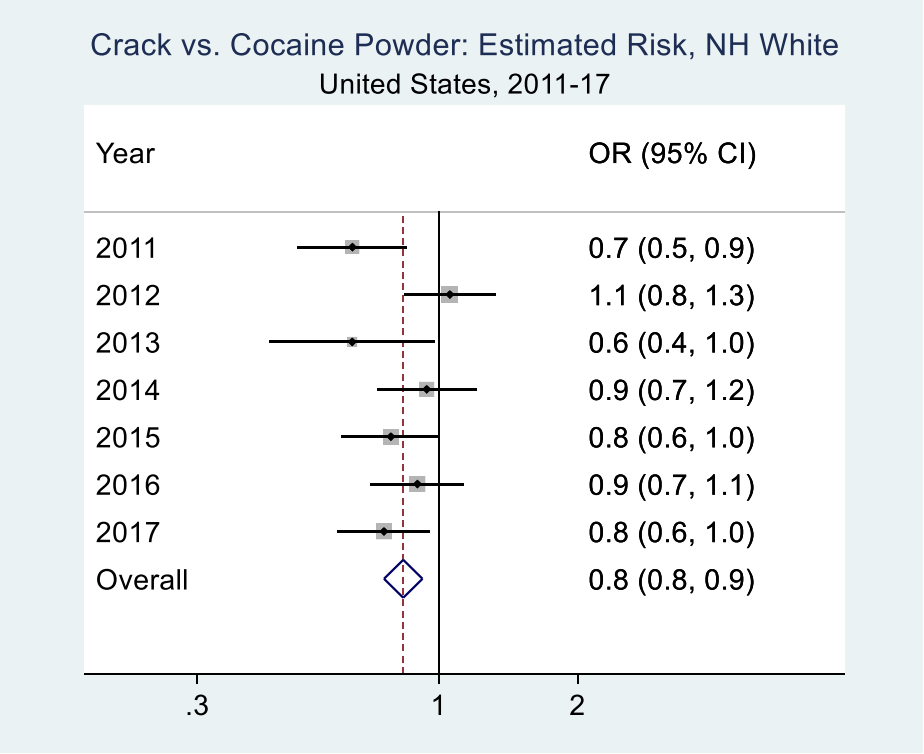

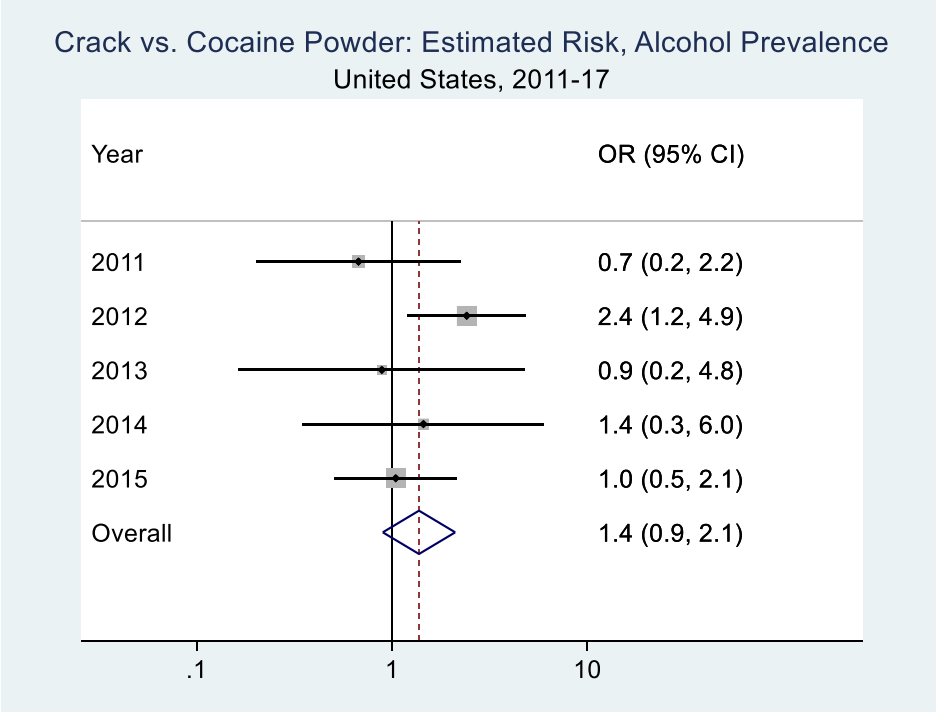

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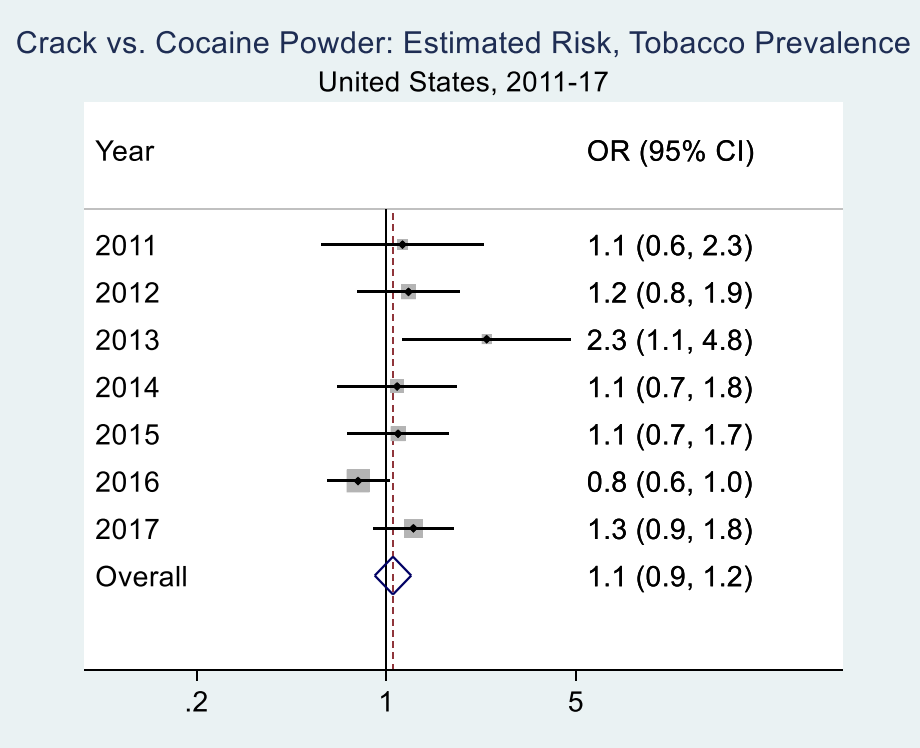

