ABSTRACT

Title of Thesis: RISK FACTORS FOR NONMEDICAL
                               PRESCRIPTION ANALGESIC USE AMONG
                               COLLEGE STUDENTS: RESULTS OF A
                               PROSPECTIVE STUDY

                               Christine Kempsell Morioka, Master of Public
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Thesis Directed By: Associate Professor Donna Howard,
                               Department of Behavioral and Community
                               Health

Nonmedical Prescription Analgesic (NPA) use is a serious public health concern and studies on risk factors for NPA use are lacking. This investigation used preexisting data from a landmark longitudinal, prospective study of college students to examine relationship between four suspected risk factors and NPA use. The sample was comprised of 1,253 young adults originally recruited as first-year college students from a large, mid-Atlantic university. 10.5% (n=103) of the participants during year 3 of the study reported past year NPA use, of which 55.3% (n=57) were male and 81.6% (n=84) were white. Affective dysregulation and conduct problems were found to be significantly and longitudinally associated with incident NPA use after controlling for gender, parents' education, and race/ethnicity. Affective dysregulation and conduct disorder are longitudinally associated with NPA use among college students. These findings might aid in prevention efforts to reduce NPA use among college students.

**RISK FACTORS FOR NONMEDICAL PRESCRIPTION ANALGESIC USE
AMONG COLLEGE STUDENTS: RESULTS OF A PROSPECTIVE STUDY**

by

CHRISTINE KEMPSELL MORIOKA

Thesis submitted to the Faculty of the Graduate School of the
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Advisory Committee:
Associate Professor Donna Howard, Chair
Associate Professor Amelia Arria
Professor Min Qi Wang

Dedications

This thesis is dedicated to my husband, Travis, my parents, Mark and Susan, and to all the professors and mentors who have helped me get to this point in my academic career. Thank you all for your endless support, enthusiasm, and inspiration as I embark on a career in public health. This thesis is also dedicated to anyone who has been negatively affected by substance use—may this research aid in our understanding of how to prevent such problems in the future.

Acknowledgements

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Chapter 1: Overview of the Study

1.1 Introduction

Adequate pain control is a fundamental right of every patient and the

consequences of not treating pain are significant (e.g. maladaptive physiological,

psychological, family, and social consequences) (Brennan, Carr, & Cousins, 2007;

Rosenblum, Marsch, Joseph, & Portenoy, 2008). Prescription analgesics (i.e. prescription

pain relievers) are used in the treatment of pain. The increasing availability of

prescription analgesics for the treatment of pain has led to diversion of these medications

for nonmedical use (Blanco et al., 2013; Rosenblum et al., 2008). Nonmedical

prescription analgesic (NPA) use—defined as taking an analgesic prescription drug for

reasons or in ways or amounts not intended by a doctor, or taken by someone other than

the person for whom they are prescribed —has received significant public health

attention during the past decade, and is a concerning trend among college students

(Garnier et al., 2009; Zacny et al., 2003).

Data from the National Survey of Drug Use and Health (NSDUH) indicate that

NPA use is more common among young adults (18-25 years old) than for individuals

over 25 years old (12% versus 3% for past year use) (Substance Abuse and Mental

Health Services Administration, 2006). Among college students, estimates of past-year

NPA use range from 7% to 9%, with lifetime use ranging from 12% to 14% (McCabe,

Boyd, & Teter, 2006; McCabe, Teter, Boyd, Knight, & Wechsler, 2005).

Few risk factors for NPA use aside from demographic characteristics have been

identified. Younger age (18–25 vs. 35+ years old) (Back, Payne, Simpson, & Brady,

2010; Blanco et al., 2013), being white (Back et al., 2010; Blanco et al., 2013; McCabe et al., 2005), having more intense pain (Back et al., 2010; Blanco et al., 2013), mental health problems (Back et al., 2010; Blanco et al., 2013), and heavy use of alcohol and other illicit drugs (e.g. cocaine, ecstasy) (Back et al., 2010; McCabe et al., 2006) have all been found to be associated with nonmedical use of prescription analgesics. Several other risk factors have been suggested to play a role in NPA use including depressive symptoms (Grattan, Sullivan, Saunders, Campbell, & Von Korff, 2012; Nekovarova et al., 2014; Scherrer et al., 2014), affective dysregulation (Back et al., 2010), conduct problems (UNODC, 2011; Zullig & Divin, 2012) and general psychological health (Back et al., 2010; Zullig & Divin, 2012), but few studies have systematically investigated their impact among the college student population. This investigation aims to address this gap in the literature.

1.2 Research Questions and Hypotheses

Research Question 1: Is affective dysregulation associated with NPA use among college students?

> Hypothesis 1a: Higher levels of affective dysregulation will be observed in NPA users compared to non-users.
>
> Hypothesis 1b: Higher levels of affective dysregulation will be observed in NPA users compared to drug users with no NPA use.
>
> Hypothesis 1c: Higher levels of affective dysregulation will be observed in drug users with no NPA use compared to non-users.

Research Question 2: Are childhood conduct problems associated with NPA use among college students?

> Hypothesis 2a: Higher levels of childhood conduct problems will be observed in NPA users compared to non-users.
>
> Hypothesis 2b: Higher levels of childhood conduct problems will be observed in NPA users compared to drug users with no NPA use.
>
> Hypothesis 2c: Higher levels of childhood conduct problems will be observed in drug users with no NPA use compared to non-users.

Research Question 3: Are depressive symptoms associated with NPA use among college students?

> Hypothesis 3a: Higher levels of depressive symptoms will be observed in NPA users compared to non-users.
>
> Hypothesis 3b: Higher levels of depressive symptoms will be observed in NPA users compared to drug users with no NPA use.
>
> Hypothesis 3c: Higher levels of depressive symptoms will be observed in drug users with no NPA use compared to non-users.

Research Question 4: Is poor psychological health associated with NPA use among college students?

> Hypothesis 4a: Higher levels of poor psychological health will be observed in NPA users compared to non-users.
>
> Hypothesis 4b: Higher levels of poor psychological health will be observed in NPA users compared to drug users with no NPA use.

Hypothesis 4c: Higher levels of poor psychological health will be observed in drug users with no NPA use compared to non-users.

1.3 Definition of Terms

1.3.1 Definitions of the three mutually exclusive groups of interest

1. *NPA users:* Any participant who reports past-year (i.e. 12 months prior to data collection) history of nonmedical prescription analgesic use (see below).

