5-9-2014

Prescription Opioid Abuse: A Gateway to Abuse of Other Prescription Medications?

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B.S., University of Connecticut, 2009

A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Public Health

University of Connecticut

2014

APPROVAL PAGE

Master of Public Health Thesis

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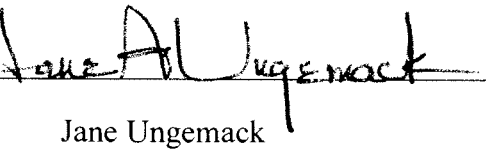
Major Advisor 

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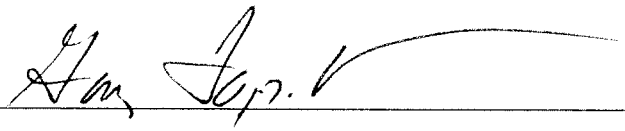
Associate Advisor 

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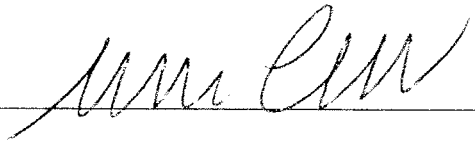
Associate Advisor 

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2014

Acknowledgements

I would like to express my appreciation to all those who provided me the possibility to complete this report. A special thanks to Dr. Jane Ungemack who has advised me on this project. She continually encouraged my excitement in regards to research and has showed me the good that can arise from the study of public health and medicine together.

I am thankful to my advisor, Dr. Miranda Lynch, who helped guide me through the statistical components of this study and help me gain great appreciation for the careful manipulation and interpretation of data.

Another special thanks to Gary Lapidus, who early in my public health studies instilled in me a love for injury prevention. This eventually blossomed and served as inspiration for this project.

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Introduction

Drug overdose deaths more than tripled from 1990 to 2008 (CDC, 2011). The majority of this rise in drug-related mortality has been attributed to prescription drug abuse, particularly abuse of prescription opioids and stimulants. The epidemic of opioid abuse with origins in the medical establishment has gained the attention of Federal and State officials and has resulted in policy changes to try and mitigate this alarming trend (Worley, 2012). With rates of prescription drug use and abuse rising, it is more important now than ever to have a more complete understanding of the nature of substance abuse, particularly involving prescription drugs.

Most research on the onset of drug abuse has focused on 'licit to illicit' drug use, where prescription drugs are generally grouped in the same category as 'illicit' drugs. There is little known about how initiation of differing prescription drugs may be associated with or may affect one another, and in turn how policy changes set to mitigate the opioid epidemic will affect the rates of abuse of other prescription drugs. The purpose of this study is to apply a "gateway hypothesis" analysis on age of initial misuse of major subtypes of prescription medications (i.e., pain relievers/prescription opioids, tranquilizers, stimulants, and sedatives) to better understand the relationship between different prescription medications. A review of the background surrounding this issue and a proposed model for prescription drug abuse initiation is provided and the model tested.

There is often some confusion in the literature of prescription drug misuse. The terms "misuse" and "abuse" are often erroneously used interchangeably. Abuse describes intentional aberrant behavior by individuals seeking a feeling of euphoria. This behavior

is typical of drug addicts. On the other hand, misuse describes a more general definition, using the prescription medication for any purposes other than what it's intended. It can be difficult to differentiate the two in research studies, thus this paper will use these terms interchangeably. Also this study will use the terms pharmaceutical pain relievers interchangeably with prescription opioids and prescription narcotics.

Background

From 1985 to 1995, there was a 25% increase in mortality due to overdose or drug poisoning in the U.S. general population (Fingerhut and Cox, 1998). This report indicated that the rise was largely due to opiate abuse, but it was not possible to determine whether the drugs responsible were prescription opioids or heroin. By 2004, the Center for Disease Control and Prevention (CDC) reported that from 1999 to 2000 more deaths were associated with prescription narcotics than heroin (CDC, 2004). By 2007, opioid analgesics were responsible for approximately 12,000 unintentional deaths compared to 2,000 deaths from heroin abuse. Prescription drug abuse and associated deaths continued to grow at a steady rate through to 2009, when prescription drug overdose death rates (37,500 deaths/year), mostly due to opioids, surpassed motor vehicle crash deaths (36,000 deaths/year) (SAMHSA, 2011). Today in the U.S., rates of prescription opioids are abused by an estimated 2.1 million persons, second only to abuse of marijuana (4.3 million) (SAMHSA, 2013).