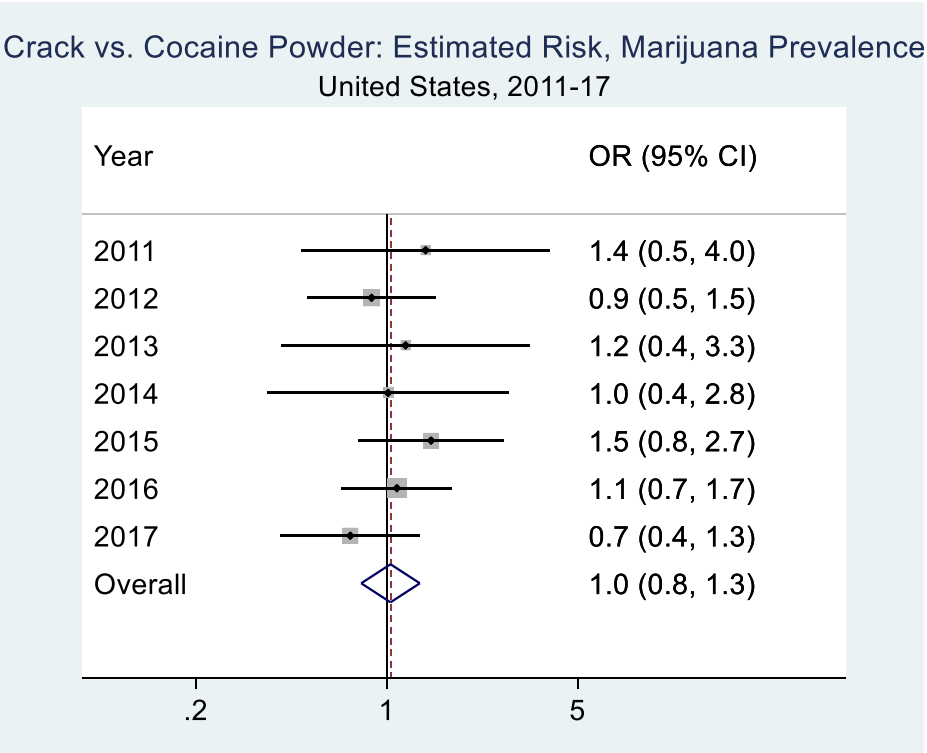

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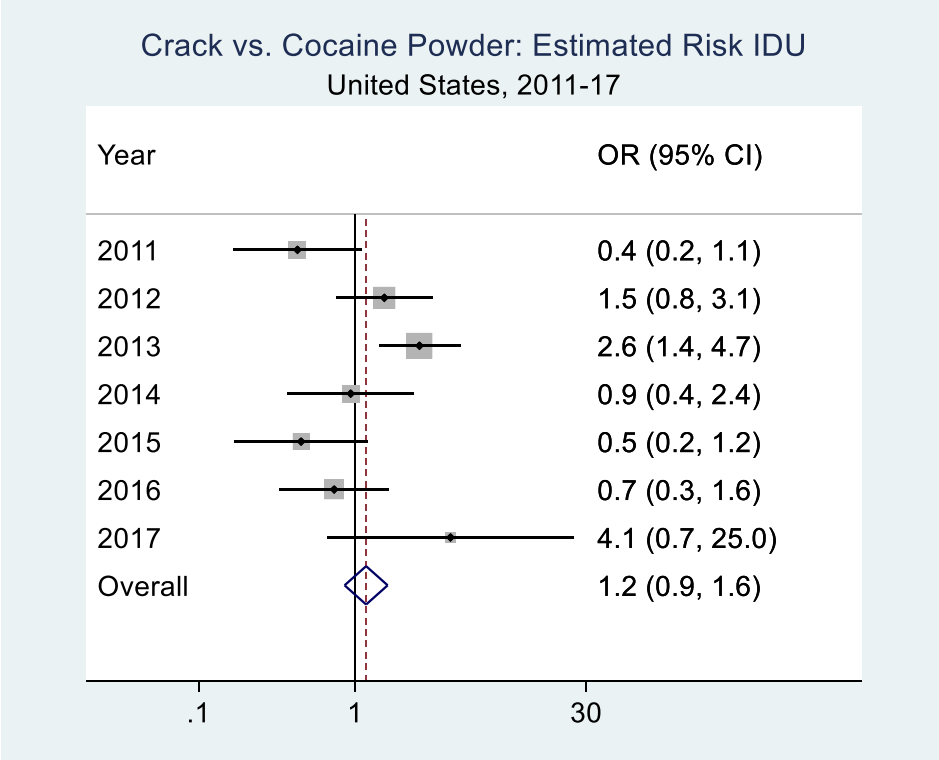
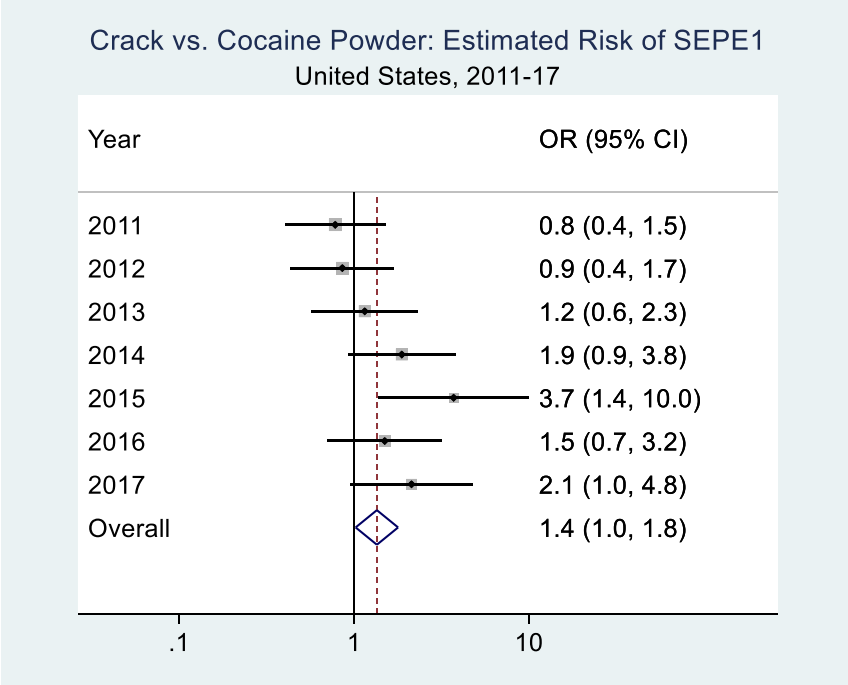
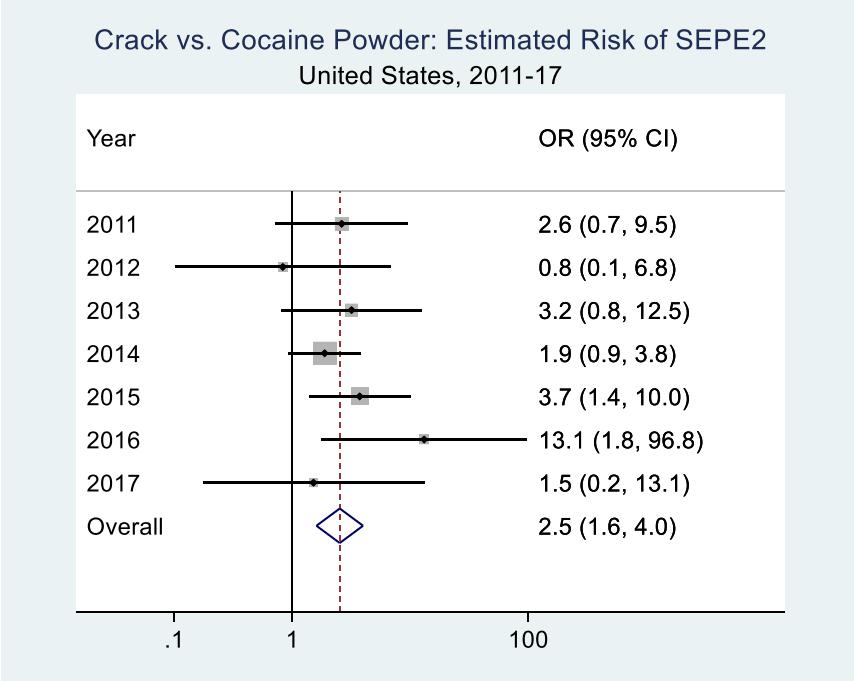


Figure C4. Meta-Analysis Forest Plot Estimates with Unweighted Covariate-Adjusted (Age, Sex, Race-Ethnicity & SES) Odds Ratios from a GZLM/GEE Model, Illustrating Cocaine Side Effect Problems & Experiences Among Newly Incident Crack Users as Contrasted with Powder Only Users. Data from the United States, National Surveys on Drug Use & Health, 2011-2017.





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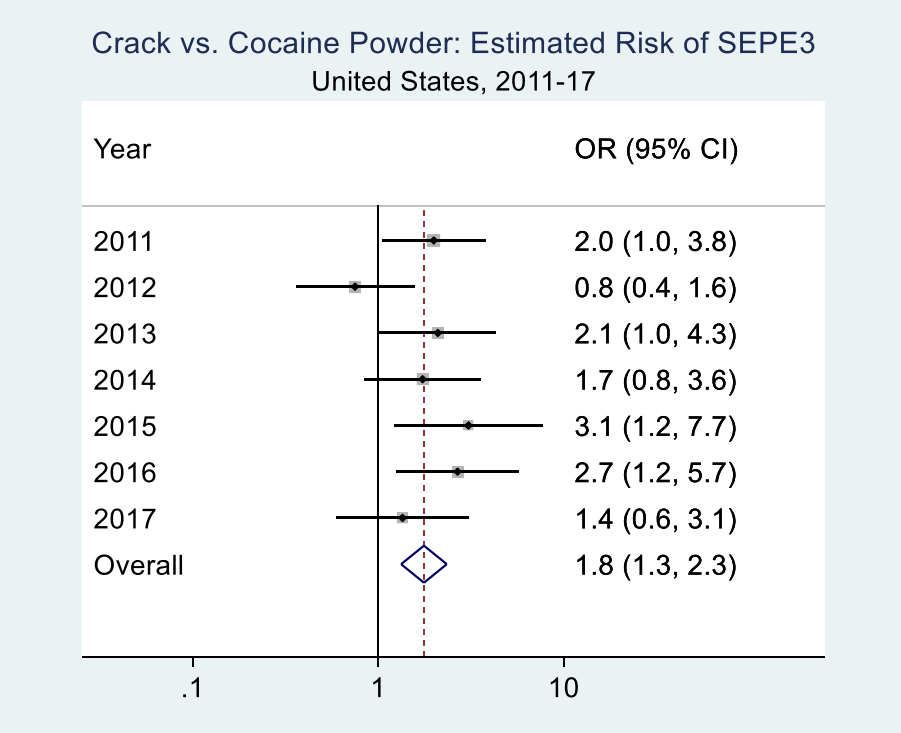