2. *Illicit drug user without NPA use*: Any participant who reports past-year history of illicit or nonmedical drug use, other than nonmedical use of prescription analgesics (i.e. does not report nonmedical use of prescription drugs).

3. *Non-users*: Any participant who does not report past-year history of illicit or nonmedical drug use.

1.3.2 Definitions of all other terminology

- *Affective Dysregulation:* The degree to which individuals are unable to flexibly respond to and manage emotions (Carpenter & Trull, 2013).

- *Analgesic (i.e. pain reliever)*: A substance that reduces pain and may or may not have psychoactive properties (UNODC, 2003). A medicine that reduces or relieves headaches, sore muscles, arthritis, or other aches and pains. Comprises of approximately 30 separate pain relieving medications, including scheduled opioid analgesics (fentanyl, hydrocodone-combinations products, methadone, morphine, oxycodone, and oxycodone-combination products, and propoxyphene) and nonscheduled drugs such as tramadol ("MedlinePlus," 2015).

- *Conduct problems:* Behaviors that violate the rights of others (e.g., aggression, destruction of property) and/or that bring the individual into significant conflict

with societal norms or authority figures (*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, 2013).

- *Dependence*: The term was introduced in 1964 by a WHO Expert Committee to replace "addiction" and "habituation". "Drug dependence" comprises a cluster of physiological, behavioral and cognitive phenomena of variable intensity, in which the use of a psychoactive drug (or drugs) takes on a high priority. It implies a need for repeated doses of the drug to feel good or avoid feeling bad despite experiencing problems associated with drug use (UNODC, 2003).

- *Diversion*: transfer of any legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use (UNODC, 2003).

- *Illicit drug use:* The use of marijuana/hashish, cocaine (including crack), inhalants, hallucinogens, heroin, or prescription-type drugs (i.e. analgesics, tranquilizers, stimulants, or sedatives) nonmedically (Substance Abuse and Mental Health Services Administration, 2013a).

- *Nonmedical prescription analgesic use:* Taking a prescription analgesic drug for reasons, or in ways, or amounts not intended by a doctor, or taken by someone other than the person for whom they are prescribed (e.g. use without a prescription, too much or too little use). Nonmedical use of any prescription-type drug does not include over-the-counter drugs ("Prescription Drugs & Cold Medicines," 2014, UNODC, 2003).

- *Nonmedical prescription drug use*: Taking a drug for reasons or in ways or amounts not intended by a doctor, or taken by someone other than the person for

whom they are prescribed (e.g. use without a prescription, too much or too little use). Nonmedical use of any prescription-type drug does not include over-the-counter drugs ("Prescription Drugs & Cold Medicines," 2014, UNODC, 2003).

- *Opioid*: A generic term applied to opiates and their synthetic analogues, with actions similar to those of morphine, in particular the capacity to relieve pain (UNODC, 2003).

- *Overdose*: The use of any drug in such an amount that acute adverse physical or mental effects are produced (UNODC, 2003).

- *Depressive symptoms:* Screen "high" for depressive symptoms on a validated and reliable scale for measuring depressive symptoms (e.g. Beck Depression Inventory, Center for Epidemiologic Studies Depression scale)

- *Prescription medications:* Pharmaceuticals dispensed by a pharmacist on the presentation of a prescription written by a physician, dentist, or other health care provider who is legally authorized to write prescriptions (Lessenger & Feinberg, 2008).

1.4 Public Health Significance

NPA use is associated with a myriad of negative health consequences including injection drug use, drug dependence, and fatal overdose (McCabe et al., 2005; Schrager et al., 2014). Prescription analgesic overdose rates continue to steadily increase. In 2010, there were 13,652 unintentional deaths from opioid analgesics, the most common type of prescription analgesic (82.8% of the 16,490 unintentional deaths from all prescription drugs) (Volkow, 2014), and there was a five-fold increase in treatment admissions for prescription analgesics between 2001 and 2011 (from 35,648 to 180,708, respectively)

(Substance Abuse and Mental Health Services Administration, 2013b). In the same decade, there was a tripling of the prevalence of positive opioid analgesic (a common type of prescription analgesic) tests among drivers who died within one hour of a crash (Volkow, 2014).

National prevalence estimates demonstrate that illicit drug use is most prevalent among the young adult (aged 18-25) age category. In 2008, current use of illicit drugs (19.6%) was higher among young adults aged 18 to 25 than for youths aged 12 to 17 (9.3%) and adults aged 26 or older (5.9%) (Substance Abuse and Mental Health Services Administration, 2009). Furthermore, nonmedical prescription analgesic (NPA) use is the second most common type of illicit drug use (Substance Abuse and Mental Health Services Administration, 2015a). According the most recent national surveillance data, an estimated 978,000 young adults aged 18 to 25 were current nonmedical users of analgesics in 2014, which represents 2.8% of young adults (Substance Abuse and Mental Health Services Administration, 2015a).

NPA use among young adults is a growing public health concern and additional research on the risk factors leading to NPA use among college students is needed. This novel study aims to examine several potential correlates of NPA use among a college student population.

Chapter 2: Literature Review

2.1 Prevalence of Drug Use

2.1.1 Prevalence of Illicit Drug Use

Illicit drug use is defined as the use of marijuana/hashish, cocaine (including crack), inhalants, hallucinogens, heroin, or prescription-type drugs (i.e. pain relievers, tranquilizers, stimulants, or sedatives) nonmedically (Substance Abuse and Mental Health Services Administration, 2013a). According to the latest national surveillance data on drug use (Substance Abuse and Mental Health Services Administration, 2015a), 27.0 million individuals aged 12 or older used an illicit drug in the past 30 days, which corresponds to about 1 in 10 Americans (10.2%). The illicit drug use estimate for 2014 is driven primarily by marijuana use and the nonmedical use of prescription pain relievers, with 22.2 million current marijuana users aged 12 or older (i.e. users in the past 30 days) and 4.3 million people aged 12 or older using prescription analgesics nonmedically (Substance Abuse and Mental Health Services Administration, 2015a).

In 2013, 22.3 % of full-time college students aged 18 to 22 years old used an illicit drug. This was similar to the rate among other persons aged 18 to 22 years old (23%), which included part-time college students, students in other grades or types of institutions, and nonstudents. Male (26.0%) college students were more likely to use drugs compared to females (19.2%). With respect to race/ethnicity, whites were the highest (25.1%), followed by Hispanics (21.5%), blacks (19.7%), and Asians (9.4%) (Substance Abuse and Mental Health Services Administration, 2013a).