Although abuse of prescription opioids have garnered the greatest attention, abuse of all major categories of prescription drugs (pain relievers, tranquilizers, stimulants, and sedatives) have increased over the past decade (SAMHSA, 2013). From 2000 to 2011,

stimulant abuse increased among 19-28 year olds from 6.6% to 9.3% for college students and 5.4% to 7.2% for non-college adults (Johnston, 2013). The number of people who initiated misuse of tranquilizers rose from 573,000 in 2004 to 1.4 million in 2012. People who began abusing sedatives rose from 128,000 in 2004 to 166,000 in 2012 (SAMHSA, 2013; Coliver, 2006).

Over-prescription by the medical establishment has been identified as playing an important role in causing the epidemic (Paulozzi, 2012). Paulozzi (2012) found a close correlation between rising rates of sales for prescription opioids and prescription opioid-related deaths. Studies have shown these individuals most often get prescription drugs from friends with access to these medications from physicians (Rabiner, 2013). This was further supported by the 2012 National Survey on Drug Use and Health (NSDUH) results showing that the majority of individuals who abuse prescription opioids obtain the medications either directly from a single provider or free from a friend/ relative who received them from a single medical provider (SAMHSA, 2013).

Various forms of interventions have been established at the State and Federal level to mitigate this alarming trend. For instance, the Prescription Drug Monitoring Program, allowing medical professionals to see when and where their patients have been prescribed narcotics, have been implemented in states across the U.S. to increase medical provider accountability. Likewise, Medication Restrictions Programs have been implemented to limit patients obtaining prescription narcotics from a single designated pharmacy (Hernandez and Nelson, 2010).

These interventions and policy changes are meant to act on the medical system and mitigate over-prescription practices at the level of the doctor's office and pharmacy. These policies target general prescription medications defined as "class II to IV drugs," encompassing all commonly abused prescription medications. These policies are almost always directed toward general prescriptions written within the context of pain management and primarily address the issue of prescription opioids and less so the abuse of other prescription medications (Manchikanti, 2007). This is due to prescription opioids being the only medications independently associated with the rising death rates from overdoses (Manchikanti, 2007). Thus, these interventions do little to address the problem of non-opioid prescription drug abuse.

More information about the initiation of prescription drug abuse is needed before appropriate steps can be taken to address the broader problem of prescription drug abuse. Until now, the majority of research on drug abuse with respect to patterns of initiation has been focused on the association between licit and illicit drugs. Typically, these studies equate prescription drug use patterns to illicit drug use (Kandel, 2002; Yamaguchi & Kandel, 1984; Kirby, 2012). Few studies have looked at potential differences in abuse patterns between illicit drug abuse and prescription drug abuse. One study found that a modeling sequence used to explain generalized substance abuse did a poor job describing the pattern of abuse when applied to prescription drugs (Kandel, Yamaguchi, & Chen, 1992). Kandel and her colleagues noted that a generalized gateway model between licit and illicit drugs, where prescription medications were equated to illicit drugs, could only account for 60% of prescription drug abuse whereas the same model was predictive of at least 80% for all other substances studied. In other words, only 60% of individuals

abusing prescription drugs could be accounted for when they were assumed to fall within the same sequence of drug abuse as illicit drugs.

Despite being grouped with illicit drugs by researchers, patterns of misuse of prescription drugs have very striking differences. Unlike illicit drugs, 77% to 89% of prescription drugs that are abused are obtained *legally* through pharmaceutical prescriptions and then illegally trickled down to other members of the community (Manchikanti, 2007). Because of their association with medicine, these substances are often regarded by the general public as safer and less stigmatizing compared to their street drug alternatives (SAMHSA, 2013).

These findings suggest that the initiation of prescription drug abuse may follow a different sequence and pattern of initiation than is seen in other types of illicit substance abuse. Unfortunately, not enough research has been done on the subject to suggest an alternative model that would explain initiation of prescription drug use.

Prescription drug abuse is on average initiated in the early to mid-twenties, whereas use of most illicit drugs begins in teenage years. Marijuana has been identified as a gateway drug to other illicit substance use (Kandel, 1978; Kandel & Yamaguchi, 2002). The average age of first use of marijuana has been found to be 17.9 years in the population 12 to 49, whereas the average age of initiation for stimulants is 22.1 years, pain killers (22.3 years), tranquilizers (23.6 years), and sedatives (26.6 years), long after marijuana use may be initiated (SAMHSA, 2013). Prescription opioids far outnumber other prescription drugs in rates of abuse, and in turn may serve as a "gateway" to augment future risk of exposure to other similar yet less popular prescription drugs. An

independent prescription opioid gateway theory could potentially help explain some of the inconsistencies seen between prescription drugs. Further, if proven true, this information could give some indication of what can be expected after government interventions are put in place to reduce or prevent prescription opioid use.