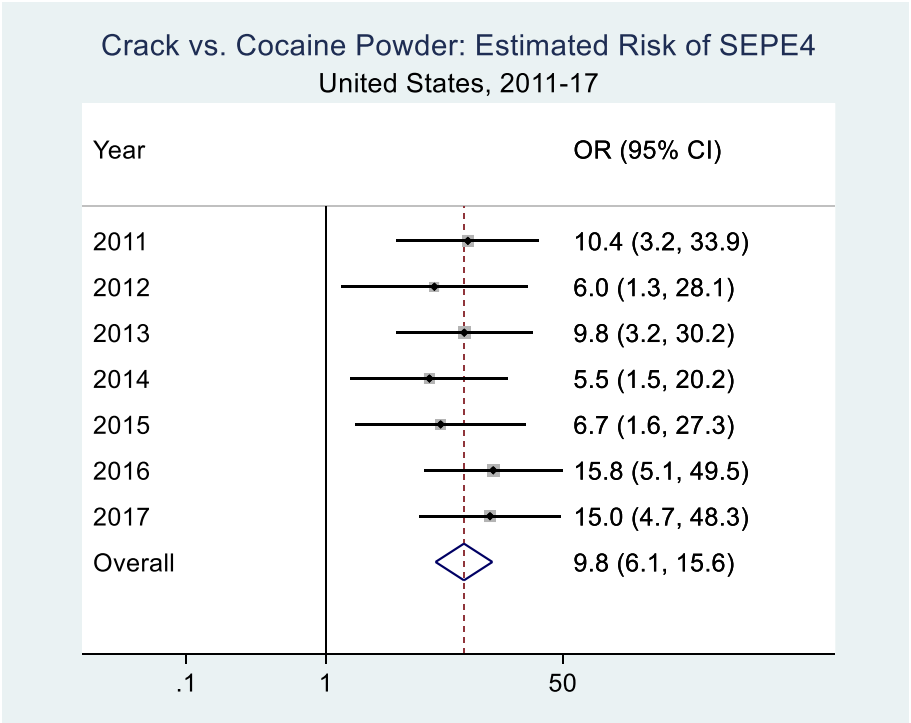

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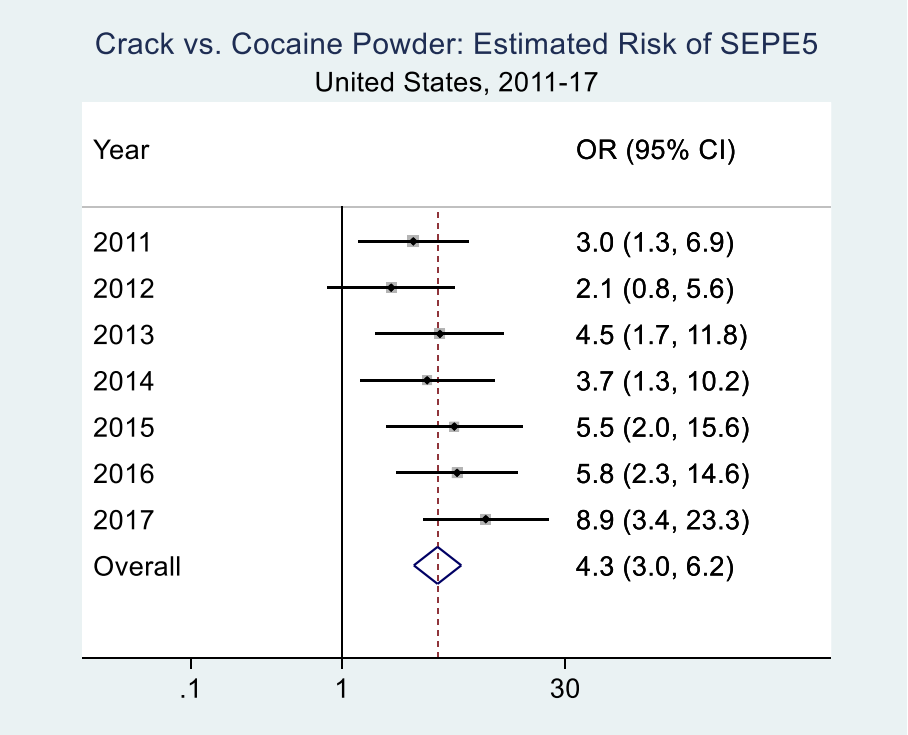

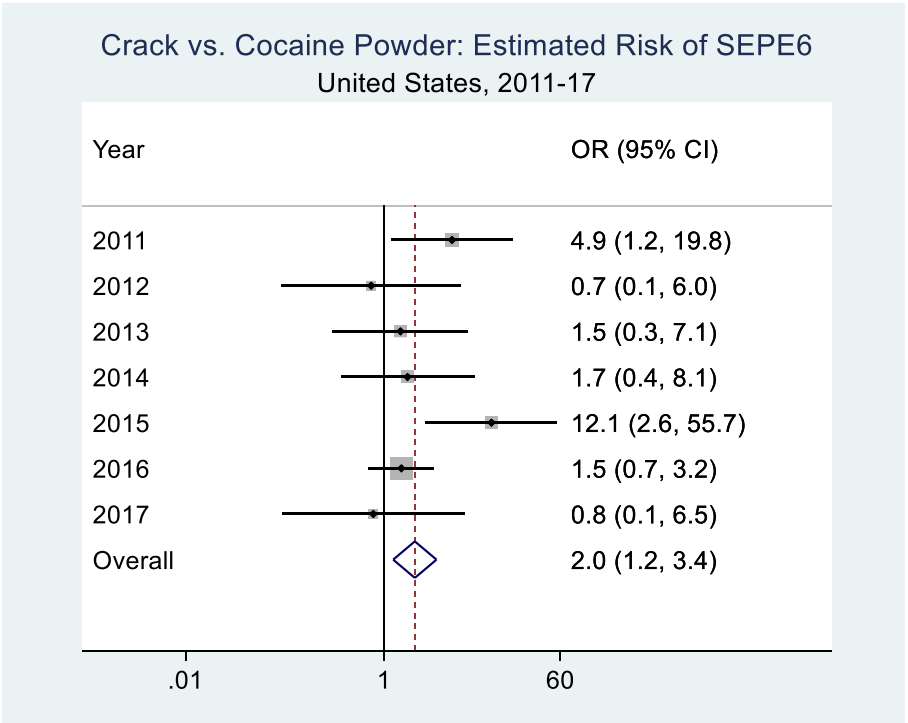

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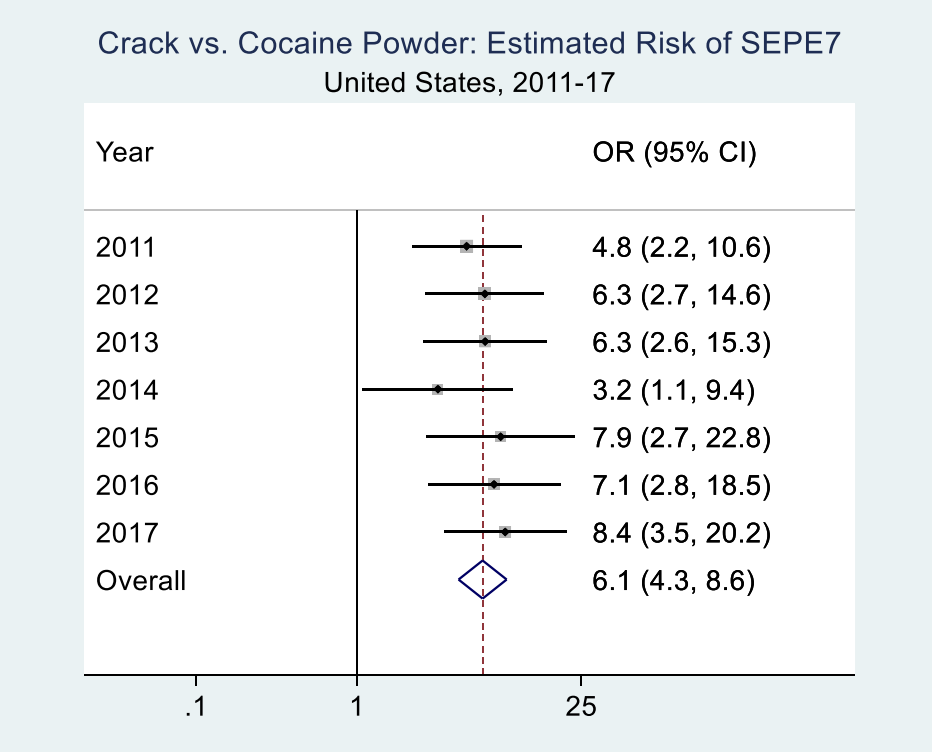