2.1.2 Prevalence of NPA Use Among College Students

Nonmedical prescription analgesic (NPA) use is the second most common type of illicit drug use (Substance Abuse and Mental Health Services Administration, 2015a). According the most recently reported national surveillance data, an estimated 978,000 young adults aged 18 to 25 were current nonmedical users of analgesics in 2014, which represents 2.8% of young adults (Substance Abuse and Mental Health Services Administration, 2015a).

Data on the prevalence of NPA use at individual colleges or universities remains very limited (McCabe et al., 2005). McCabe et al estimated that the lifetime prevalence of nonmedical prescription opioid use was 12% and the past year prevalence was 7% among a nationally representative sample of college students. Approximately one in every four colleges had a prevalence of 10% or higher for past year nonmedical use of prescription opioids (McCabe et al., 2005). The Monitoring the Future (MTF) study—an ongoing study of the behaviors, attitudes, and values of American secondary school students, college students, and young adults—reported that 10% of college students had used Vicodin and 2% had used OxyContin (commonly used prescription analgesics) nonmedically within the past year (Johnston, O'Malley, Bachman, & Schulenberg, 2006).

2.2 Correlates of NPA Use

Limited epidemiological research exists that accurately assesses the characteristics of those subpopulations among college students most at risk for nonmedical use of prescription opioid analgesics (McCabe et al., 2005; Zacny et al., 2003). The information below summarizes what is currently known about correlates for

adolescent and young adult NPA use including demographic characteristics, developmental maturity, drug accessibility, social acceptability, and psychological factors.

2.2.1 Demographic Characteristics

2.2.1.1 Age

Data from the National Survey of Drug Use and Health (NSDUH) indicate that nonmedical use of prescription analgesics is more common among young adults (18-25 years old) than older individuals (Substance Abuse and Mental Health Services Administration, 2015b). Research has also shown that the key risk periods for drug abuse are during major transitions in a young person's life. When young adults leave home for college or work and are on their own for the first time, their risk for drug and alcohol abuse can be very high (NIDA, 2003).

2.2.1.2 Race/Ethnicity

Nationally, nonmedical pain reliever use is least common among Asian Americans (1.8 %) (Substance Abuse and Mental Health Services Administration, 2015b). The rate of nonmedical use of prescription pain relievers among Asian Americans was lower than rates for whites (4.3 %), blacks (3.6 %), American Indian or Alaska Natives (6.9 %), two or more races (8.1 %), or Hispanics (4.5 %). Native Hawaiians or other Pacific Islanders do not have the same low prevalence of nonmedical use of prescription pain relievers as the Asian community although they are often grouped together. Past year nonmedical use of prescription pain relievers among Native Hawaiians or other Pacific Islanders (3.9 %) did not differ from the national average or

the other race/ethnic groups (Substance Abuse and Mental Health Services Administration, 2015b). Among college students, NPA use is most common among whites (McCabe et al., 2005).

2.2.2 Developmental Maturity and Conduct Problems

NPA use among college students might also be related to incomplete developmental maturity. The past part of the brain to fully mature is the prefrontal cortex, a region that governs judgment and decision-making functions (Compton & Volkow, 2006). The prefrontal cortex is still developing in most college-aged individuals, which can have a profound effect on their decision to experiment with alcohol and drugs. High rates of risky behavior, including using alcohol and other drugs, is common among nonmedical prescription drug users (McCabe et al., 2005; UNODC, 2011).

This lack of developmental maturity might also help to explain why college students are prone to conduct problems. The association between early conduct problems and substance use is well documented (Boyle et al., 1993; Brook, whiteman, Cohen, & Tanaka, 1992; Falls et al., 2011; Johnson, Arria, Borges, Ialongo, & Anthony, 1995; Nurco, Blatchley, Hanlon, & O'Grady, 1999), however, the association between conduct problems and NPA use in a college student population has never been previously examined.

2.2.3 Drug Accessibility and Social Acceptability

Drug accessibility has been correlated with NPA use. There are more young people being prescribed analgesics than was the case 15 years ago (Fortuna, Robbins, Caiola, Joynt, & Halterman, 2010) and due to a greater volume of drugs in circulation,

the opportunity for nonmedical use and diversion (i.e. transfer of any legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use) has increased. National data indicates that prescription drugs that are used for nonmedical purposes are typically obtained from a family member or a friend who has had a prescription from a doctor (Substance Abuse and Mental Health Services Administration, 2014). The concept of social acceptability has also been correlated with NPA use. There is a trending belief—especially among adolescents and young adults—that prescription drugs are safer than the common illicit drugs or "street drugs" (U.S. Food and Drug Administration, 2010), because they are prescribed by health professionals, can be purchased from pharmacies, are often used by family members or friends (Compton & Volkow, 2006), and information about their effects is widely available in package inserts and advertisements, and on the internet (UNODC, 2011).

2.2.4 Psychological Factors

The psychosocial changes experienced during the transition years of college may leave students highly stressed, depressed, or anxious (Zullig & Divin, 2012). Prescription analgesics elevate levels of the neurotransmitter dopamine, which is linked with pleasurable experiences and individuals might use analgesics to achieve a euphoric high (National Institute on Drug Abuse, 2010). The physiological and psychological effects of NPA use may offer a means to get high, thereby regulating the feelings of distress and/or achieving emotional stability (Zullig & Divin, 2012). It has been previously shown that those who suffer from mental illness or psychological distress often self-medicate with alcohol or drugs as an inappropriate coping mechanism (Cicero, Lynskey, Todorov,

Inciardi, & Surratt, 2008; Sullivan, Edlund MJ, Zhang L, Unützer J, & Wells KB, 2006; Zullig & Divin, 2012).

A growing amount of research suggests that one of the primary motives for NPA use among college students is as a form of self-medication, self-treatment, or 'non-deviant coping' for psychological distress, depression, or other mental health disorders (Carol J Boyd, 2009; Sean Esteban McCabe, 2009). The association between general psychological health and initiation and use of prescribed opioids in the general population has been suggested previously (Sullivan et al., 2006). Furthermore, several studies among the general population have demonstrated an association between individuals suffering from mood or anxiety disorders and subsequent NPA use, especially among females (Back et al., 2010; Wu, Woody, Yang, & Blazer, 2010).

