USING PARALLEL LATENT GROWTH CURVE MODELS TO BETTER UNDERSTAND
CO-MORBIDITY IN TWO RANDOMIZED CLINICAL TRIALS: SMOKING WITH
CO-MORBID ADHD AND CO-MORBID SUD

By

MARY ROSE MAMEY

A dissertation submitted in partial fulfillment of
the requirements for the degree of

DOCTOR OF PHILOSOPHY

WASHINGTON STATE UNIVERSITY
Department of Psychology

DECEMBER 2015
To the Faculty of Washington State University:

The members of the Committee appointed to examine the dissertation of MARY ROSE MAMEY find it satisfactory and recommend that it be accepted.

_________________________________________________
G. Leonard Burns, Ph.D., Chair

_________________________________________________
Sterling McPherson, Ph.D.

_________________________________________________
Celestina Barbosa-Leiker, Ph.D.

_________________________________________________
Craig Parks, Ph.D.
ACKNOWLEDGMENT

I am greatly indebted to Dr. Leonard Burns, Dr. Sterling McPherson, Dr. Celestina Barbosa-Leiker, and Dr. Craig Parks, whose endless guidance and mentorship made it possible for me to work in an area of such interest to me. Without their expertise and consistent advising throughout the duration of this program, this project would not be possible. I would like to thank my cohort, all of whom have been there from start to finish, and through all of the ups and downs throughout the duration of this program. Lastly, I would like to express my deepest appreciation to my family and friends, who have been encouraging throughout this entire journey. I could not have succeeded without the unwavering support of these incredible people and cannot express my gratitude enough.
This study investigated relationships between cigarette smoking and ADHD (Study A) and cigarette smoking and stimulant use (Study B). While cigarette smoking is highly comorbid with these two disorders, the relationships are rarely evaluated simultaneously in order to fully understand the association between them and how they influence one another over time while receiving treatment for one or both of them. To more precisely evaluate these relationships, a parallel latent growth curve model (LGCM) was applied to two randomized clinical trials datasets. The impact of treatment for the targeted and non-targeted disorders to further understand the link between the two comorbid disorders, and how one treatment indirectly affected the non-targeted disorder were evaluated.

Study A involved adults with ADHD and positive carbon monoxide (CO) levels. Participants were randomly assigned to either the experimental (osmotic-release methylphenidate, OROS-MPH) or placebo group to treat ADHD (targeted disorder), and
smoking (non-targeted disorder). Study B included adults with stimulant use disorder (SUD) and positive CO levels. Participants were randomly assigned to the experimental group (smoking cessation treatment with treatment-as-usual) or placebo group (treatment-as-usual).

LGCMs were first used to determine best fitting models for each disorder within each study. Due to the complexity of the model within Study A, a parallel LGCM was then applied only to Study B to help determine whether initial levels of one disorder predicted growth trajectories of the other, whether initial levels are related, and whether growth trajectories are related over time. There were significant relationships across disorders for Study B. Treatment was added to both studies (separate LGCMs for Study A, and a parallel LGCM for Study B) to predict change scores and to examine whether treatment had an impact on either disorder. Both studies found a significant treatment effect on the targeted disorders and no significant effect on the non-targeted disorders, in line with the original findings. Through the use of a parallel LGCM, researchers can test general hypotheses of how treatment may have an effect on the off-target disorders, especially when the effect is routed through change in the targeted disorder.
TABLE OF CONTENTS

ACKNOWLEDGMENT ................................................................................................................ iii

ABSTRACT................................................................................................................................... iv

LIST OF TABLES.......................................................................................................................... viii

LIST OF FIGURES ....................................................................................................................... ix

INTRODUCTION .......................................................................................................................... 1

1.1. General Introduction ............................................................................................................. 1

1.2. Comorbidity of Smoking ....................................................................................................... 4

1.3. Latent Growth Curve Modeling ............................................................................................ 11

1.4. Purpose ............................................................................................................................. 14

1.5 Hypotheses .......................................................................................................................... 15

METHOD ..................................................................................................................................... 16

2.1 Study A Method ..................................................................................................................... 16

2.2. Study B Method .................................................................................................................... 18

ANALYSIS ................................................................................................................................... 20

3.1 Preliminary Analyses ............................................................................................................. 20

3.2 Parallel Latent Growth Curve Model .................................................................................... 25

RESULTS ..................................................................................................................................... 28

4.1 Preliminary Results ................................................................................................................. 28

4.2 Latent Growth Curve Models ............................................................................................... 29

4.3 Parallel Latent Growth Curve Model .................................................................................... 31
4.4 Parallel Latent Growth Curve Model Regressed onto Treatment.............................. 33

GENERAL DISCUSSION ........................................................................................................... 35

5.1 Summary of Findings........................................................................................................ 35

5.2 Implications, Limitations, and Future Directions ............................................................. 42

REFERENCES ............................................................................................................................. 76
LIST OF TABLES

Table 1. Study A: Means of ADHD symptoms across 8 time points ........................................... 46
Table 2. Study A: Percentage of positive CO levels across 12 time points............................... 47
Table 3. Study B: Percentage of positive drug levels across 19 time points .............................. 48
Table 4. Study B: Percentage of positive stimulant UA levels (amphetamines, cocaine, and methamphetamine) across 19 time points .............................................................................. 49
Table 5. Study B: Percentage of positive CO levels across 18 time points .............................. 50
Table 6. Study A: Model fit for ADHD levels............................................................................ 51
Table 7. Study A: Model fit for CO levels.................................................................................. 52
Table 8. Study B: Model fit for stimulant use .......................................................................... 53
Table 9. Study B: Model fit for CO levels.................................................................................. 54
Table 10. Study A: Correlations within disorders ..................................................................... 55
Table 11. Study B: Correlations within and across disorders..................................................... 56
Table 12. Study A: Regressions of treatment on slopes ............................................................. 57
Table 13. Study B: Regressions of slopes on different-disorder intercepts and regressions of treatment on slopes ..................................................................................... 58
LIST OF FIGURES

Figure 1. Study A: ADHD Rating Scale total score ................................................................. 59

Figure 2. Study A: Percentage of participants with positive CO-levels ............................... 60

Figure 3. Study B: Percentage of participants with positive UA for amphetamine .................. 61

Figure 4. Study B: Percentage of participants with positive UA for cocaine ....................... 62

Figure 5. Study B: Percentage of participants with positive UA for methamphetamine ........... 63

Figure 6. Study B: Percentage of participants with positive UA for stimulant use
   (amphetamine, cocaine, and methamphetamine) ................................................................. 64

Figure 7. Study B: Percentage of participants with positive CO levels .................................. 65

Figure 8. Study B: Percentage of participants with positive CO-levels and positive UA for stimulants .......................................................................................................................... 66

Figure 9. Study A: Final model of latent growth curve model for ADHD ......................... 67

Figure 10. Study A: Final model of latent growth curve model for CO-levels ....................... 68

Figure 11. Study B: Schematic model of latent growth curve model for stimulant use......... 69

Figure 12. Study B: Schematic model of latent growth curve model for CO levels ............... 70

Figure 13. Study A: Schematic model of parallel latent growth curve model for ADHD and CO levels with correlations across disorders and model regressed on treatment .......... 71

Figure 14. Study A: Schematic model of latent growth curve model for ADHD regressed onto treatment ............................................................................................................................. 72

Figure 15. Study A: Schematic model of latent growth curve model for CO levels regressed onto treatment ............................................................................................................................. 73

Figure 16. Study B: Schematic model of parallel latent growth curve model for stimulant
use and CO-levels with correlations across disorders. .......................................................... 74

Figure 17. Study B: Schematic model of parallel latent growth curve model for stimulant
use and CO-levels with regressions across disorders and model regressed on treatment ..... 75
CHAPTER ONE

INTRODUCTION

1.1. General Introduction

Cigarette smoking has several severe health consequences, though its use in the United States remains high (CDC, 2011). It is the leading cause of preventable death in the United States, accounting for one in every five deaths each year (US Department of Health and Human Services). Although smoking has declined in recent years, it is estimated that approximately 18.1% of adults are smokers (CDC, 2010). Roughly 70% of smokers want to quit, with a little over half attempting, and just over 6% succeeding in quitting every year (Abrams, et al., 2010; CDC, 2011). Nicotine is suggested to be just as addictive as, if not more addictive than heroin or cocaine (US Department of Health and Human Services, 2014), making smoking cessation treatment very difficult and positive long-term outcomes an ongoing challenge.

Evidence has suggested that people respond well to smoking cessation treatment, as it is considered a highly responsive type of preventative service, and should be a top priority (Maciosek et al., 2006). Several types of treatment are available for those who would like to stop cigarette smoking (Shah, Rao, & Mayo, 2008), and a combination of multiple treatments simultaneously may yield higher success rates in long-term cigarette abstinence and ease in quitting (Wu, Wilson, Dimoulas, & Mills, 2006; Ebbert, et al., 2009; Gray, et al., 2011). One form of treatment that has become increasingly popular in aiding smoking cessation is antidepressants, of which bupropion is commonly used. Bupropion is believed to work as a dopamine reuptake inhibitor, which produces similar rewards achieved by smoking a cigarette by causing additional dopamine build up in the synapse (Slemmer, Martin, & Dimaj, 2000; Ebbert,
et al., 2009; McGeary, et al., 2012; David, et al., 2013). It seems as though bupropion may imitate the effects that nicotine provides for the smoker, thus allowing for less cravings (Warner & Shoaib, 2005). According to Hughes and colleagues (2014), antidepressants may not only be useful as a direct neurological smoking cessation aid, but may also help with the depressive symptoms stemming from nicotine withdrawal (David, et al., 2013). Hughes and colleagues (2014) reviewed 65 trials that used Bupropion as a treatment for smoking cessation, and overall found that it significantly increased long-term cigarette abstinence. It has also been shown to relieve nicotine withdrawal and nicotine cravings (Paterson, 2009; Gray, et al., 2011; Durcan, et al., 2002).

Nicotine inhalers are also a commonly used smoking cessation aid. Nicotine inhalers mimic asthma inhalers, in that they are puffed or inhaled orally (Shneider, Olmstead, Franzon, & Lunell, 2001). Inhalers contain small levels of nicotine and are used to minimally replace the nicotine that a smoker would get from cigarettes to ease the withdrawal effects (Schneider, Olmstead, Franzon, & Lunell, 2001). Studies have shown that nicotine inhalers are beneficial in long-term abstinence rates (Leischow, et al., 1996; Schneider, et al., 1996; Croghan, et al., 2007). Researchers have found that this is safe and effective in promoting the discontinuance of cigarettes with minimal side effects (Silagy, Lancaster, Stead, 2005; Burkett, 2005). It is continually found that its use with other treatments (i.e., brief counseling on the dangers of smoking or the nicotine patch) for smoking cessation can increase the rates of cigarette abstinence (Bohadana, Nilsson, Rasmussen, & Martinet, 2000; Shneider, Olmstead, Franzon, & Lunell, 2001). Another form of treatment is smoking-cessation counseling, which has been shown to increase the likelihood of quitting, especially when used in combination with another type of intervention such as pharmacotherapy (Stead & Lancaster, 2012; Valery, Anke, Inge, &
Some form of pharmacotherapy, even when brief in session length, can provide smokers with the tools and encouragement necessary to quit smoking (Goldstein, et al., 1998; Fiore, 2008; Croghan, et al., 2012).