Gateway Drug Hypothesis

The concept of a gateway hypothesis assumes that progression in drug abuse follows a pattern of developmental staging. This manifests as a hierarchical sequence of use of different drugs that individuals progress through as they continue to abuse drugs. This hypothesis was first investigated 40 years ago (Kandel, 1975). Although the sequence of drugs abused has varied slightly between studies, over the years a definite pattern of abuse has been established and well supported (Vanlenzuela, 2011). The hierarchy usually starts with use of licit drugs (i.e., tobacco and/or alcohol) followed by marijuana, then later 'harder drugs' such as cocaine and eventually heroin. The testing of this hypothesis ultimately led to recognition of marijuana as a "gateway" drug (Kandel, Yamaguchi, & Chen, 1992, Kandel, 2002). The basic assertion of the gateway hypothesis is that sequenced drug use is not random in nature but rather follows a defined pathway. Use of licit drugs facilitate or "open the door" to marijuana use and in turn marijuana facilitates the progression to more addictive and dangerous illicit drugs (Kandel, 2002).

The gateway phenomenon is based on three propositions: sequencing, association, and causation (Kandel, 2002). *Sequencing* requires a relationship between different substances such that one substance is regularly initiated before another. *Association* implies that initiation of one substance increases the likelihood or risk of initiating the

second substance. *Causation* posits that the use of the first substance actually causes the use of the second (Valenzuela & Fernández, 2011). Although the gateway hypothesis has substantial support from multiple research studies that overwhelmingly show *sequencing* and *association*, it has been difficult to establish causality between substances (Kandel, Yamaguchi, & Chen, 1992; Hall & Pacula, 2003; Lynskey, Heath, Bucholz et al., 2003; Bretteville-Jensen, Melberg, & Jones, 2005). Typically a single variable sequencing analysis, usually a Guttman analysis, is performed to show the presence of and describe a drug sequence to support a gateway hypothesis (Kirby, 2012).

As stated earlier, prescription opioids have been studied in generalized gateway drug models but the results have shown that their adherence to the models were significantly less than expected, especially compared to illicit drug abuse. In a report by Kandel and her colleagues (1992), prescription drugs were the only substances noted to have two distinct branching patterns stemming from the hierarchical sequence of the gateway drug hypothesis. The first branch showed prescription use before the initiation of marijuana, which is contrary to the marijuana gateway drug theory. In the second, however, use of prescription drugs came after marijuana use, consistent with the gateway drug theory. These ambiguities in the results of the study were interpreted as potentially being due to initiating use of prescription medications at different stages in time (Kandel, Yamaguchi, & Chen, 1992). The study did not distinguish between different types of prescription medications. The most interesting part of these results was that the rates reported for initial prescription drug use prior to marijuana use were consistently higher than post-marijuana use. This suggests that most prescription drug use is initiated

independent of marijuana use and in turn could potentially act like a gateway drug itself.

Factors in Progression

An underlying principle of the gateway model is that there will be increased likelihood of progression through the sequence once drug use has been initiated. Although some authors adamantly hold to the idea of unavoidable progression once the sequence has started, others perceive the pattern of progression to work under more facilitative principles (Goode, 1972; Leshner, 2002). The idea of unavoidable progression largely does not explain why many individuals who initiate substance use often stop at certain stages along the sequence without continuing on to "harder" drugs. A more facilitative perspective describes the push to get to the next drug in the sequence as "transition proneness" (Donovan, Jessor, & Costa, 1988; Osgood, Johnston, O'Malley et al., 1988; Kandel, Yamaguchi, & Chen, 1992). This "proneness" is considered a vulnerability of certain individuals to use different classes of drugs and thus more easily move through the stages of drug use development. These individuals are often prone to other behavioral and social problems, as well. Their actions are described as an opportunistic response to environmental conditions by which these individuals are 'prone' to advancing to harder drugs (Kandel, Yamaguchi, & Chen, 1992).

Many studies have looked at factors that are associated with progression through the illicit drug sequence. One of the most important factors identified as predictive of progression is age of initiation (CITE). Initiating substance use at a younger age is associated with greater risk of progression, thus increasing exposure to more addictive and potentially dangerous drugs down the sequence. Individuals that initiate drug use at a later age have less time to progress through the sequence. This essentially describes a

window period of risk to drug abuse; it also helps to explain why general drug use often stops in adulthood (Labouvie & White, 2002). Researchers have described age of initiation as being so strong a factor that some reports predict drug trajectories from only age of initiation (Labouvie & White, 2002; Kandel & Yamaguchi, 2002; Lynskey, Heath, Bucholz et al., 2003; Agrawal, Neale, Prescott et al., 2004; Lynskey, Vink, & Boomsma, 2006).