Most of the research linking mental health problems to analgesic use is limited to studies involving patients with chronic pain (Scherrer et al., 2014). Cross sectional studies have shown that patients with mental health problems compared with those without, are more likely to receive prescription analgesics (Seal et al., 2012; Sullivan et al., 2006), use prescription analgesics for longer periods of time (Braden et al., 2009; Psaty et al., 1999), use higher daily morphine equivalent doses (Merrill et al., 2012), and use prescription opioids nonmedically (Seal et al., 2012). Grattan et al (2013) examined the association between depression and opioid misuse in patients receiving chronic opioid therapy (COT) who had no history of substance abuse (Grattan et al., 2012). Patients (N=1334) on COT for non-cancer pain (i.e. pain that is not derived from cancer or cancer treatment) who had no history of substance abuse were asked about 3 forms of opioid misuse (self-medicating for symptoms other than pain; self-increasing doses; giving to or

getting opioids from others) and evaluated for depression by the 8-item Patient Health

Questionnaire (PHQ-8). It was shown that in patients with no substance abuse history,

depressive symptoms were associated with increased risk of some forms of opioid

misuse. The authors concluded that clinicians should be alert to the risk of misuse that

depressive symptoms pose for patients who are being prescribed analgesics (Grattan et

al., 2012).

Only one longitudinal study examines the relationship between depression and

nonmedical analgesic use. Sullivan et al (2006) performed an analysis of longitudinal

data from 6439 participants in the 1998 and 2001 waves of Healthcare for Communities,

a nationally representative telephone community survey (Sullivan et al., 2006). In a

community cohort they found that participants who had a psychiatric illness, including

depression, were twice as likely to use analgesics nonmedically 3 years later compared to

participants who were free of a diagnosis at baseline. The authors concluded that

common mental health disorders and problem drug use are associated with initiation and

use of prescribed opioids in the general population (Sullivan et al., 2006).

2.3 Consequences of NPA Use

2.3.1 Burden on Individual Health

The nonmedical use of prescription analgesics may result in serious medical

consequences such as respiratory depression (i.e. hypoventilation, slowed breathing),

coma, and death (McCabe et al., 2005). Cardiovascular disease (Qureshi WT, O'Neal

WT, Khodneva Y, & et al, 2015) stroke (Esse, Fossati-Bellani, Traylor, & Martin-Schild,

2011), cancer (Cronin-Fenton et al., 2015), infection with the human immunodeficiency

virus (HIV) (NIDA, 2012; Partanen, Vikatmaa, Tukiainen, Lepäntalo, & Vuola, 2009),

and hepatitis (NIDA, 2013) have also been associated with NPA use in various populations. Some of the negative health effects occur when drugs are used at high doses or after prolonged use. However, other adverse effects can occur after only one or a few occasions of use. ("Prevention of Substance Abuse and Mental Illness," 2014; Substance Abuse and Mental Health Services Administration, 2015a). A large single dose of an opioid could cause severe respiratory depression that can lead to death, while long-term use can lead to physical dependence and/or addiction (NIDA, 2014).

NPA use may also result in numerous behavioral consequences such as dependence and depression (Ali et al., 2015). Persons who report using controlled prescription analgesics nonmedically also report experiencing emotional or mental health problems that were caused or worsened by their abuse of the drugs (UNODC, 2011). Chronic NPA use has been associated with subsequent mental health problems in several cross-sectional studies (Grattan et al., 2012; Seal et al., 2012; Sullivan et al., 2006) and one longitudinal study (Scherrer et al., 2014). Additionally, persons who begin using prescription drugs nonmedically early in their youth (13 or younger) are more likely to be diagnosed as having lifetime dependence. One study showed that an estimated 42% of those who reported having started to use prescription drugs nonmedically at age of 13 or younger went on to develop prescription drug abuse (DSM-IV criteria) (McCabe, West, & Wechsler, 2007).

2.3.2 Burden on the U.S. Health System

Nonmedical prescription drug use has also placed a significant burden on the United States health system. Persons who use analgesics nonmedically are more likely to utilize medical services, such as the emergency department, physician outpatient visits,

and inpatient hospital stays (Meyer, Patel, Rattana, Quock, & Mody, 2014).

Additionally, for individuals with both private and government sponsored insurance (e.g. Medicaid), health care costs are greater for those who use prescription analgesics nonmedically compared to those who do not (Meyer et al., 2014). National surveillance data demonstrate that the number of young adults (aged 18-25) seen in an emergency department for the use of prescription drugs nonmedically has been increasing in recent years (Substance Abuse and Mental Health Services Administration, 2014). Many of these emergency room visits are related to drug poisoning or drug overdose. According to national surveillance data, opioid analgesics were involved in 37% of drug poisoning deaths in 2013 (16,235 out of 43,982 deaths) (National Center for Health Statistics, 2013).

2.3.3 Burden on Society

Significant monetary costs are associated with prevention of nonmedical use, treatment programs for misusers, decreased economic productivity, and the indirect effect on access to appropriate health care (Gilson & Kreis, 2009). It has been estimated that the direct costs of health care for people who use opioids for nonmedical purposes alone are more than eight times those who do not use them for nonmedical purposes (Meyer et al., 2014). Addressing the impact of substance use alone is estimated to cost Americans more than $600 billion each year (Substance Abuse and Mental Health Services Administration, 2015a) and societal costs attributable specifically to prescription opioid abuse are estimated at $55.7 billion (Birnbaum et al., 2011). Of this amount, 46% was attributable to workplace costs (e.g., lost productivity), 45% to healthcare costs (e.g.,

abuse treatment), and 9% to criminal justice costs (Birnbaum et al., 2011; U.S. Department of Health and Human Services, 2013).

Nonmedical use of prescription drugs has also been associated with crime. Property crime, drug dealing, violence, intoxicated driving, uninhibited and aggressive behavior have been attributed in particular to the nonmedical use of prescription medications in various populations (NDLERF, 2015). Furthermore, the demand created by the nonmedical use of prescription drugs has resulted in the formation of an illicit supply chain for prescription drugs (UNODC, 2011). Prescription shopping (i.e. when someone deliberately gets more medicine than they need), pharmacy thefts, and diversion from holders of legal prescriptions (i.e. obtaining drugs from someone who holds a legal prescription) (NDLERF, 2015).