Contingency management (CM) can be used as a system in which reinforcers encourage a targeted behavior. Specifically, in CM frameworks involving smoking, the objective is to design an intervention that promotes and maintains cigarette abstinence (Stitzer, Rand, Bigelow, & Mead, 1986) by providing smokers with tangible incentives in exchange for CO-free breath samples or cotinine free urine samples to reduce smoking cigarettes (on a schedule that is inconsistent with smoking) (Romanowich & Lamb, 2013; Secades-Villa, Garcia-Rodriguez, Lopez-Nunez, Alonso-Perez, & Fernandez-Hermida, 2014). For example, Roll and Howard (2008) found that when money was used as a reinforcer within a CM framework contingent on smoking abstinence, smokers were significantly found to increase smoking abstinence. CM has been used with a variety of types of reinforcers depending on the context, including vouchers for gas, diapers, food, clothing, and more (McDonell, et al., 2013; McDonell, et al., 2014). The reinforcer within CM can be any item that is consistent with a drug-free lifestyle, though money is most commonly used in treatment analog investigations that are designed to provide ‘proof of concept’ for a promising new type of CM delivery method or targeted drug.

Finally, the nicotine patch has demonstrated effectiveness in smoking cessation (Fiore, Smith, Jorenby, & Baker, 1994) by reducing the levels of cigarette cravings (Ferguson & Shiffman, 2009; Ferguson & Shiffman, 2010) and withdrawal symptoms (Shiffman, Ferguson, & Gwaltney, 2006; Ferguson & Shiffman, 2010). Shiffman and Ferguson (2008) conducted a meta-analysis across four studies and found that the nicotine patch was found to increase the odds of quitting. Overall, the nicotine patch has been found to be safe and very cost effective smoking
cessation tool. With approximately 70% of smoking cessation attempts ending in relapse (Fiore et al., 2008), a combination of psychosocial and pharmacologic interventions within smoking cessation treatment should be used to yield the most successful results in cigarette smoking abstinence (Croghan, et al., 2007; Ebbert, et al., 2009; Fiore, 2008).

1.2. Comorbidity of Smoking

Cigarette smoking is highly comorbid with other mental disorders and non-nicotine substance and alcohol use. It has been consistently shown that those with mental illness are as much as two to five times more likely to smoke compared to those without (Lasser, Boyd, Woolhandler, Himmelstein, McCormick, & Bor, 2000; Rohde, Lewinsohn, Brown, Gau, & Kahler, 2003), with approximately 44.3% of cigarettes consumed by those with a mental illness (Hall, 2007; Lasser, etc., 2000). In fact, ADHD and stimulant use are among the most common disorders associated with cigarette smoking. Research has focused on both the neurobiological and psychosocial factors surrounding the reasoning behind increased rates of cigarette use with these two disorders (Hall & Prochaska, 2009).

1.2.1. Smoking with ADHD

One of the more frequently occurring disorders with cigarette smoking is attention-deficit/hyperactivity disorder (ADHD; Rohde, Lewinsohn, Brown, Gau, & Kahler, 2003; Borland & Heckman, 1976; Pomerleau, Downey, Stelson, & Pomerleau, 1995; Milberger, Biederman, Faraone, Chen, & Jones, 1996). The positive relationship between smoking and ADHD has been long recognized (Hartsough & Lambert, 1987; Biederman, et al., 2006; Sousa, et al., 2011). ADHD is also associated with more severe smoking (Wilens, et al., 2008; Bron, et al., 2013) and more difficulty in quitting (Pomerleau, Downey, Stelson, & Pomerleau, 1995;
Covey et al., 2008). Nicotine has been shown to negate ADHD symptoms (Levin, et al., 1996; Kalil et al., 2008; Sousa, et al., 2011; Cassidy, et al. 2011), so smoking is thought to be a way to provide relief from several of the negative symptoms. Specifically, the effects of nicotine have demonstrated an improvement in both inattentiveness and response inhibition (Conners, et al., 1996; Levin et al., 1996; Potter & Newhouse, 2012), some of the more overwhelming symptoms of ADHD. Thus, addressing ADHD early on may indirectly facilitate smoking cessation.

ADHD is the persistent pattern of experiencing either inattention and/or hyperactivity-impulsivity that continually interferes with daily life (American Psychiatric Association, 2013). ADHD consists of 18 symptoms, nine of which fall under the inattention (IN) presentation, and nine of which fall under the hyperactivity-impulsivity (HI) presentation (American Psychiatric Association, 2013). Adults are required to display any five of the 18 symptoms to be diagnosed with ADHD (American Psychiatric Association, 2013). Although ADHD was originally believed to only affect children, and specifically males, studies have shown that the disorder can persist well into adulthood and across gender (Mannuzza, Klein, & Moulton, 2003; Davidson, 2008; Faraone & Beiderman, 2005; Fischer, Barkley, Smallish, & Fletcher, 2002; Barkley, Fischer, Smallish, & Fletcher, 2002), posing concerns for both early and later life comorbidity. Up to 4.4% of adults in the United States are diagnosed with this disorder (Winhusen, et al., 2011; Kessler, et al., 2005; Kessler, 2006; Spencer, Biederman, & Mick, 2007; Leithead & Freeborn, 2013), making ADHD one of the more profound mental disorders in adulthood (Kessler, et al., 2005).

Over the past several decades, research has consistently demonstrated that adults with ADHD are more likely to have impairments in everyday life. For example, adults with ADHD have been shown to have more difficulties within their job, including more frequent job changes
and lower work status, both of which may lead to lower socioeconomic status (Borland & Heckman, 1976; Morrison, 1980; Mick, 1993; Murphy & Barkley, 1996; Mannuzza, Klein, Bessler, Malloy & Hynes, 1997; Kessler, et al., 2005; Spencer, Biederman, & Mick, 2007; Barkley & Murphy, 2010; Garcia, et al., 2012). Those with ADHD have also shown to have greater problems in marital status, including higher rates of separation and divorce (Mick, 1993; Murphy & Barkley, 1996; Weiss & Murray, 2003; Sagvolden, 2005; Spencer, Biederman, & Mick, 2007). While adult ADHD follows the same criteria as childhood ADHD, the way in which these symptoms manifest themselves as the individual matures can have a detrimental effect on the person’s quality of life, and research has shifted to address this issue.

**ADHD Treatment.** ADHD is often treated with psychostimulants, some form of psychosocial or behavioral therapy, or a combination of both in order to effectively reduce symptoms. Osmotic release methylphenidate (OROS-MPH) is one of the more commonly used medications used to minimize ADHD symptoms and provides both immediate and delayed release of the drug (Schachter, King, Lagnford & Moher, 2001; Wolraich, et al., 2001; Wilens, et al., 2003; Biederman, et al., 2006; Medori, 2008). It has been demonstrated to be safe and effective (Spencer, et al., 2005; Biederman, et al., 2006; Medori, et al., 2008), with demonstrably better functioning and quality of life (Buitelaar, et al., 2012) for patients who consistently take OROS-MPH compared to a placebo. Support for such a drug has stemmed from the demonstrated therapeutic short-term benefits, as well as long-term benefits, such as normalization of certain parts of the brain (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). Research that has shown that those with ADHD who consistently take a psychostimulant have more similar brains to those without ADHD compared to those with ADHD who have not consistently taken psychostimulants (Spencer, et al., 2013; Frodl & Skokauskas, 2012). Even
with the advantages of such a drug, researchers repeatedly report the problematic side effects, such as increased blood pressure and heart rate (Biederman, et al., 2006). Furthermore, researchers have been investigating whether methylphenidate provides potential abuse similar to other stimulant drugs. For example, Wilens and colleagues (2006) found that many young adults were selling or misusing their prescribed medication (Wilens et al., 2008a; Kroutil, et al., 2005).

**Treatment to Smokers with ADHD.** ADHD medication and nicotine have similar effects on the brain, such that the reuptake of neurotransmitters are inhibited. Thus, the relationship between ADHD and smoking may exist as a self-medication theory, such that those with ADHD smoke to reduce ADHD symptoms (Bron, et al., 2012). Nicotine can thus provide treatment for adults with ADHD, as the stimulant aids in the relief of ADHD symptoms (Winnusen, et al. 2010; Levin, et al., 1996). Given the high prevalence of comorbidity between cigarette smoking and ADHD, it may be advantageous to deliver treatment modalities that capitalize on both the behavioral and neurobiological overlap between these two disorders in order to improve the outcome of each. This is especially true since they are often co-occurring disorders. This line of reasoning allows researchers to investigate whether treating ADHD will not only decrease ADHD symptoms, but also serve to increase smoking cessation.

1.2.2. Smoking with Stimulant Use

Other common co-occurring disorders with smoking are non-nicotine substance use disorders, specifically stimulants, such as cocaine or methamphetamine use disorders (Weinberger & Sofuoglu, 2009; Budney, Higgins, Hughes, & Bickel, 1993; Sees & Clark, 1993; Roll, Higgins, Budney, Bickel, & Badger, 1996). The relationship between cocaine and tobacco use is highly comorbid (Henningfield, Clayton, & Pollin, 1990; Sees & Clark, 1993), such that
75 – 85% of cocaine users smoke cigarettes (Budney, Higgins, Hughes & Bickel, 1993; Patkar, et al., 2006; Roll, Higgins, & Tidey, 1997; Roll, Higgins, Budney, Bickel, & Badger, 1996; Weinberger & Sofuoglu, 2009). Cocaine users are three to four times more likely to smoke cigarettes than their non-drug-using counterparts (Brewer, Mahoney, Nerumalla, Newton & Garza, 2013), and often report that using the drug increases the urge to smoke cigarettes (Brewer, Mahoney, Nerumalla, Newton, & Garza, 2013). Methamphetamine users are similar to cocaine users in that there is a strong relationship with cigarette smoking. In fact, methamphetamine users continually report even higher rates of cigarette use than cocaine users, upwards of 85% (Weinberger & Sofuoglu, 2009; Grant, et al., 2007). Research has also shown that the use of stimulants can lead to increased consumption of cigarettes (Roll, Higgins, & Tidey, 1997). The reasoning behind the link between nicotine and stimulant use is not definitive, but it is believed that the nicotine in cigarettes augment the dopamine levels released from stimulant use (Wooters, Neugebauer, Rush, & Bardo, 2008; Gerasimov, et al., 2000). If this is the case, then nicotine may enhance the person’s reaction to stimulant use.

Cocaine and methamphetamine are the two most common stimulants that are abused, with lifetime prevalence of cocaine (14.7%) and methamphetamine (8.5%) very high within the United States (Cicarrone, 2011). Because of the addictive nature of both of these drugs, substance dependence can occur over a relatively short period of time for cocaine and methamphetamine users (Wagner & Anthony, 2002). Substance dependence is defined as a maladaptive pattern of substance use over the course of twelve months, and can involve an increased tolerance of the drug, withdrawal, and unsuccessful attempts to disuse the drug, among other symptoms (American Psychiatric Association). The abuse of these drugs often follows a
binge-abstinence cycle, which may reinforce the behavior over a longer period of time (Gawin, 1991;

The persistent use of stimulants has been linked to criminal activity, including drug dealing and property crime (Baker, et al., 2004; Brecht, Greenwell, & Anglin, 2007; Henningfield, Clayton, & Pollin, 1990). Adults with amphetamine dependence have higher rates of other mental health disorders, and research has shown that the onset of many of these mental health problems can occur or increase preexisting symptoms after regular amphetamine use (Baker, et al., 2004; Grant, et al., 2007; Yen & Chong, 2006). Specifically, 25 – 50% of methamphetamine users report psychotic features, which may be attributed to stimulant-induced psychosis, even up to two years after the last use of the drug (Ciccarone, 2011; Mahoney, Kalechstein, De La Garza, & Newton, 2008). Furthermore, the risk of death due to overdose, among other acts, is heightened for those in this abusing population (Ciccarone, 2011).