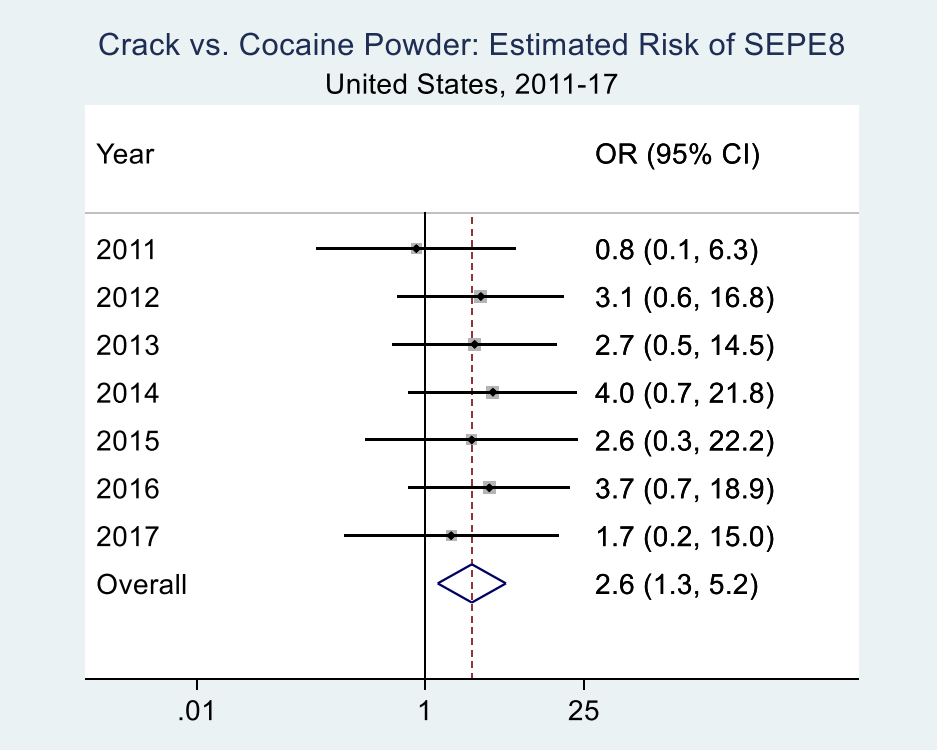

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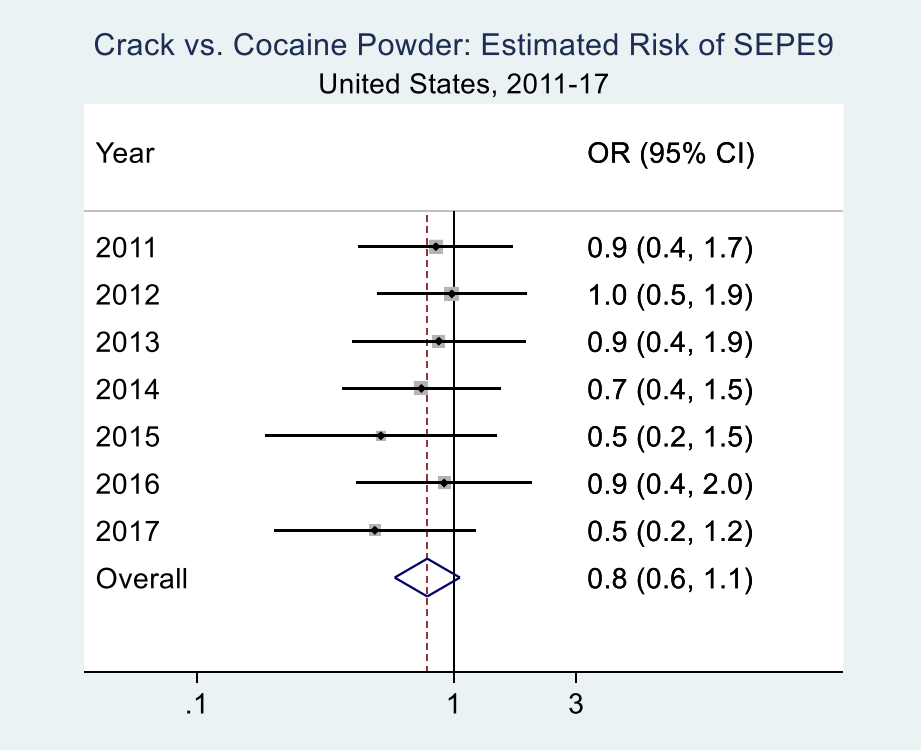