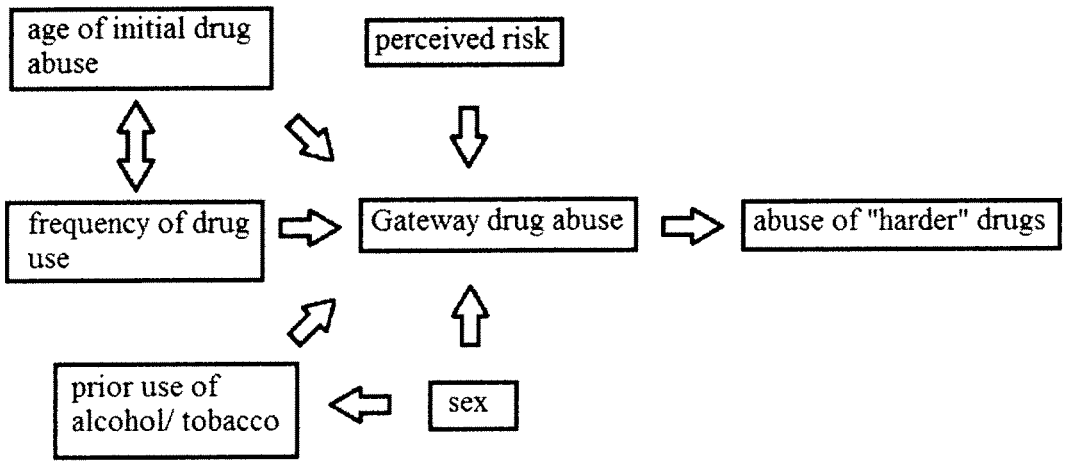
Another major factor for drug sequence progression is the intensity of drug use. Individuals with more frequent or regular patterns of use tend to proceed further along the sequence (Newcomb & Bentler, 1986; Fergusson, Boden, & Horwood, 2006; Kandel & Yamaguchi, 2002). Although frequency of drug use has been identified as an independent factor, it has also been shown to be associated with initiation of drug use at an early age, as well as engagement in precocious behaviors. Precocious behavior is used to describe recreational drug use. Precocious individuals can be difficult to discern from high intensity drug users, who are ultimately at higher risk for progressing to harder drugs. By measuring frequency of use, studies have been able to differentiate between cases of precocious behavior and high intensity substance abusers (Labouvie & White, 2002).

The use of alcohol and tobacco have also been identified as risk factors for initiation and progression of drug use. These two behaviors have such a strong correlation with initiation of other drug use that some researchers have argued that alcohol and tobacco are the true gateway drugs (Hawkins, Hill, & Battin-Pearson, 2002; Yamaguchi & Kandel, 1984). These studies have noted a difference in initiation patterns between the sexes. Males are more likely to initiate illicit drug use if they had prior exposure to either alcohol or cigarettes, with alcohol playing a larger role. Females were more likely to

initiate illicit drug use with prior exposure to only cigarettes (Yamaguchi & Kandel, 1984).

Perceived risk of drugs and social acceptability have also been identified as risk factors for progression of drug use. Research has shown that a decreased perception of risk of harm of using tobacco and marijuana was associated with increased likelihood of individuals eventually using those drugs (Hawkins, Hill, & Battin-Pearson, 2002; Kandel & Yamaguchi, 2002). This notion of perceived risk related to likelihood of substance initiation was then expanded to harder substances later in the sequence of drug abuse. This was called the "learning effect.," The learning effect is described as an individual having a decreased perception of risk for more dangerous/harder drugs because experience with preceding drugs did not lead to negative effects (Valenzuela & Fernández, 2011).

Figure 1. Model of Factors Leading to "Harder" Drug Use



Finally, "differential association," or peer influence, has been reported as a risk factor for sequence progression (Fergusson, Boden, & Horwood, 2006; Kandel, 1978).

This refers to increased opportunities for vicarious learning via peers that use drugs. This also allows accessibility to new substances if and when the individual is ready to initiate, thus facilitating the entire process of transition to harder drug use.

The present study explores whether prescription drug abuse can be described by a gateway model particular to prescription drugs. Prescription drugs are unique in regards to how they are seen in society, the manner by which they are attained, and how their misuse permeates into the community. An independent gateway model could explain the seemingly sequential order of "average age of initiation" among prescription drugs and how they seem chronologically isolated from other abused substances. This study was designed to investigate whether there is a sequence of abuse among prescription drugs and describe how well a gateway model describes the data. The results address two of the three requirements in defining a gateway model, *sequencing* and *association*. This study posits a sequence of use among different types of prescription drugs and relative risk of progressing from one prescription drug to the next in the sequence. The analysis helps elucidate how the pattern of progression works and how closely illicit and prescription drug abuse are related to one another.