**Treatment for Stimulant Use Dependence.** Outpatient clinics addressing persons suffering from severe cocaine and methamphetamine use may vary from site to site (Sholomskas, et al., 2005). Some of the more common treatments for targeting these addictions are contingency management (Dutra, et al., 2008; McDonell, et al., 2013; Pendergast, Podus, Finney, & Roll, 2006; Roll, et al., 2006), cognitive behavioral therapy (CBT; Carroll, 1996; Roll, et al., 2006), and relapse prevention (RP; McKay, et al., 2010; Roll, et al., 2006), and are considered “treatment-as-usual” (TAU) for many clinics. Contingency management to treat stimulant use is similar to that of smoking cessation; reinforcers are used in exchange for non-use, or the reduction, of cocaine or methamphetamine, and has proven very successful in this population (Higgins, Alessi, & Dantona, 2002; Rawson, et al., 2006). It is commonly used due to the rapid decline in stimulant use early on in treatment (Epstein, Hawkins, Covi, Umbricht, & Preston,
Cognitive behavioral therapy is a useful type of psychotherapy within cocaine and methamphetamine users because it is present-focused in which patients are able to understand thoughts and behaviors and correct them accordingly (Carroll, 2000; Sholomskas, et al., 2005). Unlike the immediate results often seen with CM treatment, CBT tends to be more effective later on or even after the treatment program (Epstein, Hawkins, Covi, Umbricht, & Preston, 2003; Carroll, et al., 1994). Relapse prevention (Marlatt & Gordon, 1985) is a method used to reduce and prevent relapse and is based on the cognitive-behavioral framework (Marlatt & Donovan, 2005). Patients are encouraged to recognize high-risk situations, and prevent a relapse by using coping strategies (Marlatt & Donovan, 2005), a technique that has been considered a highly efficient form of stimulant use treatment (Irvin, Bowers, Dunn, & Wang, 1999; Schmitz, et al., 1997). While many of these treatments diverge across sites, these more frequently used techniques have been proven successful when used both alone and combined with each other or other treatments.

Treatment for Smokers with Stimulant Use Dependence. Plenty of evidence has proposed a link between cigarette smoking and stimulant use (Grant, et al., 2007; Weinberger & Sofuoglu, 2009; Sees & Clark, 1993; Roll, Higgins, Budney, Bickel, & Badger, 1996), which may suggest treatment targeted for one disorder may result in the efficacy for the other disorder. Those who are dependent on stimulants may use nicotine because of its effect on dopamine levels, heightening the symptoms of the drug (Brewer, et al., 2013). While smoking cessation rates within this population remain very low (Winhusen, et al., 2014; Morphett, et al., 2013), it may be believed it is because administering treatment for cigarette smoking may heighten the craving for cocaine or methamphetamine. However, much research conducted in this field has proven that implementing smoking cessation treatment does not negatively affect substance use
outcomes (Budney, Higgins, Hughes, & Bickel, 1993; Patkar, Mannelli, Peindl, Murray, Meier, & Leone, 2006; Radzius, Gorelick, Henningfield, 1998). Given the strong relationship between cigarette smoking and stimulant use, it can be proposed that by introducing a combination of smoking cessation treatments, stimulant use may be indirectly treated as well. Thus, by decreasing cigarette smoking, cocaine and methamphetamine use may also be decreased. To test this idea, the proper methodological approaches must me used in order to determine whether the influence of one medication can provide relief for not only the target disorder, but also other related disorders.

1.3. Latent Growth Curve Modeling

Considering the high comorbid rates between both smoking and ADHD, as well as smoking and stimulant use, it seems necessary to analyze these two disorders simultaneously through the use of a latent growth curve model (LGCM; Meredith & Tisak, 1990) in order to better understand the dynamic relationship over time while receiving coordinated treatment. This type of analysis is especially important in studies that are designed to determine the level of indirect treatment effects on a secondary disorder. A latent growth curve model allows for the modeling of change in an outcome trajectory over time. This type of statistical technique is beneficial when working with longitudinal data, as researchers are able to plot latent means at each time point to understand the trend of the participants over the course of the study (Geiser, 2013), and thus study growth by mapping these developmental patterns over time (Chou, Yang, Pentz, Hser, 2004). Furthermore, researchers are able to examine the amount of within person change across time, as well as between person variability. LGCMs can provide group-level statistics, including the average amount of change over time (i.e., slope), the average starting point (i.e., intercept), and the relationship between the two (Preacher, et al., 2008; Geiser, 2013),
making this a very powerful tool for researchers involved in clinical trials research. When working with clinical trials data, the appropriate methods to measure change have been critical to obtain information on whether treatment was successful, and more specifically, how treatment may have affected the symptoms over time (Cheong, MacKinnon, & Khoo, 2003) while making the results useful at the population-level given the type of modeling utilized.

1.3.1. Parallel Latent Growth Curve Modeling

The use of a parallel latent growth model allows the modeling of two growth trajectories simultaneously. This technique allows for the researcher to model several growth processes at once to evaluate two or more intercepts and slopes in order to explore several hypotheses about the relationships between them (Muthén, 2002). This model adds the distinctive component of directional paths between growth factors, where the slope of one disorder can be regressed on the intercept of the other. For example, when working with two highly comorbid disorders, the parallel LGCM can determine whether the initial status of one disorder predicts the rate of change of the other disorder because researchers are able to incorporate direction paths between the growth factors. Furthermore, this model allows the addition of treatment effectiveness to answer a series of questions related to both the primary and secondary disorder.

This evaluation could provide critical evidence on how to best design treatment protocols with several high-risk populations and assess whether there are unique patterns in one outcome related to a pattern of change in another outcome. In addition, it is likely that different baseline covariates are related to these two outcomes in different ways, but this is not possible to understand when the outcomes are analyzed separately, as is normally the case when such trials are analyzed for the primary papers. In the domain of observational substance use research, such
a ‘parallel change analysis’ has proven useful (Neelon, O’Malley, & Normand, 2011; Witkiewitz, Hartzler, & Donovan, 2010; Witkiewitz, & Masyn, 2008; Witkiewitz, van der Maas, Hufford, & Marlatt, 2007; Wu, Witkiewitz, McMahon, & Dodge, 2010) for addressing research questions that are similar in nature. Thus, a thorough investigation of how two related outcomes are related over time and whether baseline characteristics and treatment effects can predict them can be examined.

Two studies will be used in order to illustrate the effectiveness of a parallel latent growth curve model (LGCM) on two comorbid disorders. Specifically, this paper will demonstrate how to investigate unexplored areas of completed trials in order to understand the relationship between changes in comorbid outcomes and how they impact each other. Because of this concurrent analysis, the impact of treatment can be incorporated into this model. Specifically, we are able to determine whether the treatment of one disorder will help reduce the symptoms of the other. The first study (Study A) evaluates the relationship between smoking cessation, measured by expired carbon monoxide (CO) levels (in parts per million), and ADHD, measured by the self-reported ADHD Rating Scale total score (ADHD-RS). The second study (Study B) evaluates the relationship between smoking cessation (CO levels) and stimulant use via urine analysis (UA). The use of a parallel LGCM will allow for the simultaneous evaluation of two separate but related outcomes (i.e., the biochemical measure of cigarette smoking, the self-reported ADHD symptoms, and the biochemical measure of stimulant use) with the intent of answering several interrelated questions for Study A and B.

The original aim of Study A (Winhusen, et al., 2011) was interested in determining whether the use of OROS-MPH reduced ADHD symptoms (primary target) as well as increased smoking cessation (secondary target). The researchers found that OROS-MPH did reduce
symptoms in ADHD, but did not increase smoking cessation (Winhusen, et al., 2011). The original aim of Study B (Winhusen, et al., 2014) uses a combination of four smoking cessation treatments (Bupropion, nicotine inhaler, counseling, and contingency management) to determine its effectiveness on smoking cessation (primary target), while also determining whether it lowered levels of stimulant use (secondary target). The researchers found that smoking cessation treatment increased smoking abstinence point prevalence, but did not increase stimulant-free days (Winhusen, et al., 2014). A parallel LGCM can allow for an extension to these questions in order to understand the trend in the trajectories of the disorders in relation to the treatment.

1.4. Purpose

1.4.1. Study A

We were interested in answering the following set of questions in reference to the relationship between smoking cessation and ADHD outcomes: (1) Are the initial levels of cigarette smoking (CO levels) and ADHD symptoms (ADHD RS total score) related?; (2) Are the growth trajectories of smoking cessation and ADHD symptoms related?; (3) Is the initial status of smoking cessation related to the change in ADHD symptoms over time?; (4) Is the initial status of ADHD symptoms related to change in smoking cessation?; (5) Does treatment influence change in ADHD over time?; and (6) Does treatment influence change in smoking over time?

1.4.2. Study B

We answered the following questions in reference to the relationship between smoking cessation and substance use: (1) Are the initial levels of smoking cessation (CO levels) and stimulant use (negative UA) related?; (2) Are the growth trajectories of smoking cessation and
stimulant use related?; (3) Is the initial status of smoking cessation related to change in stimulant use over time?; (4) Is the initial status of stimulant use related to change in smoking cessation?; (5) Does treatment influence change in stimulant use over time?; and (6) Does treatment influence change in smoking over time?

1.5 Hypotheses

Based on the preceding discussion, hypotheses for this paper are developed below.

**Hypothesis 1.** Relationship between initial levels of disorders: The initial levels of cigarette smoking (CO levels) and the comorbid disorder are significantly related.

**Hypothesis 2.** The growth trajectories of smoking cessation and the comorbid disorder are significantly related.

**Hypothesis 3.** The initial status of smoking cessation is related to change in the comorbid disorder over time.

**Hypothesis 4.** The initial status of the comorbid disorder is related to change in smoking cessation over time.

**Hypothesis 5.** Treatment will significantly influence change in the primary disorder over time.

**Hypothesis 6.** Treatment will significantly influence change in the secondary disorder over time.
CHAPTER TWO

METHOD

2.1 Study A Method

2.1.1 Study Design of CTN 0029

This study contained a series of secondary analyses using data from the National Drug Abuse Clinical Trials Network No. 0029 (http://www.ctndatashare.org). A complete description of this study can be found in Winhusen and colleagues (2011). This study was an 11-week treatment program in which OROS-MPH was used to determine its treatment efficacy in both ADHD and in the decrease in cigarette smoking. Participants were randomly assigned to the experimental (n = 127) or placebo (n = 128) group. Those in the experimental group received OROS-MPH, starting with 18 mg/day and titrating up to 72 mg/day (or the highest dose tolerable) over the course of the first two weeks. Those in the placebo group received a placebo pill. Both groups took their designated pills for the entirety of the 11 weeks of the study (point prevalence abstinence rate was 39%). All participants participated in smoking cessation treatment, which involved a 10-minute smoking cessation counseling session each week over the span of the 11 weeks. On the 27th day (the first day of the “post-quit” phase), all participants received a 21-mg nicotine patch to be worn daily until the end of the study. During weeks 12 and 13, participants began tapering from the nicotine patch and were given 14-mg patches. During week 14, participants were given 7-mg patches. Participants were scheduled to visit the clinic once a week and given a $25 incentive for each visit. Another $25 at week 11 was given for completing the study.
A follow-up assessment was collected one month after the completion of the study for safety data. This study involved two phases; the first 26 days of treatment were labeled the “pre-quit” phase, while the 27th day through end of treatment was considered the “post-quit” phase. The 27th day was considered the designated “quit” day. The study took place across six sites, two of which were substance abuse community treatment programs, two of which were ADHD clinics, and two of which were smoking cessation clinics.

2.1.2 Participants of CTN 0029

Adults (18 – 55) were recruited through advertising, letters, community promotions, and other networking methods to participate in this study (Winhusen, et. al., 2011). Of the 3,865 who were pre-screened, eligible participants were 255 smokers interested in quitting smoking (Winhusen, et al., 2011). “Smokers” was defined as smoking 10 cigarettes per day for at least three months, and having a Carbon Monoxide (CO) level equal to or greater than 8 ppm (Winhusen, et al., 2011). Participants had to be in good physical health and not have been involved with any other programs within the past 30 days (Winhusen, et al., 2011). The participants also had to meet the criteria for ADHD according to the DSM-IV, with an ADHD-RS total score greater than 22. Winhusen and colleagues (2011) provide a detailed list of inclusion and exclusion criteria.