2.4 Summary

In conclusion, nonmedical drug use remains a behavioral health problem among college students. Nationally, NPA use remains the second most common type of illicit drug use after marijuana use. The consequences of NPA use are severe and place a burden on the health of the individual, the U.S. medical system, and our society as a whole. Despite the severity of the problem, limited data exists on the risk factors associated with NPA use among college students. A growing amount of research suggests that one of the primary motives for NPA use among college students is as a form of self-medication or self-treatment for psychological distress, depression, or other mental health disorders. This study aims to examine the relationship between mental health— specifically depressive symptoms, affective dysregulation, conduct problems, and general psychological health—and NPA use in a large sample of college students.

Chapter 3: Manuscript

Note: The document below contains the entire manuscript (draft) to be submitted to the journal *Addictive Behaviors*.

Risk Factors for Nonmedical Prescription Analgesic use Among College Students:

Results of a Prospective Study (DRAFT)

Christine K. Morioka[1*]

Donna E. Howard, DrPH[1]

Kimberly Caldeira, MS[2]

Min Qi Wang, PhD[1]

Amelia Arria, PhD[2]

[1]Department of Behavioral and Community Health, School of Public Health, University of Maryland, College Park

[2] Center on Young Adult Health and Development, Department of Behavioral and Community Health, School of Public Health, University of Maryland, College Park

[*]Corresponding Author: Christine K. Morioka, MPH Graduate Student, Department of Behavioral and Community Health, School of Public Health, University of Maryland, College Park, Phone: 949-636-1041; christine.morioka@gmail.com

Running Head: Risk Factors of NPA Use Among College Students

ABSTRACT

1. Abstract

Purpose—Nonmedical Prescription Analgesic (NPA) use is a serious public health concern and studies on risk factors for NPA use are lacking. This investigation used preexisting data from a landmark longitudinal, prospective study of college students, the *College Life Study* (CLS), to examine the longitudinal relationship between four suspected risk factors—affective dysregulation, conduct problems, depressive symptoms, and general psychological health—and NPA use.

Methods—The sample was comprised of 1,253 young adults originally recruited as first-year college students from a large, mid-Atlantic university.

Results—10.5% (n=103) of the participants during year 3 of the study reported past year NPA use, of which 55.3% (n=57) were male and 81.6% (n=84) were white. Affective dysregulation and conduct problems were found to be significantly and longitudinally (baseline to year 3) associated with incident NPA use after controlling for gender, parents' education, and race/ethnicity.

Conclusions—Affective dysregulation and conduct disorder are longitudinally associated with NPA use among college students. These findings might aid in prevention efforts to reduce NPA use among college students.

1. INTRODUCTION

Pain control is a fundamental right of every patient and the consequences of not treating pain are significant (e.g. maladaptive physiological, psychological, family, and social consequences) (Brennan et al., 2007; Rosenblum et al., 2008). Prescription analgesics (e.g. opioid-containing pain relievers) are often used in the treatment of pain. The increasing availability of prescription analgesics for the treatment of pain along with their addictive properties have led to diversion (i.e. illegal distribution) of these medications for nonmedical use (Blanco et al., 2013; Rosenblum et al., 2008). Nonmedical prescription analgesic (NPA) use—defined as taking a prescription analgesic drug for reasons or in ways or amounts not intended by a doctor, or taken by someone other than the person for whom they were prescribed —has received significant public health attention during the past decade and is a concerning trend among college students (Garnier et al., 2009; Zacny et al., 2003). Data from the National Survey of Drug Use and Health (NSDUH) indicate that NPA use is more common among young adults (18-25 years old) than for individuals over 25 (12% versus 3% for past year use) (Substance Abuse and Mental Health Services Administration, 2006). Among college students, estimates of past-year NPA use range from 7-9%, with lifetime use ranging from 12-14% (McCabe et al., 2006, 2005).

The consequences of NPA use are severe and place a burden on the health of the individual, families and healthcare systems. NPA use can result in serious medical consequences such as respiratory depression (i.e. hypoventilation), coma, and death (McCabe et al., 2005). Cardiovascular disease (Qureshi WT et al., 2015), stroke (Esse et al., 2011), cancer (Cronin-Fenton et al., 2015), infection with the human

immunodeficiency virus (HIV) (NIDA, 2012; Partanen et al., 2009), and hepatitis (NIDA, 2013) have also been associated with NPA use in various populations. NPA users also report experiencing emotional or mental health problems that were caused or worsened by their abuse of the drugs (UNODC, 2011). Additionally, persons who use analgesics nonmedically are more likely to utilize medical services, such as the emergency department, physician outpatient visits, and inpatient hospital stays (Meyer et al., 2014). Estimates suggest that the direct costs of health care for people who use opioid prescription painkillers solely for nonmedical purposes are more than eight times higher than those who use opioids strictly for medical purposes (Meyer et al., 2014). Addressing the impact of substance use alone is estimated to cost Americans more than $600 billion each year (Substance Abuse and Mental Health Services Administration, 2015a). Costs attributable specifically to prescription opioid abuse are estimated at $55.7 billion (Birnbaum et al., 2011), of which 46% is attributable to workplace costs (e.g., lost productivity), 45% to healthcare costs (e.g., abuse treatment), and 9% to criminal justice costs (Birnbaum et al., 2011; U.S. Department of Health and Human Services, 2013).

The prevention of NPA use presents a significant challenge to physicians and health care providers, and there is a critical need to better understand factors involved in susceptibility (Back et al., 2010); however, limited epidemiological research exists that accurately characterizes subpopulations among college students most at risk for NPA use (Brennan et al., 2007; Rosenblum et al., 2008). Demographically, younger age (18–25 vs. 35+ years old) (Back et al., 2010; Blanco et al., 2013) and white race (Back et al., 2010; Blanco et al., 2013; McCabe et al., 2005) have been previously associated with NPA use. Other correlates include heavy use of alcohol and other illicit drugs (e.g. cocaine, ecstasy)

(Back et al., 2010; McCabe et al., 2006) as well as mental health problems (Back et al., 2010; Blanco et al., 2013).

To further investigate the role of mental health problems and NPA use, the current study used a large sample of college students to examine several suspected risk factors of NPA use—affective dysregulation, conduct problems, depressive symptoms and general psychological health. A growing amount of research suggests that one of the primary motives for NPA use among college students is self-treatment, or 'non-deviant coping' for psychological distress (Sullivan et al., 2006), depression, or other mental health disorders (Carol J Boyd, 2009; Sean Esteban McCabe, 2009). Patients with mental health problems, compared to those without, are more likely to receive prescription analgesics (Seal et al., 2012; Sullivan et al., 2006), use prescription analgesics for longer periods of time (Braden et al., 2009; Psaty et al., 1999), use higher daily morphine equivalent doses (Merrill et al., 2012), and use prescription opioids nonmedically (Seal et al., 2012).