Methods

This study is based on a secondary analysis of the 2012 U.S. National Survey on Drug Use and Health (NSDUH), an annual national population survey conducted by Substance Abuse and Mental Health Services Administration (SAMHSA). The data analysis examines sequencing of prescription drug use based on the gateway hypothesis model independent of other legal and illegal substances, estimates the relative risk of progressing throughout the drug sequence, and performs a chronological assessment to

elucidate which prescription drugs are used first based on self-reported data regarding age of initiation of each drug.

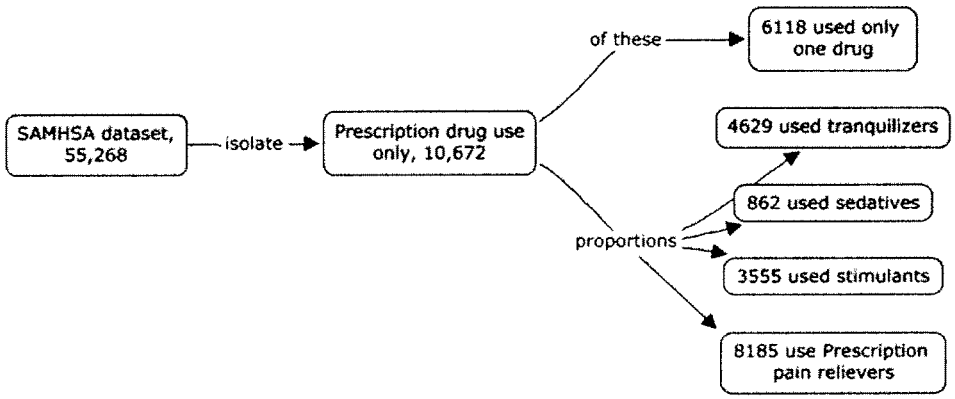
Data Source

The NSDUH is an annual, household survey of civilian, non-institutionalized U.S. population aged 12 and older. The purpose of the survey is to provide national, state, and substate estimates on substance abuse and mental health issues. Potentially sensitive topics, which constitute a large proportion of the survey, are queried using a computer-assisted, self-administered platform. Youths are oversampled and larger states contribute more respondents in attempt to be better representative at both the state and national levels. This study was considered exempt from full Institutional Review Board (IRB) review by the University of Connecticut since it is a secondary analysis of de-identified data.

Analytic Sample

The original data set obtained by SAMHSA contained 55,268 individuals. Of this large initial pool, only individuals who had reported an age of initiation for at least one of the four prescription drug types (pain killers, tranquilizer, stimulants, and sedatives) were retained, decreasing the number in the analytical data set to 10,672 observations. Of these, 6,118 were found to have used only one prescription drug. Of the 10,672 observations, 8,185 were found to have used prescription pain relievers, 4,629 used tranquilizers, 3,555 reported use of stimulants, and 862 used sedatives.

Figure 2. Flowchart of Prescription Drug Users in the 2012 NSDUH



A small portion of the 10,672 individuals (172) were noted to have very young ages of initiation recorded for one or more of the prescription drugs of interest. For instance, the youngest report of initial prescription drugs use for non-medical purposes was one year of age. These cases with excessively young ages were removed. A cut off was made at 10 years of age, so all those who reported 9 years of age and younger for any of the four drug types were removed from the study analysis. It is understood that making this type of cut off can exclude some legitimate points from the data set, but considering they comprise only a small subset of all individuals who reported using prescription drugs for non-medical purposes (1.6%) the data removal is justified. Upon limiting the dataset by prescription drug use to age 10 years or older, 10,500 individuals comprised the final data set used for analysis.

The analytic sample only included individuals who self-reported age of initial prescription drug use for non-medical purposes. The four types of prescription medications assessed in the survey were prescription pain relievers, tranquilizers, stimulants, and sedatives, as defined by the NSDUH 2012 codebook pages 65-75, 83-89, 93-99, 105-109, respectively (SAMHSA, 2013). The variables used in coding to obtain

numeric age of initiation for each prescription drug per individual were "ANALAGE" (pain relievers), "TRANAGE" (tranquilizers), "STIMAGE" (stimulants), and "SEDAGE" (sedatives).

Pain relievers were defined by the NSDUH survey as prescription narcotics (i.e., oxycodone, dilaudid, demerol, Tylenol with codeine, etc.). Tranquilizers were defined as prescription anti-anxiety benzodiazepines drugs (i.e., clonazepam, alprazolam, lorazepam, diazepam, etc.). Stimulants were defined as prescription amphetamines (i.e., methamphetamine, desoxyn, methedrine, etc.). Sedatives were defined as a heterogeneous group of prescription "sleeping pills" used for sedation which includes barbituates, benzodiazepines, and numerous other classes and class derivatives (i.e., methaqualone, sopor, quaalude, nembutal, restoril, temazepam, etc.).