2.1.3 Measures of CTN 0029

A 7-day time-line follow-back (TLFB) was used to determine cigarette use weekly (Winhusen, et al., 2011). Participants were asked to report the number of cigarettes smoked in the past week (Winhusen, et al., 2011). These reports were confirmed by CO-levels, which were also measured weekly (Winhusen, et al., 2011). The DSM-IV ADHD-RS total score was used to
measure ADHD, and the Clinical Global Impression (CGI) severity scale was used to measure ADHD severity (Winhusen, et al., 2011). Both ADHD assessments were measured weekly during the pre-quit phase, and bi-weekly during the post-quit phase (Winhusen, et al., 2011).

2.2. Study B Method

2.2.1. Study Design of CTN 0046

This study contained the use of several analyses of data from the National Drug Abuse Clinical Trials Network No. 0046 (http://www.ctndatashare.org). A complete description can be found in Winhusen and colleagues (2014). This was a 10-week intent-to-treat (ITT) randomized clinical trial across 12 substance use disorder program sites to establish the efficacy of smoking cessation treatment (SCT) on both smoking and stimulant use. Two phases of the study existed; the pre-quit phase existed from Week 1 – Week 4 (day 20), followed by the “post-quit” phase, lasting from Week 4 through the end of the trial.

Participants were randomly assigned to either the treatment-as-usual (TAU) condition (n = 271) or the TAU plus smoking cessation treatment (TAU + SCT) condition (n = 267). All participants received treatment for substance use as per the study site. This required a minimum of one treatment session per week over the course of the full 10 weeks. Those who were assigned to the TAU + SCT condition also received several forms of smoking cessation treatment. During the pre-quit phase (Weeks 1 – 4), the TAU + SCT participants received smoking-cessation counseling (10-minute counseling sessions over the course of the full 10 weeks), as well as extended-release (XL) bupropion (titration to 300/mg over the first 4 days until the end of the study). During the post-quit phase, the TAU + SCT participants also received a nicotine inhaler (6 – 16 nicotine cartridges per day ad libitum) and contingency management for smoking
abstinence. Contingency management was prize-based (fishbowl from which chips were drawn) to reinforce negative CO levels (i.e., CO < 8 ppm). The number of draws increased with each successive week of abstinence.

2.2.2. Participants of CTN 0046

Adults were recruited through the participating sites upon entering treatment. Participants were also recruited through advertising and direct community promotions. Participants were adults enrolled in an outpatient SUD treatment program, interested in quitting, and met the DSM-IV-TR criteria for a current cocaine or methamphetamine dependence. Eligibility also required that the adults smoked at least seven cigarettes per day, had a carbon monoxide level (CO level) of ≥ 8 ppm, and smoked cigarettes for the past three months. Of the 2,244 that were prescreened, 538 participated in the study. Winhusen and colleagues (2014) provide a detailed list of inclusion and exclusion criteria.

2.2.3. Measures of CTN 0046

Stimulant use was measured weekly by both urine analysis (UA) as well as a time-line follow-back (TLFB) self-report of no stimulant use over the previous seven days (Winhusen, et al., 2014). Smoking was measured weekly by a self-report of not smoking in the past seven days, and confirmed by CO levels (< 8ppm; Winhusen, et al., 2014).
CHAPTER THREE

ANALYSIS

3.1 Preliminary Analyses

Several models were estimated before reaching the final models. Raw means were plotted for both Study A and Study B to determine the trajectories of the two disorders (i.e., smoking and ADHD or smoking and stimulant use) within each. Models were analyzed using Mplus 7.11 (Muthen & Muthen, 1998-2012). Robust maximum likelihood (MLR) was used in order to account for any nonnormality. To measure good model fit for continuous outcome variables, the chi-square, comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR) with cutoffs greater than 0.95, less than .05, and less than .05, respectively, were used (West et al., 2012). The BIC was included, where lower values represented better fit. For binary outcome variables, the chi-square, BIC, AIC, and log likelihood (LL) were used to determine the best fitting model.

Considering the first series of models estimated each disorder symptom outcomes separately, these guidelines helped build an accurate latent growth model for each disorder. That is, the plotted means helped establish the best fitting latent growth model based on the trend of the data and allowed us to implement and compare the appropriate function (e.g., linear, quadratic, cubic, piecewise). Adjacent correlated residuals (Kline, 2010) were added to any model with continuous outcome variables in order to improve the model fit as the different functions are estimated. Taking these initial steps ensured the optimal model on the outcomes of interest before exploring the parallel growth model and impact of various covariates. Specifically, the first latent growth curve model allowed for modeling of intraindividual change.
for each adult by estimating the mean intercept for the symptom outcome as well as estimating
the slope across time for the disorder.

The next sets of models were done in tandem for both (i.e., smoking cessation and
ADHD or smoking cessation and stimulant use) of the growth processes at the same time (i.e.,
parallel growth model). Finally, it was planned to have treatment integrated into the model, such
that the model would be regressed onto treatment.

3.1.1. Study A

Study A plotted eight means from Weeks 0, 1, 2, 3, 4, 7, 9, and 11 for ADHD (Table 1;
Figure 1) and twelve means for cigarette smoking (Weeks 0 – 11; Table 2; Figure 2). CO levels
were taken weekly while the ADHD-RS scores were only taken weekly during the pre-quit stage
(i.e., the start of the study through day 26) and bi-weekly during the post-quit stage (i.e., day 27
through the end of the study). To ensure accurate mapping of the data, all eight given means for
ADHD (i.e., Weeks 0, 1, 2, 3, 4, 7, 9, and 11) and all twelve CO level means were used (Weeks
0 – 11) to estimate the models. The ADHD Rating Scale was used to determine ADHD symptom
levels over time. This measure contains 9 ADHD-inattention (ADHD-IN) items, and 9 ADHD-
hyperactivity/impulsivity (ADHD-HI) items for a total of 18 items. Each of the items is rated on
a 4-point Likert-type scale (0 = never/rarely; 1 = sometimes; 2 = often; and 3 = very often), and
were treated as continuous. The CO levels were used as the smoking outcome in order to
determine smoking status. The CO levels were coded as either “positive” for high CO levels (i.e.,
≥ 8 ppm) or “negative” for low CO levels (i.e., < 8 ppm), and were treated as a binary outcome.
Percentages were used to determine the ratio of positive CO levels each week.
**ADHD Latent Growth Curve Model.** The first ADHD model imposed a fixed intercept to estimate the initial starting point (population mean) and to estimate the common residual (disturbance) variance. This null model allowed no variance to be accounted for in the eight measures of ADHD. This model does not have a slope factor and therefore does not account for change over time, nor does it have intercept variability, and therefore no variability in the overall mean level. Thus, subjects had the same score and that score did not change over time.

The second model imposed a random intercept model in which the mean and common residual variance was estimated for each measure, as well as variability around the estimated population mean (estimation of the intercept mean, intercept variance, and the residual variance). This allowed for differing initial statuses across the participants. The third model imposed a fixed intercept, fixed slope model to estimate three parameters: the mean intercept, the mean slope, and the residual. Because both intercept and slope were fixed, there was no individual variability around the intercept mean (participants did not vary in initial status) or slope mean (participants did not vary in trajectory over time). Loadings were fixed to 1 on the intercept factor reflect the fact that each subject’s intercept remains constant over the repeated measures. Loadings on the slope factor reflected the hypothesis of linear growth.

The fourth model allowed for the estimation of the intercept mean, the intercept variance, the slope mean, and the residual variance. This model allowed for variability around initial status, but did not allow for variability around the slope (i.e., participants were allowed to vary in initial status, but did not vary in change across time). The random intercept, random slope model (the fifth model) allowed for the modeling of interindividual change for each participant by estimating the mean intercept for the group, as well as estimating the slope across time for the group. This model also estimated the variations in participants’ scores at time 0 around the
average intercept, the variations in the participants’ slopes around the average slope, and the variations in the time specific assessments not accounted for by the model. Finally, this model allowed for the assessment of the residual covariances (covariance of the variations between the intercept and slope), and will answer the question: *Does initial status differentially predict rate of change in ADHD?* That is, is initial status of ADHD levels related to the rate of change or growth over time?

Once this model had been established, adjacent correlated residuals (Kline, 2010) as well as different slope functions were added to the model (in successive steps) in order to accurately describe the trend in the data. Table 6 describes the model fit of each of these added components. Based on the plotted means, we imposed a linear (Model 5), quadratic (Models 6, 7, and 7A), and shape (Models 8, 8A, and 8B) function to our model.

**Smoking Latent Growth Curve Model.** As stated previously, the first set of models involved the use of a latent growth curve model that projected the trend of change over time for each individual disorder (i.e., one latent growth curve model for smoking and one latent growth curve model for ADHD). Table 7 shows the model fit of each model starting with the null (no slope, no variability in the intercept) and building to our final model for the CO level outcome variable. This process followed the same model steps as the ADHD outcome variable: fixed intercept, random intercept, fixed intercept-fixed slope, random intercept-fixed slope, and random intercept-random slope.

Once the random intercept-random slope model had been established, different slope functions were added to the model (Table 7). Given the nature of the plotted data, it seemed best to impose both a three-slope piecewise model (Table 7, Model 8 and Model 8A) and a two
intercept-two slope piecewise model (Table 7, Model 9). A random quadratic and random cubic model were also estimated for comparison purposes.

The three-slope piecewise model estimated the first linear slope from baseline through Week 4, the second linear slope from Week 4 to Week 5, and the third linear slope from Week 5 through Week 11. This model was an improvement from the linear, quadratic, and cubic models ($\Delta$BIC = -378, -139, and – 139, respectively). The estimation between Week 4 to Week 5 was the time in which treatment was introduced, and thus created an expected dramatic drop in symptoms. However, the line between these time points can be explained by the implementation of treatment. Instead, removing the second “slope” between Week 4 and Week 5 and creating a two-slope model that is separated by treatment would provide us with two intercepts and better theoretical justification.

3.1.2 Study B

Data on six different substances were collected in the original clinical trial (Table 3), though the focus of Study B was solely on stimulant use. Stimulants involved three of these six substances, including amphetamine (Figure 3), cocaine (Figure 4), and methamphetamine (Figure 5). Study B plotted 19 means for both stimulant use (UA; Table 4; Figure 6) and smoking status (CO levels; Table 5; Figure 7) from baseline through Week 10: one mean from baseline (1) and two means from Weeks 2 through 10 (18) were charted because data was collected for both disorders at all of those time points. Biochemical urine analysis (UA) was used to determine stimulant use. Participants were coded as “positive” for a positive UA indicating recent stimulant use in at least one of the stimulants (amphetamine, cocaine, and/or methamphetamine), or “negative” for a negative UA indicating abstinence from stimulants. The
CO levels of the participants were coded as “positive” for CO levels equal to or greater than 8 ppm, or “negative” for CO levels less than 8 ppm. Both of these outcome variables were treated as binary.

**Stimulant Use Latent Growth Curve Model.** Model estimation for stimulant use followed the same steps as Study A, starting with a null model (fixed intercept), and building up to different slope models based on the trajectory of the means (ratios of positive UA). The plotted means of amphetamine (Figure 3), cocaine (Figure 4), and methamphetamine (Figure 5) were combined, where those participants who were positive for any or all of the stimulants at a given time point were positive for stimulant use at the time point. This revealed a linear slope across the 19 time points (Figure 6), so a random intercept-random slope model was used (Model 5, Table 8). A fixed quadratic and random quadratic slope were incorporated into the model to compare change in BIC, but the trend of the means suggested that these did not fit the data as well as a linear slope.

**Smoking Latent Growth Curve Model.** CO levels were also estimated across the 19 time points (Table 5, Figure 7). However, because 100% of participants had positive CO-levels at baseline (Week 0), this estimated time point was removed in order for the model to run. The remaining 18 time points were used in the model (two time points per week, from Week 2 through Week 10). This trajectory also showed a linear growth process, and thus a random intercept-random slope model was used (Model 5, Table 9). While a random quadratic model had an improved BIC (Δ165), the linear trend seemed to fit the data better.