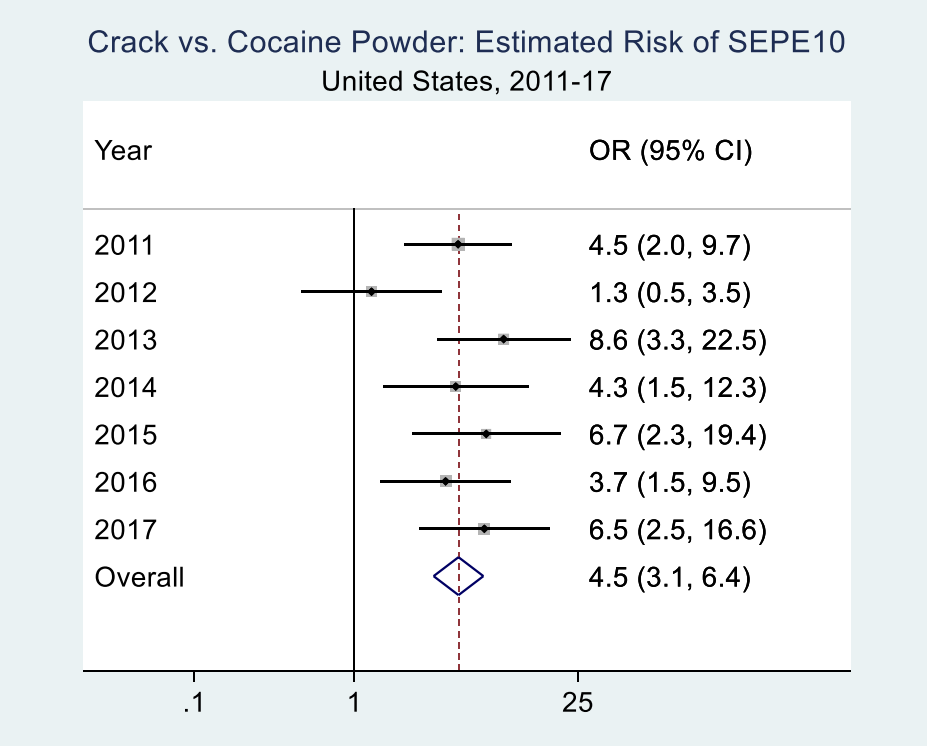

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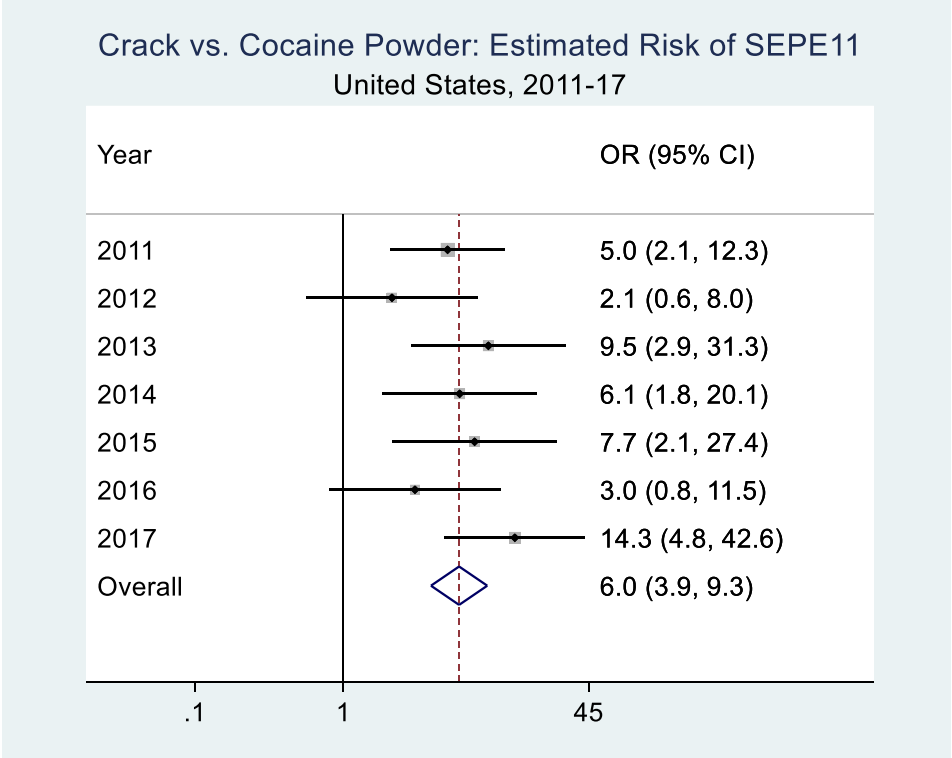

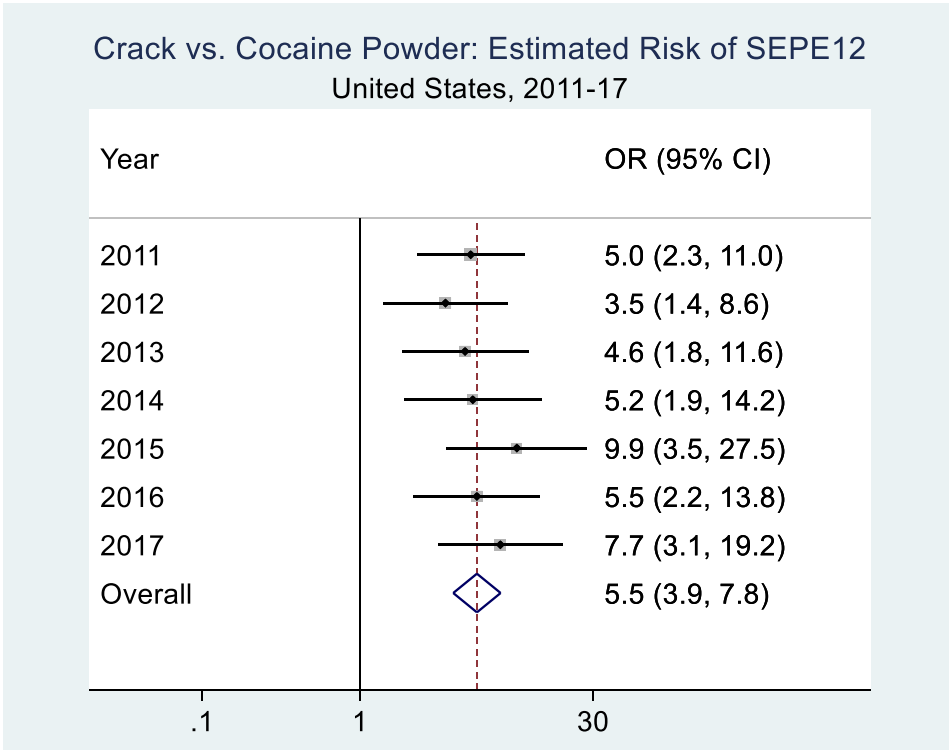

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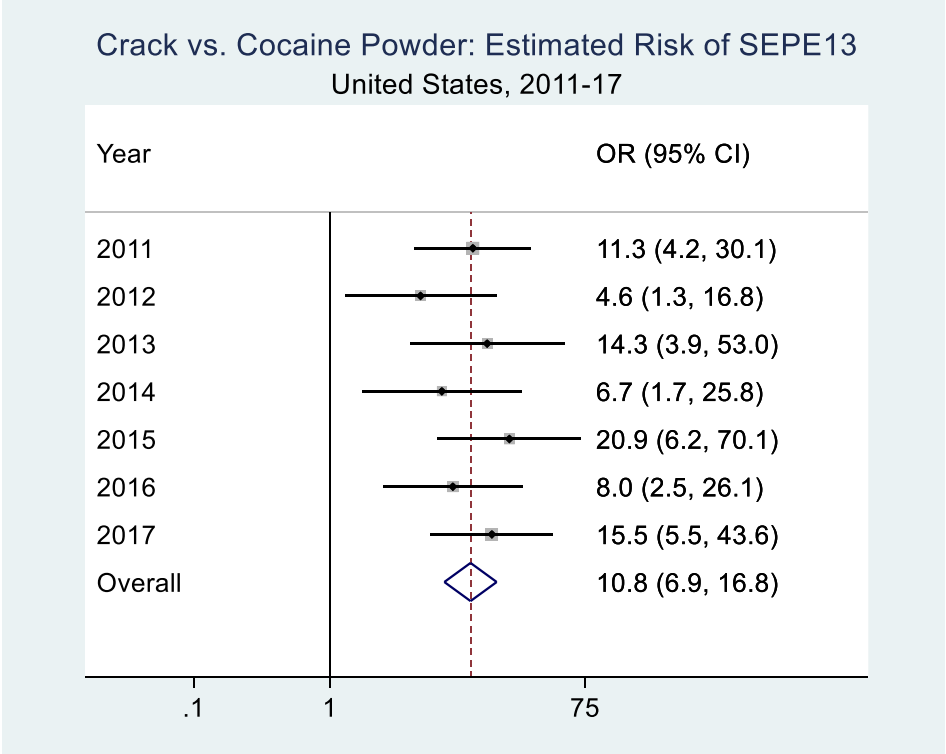