Analysis

All statistical analyses were performed using SAS 9.3. A Guttman sequence was created by converting all reported numerical ages into binary outputs. The binary variable was defined as "1"to represent 'had used specific prescription drug in the past' and "0" to represent 'not used specific prescription drug in the past.' The actual sequence was obtained through a point system. A point was given for every substance an individual reported using. Thus individuals who reported only using one type of medication would have a cumulative score of 1. If they had used two different medications of any combination they would have a score of 2. If they reported using any combination of three medications, their cumulative score would be 3. Individuals that reported using all four drugs, at any point in time would be given a cumulative score of 4. In this manner a "frequency" procedure was used to count the occurrence for each possible two drug

combination and three drug combination. The Guttman sequence is then derived by tabulating the frequency of all combinations from a score of 1 through 4, as shown in Table 1. By selecting the combinations with the highest frequencies for scores 1, 2, 3, and 4, the sequence is created, as shown in Table 2. A coefficient of reliability (CR) was used to assess a goodness of fit between the observed and predicted ideal response pattern (CR = 1 – (# errors / total responses), where total responses = (# items) x (# respondents)) (Kirby and Barry 2012). CR will be used to assess the extent to which the Guttman sequence reflects the data. A CR value of 0.90 is considered to be the minimum standard of acceptability. A CR of 0.90 means that one can predict with 90% accuracy the drugs used by of any survey responder by simply knowing their scale score, and also that sequence of drug use can be predicted with 90% accuracy (Howell, 2010).

The Guttman analysis' binary output ignores time as a variable, thus making no use of the chronologic nature of the dataset. To incorporate a time variable into the analysis a frequency procedure was done to count each time a specific drug's age of initiation was less than the age of initiation of another drug. In effect, for example, counting how often a pain relievers' age of initiation was less than a tranquilizer's age of initiation for individuals that used both substances. This process was then expanded to assess pain relievers being less than stimulants and pain relievers being less than sedatives. This was repeated for tranquilizers (frequency of tranquilizers being less than pain relievers, stimulants, sedatives), stimulants (frequency of stimulants being less than pain relievers, tranquilizers, sedatives), and sedatives (frequency of sedatives being less than pain relievers, tranquilizers, stimulants).

Relative risk of progression through the sequence was then estimated by calculating the odds ratio with its associated 95% confidence interval. This was done by calculating the odds ratio between the first and second prescription drugs in the Guttman sequence with the first serving as the independent variable, then the second and third (i.e., the second serving as the independent variable), and finally the third and fourth drugs (i.e., the third serving as the independent variable).

Results

As seen in Table 1, the majority of prescription drug users were single substance users; they comprised 57% of the population studied. Among these, pain relievers comprised the majority of observations with 36.8% of the cases. Tranquilizers comprised 8.9% of findings, 10% for stimulants, and 1.4% for sedatives. The mean age of initiation for all individuals that used pain relievers was 19.38 years, 20.53 years for tranquilizers, 18.85 years for stimulants, and 20.12 years for sedatives.

Guttman Sequence

The results for the Guttman analysis are shown in Table 1 with the proposed sequence shown in Table 2. The most common prescription drug used in isolation was pain relievers, or prescription narcotics. This pattern accounted for 3,860 of the total 10,500 observations, 37% of all individuals who reported using prescription medication. It was more than triple the size of any other single prescription drug used. Of the possible two drug combinations, Pain killers + Tranquilizers (17%) was the most common accounting for 1,803 observations, which was almost three times more frequent then the second most frequent combination. The most frequent three drug combination found was Pain killers + Tranquilizers + Stimulants at 1,153 (11%) observations and almost ten

times more frequent then the second leading three drug combination. Three hundred eleven cases reported using all four substances. The four drug combination comprised only 2.9% of all individuals that reported using any prescription drugs. The CR, used to assess goodness of fit of this sequence, was found to be 0.8303, indicating that you could predict the pattern of prescription drug use with 83% accuracy, below the 0.90 criterion level.