### 3.2 Parallel Latent Growth Curve Model
Outcomes were first estimated separately in order to establish a reliable and accurate latent growth model for each. The best fitting model was chosen based on criterion for fit for each disorder. This series of analyses allowed us to focus on the form and strength of change for each, the average baseline value (i.e., intercept), change over time (i.e., slope), and whether the intercept and slope within each disorder was correlated. Once a good fitting model for both disorders was established (within Study A and Study B), a parallel LGCM was estimated.

3.2.1 Study A

The ADHD and CO-level trajectories were attempted to be estimated together in a parallel LGCM to determine whether the two disorders were related over time. This specific model would allow the correlation between the initial starting points intercepts (Question 1), and the correlation between slopes of both disorders (Question 2) to be included in this model in order to determine whether initial status of each disorder, and whether change over time across disorders is related. If this model was able to converge, then a regression from the ADHD slope onto the smoking intercept (Question 3), and a regression from the smoking slope onto the ADHD intercept (Question 4) could determine if the initial status of one disorder is related to the change in the other. Once a regression model was run, treatment could be added to the model. Allowing the slopes of smoking and ADHD to regress onto treatment could determine whether treatment influenced change in symptoms of each disorder (Questions 5 and 6). Specifically, this could determine whether OROS-MPH helped reduce ADHD symptoms (primary target) as well as smoking habits (secondary target) with more information as to the form of change across the study.

3.2.2 Study B
The disorders of interest (stimulant use and cigarette smoking) were estimated together in a parallel LGCM to determine the relation between the two. A correlation was estimated between the slope of smoking and the slope of stimulant use (Question 1) to determine whether the initial statuses of both are related. Another correlation between the slopes of smoking and stimulant use determined whether change over time in one disorder is related to change over time in the other (Question 2). A regression of the stimulant use slope onto the smoking intercept (Question 3) and a regression of the smoking slope onto the stimulant use intercept (Question 4), allowed us to determine whether the initial status of one disorder is related to change in the other. Treatment was also incorporated into the model to allow the slopes of both smoking and stimulant use to regress onto treatment. This helped us determine whether smoking cessation treatment does in fact increase smoking cessation and decrease stimulant use.
CHAPTER FOUR

RESULTS

4.1 Preliminary Results

4.1.1 Study A Model Fit

The first several models of ADHD did not meet criterion fit (Table 6). Each model improved upon the previous, and the final model for ADHD consisted of a shape model with adjacent correlated residuals, and one additional correlated residual between Week 7 and 11 (Model 8B, Table 6). The addition of a shape factor allowed for the growth trajectory to be estimated from the data, rather than specified a priori. The first and last time points (i.e., Week 0 and Week 11) were fixed to 0 and 1, respectively, while the rest of the time points (i.e., Weeks 1, 2, 3, 4, 7, and 9) were estimated in order to reveal the shape of the growth process. This showed the best fit and made theoretical sense ($\chi^2(32) = 179$; CFI = .857; RMSEA = .135; SRMR = .123).

The final model for CO levels consisted of the two slope-two intercept model (Model 9, Table 7). This model estimated two linear slopes: the first from Week 1 through Week 4 (i.e., pre-quit phase), and the second from Week 5 to Week 11 (i.e., post-quit phase). While the three-slope model provided better fit, treatment occurred between Week 4 and Week 5, which explained the dramatic decrease in symptoms. Including this slope does not provide us with much more clinical explanation, and we can gather more information by separating these trajectories by removing the second slope. Thus, we removed the “slope” that estimated only two time points (i.e., the second linear slope from Week 4 to Week 5). This allowed our new model to have two intercepts (i.e., Baseline and Week 5). The model did not improve from the three-
4.1.2 Study B Model Fit

The final model for stimulant use consisted of random intercept-random slope model, where the intercept and slope were allowed to vary across participants (Model 5, Table 8). This imposed a linear slope, based off of the means of the outcome variable each week and was an improvement in fit compared to previous models (BIC = 4214). A fixed quadratic (BIC = 4205) and random quadratic (BIC = 4211) slope were added to the model, though we believed that the decrease in BIC was not sufficient, and more importantly, the trend of the data did not justify a quadratic slope addition to the model.

The final model for CO levels also used a random intercept-random slope (Model 5, Table 9). Based on the trend of the data, this was believed to be the best fitting model and did show and improvement from previous models (BIC = 13465). We added a fixed quadratic and random quadratic slope to this model as well to determine whether there was an improvement in fit. However, a linear slope was thought to fit the plotted data best.

4.2 Latent Growth Curve Models

4.2.1 Study A

ADHD. The ADHD model used eight time points (Weeks 0, 1, 2, 3, 4, 7, 9 and 11) to estimate the latent growth curve model (Figure 9). Means were estimated for each of these time points. There was a large average decline in ADHD symptoms across the 11-weeks ($M = -14.71$). The intercept and slope had a moderate positive relationship ($r = .301, p = .081$), suggesting that
those who had higher ADHD symptoms had more of a decrease in symptoms over the course of the clinical trial (Table 10).

**CO Levels.** CO levels were estimated using the 12 time points provided (Weeks 0 – 11; Figure 10). Two growth processes were estimated: the first between Week 0 and Week 4 (designated as the pre-quit phase), and the second between Week 5 and Week 11 (designated as the post-quit phase). There was a small decrease in CO levels in the pre-quit phase ($M = -2.839$). There was a small decrease in symptoms during the second part of the study (between Week 5 and week 11; $M = -.579$). However, there was a dramatic drop between the pre- and post-quit phases, which can be seen in Table 2.

The relationship between the intercept and slope of the first trajectory approached significance ($r = -.735$, $p = .061$), which shows that those who had higher levels of CO at Week 0 decreased much more quickly than those with lower levels of CO at Week 0. There was a strong, significant correlation between the intercept and slope of the second trajectory ($r = .944$, $p = .000$), suggesting that those with higher levels of CO at Week 5 had a slower rate of decrease during the post-quit phase of the study. The small, negative relationship between the two intercepts approached significance ($r = -.015$, $p = .074$); those with higher levels of CO level at the start of the pre-quit phase had lower levels at the post-quit phase, and vice versa. There was also a negative, moderate relationship between the slopes of the pre- and post-quit phases ($r = -.432$, $p = .000$), where those who had a steeper decrease in the first part of the study had a slower decrease in the second part of the study, and vice versa. We also examined the relationships between the initial status of the pre-quit phase with the slope of the second trajectory, as well as the initial status of the post-quit phase with the slope of the first trajectory. We found that there was no significant relationship between either of these.
4.2.2 Study B

**Stimulant Use.** The means of the 19 time points were used to estimate the final model of the latent growth curve model for stimulant use (Figure 11). There was a small average linear change in stimulant use symptoms over the 10 weeks ($M = -.062$). There was no relationship between the initial level of stimulant use symptoms and the change in symptoms ($r = .048$, $p = .735$). This suggests that the starting levels of stimulant use were not related to the increase or decrease in symptoms over the course of the clinical trial.

**CO Levels.** The CO level outcome variable used 18 time points to model a LGCM (Figure 12). While we originally started with 19 time points, 100% of the participants were positive for CO levels. Due to the lack of variability in the first time point amongst our participants, this was dropped in order for the model to run. Thus, Week 2 assumes the role of the intercept. There was a small average linear change in CO levels ($M = -.180$), suggesting that CO levels decreased over the course of the trial. There was no relationship between the intercept and the slope ($r = -.030$, $p = .685$). If baseline scores were incorporated, we may have seen a significant relationship between the initial status of CO levels and change scores, as Week 0 had 100% and Week 2 had 76.6%.

4.3 Parallel Latent Growth Curve Model

4.3.1 Study A

A parallel latent growth curve model was estimated in order to combine the two separate models of ADHD and CO levels. While this model can still answer questions about the relationships within a disorder, more interesting are the questions that can be answered about the relationships across two disorders. Correlations were first estimated across the disorders (e.g., the
intercept of ADHD correlated with the intercept of CO levels) in hopes to next add a slope-intercept regression, where the slope of one disorder would be regressed onto the intercept of the different-disorder to determine whether initial status of one disorder predicted the change in the other disorder.

**Correlations.** The separate LGCMs for both stimulant use and CO levels utilized a MLR estimator. When the two LGCMs were combined into a parallel LGCM, the model did not converge. The number of iterations for the EM algorithm were increased in an attempt to have the model run, as suggested by the output warnings, though this adjustment did not force the model to converge. The model did converge when the WLSMV estimator was used. However, when comparing the correlation values within disorder (e.g., correlation of ADHD intercept with ADHD slope) and the fixed effects (i.e., means of intercepts and slopes) of the LGCMs for both stimulant use and CO levels to the parallel LGCM, there was an incredible discrepancy. These new values did not make theoretical sense. For example, the large, positive, and significant relationship between the intercept and slope of the second trajectory of CO levels within the CO level LGCM ($r = .944, p = .000$) became a very small, negative, and nonsignificant relationship in the parallel LGCM ($r = -.111, p = .918$). Considering the change in the estimator, and seeing how the MLR estimator did not allow for the convergence of the parallel LGCM, the final models for Study A became the LGCM for ADHD, as well as the LGCM for CO-levels. Treatment was thus regressed onto these two separate models. The parallel LGCM that was attempted can be found in Figure 13.

### 4.3.2 Study B
A parallel latent growth curve model was run for Study B (Figure 16). This model incorporated the LGCM of stimulant use and the LGCM of CO levels to answer several questions. As questions within a disorder (e.g., relationship of slope and intercept) had already been answered in the separate LGCM of each disorder, we were interested in the information pertaining to the across-disorder relationship.

**Correlations.** There was a significant negative relationship between the intercepts \( r = -0.130, p < .05 \), suggesting that those who had higher levels of stimulant use at baseline had lower CO levels at Week 2 of the study, or that those who had lower levels of stimulant use at baseline had higher levels of CO levels at Week 2 of the study. There was no relationship between the initial level (Week 2) of CO levels and change in stimulant use symptoms \( r = .033, p = .707 \). There was also no relationship between the initial status of stimulant use symptoms and the change in CO levels \( r = .035, p = .623 \). Finally, there was a small negative relationship between the slopes, but this was nonsignificant \( r = -.117, p = .208 \). These values can be found in Table 11.

**Regressions.** Although there was no significant relationship between the initial status of one disorder with the slope of the other disorder, adding a regression component to the model allowed us to determine whether intercepts *predicted* the different-disorders’ slopes (Table 13). The initial status of CO-levels were not predictive of the change in stimulant use levels \( \beta = -.093, p = .157 \). However, the initial status of stimulant use did predict the change in CO-levels over the course of the clinical trial \( \beta = .838, p = .000 \). This means that higher levels of stimulant use predicted slower change in CO-levels.

**4.4 Treatment**
4.4.1 Study A

Two final models were used for Study A to determine treatment effectiveness. Because the parallel LGCM would not converge, the ADHD LGCM model was regressed onto treatment (Figure 14) and the CO LGCM was regressed onto treatment (Figure 15). This helped determine whether OROS-MPH had any impact on either ADHD (targeted disorder) or smoking cessation (secondary disorder; Table 12). By regressing the slopes of each disorder (one slope for ADHD, and two slopes for CO levels) onto treatment, we can propose ideas as to whether treatment significantly impacted the change in symptoms over the clinical trial. There was a significant treatment effect of change in ADHD ($\beta = -.337$, $p = .000$), suggesting that those who received OROS-MPH decreased more in ADHD symptoms than those who received the placebo. There was no treatment effect of change in CO levels (pre- or post-quit stages). These findings are in line with the original findings (Winhusen, et al., 2011).