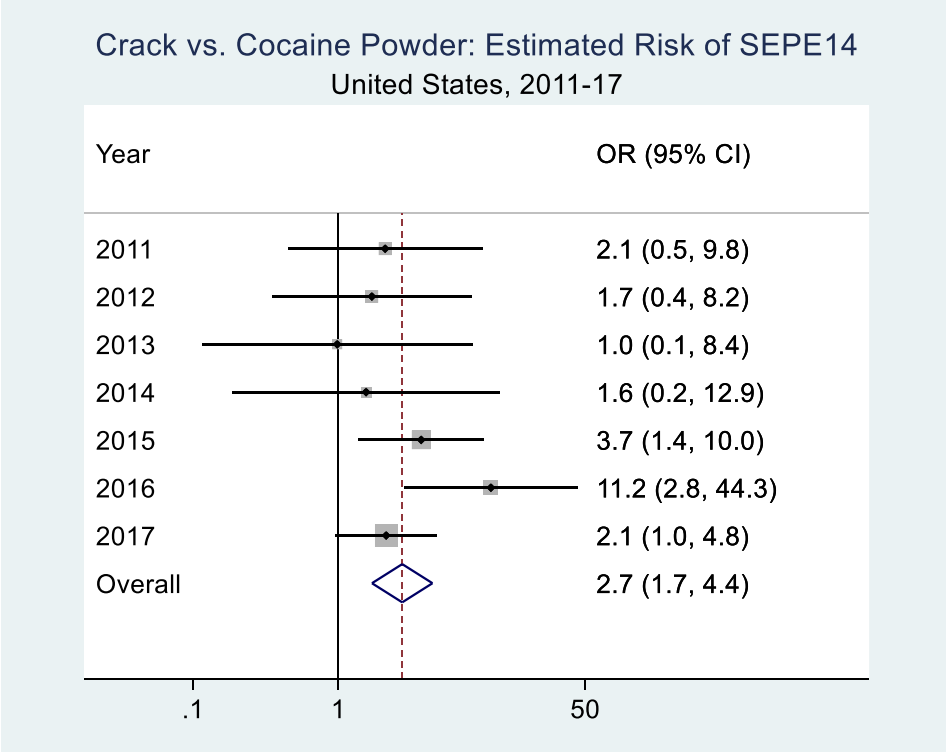

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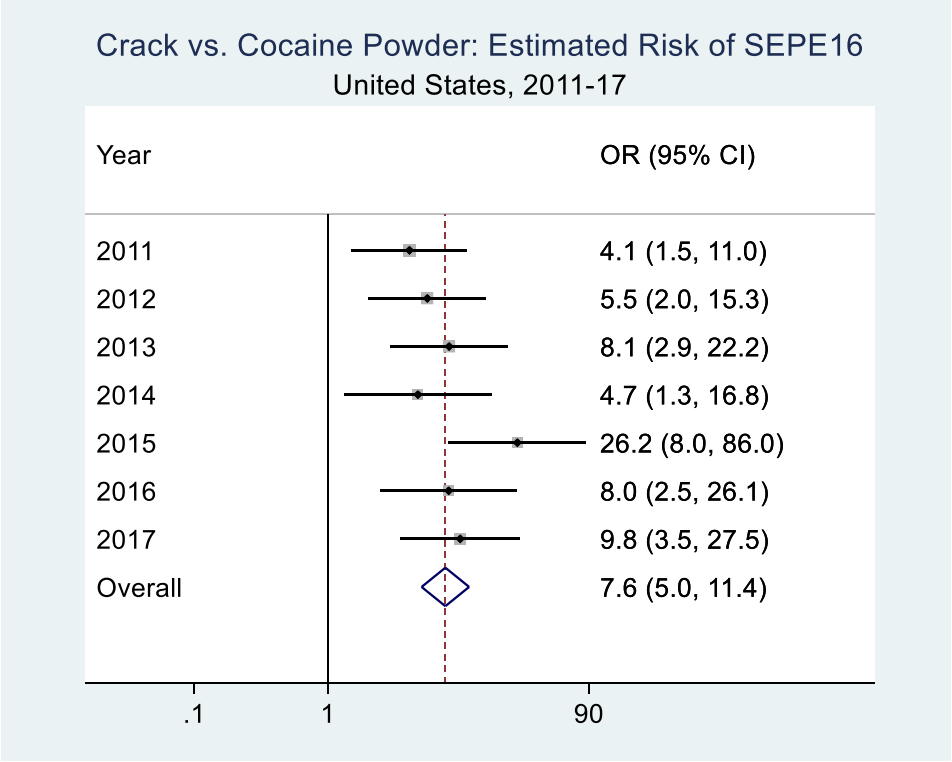

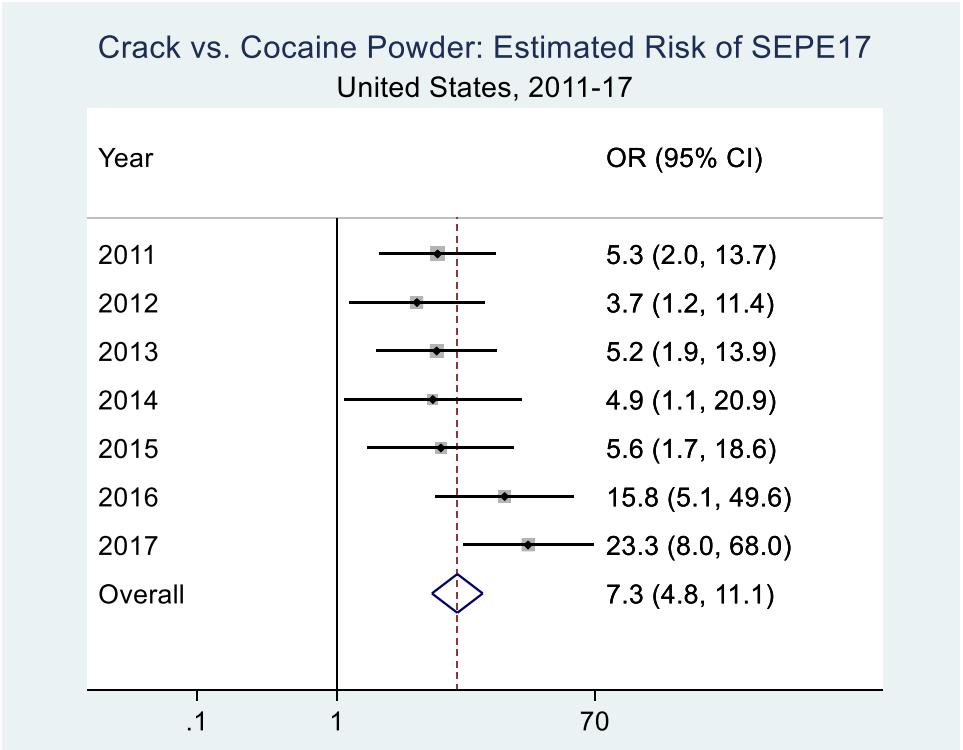

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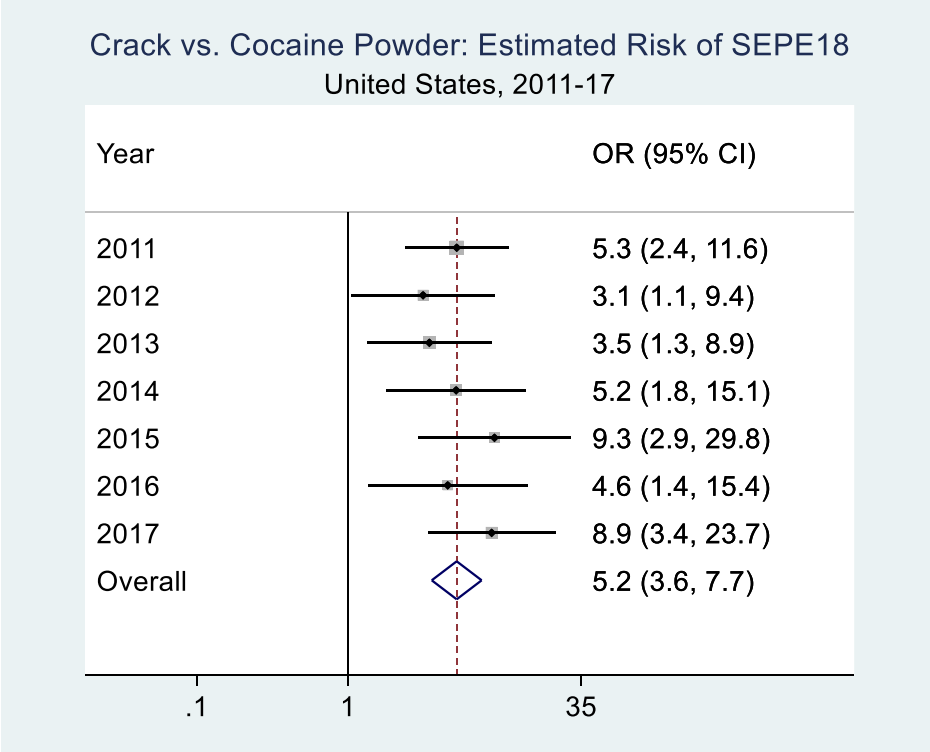