Table 1. Drug Combination Frequencies

Prescription Drug Combination	Number of Cases	% of total
Pain reliever (A) only	3860	36.76
Tranquilizers (B) only	932	8.87
Stimulants (C) only	1051	10.01
Sedatives (D) only	151	1.44
A + B only	1803	17.17
A + C only	663	6.31
A + D only	75	0.71
B + C only	193	1.84
B + D only	32	0.31
C + D only	64	0.61
A + B + C only	1153	10.98
A + B + D only	125	1.19
A + C + D only	41	0.39
B + C + D only	46	0.44
A + B + C + D	311	2.96
Total Number of Individuals	10,500	

Table 2. Guttman Sequence

Pain relievers	Tranquilizers	Stimulants	Sedatives	Scale Score	Total Number of Individuals
1	1	1	1	4	311
1	1	1	0	3	1153
1	1	0	0	2	1803
1	0	0	0	1	3860

Frequency of Progression by Chronology

The results showing how often a specific type of medication was used before another type are shown in Table 3. The most frequent medication used prior to use of other medications were pain killers. This is shown by the 1,348 observations noting pain relievers being used prior to tranquilizers, 778 observations prior to using stimulants, and 245 observations used prior to sedatives. Stimulants are the second most common drug used prior to other prescription medications with 745 observations prior to pain killers, 761 observations prior to tranquilizers, and 181 observations prior to sedatives. The third most common drug type were tranquilizers with 602 observations noted prior to pain killers, 410 observations prior to stimulants, and 245 observations prior to sedatives. The least common drug type to be used prior to other prescription drugs were sedatives with 142 observations prior to pain killers, 144 observations prior to tranquilizers and 103 observations prior to stimulants.

Further analysis showed that among individuals that used more than one prescription drug, 65% used pain relievers first. Stimulants were the second most common type, with 18% of individuals having used stimulants as their first prescription drug among multi-prescription drug abusers.

Table 3. Frequencies of Drug Pairs by Chronological Order

Type of Prescription Drug Sequence	# that reported using one drug before another	# that used both drugs, regardless of order	# that reported drug initiation at the same age
Pain reliever before Tranquilizers	1348	3392	1442
Pain reliever before Stimulants	778	2168	645
Pain reliever before Sedatives	245	552	165
Tranquilizers before Pain killers	602	3392	1442
Tranquilizers before Stimulants	410	1703	532
Tranquilizers before Sedatives	174	514	196
Stimulants before Pain killers	745	2168	645
Stimulants before Tranquilizers	761	1703	532
Stimulants before Sedatives	181	462	178
Sedatives before Pain killers	142	552	165
Sedatives before Tranquilizers	144	514	196
Sedatives before Stimulants	103	462	178

Estimation of Relative Risk across Guttman Sequence

Estimation of relative risk via odds ratio (OR) from one drug type to the next along the Guttman sequence showed an OR of 0.7695 (0.7029, 0.8424; 95% CI) for using tranquilizers if they report using pain killers (independent variable). The OR for using stimulants if they also reported using tranquilizers (independent variable) was 1.3228 (1.2193, 1.4350; 95% CI). The OR for using sedatives if they also reported using stimulants (independent variable) was 2.5998 (2.2555, 2.9966; 95% CI). None of these CIs include the value 1, indicating a significant finding.

Discussion

The major finding of this thesis is that the data did not support a gateway hypothesis explaining trends in misuse of different types of prescription drugs among prescription drug users. The analysis showed that among multi-prescription drug users, pain relievers most often served as the first abused drug. Despite the data supporting a common initial substance, the data suggests an interchangeable nature between the second and third substances in the sequence, contradicting the presence of a common recurring sequence. The relative risk findings also contradicted the gateway hypothesis by suggesting a decreased risk of tranquilizer use if already using pain relievers.

Nineteen percent of the general population aged 12 or older in the U.S. have reported lifetime use of at least one prescription medications for non-medical purposes. Of these prescription drug abusers, the majority (57%) reported misusing only one prescription medication. The remaining 43% of prescription drug abusers were multi-substance abusers. Because only interactions among multi-prescription drug abusers were used to explore whether there is a gateway sequence of prescription drug abuse, findings and applications of this study are only reflective of a small proportion of substance users. Since the NSDUH survey is representative of total U.S. population, this would involve only 8% of the population 12 or older in the United States. The results of this study only apply to a small fraction of individuals who abuse prescription narcotics, and for whom drug monitoring programs and pharmacy restrictions are intended to effect.

The Guttman sequence derived from this data showed that pain relievers are most likely to be the first drug used by polyprescription drug users, followed by tranquilizers, stimulants, and finally sedatives. Although the gradual decline in frequency from one stage to the next in the sequence is expected, a CR of 0.8303 is less than the 0.90

minimum standard of acceptance (Kirby, 2012). This means that the proposed sequence by the Guttman analysis does not include enough observations to support the viability of this sequence and application of the gateway hypothesis in this manner. Although the minimum standard was not met, the CR was still high enough to suggest the possibility of other underlying patterns of progression.