4.4.2 Study B

Smoking cessation treatment was incorporated into the parallel LGCM (Table 13; Figure 17). This allowed us to understand how treatment impacted the change in both smoking cessation (targeted disorder) and stimulant use (secondary disorder). There was a significant treatment effect on the change in CO levels ($\beta = .523$, $p = .000$). However, there was no treatment effect on change in stimulant use ($\beta = .005$, $p = .948$).
CHAPTER FIVE
GENERAL DISCUSSION

5.1 Summary of Findings

The current study applied a parallel latent growth curve model to smoking with one of two comorbid disorders to determine the association between the two and to model treatment effectiveness on each of the disorders. It was expected that by modeling two disorders simultaneously, further information regarding the comorbidity between them could be established. More specifically, by incorporating treatment into a parallel LGCM, more questions could be answered regarding the efficacy on both the targeted and secondary disorders. To demonstrate this methodology, two datasets were used. Study A evaluated the relationship between cigarette smoking and ADHD. OROS-MPH was used to treat both ADHD (targeted disorder), as well as cigarette smoking (secondary disorder). The original researchers found that there was a treatment effect of OROS-MPH on ADHD, but no treatment effect on cigarette smoking. Study B evaluated the relationship between cigarette smoking and stimulant use. Several forms of smoking cessation treatment were used to increase cessation (targeted disorder) and decrease stimulant use (secondary disorder). The original findings found smoking cessation treatment significantly increased abstinence in cigarette smoking, though there was no treatment effect for stimulant use. While there was no treatment effect on the secondary disorder of either Study A (smoking) or Study B (stimulant use), the purpose of this paper was to demonstrate a different way to model these data in order to answer a series of different questions.

The association between smoking and ADHD, as well as between smoking and stimulant use is strong enough where the application of a parallel latent growth curve model is appropriate.
It was expected that by running a parallel latent growth curve model, we would be able to answer a series of questions that had not been asked in the original study. First, we could determine whether initial levels of cigarette smoking were related to initial levels of the corresponding comorbid disorder (ADHD or stimulant use). Second, we could determine whether the trajectories of smoking with the corresponding comorbid disorder were related over time. Third, we could determine whether the initial level of one disorder were related to or predictive of the different-disorder slope. And finally, we could regress the slope of each disorder onto treatment to understand whether efficacy influenced change over the course of the clinical trial.

We first applied a latent growth curve model to each of the disorders separately to allow for the best fitting model before moving into our final models. We then combined the disorders into parallel latent growth curve models.

5.1.1 Study A

Study A was an 11-week clinical trial in which participants received OROS-MPH or a placebo throughout the entirety of the study. All participants received a nicotine patch on the designated “quit” day (occurring between Week 4 and Week 5). Due to the design of the clinical trial, it was expected to see that the trajectory of ADHD slowly decreased over the course of the study, while CO-levels had a dramatic decrease in symptoms after the designated quit day. A shape model fit the ADHD trajectory best by fixing the first and last time points and estimating the other time points. CO-levels had a more complex trajectory. The study simulated a pre-quit/post-quit study: there was a stable, linear slope during the pre-quit phase, and a stable, linear slope during the post-quit phase. As expected, a dramatic drop in CO-levels occurred in between these two time periods (on the designated quit day). This allowed us to use a nontraditional
approach to describing this data. One approach we considered was the use of a piecewise model that included three slopes: pre-quit phase (Week 0 – Week 4), designated quit day (Week 4 – Week 5), and post-quit phase (Week 5 – Week 11). While the fit of this model was good, the theoretical justification was not strong enough to move forward with this latent growth curve model. Considering the designated quit day occurred between Week 4 and Week 5, the dramatic decrease in CO-levels was already explained. Instead, by allowing for two disconnected slopes, we were given two intercepts and the ability to answer additional questions about the relationship of CO-levels with ADHD and treatment. Specifically, we could determine whether CO-levels at the start of the study were related to CO-levels after the designated quit day (e.g., did participants with higher CO-levels at the start of the pre-quit phase have higher or lower CO-levels at the start of the post-quit phase?). We could also model whether CO-levels at the start of the study were at all predictive of the change during the post-quit phase, and whether the change in the pre-quit phase was related to CO-levels at the start of the post-quit phase.

The initial status of ADHD was significantly related to the change in ADHD over the course of the clinical trial; those with higher levels of ADHD at the start of the study decreased at a steeper rate than those with lower levels of ADHD at the start of the study. This could be due to a ceiling effect, where those with higher scores have more room for a decrease in symptoms over time. This may also be due to the response to treatment; those with high levels of ADHD may have more symptoms needing to be treated, and thus produce more change. The relationship between the initial status and slope of CO during the pre-quit phase approached significance, but this moderate, negative relationship does show that those who had positive levels of CO at intake had a greater decrease in symptoms in the pre-quit phase. This finding is interesting, as smoking cessation treatment had not been fully implemented during the pre-quit phase of the study.
However, this may be explained by reactivity. That is, the behavior begins to change even before treatment is implemented because the person is enrolled in a program. There was a strong, significant relationship between the initial status and slope of CO-levels during the post-quit phase. This means that those with higher CO levels at the start of the post-quit phase did not decrease as much as those with lower CO-levels. The initial levels of the pre-quit and post-quit phase approached significance, where higher levels at the start of the pre-quit phase resulted in lower levels at the start of the post-quit phase. Again, the ceiling effect may explain this; those who score higher at the start of the study have more room to decrease. While those with the higher scores may not have decreased as much as those with lower scores. There was a significant relationship between the slope of the pre-quit phase and the slope of the post-quit phase. A larger decrease in the first phase of the study resulted in a smaller decrease in the second phase of the study, and vice versa. Finally, there was no significant relationship between the initial status of the pre-quit phase with the slope of the post-quit phase, or between the initial status of the post-quit phase with the slope of the pre-quit phase.

The parallel LGCM would have allowed us to answer questions across disorders. In order to allow for the model to converge, the robust weighted least squares (WLSMV) estimator was used instead of the robust maximum likelihood (MLR). While the WLSMV estimator may not be as efficient as MLR, the disadvantages are small and should produce similar results. While the MLR estimator can handle missing data under the missing at random (MAR) assumption, WLSMV cannot given its pairwise variable orientation. However, the retention rate in this study was high (84.4%), so using the WLSMV estimator seemed appropriate. We set the intercept of the pre-quit phase for CO-levels to 0; this allowed for no variability among the initial status of
participants. Once these adjustments were made, we were able to run the parallel latent growth model involving both ADHD and CO-levels.

Unfortunately, the new estimator created several problems. First, the correlations were vastly different within each disorder; while estimators should produce similar results when retention rates are high, this was not the case. We also examined the fixed effects to determine whether the means of the intercepts and slopes within the parallel LGCM also differed from the separate LGCMs. For example, while the LGCM for CO levels showed a small, negative decrease in cigarette smoking (in line with the growth trajectory), the parallel LGCM suggested a very large increase in cigarette smoking. Furthermore, the fixed effects (i.e., the means of the intercepts and slopes) were also vastly different and did not make sense based on the both the calculated means from previous models, as well as the trends in the data. We were therefore unable to move forward with a parallel LGCM, and instead used the two final LGCMs for each disorder separately to regress onto treatment.

Accordingly, the ADHD LGCM and the CO LGCM were both regressed onto treatment separately. Specifically, the slope of ADHD was regressed onto treatment, and the two slopes of CO levels were regressed onto treatment to determine whether treatment influenced change in symptoms over the course of the clinical trial. There was a significant treatment effect on the change in ADHD. This was expected, as ADHD was the targeted disorder of the OROS-MPH treatment, and is in line with the original researchers’ findings. There was no treatment effect on the change in either slope of CO levels; OROS-MPH did not predict the trajectory of growth for the pre-quit or post-quit phase of cigarette smoking. Again, this is in line with the original researchers’ findings, which found that OROS-MPH did not significantly reduce the number of cigarettes smoked at the end of the clinical trial.
5.1.2 Study B

Study B involved a 10-week intent to treat clinical trial in which participants received either treatment-as-usual (TAU) for stimulant use (placebo group) or TAU for stimulant use and smoking cessation treatment (experimental group). Nineteen data points were used for each of these variables: one baseline data point and two data points per week thereafter (Weeks 2 – 10), totaling eighteen. The baseline data point for CO-levels was dropped before analyses started. Each participant of the study scored “positive” (> 8ppm) for CO-levels at the start of the study, which was expected because a requirement to participate in the study was to smoke at least seven cigarettes per day. Thus, Week 2 of the study became the initial status for CO-levels due to the homogenous nature of the baseline data point. Once this adjustment was made, both sets of plotted means for stimulant use and CO-levels revealed linear slopes. While there was a decrease in symptoms for both disorders over the course of the clinical trial, these changes were minimal. The final latent growth curve model for each used a random intercept-random slope model, where variability around both the initial status and slopes were allowed.

The relationship between the initial status of stimulant use and its slope was nonsignificant. The relationship between the initial status of CO-levels and its slope was also nonsignificant. Due to both of the linear, and relatively stable trajectories of the disorders during the study, it seems reasonable that positive or negative values of the disorder at initial status would not be related to the small decline in symptoms. However, given the allowance of the baseline data point for CO-levels, these results may have been significant, as 100% of participants had positive CO-levels at intake, and 50.6% had positive levels of CO by the end of Week 10.
The parallel latent growth curve model allowed for questions regarding the relationship across disorders to be answered. Specifically, (1) Are the initial levels of stimulant use and CO-levels related to each other?, (2) Are the slopes of CO and stimulant use related to each, (3) Were initial levels of CO related to the change in stimulant use?, and (4) Were initial levels of stimulant use related to CO change? There was a significant relationship between the intercepts, where higher levels of one disorder were related to lower levels of the other disorder (Question 1). There was no relationship between the two slopes of the disorders (Question 2), nor were there relationships between the initial status of one disorder on the slope of the other disorder (Question 3 and 4). Though we found only one significant relationship in the parallel latent growth curve model, adding a regression between the slope and the different-disorder intercept could provide more information. Thus, we regressed the slope of stimulant use onto the intercept of CO, and we regressed the slope of CO onto the intercept of stimulant use. While the initial status of CO did not predict the slope in stimulant use, the initial status of stimulant use predicted change in CO-levels. Specifically, higher levels of stimulant use predicted slower change in CO-levels. Because both are stimulants and the nicotine from cigarettes produce similar responses, it is understandable that those with higher stimulant use would continue to smoke cigarettes to continue the effects of the drug.

Treatment was then added to this model and revealed a treatment effect on the change in CO-levels (primary disorder). Those who received the TAU for stimulant use and smoking cessation treatment decreased more than those who only received TAU. This corroborates the original authors’ findings, where the experimental group involving smoking cessation treatment reduced cigarette smoking. We found no treatment effect on change in stimulant use (secondary disorder).
5.2 Implications, Limitations, and Future Directions

This study has several empirical and theoretical implications by making an important attempt at demonstrating the usefulness of a parallel latent growth curve model for psychological and pharmaceutical research. Much of the research that studies two comorbid disorders uses statistical techniques that do not incorporate the analyses of both disorders simultaneously, but rather uses methodological approaches that allow the researchers to only answer one question per analysis. While parallel latent growth curve models have been previously established across several disciplines, there is a deficit in the number of studies that utilize this type of analysis, especially when many studies have collected the appropriate data in order to run them. By modeling a parallel latent growth curve model, we are able to answer a series of questions across disorders that are otherwise overlooked and are unable to be answered unless this approach is applied to the dataset. Specifically, we can further the understanding of the relationship between initial status of two disorders, changes over the course of clinical trials across the two disorders, and whether treatment affects these changes. Most importantly, it seems more and more appropriate to model these data in such a way, as it is extremely common for those with one disorder to have a second, related disorder. Cigarette smoking is among one of the most commonly occurring comorbid disorders, where those with ADHD or a stimulant use disorder are much more likely to smoke than those without either of the disorders (Hall & Prochaska, 2009). Thus, modeling these disorders separately could lead to incorrect assumptions, as the incorporation of the second disorder within a model may reveal different trends and results.