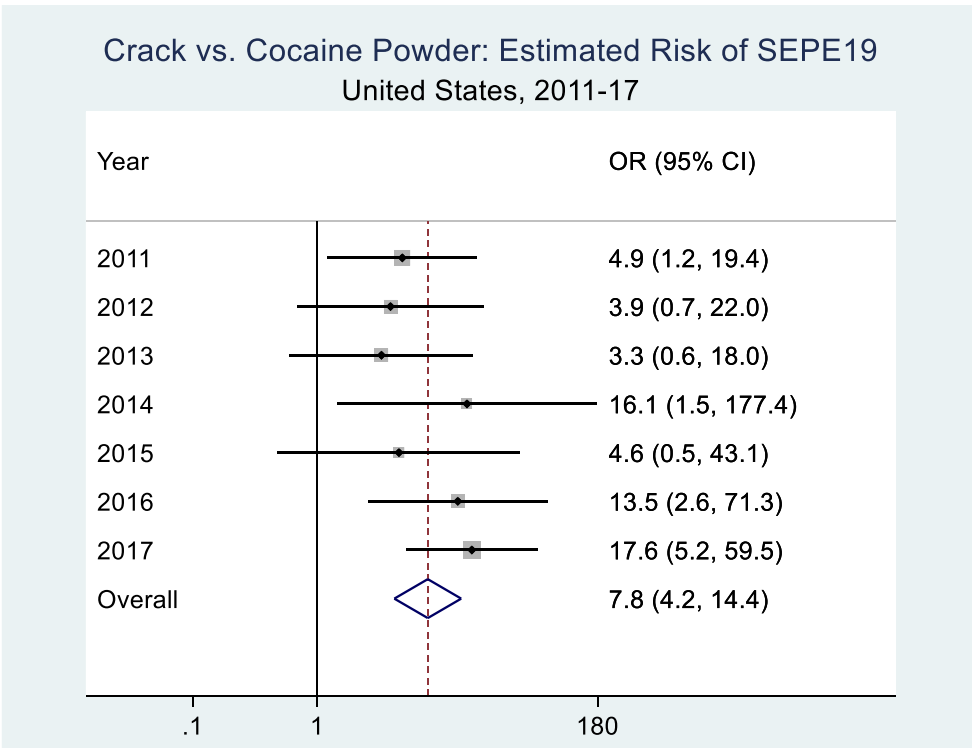

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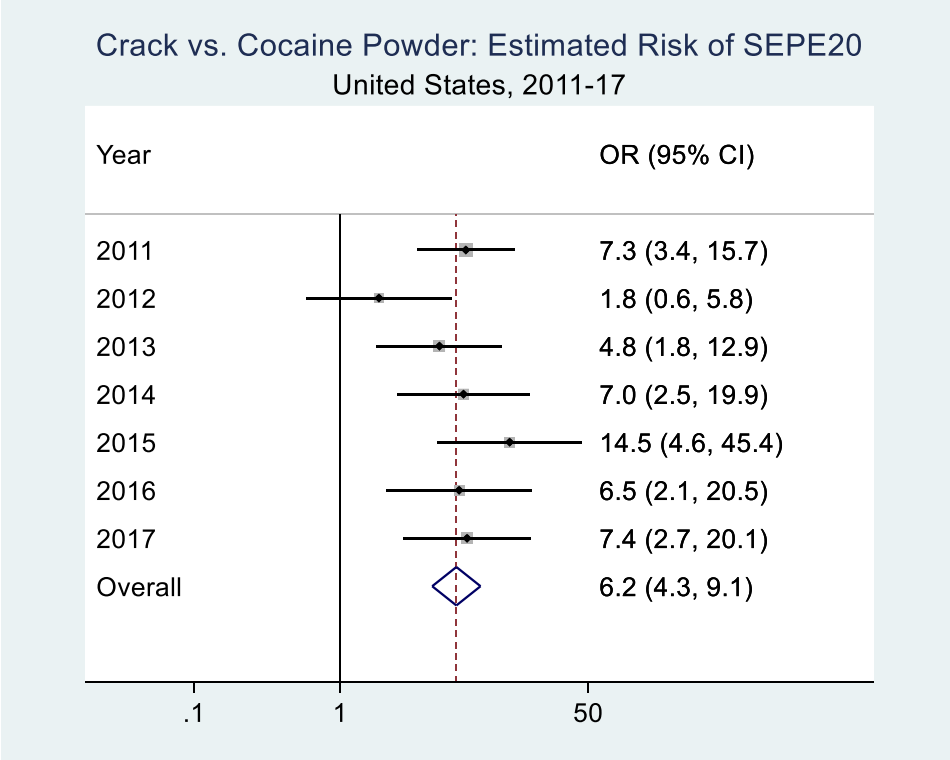

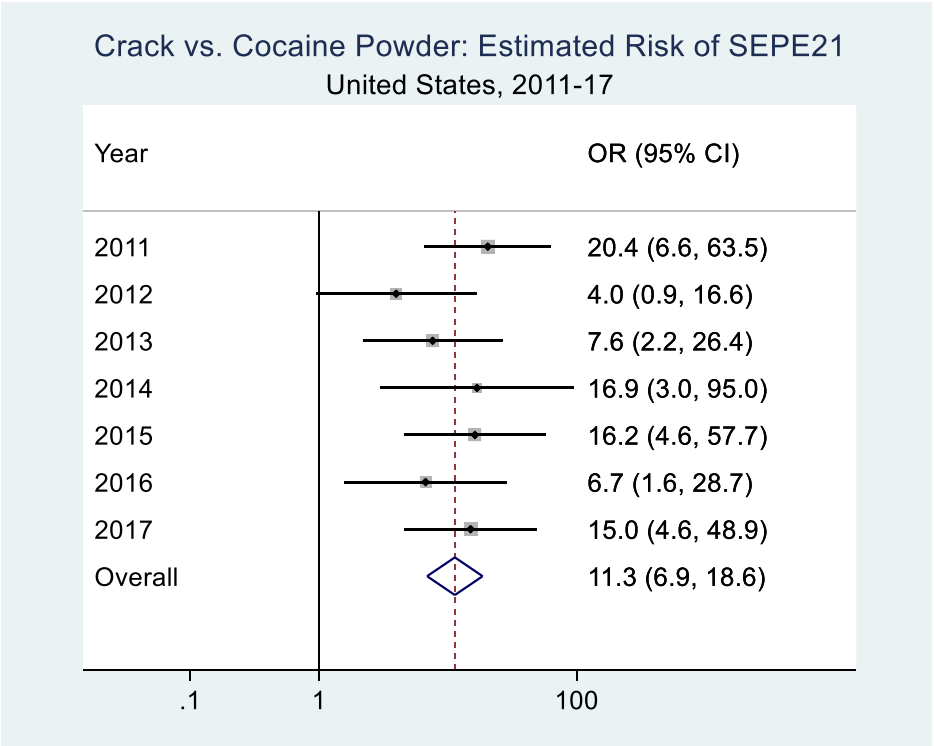

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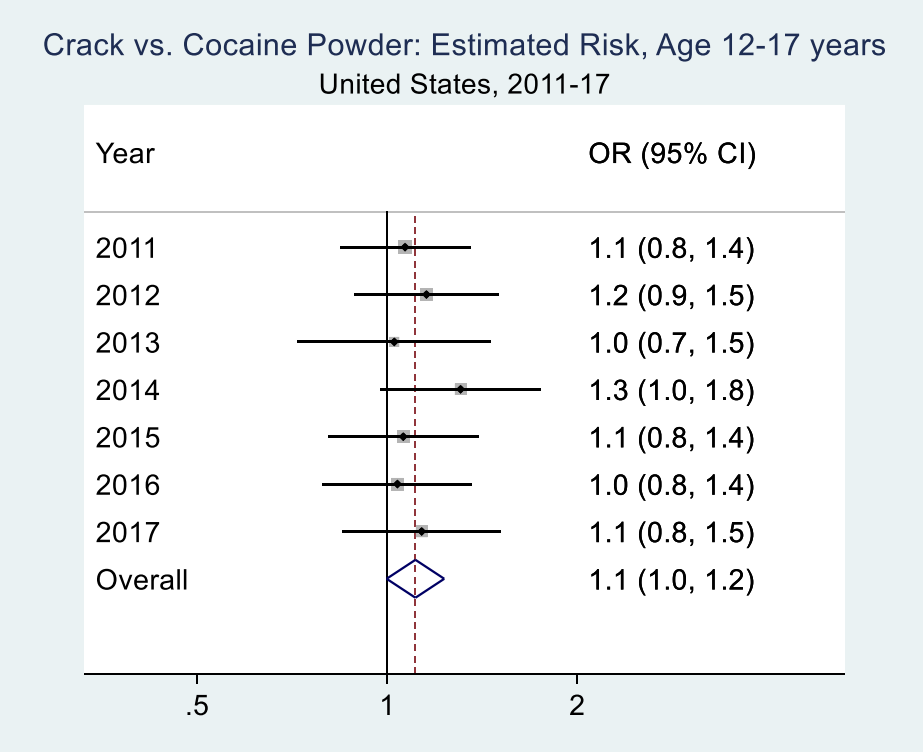