Affective dysregulation, a deficiency in the capacity to modulate affect such that emotions become uncontrolled, expressed in intense and unmodified forms, and overwhelm reasoning (Carpenter & Trull, 2013; van Dijke et al., 2011), is of particular interest in this investigation. Problems with affective dysregulation are characterized by heightened emotional reactivity, violent outbursts, reckless or self-destructive behavior, or a tendency towards experiencing prolonged dissociative states when under stress (Ford & Courtosis, 2014). Additionally, there may be emotional numbing and a lack of ability to experience pleasure or positive emotions (Ford & Courtosis, 2014). Several cross sectional studies among the general population have demonstrated an association between individuals suffering from temperament problems and subsequent NPA use, with a strong

association found among females (Back et al., 2010; Wu et al., 2010), so the argument could be made that NPA use is a form of self-treatment or coping for individuals who are not able to properly manage or deal with their emotions. This investigation aims to expand on the limited literature on this topic to specifically examine the longitudinal relationship between affective dysregulation and NPA use.

The relationship between conduct problems and NPA use is also of particular interest in this investigation. Conduct problems, or behaviors that violate the rights of others (e.g., aggression, destruction of property) and/or that bring the individual into significant conflict with societal norms or authority figures (*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, 2013). The association between early conduct problems and substance use (e.g. alcohol abuse) is well documented (Boyle et al., 1993; Brook et al., 1992; Falls et al., 2011; Johnson et al., 1995; Nurco et al., 1999), however, the association between conduct problems and NPA use in a college student population has never been previously examined.

In summary, this study aims to examine the longitudinal relationship between several suspected risk factors and NPA use in a large sample of college students. It is hypothesized that higher levels of all suspected risk factors—affective dysregulation, conduct problems, depressive symptoms, and general psychological health—will be observed in NPA users compared to both illicit drug users without NPA use and non-users.

2. METHODS

2.1. Study Design

Data for this study were drawn from a longitudinal, prospective study of college students, the *College Life Study* (CLS), which was launched in 2004 (Arria et al., 2008). The CLS sample was derived from a cohort of incoming first-year students recruited from one large public university in the mid-Atlantic region. Participants were recruited in two stages. First, all incoming first-time matriculating, first-year students who were between 17 and 19 years old were invited to complete a brief survey (primarily administered online, but paper versions were also available) during new student orientation in the summer of 2004 (*N*=3,401). University records indicate that approximately 90% of incoming students attend orientation; however, incoming students who did not attend orientation were invited to participate in the screening survey via U.S. Mail. The response rate was 89% for the survey.

Next, a stratified random sample of stage one respondents was selected for participation in the longitudinal study, beginning with a two-hour, face-to-face interview administered sometime during their first year of college (*N*=1,253) from 2004-2005. The interview response rate was 86%. Over-sampling was used to obtain a disproportionate number of students who had used an illicit drug at least once during high school, based on their initial survey. The sample was demographically representative of the entire first-year class of students.

Follow-up assessments were conducted annually for eight years after the year 1 baseline assessment, and consisted of a 2-hour personal interview and self-administered

questionnaires covering a broad range of topics (e.g. Drug use patterns, mental health). Follow-up participation exceeded 87% of the original sample every year thereafter.

The CLS was reviewed and approved by the university's Institutional Review Board (IRB). Informed consent was obtained for participation in all waves of data collection, and a federal Certificate of Confidentiality was also attained. Respondents received $5 for participating in the screener survey and $50 for completing each annual interview. Additional information on the CLS study design is available elsewhere (Arria et al., 2008; Vincent et al., 2012).

2.2. Sample

The current analysis used data from the first (Year 1= Y_1) and third (Year 3= Y_3) annual assessments (N=1253, response rate=86%, n=1101, response rate=88%, respectively). The Y_3 data was specifically selected for this analysis because the prevalence of NPA use (14.3%) peaked in Y_3.

2.3. Measures

2.3.1. Nonmedical Prescription Analgesics Use

Data on nonmedical prescription analgesic (NPA) use was collected during the annual interview. The NPA use questions were adapted from the questions asked in the 2002 NSDUH (Substance Abuse and Mental Health Services Administration, 2003). The interviewer provided the definition of nonmedical use and presented cards with the names and color photos of various pills. Interviewers explained that nonmedical use involved taking any medication "that was not prescribed for you or that you took only for the experience or feeling they caused," excluding any over-the-counter medications. Students

were asked the number of occasions they had used prescription analgesic for nonmedical reasons in the past 12 months and in the past 30 days. Each type of drug (Vicodin®, OxyContin®, Percocet®, Codeine®, Other) was dichotomized as "ever" versus "never" use.

2.3.2. Conduct Problems

The College Early Conduct Problems Index (CECPI) was used to measure conduct problems (Falls et al., 2011). The self-administered survey asked about 16 behaviors corresponding to the DSM-IV criteria for conduct disorder (*DSM IV*, 2000). Respondents were asked to indicate the frequency of the behavior problem in the past 12 months. The scoring rules—indicating a high likelihood of conduct disorder—require responses of "*three or more times*" in the past year for the following problem behaviors (i.e. if the respondent answered "*three or more times*" for any or all of the following problem behaviors, conduct disorder is present) (Johnson et al., 1995): "took property belonging to others," "damaged other people's property on purpose," "lied," "started physical fight with other youths," and "broke rules." The scoring rules require a response of "*two or more times*" in the past year for the following behaviors: "hurt others physically," "skipped school," "ran away from home overnight," "used a weapon in a fight," "broke into someone's house, building, or car," and "set fires."

2.3.2. Mental Health

Depressive symptoms were measured using the Beck Depression Inventory (BDI) (A. T. Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977). The BDI and CES-D are valid and reliable screening instruments to measure depressive symptoms (A. T.

Beck, Steer, & Carbin, 1988; Besier, Goldbeck, & Keller, 2008; Knight, Williams,

McGee, & Olaman, 1997). The BDI and CES-D were used in the analyses as continuous

variables.

General psychological health was measured using the 12-item General Health

Questionnaire (GHQ-12), which was interview-administered. Scoring was based on the

3-point Likert Scale method (Kelly & Watson, 2014) and the sum of all 12 items were

calculated for a possible total range of 0 to 36 (Goldberg & Williams, 1988). The GHQ-

12 was used in the analyses as a continuous variable.