Findings from this study are meaningful in that they provide insight into how treatment for one disorder can subsequently affect the comorbid disorder. As some scholars have suggested, the incorporation of smoking cessation treatment when targeting another disorder
(e.g., ADHD or stimulant use) may negatively affect the results of one or both disorders. In other words, implementing smoking cessation treatment while simultaneously treating ADHD or stimulant use may actually increase ADHD or stimulant use. This idea stems from the fact that nicotine, the stimulant found in cigarettes, helps diminish the effect of ADHD and helps fuel the effect of stimulants. By reducing cigarette consumption through smoking cessation treatment, participants may turn to another stimulant to help reduce their ADHD, or those with stimulant use disorder may increase their drug use. Though this idea has little to no theoretical backing (Budney, Higgins, Hughes, & Bickel, 1993), many studies do not account for two disorders simultaneously with the fear that one disorder will increase while the other will increase. This specific study was able to test this theory on two different datasets. Each of the four disorders used in this study (i.e., cigarette smoking and ADHD in Study A, and cigarette smoking and stimulant use in Study B) decreased over the course of the clinical trial, regardless of whether the disorder was the targeted or secondary disorder. Furthermore, treatment only affected the targeted disorder and had little to no effect on the secondary disorder. This advocates for the concurrent treatment and evaluation of two comorbid disorders in order to decrease the symptoms of each, as treatments for ADHD and stimulant use rarely address cigarette smoking. By incorporating smoking cessation treatment when treating another disorder, researchers may successfully be able to reduce two disorders simultaneously. While there was no treatment effect on the secondary disorder, the aim of this paper was to demonstrate how researchers could analyze data when participants are diagnosed with two disorders.

The use of a latent growth curve model allows for much flexibility in modeling data within longitudinal data; this type of analysis focuses on change, but more importantly, it allows for the modeling of the form of change over time. As mentioned previously, different functions
could be incorporated into the model (e.g., linear, quadratic, shape) to determine which best describes the data to allow for a more accurate trajectory that other models may not able to produce. The evaluation of studies through the use of a parallel latent growth curve model could provide important evidence on how to best design treatment practices with these high-risk populations. In addition, it is likely that different baseline covariates are related to these two outcomes in different ways, but this is not possible to understand when the outcomes are analyzed separately, as is normally the case when such trials are analyzed for the primary papers.

While the current study contains important implications, this was not without limitations. First, several adjustments to the final parallel latent growth curve model were made for Study A in order to allow for its convergence. While it was originally planned to use MLR for each of the analyses because this estimator usually produces more accurate results, the WLSMV estimator was used. This option is appropriate because Study A contained both continuous and binary outcome variables. However, the WLSMV estimator handles missing data differently than the MLR estimator. When working with longitudinal data, it is likely that the rate of attrition is substantial enough where researchers should be aware of how a model handles missing data. However, the retention rate of this specific study was high enough where the WLSMV estimator should not have significantly influenced the output. Unfortunately, the incredible discrepancy in values between the LGCMs and the parallel LGCM were substantial enough where we could not justify using the parallel LGCM. While our final models were able to answer questions pertaining to the relationship within the disorders, and the influence of treatment on each disorder, we were unable to answer any questions pertaining to the relationship across disorders.

The models involving CO-levels for Study B were also adjusted in order for the model to run. The first time point (baseline) was removed due to the homogeneity of the variable; each
participant scored positive for CO during intake because this was a requirement of the study. This removal could have produced different results—that is, by keeping the baseline data point in the analysis, there may have been a significant decrease in symptoms over the course of the clinical trial. There also may have been significant relationship between the intercept of CO-levels and the slope of stimulant use, as we found a significant relationship between the intercept of stimulant use and the decline in CO-levels.

Cigarette smoking has continually been found to have high comorbidity rates with both ADHD and stimulant use. While we could not further understand the relationship between cigarette smoking and ADHD within Study A, Study B found the intercept and slope of cigarette smoking were not related to the intercept and slope of stimulant use. This contradicts previous research, though the adjustments made to the growth models mentioned previously may have affected these results.

Future research is needed in order to continue the evaluation of comorbid disorders through the use of a parallel latent growth curve model. This line of statistical analyses can provide more in-depth discussions to the extent of how two disorders are related over time. The high rate of comorbidity between cigarette smoking and both ADHD and stimulant use should continue to utilize parallel latent growth model to analyze the data. Researchers must conduct research on both disorders simultaneously to understand these intricate and complex relationships. Furthermore, the incorporation of several types of treatment to address both disorders should be used in order to decrease both disorders.
Table 1

Study A: Means of ADHD symptoms across 8 time points

<table>
<thead>
<tr>
<th>Time</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 7</th>
<th>Week 9</th>
<th>Week 11</th>
</tr>
</thead>
</table>
Table 2

*Study A: Percentages of positive CO levels across 12 time points*

<table>
<thead>
<tr>
<th>Time</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Week 9</th>
<th>Week 10</th>
<th>Week11</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>98.0</td>
<td>94.9</td>
<td>93.5</td>
<td>92.8</td>
<td>90.6</td>
<td>26.7</td>
<td>31.3</td>
<td>31.5</td>
<td>32.5</td>
<td>33.3</td>
<td>33.7</td>
<td>41.5</td>
</tr>
</tbody>
</table>
Table 3

Study B: Percentages of positive drug levels across 19 time points

<table>
<thead>
<tr>
<th>Time</th>
<th>1</th>
<th>2.1</th>
<th>2.2</th>
<th>3.1</th>
<th>3.2</th>
<th>4.1</th>
<th>4.2</th>
<th>5.1</th>
<th>5.2</th>
<th>6.1</th>
<th>6.2</th>
<th>7.1</th>
<th>7.2</th>
<th>8.1</th>
<th>8.2</th>
<th>9.1</th>
<th>9.2</th>
<th>10.1</th>
<th>10.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>1.49</td>
<td>.193</td>
<td>.622</td>
<td>.216</td>
<td>.668</td>
<td>.414</td>
<td>.895</td>
<td>.624</td>
<td>0</td>
<td>.842</td>
<td>.478</td>
<td>1.08</td>
<td>.733</td>
<td>1.09</td>
<td>.744</td>
<td>.419</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>4.09</td>
<td>1.93</td>
<td>1.24</td>
<td>2.37</td>
<td>1.30</td>
<td>2.01</td>
<td>1.85</td>
<td>1.79</td>
<td>1.46</td>
<td>1.39</td>
<td>1.68</td>
<td>1.44</td>
<td>1.73</td>
<td>2.44</td>
<td>1.97</td>
<td>.992</td>
<td>1.47</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>19.9</td>
<td>11.6</td>
<td>10.4</td>
<td>10.7</td>
<td>9.52</td>
<td>12.1</td>
<td>9.35</td>
<td>13.3</td>
<td>11.6</td>
<td>13.1</td>
<td>10.2</td>
<td>13.3</td>
<td>11.5</td>
<td>12.8</td>
<td>13.2</td>
<td>13.5</td>
<td>13.2</td>
<td>14.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Methamphet</td>
<td>5.94</td>
<td>2.32</td>
<td>2.70</td>
<td>2.97</td>
<td>2.17</td>
<td>2.83</td>
<td>2.01</td>
<td>2.46</td>
<td>2.69</td>
<td>2.29</td>
<td>2.78</td>
<td>2.96</td>
<td>2.64</td>
<td>3.26</td>
<td>3.69</td>
<td>3.50</td>
<td>1.99</td>
<td>2.52</td>
<td>1.75</td>
</tr>
<tr>
<td>Opioids</td>
<td>2.60</td>
<td>1.35</td>
<td>1.24</td>
<td>.988</td>
<td>1.30</td>
<td>1.41</td>
<td>2.00</td>
<td>1.85</td>
<td>2.01</td>
<td>1.66</td>
<td>3.01</td>
<td>2.74</td>
<td>2.63</td>
<td>2.16</td>
<td>1.71</td>
<td>2.83</td>
<td>2.98</td>
<td>2.10</td>
<td>2.00</td>
</tr>
</tbody>
</table>
Table 4

Study B: Percentages of positive UA levels for stimulants (amphetamines, cocaine, methamphetamine) across 19 time points, CTN 46

<table>
<thead>
<tr>
<th>Time</th>
<th>1</th>
<th>2.1</th>
<th>2.2</th>
<th>3.1</th>
<th>3.2</th>
<th>4.1</th>
<th>4.2</th>
<th>5.1</th>
<th>5.2</th>
<th>6.1</th>
<th>6.2</th>
<th>7.1</th>
<th>7.2</th>
<th>8.1</th>
<th>8.2</th>
<th>9.1</th>
<th>9.2</th>
<th>10.1</th>
<th>10.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant UA</td>
<td>25.1</td>
<td>13.7</td>
<td>12.7</td>
<td>13.6</td>
<td>11.4</td>
<td>14.5</td>
<td>7.64</td>
<td>15.4</td>
<td>13.9</td>
<td>15.4</td>
<td>12.7</td>
<td>16.0</td>
<td>13.6</td>
<td>15.8</td>
<td>16.4</td>
<td>17.0</td>
<td>14.6</td>
<td>17.0</td>
<td>16.25</td>
</tr>
</tbody>
</table>
Table 5

*Percentages of positive CO levels across 19 time points, CTN 46*

<table>
<thead>
<tr>
<th>Time</th>
<th>1</th>
<th>2.1</th>
<th>2.2</th>
<th>3.1</th>
<th>3.2</th>
<th>4.1</th>
<th>4.2</th>
<th>5.1</th>
<th>5.2</th>
<th>6.1</th>
<th>6.2</th>
<th>7.1</th>
<th>7.2</th>
<th>8.1</th>
<th>8.2</th>
<th>9.1</th>
<th>9.2</th>
<th>10.1</th>
<th>10.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO Levels</td>
<td>100</td>
<td>76.6</td>
<td>72.6</td>
<td>68.7</td>
<td>65.6</td>
<td>58.5</td>
<td>53.4</td>
<td>54.8</td>
<td>54.1</td>
<td>53.8</td>
<td>51.6</td>
<td>52.2</td>
<td>51.4</td>
<td>53.5</td>
<td>50.4</td>
<td>50.0</td>
<td>49.3</td>
<td>51.6</td>
<td>50.6</td>
</tr>
</tbody>
</table>
Table 6  

*Study A: Model fit for ADHD symptoms*

<table>
<thead>
<tr>
<th>Model Steps</th>
<th>$\chi^2$</th>
<th>df</th>
<th>CFI</th>
<th>RMSEA (90% CI)</th>
<th>SRMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fixed Intercept</td>
<td>1833*</td>
<td>42</td>
<td>.000</td>
<td>.410 (.394 - .426)</td>
<td>.836</td>
</tr>
<tr>
<td>2. Random Intercept</td>
<td>1253*</td>
<td>41</td>
<td>.000</td>
<td>.341 (.325 - .357)</td>
<td>.698</td>
</tr>
<tr>
<td>3. FI-Fixed Slope</td>
<td>1614*</td>
<td>41</td>
<td>.000</td>
<td>.389 (.373 - .405)</td>
<td>.705</td>
</tr>
<tr>
<td>4. RI-FS</td>
<td>789*</td>
<td>40</td>
<td>.277</td>
<td>.272 (.255 - .288)</td>
<td>.525</td>
</tr>
<tr>
<td>5. RI-RS</td>
<td>615*</td>
<td>38</td>
<td>.443</td>
<td>.245 (.228 - .262)</td>
<td>.379</td>
</tr>
<tr>
<td>5A. RI-RS, CR</td>
<td>406*</td>
<td>31</td>
<td>.638</td>
<td>.218 (.200 - .238)</td>
<td>.362</td>
</tr>
<tr>
<td>6. Fixed Quad</td>
<td>415*</td>
<td>37</td>
<td>.635</td>
<td>.201 (.183 - .218)</td>
<td>.299</td>
</tr>
<tr>
<td>7. Random Quad</td>
<td>283*</td>
<td>34</td>
<td>.760</td>
<td>.170 (.152 - .188)</td>
<td>.171</td>
</tr>
<tr>
<td>7A. RQ, CR</td>
<td>208*</td>
<td>27</td>
<td>.826</td>
<td>.162 (.142 - .183)</td>
<td>.176</td>
</tr>
<tr>
<td>8. Shape</td>
<td>179*</td>
<td>32</td>
<td>.857</td>
<td>.135 (.116 - .154)</td>
<td>.123</td>
</tr>
<tr>
<td>8A. Shape, CR</td>
<td>82*</td>
<td>25</td>
<td>.945</td>
<td>.095 (.073 - .118)</td>
<td>.093</td>
</tr>
<tr>
<td><strong>8B. Shape, CR + 1</strong></td>
<td><strong>69</strong></td>
<td><strong>28</strong></td>
<td><strong>.956</strong></td>
<td><strong>.086 (.063 - .110)</strong></td>
<td><strong>.089</strong></td>
</tr>
</tbody>
</table>