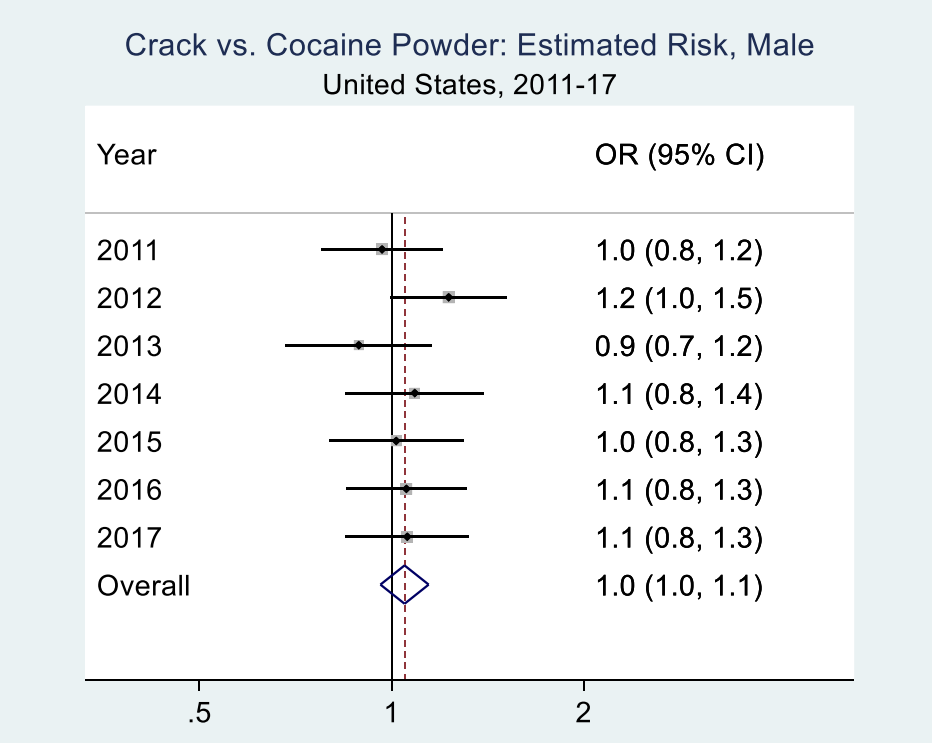

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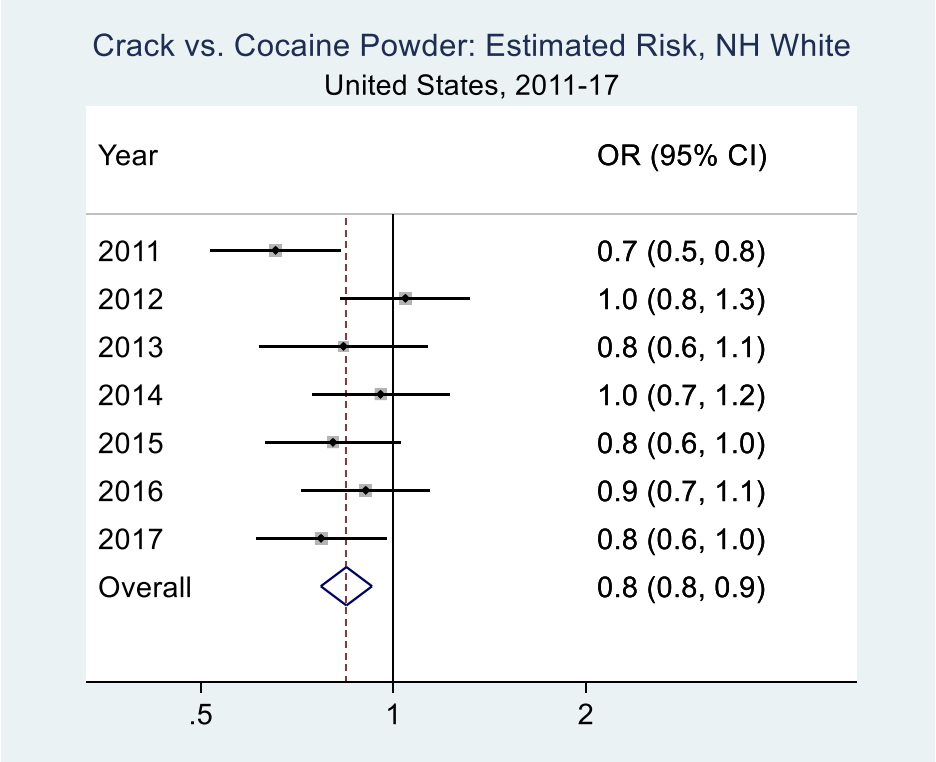

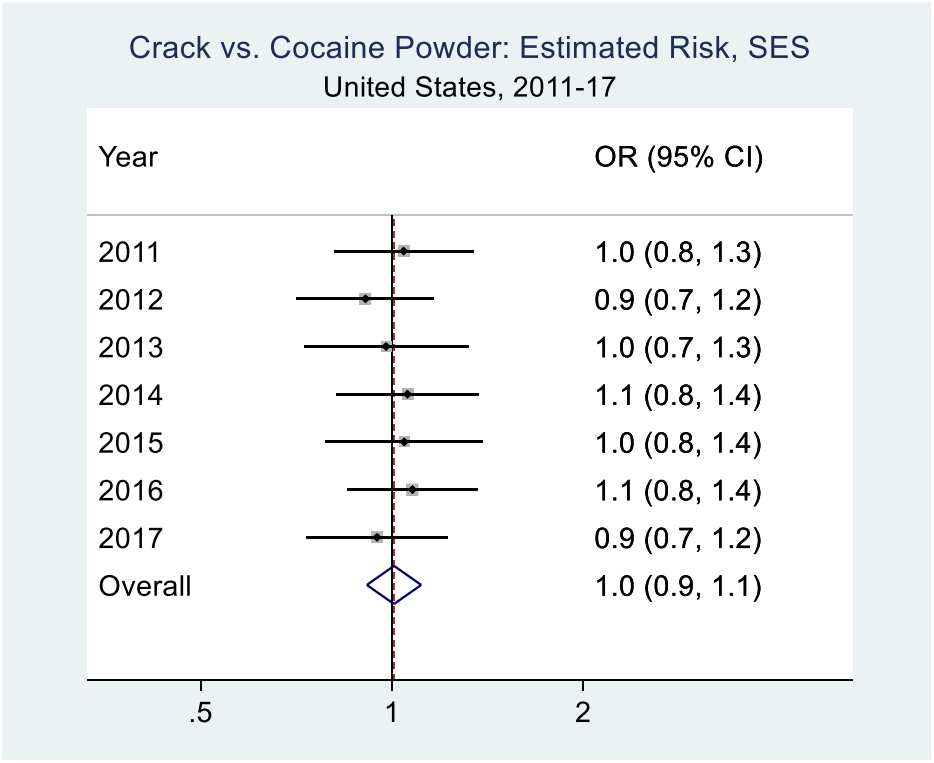

Appendix D

Manuscript 3

Table D1. Results of Patients under Oral Cocaine Agonist Treatment in Clinical Trials (1986-2006)

RESULTS OF 127 PATIENTS UNDER SUBSTITUTION THERAPY (COCALIZATION)

(Llosa T & Llosa LM 2006)

No.Sub	sex	drug	trial	oral coc dose	vehicle	time	r-avg(E)	r-avg(e)	year	Status
20	m	CCP	Open	20 mg	CCT	3 mo	12 .8 mo	4.8 mo	(1989)	Report
23	m	CCP	Open	17.7 mg	CCT	12 mo	4.35 mo	1.22 mo	(1994)	Published
8	m	CCP	Blind	60 mg	CCT-CT	5 wks	4.3 wk	0.7 wk	(1996)	Published
20	m	CCP	Open	60 mg	CT	3 mo	4.3 wk	0.3 wk	(1996)	Not published
20	m	CCP	Blind	20 mg	CT	4 wk	4.7 wk	1.18 wk	(2002)	Published
18	m	HCC	Open	100-300 mg	CCT	6 to 12 mo	3.0 wk	0.4 wk	(2003-05)	Not published
10	m	HCC	Open	100-500 mg	CCT	6 to 12 mo	2.7 wk	0.6 wk	(2004-05)	In review
8	m/f	HCC	Open	50-200 mg	CP	3 to 6 mo	3.3 wk	0.8 wk	(2006)	Published

CCP: coca paste HCC: hydrochloride cocaine CCT: coca tea CP: coca powder CT: coca tablets r-avg (E): relapse at entry (per week/ month) r-avg (e): relapse at end (per week/month) mo: month wk: week m: men f: female

Source: Table reproduced from Llosa, L. (2010). Brief review of oral cocaine for the treatment of cocaine dependence.

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BIBLIOGRAPHY

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