2.3.3. Affective Dysregulation

Affective dysregulation was measured using the affective subscale (DI-A) from

the Dysregulation Inventory (DI). The DI (Mezzich, Tarter, & Kirisci, 2001) is a 92-item

self-administered questionnaire that measures aspects of temperament and behavior

(Clark, Cornelius, Kirisci, & Tarter, 2005). Higher scores on the affective subscale

indicate high emotional reactivity and low control over one's emotional state (Wilcox et

al., 2010). For each item, participants were asked to read a statement and indicate how

well it described their own behaviors and experiences, with response options of "never

true," "occasionally true," "mostly true," and "always true." Items scores were summed

to compute the affective subscale. Reliability for the DI-A was high in the sample

(Cronbach's $\alpha = 0.89$). The DI-A was operationalized as a continuous variable.

2.3.4. Other Covariates

The following demographic characteristics were collected during the baseline

assessment (Y_1): race/ethnicity (self-reported), age (self-reported), and gender

(observation). The mean adjusted gross income (AGI), in thousands, of each student's

self-reported home zip code from the year prior to enrollment (2003) was used as a proxy for the family of origin's household income. Mother's and father's education level was self-reported and a combined variable was created to reflect the highest level of education attained by either parent.

2.4. Statistical Analyses

Three mutually exclusive groups were created: (1) NPA use (i.e. any participant who reported past-year nonmedical use of prescription analgesics); (2) illicit drug use without NPA use (i.e. past-year illicit or nonmedical drug use, other than nonmedical use of prescription analgesics); (3) no illicit drug use (i.e. no past-year illicit or nonmedical drug use). Bivariate analyses were performed to understand the relationship between each of the four suspect risk factors and NPA use, after adjusting for demographic characteristics.

Multivariate associations were examined using logistic regression. Three binary regression models were developed to determine the association between incident self-reported drug-use (NPA use; illicit drug use without NPA use; no illicit drug use) and each of suspected risk factors (i.e. affective dysregulation, conduct problems, general psychological health, depressive symptoms) when controlling for demographic characteristics (i.e. gender, mother/father education, race/ethnicity, and SES). Y_1 data was used for the independent variables (i.e. suspected risk factors) and Y_3 data was used for the dependent variables (i.e. drug use groups). Baseline NPA users (Y_1) were excluded from the analyses in order to capture only incident NPA Y_3 users.

The multivariate model was built by entering the predictor variables into the logistic regression model one at a time in the following order: depressive symptoms

(BDI, CES-D), affective dysregulation (DI-A), general psychological health (GHQ), and conduct problems (CECPI). Significant predictor variables were kept in the model and non-significant predictors variables were removed. The final model included predictor variables that were significantly ($p<0.05$) associated with the outcome variable (affective dysregulation, conduct disorder) in addition to one measure of depressive symptoms (BDI) in order to account for any relationship between depressive symptoms and affective dysregulation. Because BDI was significantly ($p<0.01$) correlated with the CES-D (.783) and the GHQ (.683), it was determined that both CES-D and GHQ were unnecessary to include in the final model. Furthermore, parent's education was significantly correlated ($p<0.01$) with AGI, so AGI was not included in the final model.

3. RESULTS

Table 1 describes the sample characteristics and compares the demographic characteristics between the three groups of interest. Approximately half of the sample was female (54.0%) and almost three quarters was white (71.1%). The prevalence of past-year NPA use was 10.5%. The prevalence of past-year non-prescription analgesic illicit drug use was 50.1%. The prevalence of no illicit drug use was 39.5%.

The results of the bivariate and multivariate logistic regression models are presented in **Table 2**. At the bivariate level, all suspected risk factors were positively associated with NPA use when compared to both other illicit drug use without NPA use and no drug use. Conduct problems was the only suspected risk factor significantly associated with illicit drug use without NPA use when compared to no illicit drug use.

At the multivariate level, in the model comparing the *NPA Use* group to the *Other Illicit Drug Use without NPA Use* group, affective dysregulation (p<0.01, AOR=1.041) was positively associated with NPA use. In the model comparing the *NPA Use* group to the *No Illicit Drug Use* group, affective dysregulation (p<0.01, AOR=1.036) and conduct problems (p<0.01, AOR=1.078) were both positively associated with NPA use. In the model comparing the *Other Illicit Drug Use without NPA Use* group to the *No Illicit Drug Use*, conduct problems (p<0.01, AOR=1.06) was positively associated with *Other Illicit Drug Use without NPA Use*.

4. DISCUSSION

The present findings provide novel evidence of a longitudinal association between affective dysregulation and NPA use. The results also corroborate prior evidence of an association between conduct problems and all categories of illicit drug use (Boyle et al., 1993; Brook et al., 1992; Falls et al., 2011; Nurco et al., 1999). A higher affective dysregulation score was significantly more likely in the *NPA Use* group compared to both the *Other Illicit Drug Use without NPA Use* and the *No Illicit Drug Use* groups, even when controlling for demographic characteristics. This pattern suggests that affective dysregulation may be a risk factor of NPA use in the college student population—a finding that has not been previously reported. Additionally, these findings expand our understanding of conduct problems as a predictor of nonmedical and illicit drug use. These findings confirm the original hypothesis that higher levels of affective dysregulation and conduct problems will be observed in NPA users compared to both other illicit drug users without NPA use and non-users.

A bivariate association was found between the suspected risk factors of depressive symptoms (BDI, CES-D) and general psychological health (GHQ) and NPA use, however, no significant multivariate association was found. One possible explanation of this is that information bias occurred, however this is unlikely because the measures used to capture this data are highly valid and reliable measures. Another more likely explanation is that there was an interaction effect between affective dysregulation and depressive symptoms as well as general psychological health.

4.1. Study Limitations and Strengths

Several limitations must be acknowledged. Because the data was collected from a

sample at one large public university, it is unclear whether the findings have generalizability to other settings (i.e. other states and countries) and populations (e.g. small private colleges). Although reliable and validated measures were used, the data were collected by self-report and, while we have no indication that under- or over-reporting occurred, social desirability bias cannot be ruled out. Although retention rates were high, attrition bias might also be present. Almost three quarters of the sample were white, indicating that the sample is slightly over-representative of whites in comparison to the larger university.

Despite such limitations, the study has several strengths. The overall design was prospective, longitudinal, and the sample was large. All study measures (e.g. Beck Depression Inventory, Center for Epidemiologic Studies Depression Scale, College Early Conduct Problems Index, Dysregulation Inventory, General Health Questionnaire) had strong psychometric properties, (i.e. reliability and validity).