Note. CFI = comparative fit index; RMSEA = root mean square error of approximation; SRMR = standardized root mean square residual.  
* $p < .05$; ns = non-significant.
Table 7

*Study A: Model fit for CO levels*

<table>
<thead>
<tr>
<th>Model Steps</th>
<th>$\chi^2$</th>
<th>df</th>
<th>BIC</th>
<th>AIC</th>
<th>LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fixed Intercept</td>
<td>3530</td>
<td>4032</td>
<td>3503</td>
<td>3499</td>
<td>-1749</td>
</tr>
<tr>
<td>2. Random Intercept</td>
<td>3036</td>
<td>4046</td>
<td>3271</td>
<td>3264</td>
<td>-1630</td>
</tr>
<tr>
<td>3. FI-Fixed Slope</td>
<td>2207</td>
<td>4047</td>
<td>2728</td>
<td>2721</td>
<td>-1359</td>
</tr>
<tr>
<td>4. RI-FS</td>
<td>1403</td>
<td>4059</td>
<td>2299</td>
<td>2289</td>
<td>-1141</td>
</tr>
<tr>
<td>5. RI-RS</td>
<td>405</td>
<td>4055</td>
<td>2067</td>
<td>2049</td>
<td>-1020</td>
</tr>
<tr>
<td>6. Random Quad</td>
<td>1087</td>
<td>4065</td>
<td>1828</td>
<td>1796</td>
<td>-889</td>
</tr>
<tr>
<td>7. Random Cubic</td>
<td>945</td>
<td>4056</td>
<td>1828</td>
<td>1777</td>
<td>-875</td>
</tr>
<tr>
<td>8. 3S Piecewise</td>
<td>577</td>
<td>4064</td>
<td>1689</td>
<td>1640</td>
<td>-806</td>
</tr>
<tr>
<td>8A. P with Shape</td>
<td>580</td>
<td>4056</td>
<td>1713</td>
<td>1645</td>
<td>-804</td>
</tr>
<tr>
<td><strong>9. 2I2S Piecewise</strong></td>
<td><strong>247</strong></td>
<td><strong>4057</strong></td>
<td><strong>2034</strong></td>
<td><strong>1989</strong></td>
<td><strong>-981</strong></td>
</tr>
</tbody>
</table>

Note. BIC = Bayesian information criteria; AIC = Akaike information criteria; LL = Log-likelihood.
Table 8

Study B: Model fit for stimulant use

<table>
<thead>
<tr>
<th>Model Steps</th>
<th>$\chi^2$</th>
<th>df</th>
<th>BIC</th>
<th>AIC</th>
<th>LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fixed Intercept</td>
<td>--</td>
<td>--</td>
<td>7495</td>
<td>4790</td>
<td>-3744</td>
</tr>
<tr>
<td>2. Random Intercept</td>
<td>--</td>
<td>--</td>
<td>4321</td>
<td>4313</td>
<td>-2154</td>
</tr>
<tr>
<td>3. FI-Fixed Slope</td>
<td>--</td>
<td>--</td>
<td>7501</td>
<td>7492</td>
<td>-3744</td>
</tr>
<tr>
<td>4. RI-FS</td>
<td>--</td>
<td>--</td>
<td>4327</td>
<td>4314</td>
<td>-2154</td>
</tr>
<tr>
<td><strong>5. RI-RS</strong></td>
<td>--</td>
<td>--</td>
<td><strong>4214</strong></td>
<td><strong>4193</strong></td>
<td><strong>-2091</strong></td>
</tr>
<tr>
<td>6. Fixed Quad</td>
<td>--</td>
<td>--</td>
<td>4205</td>
<td>4180</td>
<td>-2083</td>
</tr>
<tr>
<td>7. Random Quad</td>
<td>--</td>
<td>--</td>
<td>4211</td>
<td>4172</td>
<td>-2077</td>
</tr>
</tbody>
</table>

Note. BIC = Bayesian information criteria; AIC = Akaike information criteria; LL = Log-likelihood.
### Table 9

**Study B: Model fit for CO levels**

<table>
<thead>
<tr>
<th>Model Steps</th>
<th>$\chi^2$</th>
<th>df</th>
<th>BIC</th>
<th>AIC</th>
<th>LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fixed Intercept</td>
<td>--</td>
<td>--</td>
<td>19020</td>
<td>19021</td>
<td>-9504</td>
</tr>
<tr>
<td>2. Random Intercept</td>
<td>--</td>
<td>--</td>
<td>14496</td>
<td>14483</td>
<td>-7239</td>
</tr>
<tr>
<td>3. FI-Fixed Slope</td>
<td>--</td>
<td>--</td>
<td>18746</td>
<td>18733</td>
<td>-9363</td>
</tr>
<tr>
<td>4. RI-FS</td>
<td>--</td>
<td>--</td>
<td>13947</td>
<td>13930</td>
<td>-6961</td>
</tr>
<tr>
<td><strong>5. RI-RS</strong></td>
<td>--</td>
<td>--</td>
<td><strong>13465</strong></td>
<td><strong>13440</strong></td>
<td><strong>-6714</strong></td>
</tr>
<tr>
<td>6. Fixed Quad</td>
<td>--</td>
<td>--</td>
<td>13403</td>
<td>13373</td>
<td>-6679</td>
</tr>
<tr>
<td>7. Random Quad</td>
<td>--</td>
<td>--</td>
<td>13299</td>
<td>13257</td>
<td>-6619</td>
</tr>
</tbody>
</table>

**Note.** BIC = Bayesian information criteria; AIC = Akaike information criteria; LL = Log-likelihood.
Table 10

Study A: Correlations within disorders

<table>
<thead>
<tr>
<th>Model</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ADHD Intercept</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. ADHD Slope (Shape)</td>
<td>0.30**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. CO Intercept 1</td>
<td>NA</td>
<td>NA</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. CO Slope 1</td>
<td>NA</td>
<td>NA</td>
<td>-0.74**</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. CO Intercept 2</td>
<td>NA</td>
<td>NA</td>
<td>-0.02**</td>
<td>-0.67</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>6. CO Slope 2</td>
<td>NA</td>
<td>NA</td>
<td>-0.31</td>
<td>-0.41*</td>
<td>0.94*</td>
<td>--</td>
</tr>
</tbody>
</table>

Note. * p < .05; ** p < .10. Values taken from separate LGCM models for ADHD and CO. Across disorder values were not available.
Table 11

*Study B: Correlations within and across disorders*

<table>
<thead>
<tr>
<th>Model</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. SU Intercept</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. SU Slope</td>
<td>0.05</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. CO Intercept</td>
<td>-0.13*</td>
<td>0.03</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>4. CO Slope</td>
<td>0.04</td>
<td>-0.12</td>
<td>-0.03</td>
<td>--</td>
</tr>
</tbody>
</table>

Note. * p < .05; ** p < .10.
Table 12

*Study A: Regressions of treatment on slopes*

<table>
<thead>
<tr>
<th>Treatment Interval</th>
<th>β</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treatment on CO Slope 1</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>2. Treatment on CO Slope 2</td>
<td>-0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>3. Treatment on ADHD Slope</td>
<td>-0.34*</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Note. β = standardized regression coefficient, SE = standard error. *p < .05. Values taken from separate LGCM models for ADHD and CO. CO Slope 1 = CO level slope from Week 0 – Week 4; CO Slope 2 = CO slope from Week 5 – Week 11.
Table 13

*Study B: Regressions of slopes on different-disorder intercepts and regressions of treatment on slopes*

<table>
<thead>
<tr>
<th>Treatment Interval</th>
<th>β</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CO Slope regressed on SU intercept</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>2. SU Slope regressed on CO intercept</td>
<td>0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>3. CO Slope on Treatment</td>
<td>0.52*</td>
<td>0.04</td>
</tr>
<tr>
<td>4. SU Slope on Treatment</td>
<td>0.01</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Note. β = standardized regression coefficient, SE = standard error. *p < .05.
Figure 1. Study A: ADHD Rating Scale total score.
Figure 2. Study A: Percentage of participants with positive CO-levels.
Figure 3. Study B: Percentage of participants with positive UA for amphetamine.
Figure 4. Study B: Percentage of participants with positive UA for cocaine.
Figure 5. Study B: Percentage of participants with positive UA for methamphetamine.
Figure 6. Study B: Percentage of participants with positive UA for stimulant use (amphetamine, cocaine
Figure 7. Study B: Percentage of participants with positive CO levels.
Figure 8. Study B: Percentage of participants with positive CO-levels and positive UA for stimulants.
Figure 9. Study A: Final model of latent growth curve model for ADHD with eight time points and adjacent correlated residuals and one correlated residual between Week 7 and Week 11. * p < .05; ** p < .10.
Study A: CO Latent Growth Curve Model

Figure 10. Study A: Final model of latent growth curve model for CO-levels with twelve time points. * p < .05; ** p < .10.
Study B: Stimulant Use Latent Growth Curve Model

Figure 11. Study B: Schematic model of latent growth curve model for stimulant use with nineteen time points (Baseline contains one data point, Week 2 – Week 10 each contain two data points). * p < .05; ** p < .10.
Figure 12. Study B: Schematic model of latent growth curve model for CO levels with eighteen time points (Week 2 – Week 10 each contain two data points). * p < .05; ** p < .10.
Figure 13. Study A: Schematic model of parallel latent growth curve model for ADHD and CO levels with correlations across disorders and model regressed on treatment. Treatment represented in red. Correlations represented in orange.
Figure 14. Study A: Schematic model of latent growth curve model for ADHD regressed onto treatment.
Figure 15. Study A: Schematic model of latent growth curve model for CO levels regressed onto treatment.
Figure 16. Study B: Schematic model of parallel latent growth curve model for stimulant use and CO-levels with correlations across disorders. Correlations represented in orange.
Figure 17. Study B: Schematic model of parallel latent growth curve model for stimulant use and CO-levels with regressions across disorders and model regressed on treatment. Regressions represented in orange. Treatment represented in red.
REFERENCES


of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse.


disorders: Emphasis on integration in mental health and addiction treatment settings.

*Annual Review of Clinical Psychology, 5, 409 – 431.*


Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews: Reviews 2007, (1).*


Randomized trial of continuing care enhancements for cocaine-dependent patients following initial engagement. *Journal of consulting and clinical psychology*, 78(1), 111.


Roll, J. M., Higgins, S. T., & Tidey, J. (1997). Cocaine use can increase cigarette smoking:


Secades-Villa, R., Garcia-Rodriguez, O., Lopez-Nunez, C., Alonso-Perez, F., Fernadez-