The chronological analysis, like the Guttman analysis, indicated that pain relievers most often are used prior to other prescription drugs. Pain relievers were typically initiated before tranquilizers, stimulants, and sedatives. Among the three, tranquilizers appear to be the second drug in the sequence, because there were more instances of reported pain reliever use before tranquilizers, than either stimulants or sedatives. This is consistent with findings of the Guttman analysis. At the second stage there was some ambiguity in the pattern, the most frequently occurring prescription drug combination shows tranquilizer use most often comes before pain relievers. The next most common drug after tranquilizers, are stimulants. If a sequence exists, stimulant use would define the third stage. But, again there are divergent sequences. The majority of stimulant abusers go on to use tranquilizers after using stimulants; it is almost equally common for stimulants use to be followed by initiation of prescription pain relievers. Sedative use is typically the fourth drug in the sequence, which is expected given that it's the least prevalent type of prescription drug reported.

These findings of the chronological analysis suggest tranquilizers and stimulants are interchangeable, thus contradicting the idea of a single pattern of prescription drug sequencing. Some of the ambiguity and interchangeable nature of the drugs may be due to a competing pathway with stimulants acting as the starting drug of choice. Having an

alternative pathway run parallel starting with stimulants instead of pain relievers could possibly explain the conflicting patterns of the data, showing a strong correlation with a large subset of people using tranquilizers and pain relievers after initiating stimulants. Another element that could have played a role in masking the effect stimulants have in initiation of multi-substance use is the difference in sample size between substance groups. Pain relievers are used by 75% of individuals in this sample whereas stimulants were used by only 32% of individuals, meaning its effects on the dataset could easily have been dampened by sheer size comparison. More research should be conducted to better describe the initiation of prescription stimulant abuse and its association with other prescription drug abuse.

The odds ratio analysis on the Guttman sequence showed an increased risk among individuals that progressed from tranquilizers to stimulants (OR= 1.3) and from stimulants to sedatives (OR= 2.6). Increased risk as individuals progress from one stage to the next along the sequence is consistent with the gateway hypothesis. An OR of 0.77 depicting a protective effect of pain reliever on tranquilizer use was unexpected and does not correlate with the *association* premise of the gateway hypothesis. Considering the results are statistically significant. Possible explanations for these findings could be due to particular characteristics of the subpopulation of tranquilizer users.

Limitations of this study include a lack of risk factor assessment and limited understanding of how they could serve as confounding variables. Important potential risk factors that were not assessed by this study include psychological, medical, and social effects of drug use; some of which could help differentiate abuse from self-medication. This study was further limited by the use of only multi-prescription drug users, thus

making the findings only generalizable to a very particular group. Also it is understood the Guttman sequence is a dated statistical analysis. The Guttman analysis uses a single variable regression model, yet the use of a multivariable analysis (one that includes the time variable) to derive the sequence would be significantly more compelling. Further research is needed to address these unexpected findings in determining what factors are predictive of certain types of substance abuse and patterns of use.

Furthermore, future studies should consider controlling for demographic factors such as race, sex, and age-specific patterns. The literature shows that stimulant abuse strongly correlated with high school and college aged individuals, whereas prescription pain reliever abuse can be initiated throughout a larger age range since it is not limited to recreational use by youths, but also due to self-medication among adults and the elderly (Johnston, 2013). There is still little known about how these factors effect trends of prescription drug abuse or even how these factors may correlate with prescription drugs inducing the use of illicit drug independently. Although this study did not examine prescription drug misuse in the context of illicit drug use, recent literature ties use of prescription opioids with heroin subsequent use (McHugh, 2014).

Conclusion

Overall the results of the study did not support the application of the gateway hypothesis to prescription medication abuse with prescription narcotics as the gateway drug. The analysis failed to support the gateway hypothesis premise of both *sequencing* and *association*. *Sequencing* was not supported, visible in the CR < 0.90 and by the chronological assessment suggesting tranquilizers and stimulants could serve interchangeably instead of describing a linear relationship. *Association* was not supported

by the results because the OR of pain relievers to tranquilizers suggested a protective effect rather than posing higher risk. Although it is possible this result is due to confounding variables or independent characteristics of the sub-population, this was beyond the scope of this study. It also was noted due to the small size of the population that abuse of multiple prescription drugs, the results of this study are likely inadequate to draw a conclusion about how future legislation on prescription opioid abuse will effect abuse of other prescription drugs. Much research still remains to be conducted to better understand trends in prescription drug abuse, although a single prescription drug sequence may not be adequate to describe the findings, correction for other risk factors and even looking for alternative parallel sequencing may help explain the some of the ambiguities noted in this study.

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