4.2. Implications and Future Research

The present findings might have important implications for prevention of nonmedical use of prescription analgesics among college students. Providers and other clinical staff (e.g. psychologists, nurses, nurses assistants) must be aware and cautious of the warning signs for NPA use and diversion among college students (American College of Preventive Medicine, 2011; Dowell, Haegerich, & Chou, 2016). Additionally, providers should be encouraged to educate their patients –especially college students and parents of college students – about the negative consequences of using prescription analgesics nonmedically and provide explicit guidance on how to prevent diversion of their medication (e.g. bring unused prescription drugs to Drug Enforcement Agency registered prescription drug collection centers or local pharmacist) (U.S. Food and Drug

Administration, 2015).

Future research should examine whether this phenomenon is unique to the college student population or if affective dysregulation and conduct disorder is associated with NPA use in all age groups (e.g. adolescents, adults). While no single factor can predict whether or not a person will become a nonmedical prescription analgesic user, the more risk factors an individual has, the greater the chance they have of becoming a user (American College of Preventive Medicine, 2011; National Institute on Drug Abuse, 2012), thus, there is an urgent need for future research to examine other predictors of NPA use to better inform health professionals about potential targets for primary, secondary and tertiary preventive interventions.

4.3. Conclusions

The current findings help alert clinicians to specific characteristics that may confer greater risk of NPA use—including affective dysregulation and conduct problems—and they underscore the importance of considering risk factors when designing prevention, treatment, and recovery programs. Additionally, given that NPA use is more common among young adults (18-25 years old) than older individuals (Back et al., 2010; Blanco et al., 2013; Substance Abuse and Mental Health Services Administration, 2015b), urgent attention on preventative strategies for this age group is warranted.

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TABLES/FIGURES

Table 1. Sample demographics listed by drug use groups (self-reported).

	Self-Reported Drug Use (Y_3)			
	NPA use (n=103)	Other Illicit Drug Use w/o NPA Use (n=492)	No Illicit Drug Use (n=388)	Total (N=983)
Demographic Characteristics				
Gender [*n* (%)]				
Female	46 (44.7%)	255 (51.8%)	230 (59.3%)	531 (54.0%)
Male	57 (55.3%)	237 (48.2%)	158 (40.7%)	452 (46.0%)
Race/Ethnicity [*n* (%)]				
white	84 (81.6%)	372 (75.6%)	243 (62.6%)	699 (71.1%)
black	4 (3.9%)	38 (7.7%)	55 (14.2%)	97 (9.9%)
Asian	7 (6.8%)	34 (6.9%)	54 (13.9%)	95 (9.7%)
Hispanic	2 (1.9%)	28 (5.7%)	18 (4.6%)	48 (4.9%)
Other	6 (5.8%)	20 (4.1%)	18 (4.6%)	44 (4.5%)
Parent's Education[a] [*n* (%)]				
Less than high school	0 (0.0%)	3 (0.7%)	5 (1.4%)	8 (0.9%)
High school or GED	7 (7.2%)	38 (8.3%)	27 (7.4%)	72 (7.8%)
Some college or technical	4 (4.1%)	17 (3.7%)	31 (8.5%)	52 (5.7%)
Bachelor's degree	31 (32.0%)	121 (26.5%)	93 (25.5%)	245 (26.7%)
Graduate degree	55 (56.7%)	277 (60.7%)	209 (57.3%)	541 (58.9%)
Adjusted Gross Income[b] [$\bar{x}$ (sd)]	$76,958 ($34,265)	$75,615 ($32,619)	$68,392 ($32,675)	$72,899 ($32,986)
Suspected Risk Factors				
Affective Dysregulation [$\bar{x}$ (sd)]	27.27 (13.51)	23.03 (9.87)	23.25 (10.35)	23.55 (10.55)

Conduct Problems [$\bar{x}$ (sd)]	7.86 (4.72)	6.72 (4.63)	5.59 (4.25)	6.39 (4.55)
Depressive Symptoms (BDI) [$\bar{x}$ (sd)]	6.42 (6.88)	5.16 (4.98)	5.20 (4.98)	5.31 (5.22)
Depressive Symptoms (CES-D) [$\bar{x}$ (sd)]	12.79 (9.34)	10.02 (7.38)	10.56 (7.27)	10.53 (7.60)
General Psychological Health [$\bar{x}$ (sd)]	10.24 (4.45)	9.39 (4.00)	9.76 (4.22)	9.63 (4.14)

a   Highest reported education level between the respondent's mother and father.

b   Mean adjusted gross income (AGI) of the respondent's self-reported home zip code in 2003.

Table 2. The results of the bivariate and multivariate logistic regression models comparing the three drug use groups, controlling for sex, race/ethnicity, and parents education level.

| | | Self-Reported Drug Use | | | | | | | | | | | |
| | | NPA Use[a] vs Illicit drug use, w/o NPA use[b] | | | | NPA Use[a] vs No Drug Use[c] | | | | Illicit drug use, w/o NPA use[b] vs No Drug Use[c] | | | |
		p	AOR	Lower	Upper	p	AOR	Lower	Upper	p	AOR	Lower	Upper
Bivariate	Affective dysregulation	.000	1.045	1.023	1.067	.000	1.044	1.021	1.067	.534	1.005	.990	1.020
	Conduct problems	.041	1.052	1.002	1.104	.000	1.099	1.042	1.158	.002	1.057	1.021	1.095
	Depressive symptoms (BDI)	.009	1.053	1.013	1.094	.007	1.058	1.015	1.103	.607	1.008	.978	1.038
	Depressive symptoms (CES-D)	.000	1.051	1.023	1.080	.001	1.052	1.022	1.083	.966	1.000	.980	1.020
	General psychological health	.023	1.062	1.008	1.118	.039	1.058	1.003	1.116	.690	.993	.958	1.029
Multivariate	Affective dysregulation	.001	1.041	1.016	1.067	.007	1.036	1.010	1.063	.982	1.000	.983	1.018
	Conduct problems	.235	1.032	.980	1.087	.009	1.078	1.019	1.140	.002	1.060	1.022	1.100
	Depressive symptoms (BDI)	.772	1.007	.960	1.057	.701	1.010	.960	1.062	.901	1.002	.967	1.039

a   n = 97 included in the regression analyses

b   n = 456 included in the regression analyses

c   n = 365 included in the regression analyses

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