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Concomitant Use of Central Nervous System Stimulants and Depressants Prescribed in Rhode Island

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CONCOMITANT USE OF CENTRAL NERVOUS SYSTEM STIMULANTS AND DEPRESSANTS PRESCRIBED IN RHODE ISLAND

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ABSTRACT

Background: Risks of morbidity and mortality may arise when prescription stimulants are used in combination with prescription central nervous system (CNS) depressants. The RI Prescription Drug Monitoring Program (PDMP) captures all prescriptions for schedule II to IV, as well as information on certain schedule V medications.

Objective: This study examines the pattern of using a combination of controlled substance prescription CNS stimulants with CNS depressants in RI. We also seek the predictors of concomitant use of these two drugs classes in patients.

Methods: This was a cross-sectional study using de-identified data from the RI PDMP in 2015. We included all patients who filled a prescription for stimulants or CNS depressants. Medications that are not in these two study drug classes were excluded. The outcome of interest was concomitant use of stimulants and CNS depressants, which was defined as patients who filled any stimulants and any depressants with at least 60 days of combined fill and less than 15 days' gap in filling. Demographic characteristics of patients were used in the statistical analyses to identify the predictors of concomitant use of stimulants and depressants.

Results: In the complete RI PDMP data set, there was a total 409,740 patients who filled 2,516,314 prescriptions of schedule II to V medications. The patients using both stimulants and CNS depressants tended to be younger females, which used private pay (cash) more frequently than their male counterparts. Patients in the stimulants and CNS depressants cohort were older women who used

commercial pay type at a higher percentage than their counterparts in the stimulants only cohort. A difference existed in the percent of patients that filled an average days' supply of less than or equal to 30 days compared with greater than 30 days, between those who take both prescription controlled substance stimulants and depressants chronically compared with those who fill only stimulants. In hypothesis 3, patients in the Attention Deficit Hyperactivity Disorder cohort were younger with a lower percentage average daily dose (less than or equal to 25 milligrams) of stimulant, more likely to be of male sex, and use commercial insurance as the primary pay type compared to the usage of stimulants in the stimulants and CNS depressants cohort.

Conclusion: The prevalence of chronic concomitant therapy of stimulants with CNS depressants was associated with prescribing longer days of supply and higher dose of stimulants. The most prevalent pay type of all cohorts was commercial insurance.

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CHAPTER 1

INTRODUCTION

The most commonly prescribed medications for Attention-Deficit/Hyperactivity Disorder (ADHD) in adults in the United States are the controlled substance stimulant class of medications, including amphetamine salt and methylphenidate.[1] Common adverse effects associated with these medications include irritability, anxiety, and difficulty falling asleep or staying asleep.[2] To combat the aforementioned adverse effects, patients may be prescribed central nervous system depressants which can slow down the central nervous system and reduce the stimulant adverse effects.[3,4] Included in these medication classes are tranquilizers, barbiturates/sedatives, muscle relaxants and other prescription sedatives such as zolpidem, eszopiclone and zaleplon. Their desirable side effects or undesirable adverse effects often include: drowsiness, dizziness, tiredness, or in more severe cases respiratory depression leading to coma and death.[3,4] The combination of stimulants and depressants, however, can cause mixed signals within the brain, and can lead to adverse events including coma and death.[4]

A 2015 National Survey of Drug Use and Health (NSDUH) surveyed the use and misuse of individual medications in the four groups separately, but not in concomitant use with medications from the other groups.[1] We analyzed potential signs of misuse by way of comparing overutilization of controlled substances in combination according to the definitions from the Center for Medicare and Medicaid Services (CMS)[5] and the Center for Disease Control.[6] Overutilization has also been termed polypharmacy, or use of more than one pharmacy to fill a

prescription, or an inappropriate medication regimen. Adverse outcomes from unnecessary over-prescribing of medications, particularly in the elderly, may occur from this practice.[7-9] In addition, there is concern for patients of all ages who have taken prescribed stimulants with non-prescribed controlled substances.[10-16] By creating awareness of the prevalence and potential risk factors of this type of antagonistic medication usage, prescribers may be able to target at-risk populations more readily to avoid potential adverse outcomes.

To-date there has been no published study conducted with information from the Rhode Island State Prescription Drug Monitoring Program (PDMP) which describes chronic concomitant therapy of prescription stimulants with prescription depressants. This study sought to discover if there are significant risk factors associated with patients using a combination of prescription central nervous system (CNS) stimulants with prescription CNS depressants based on the demographic characteristics provided by the data source, including age, sex, and payment type.

To better understand the relationship among different subpopulations represented by claims in the RI PDMP and how their baseline demographics and fill history affect the combined use of CNS stimulants and depressants, three hypotheses were developed:

1. There is no difference in baseline characteristics among patients of combination use of stimulants and CNS depressants in consideration of days of concomitant use.
2. There is no difference in the percentage of patients' average days of supply of either less than and equal to 30 days or more than 30 days for those who

chronically fill only a prescription stimulant compared with those who fill prescriptions stimulant(s) with a depressant(s).

3. For those who chronically fill the two most commonly prescribed medication bases for ADHD, there is no difference in the percentage of average daily dose of either less than or equal to 25 milligrams or more than 25 milligrams for patients taking only the ADHD medication base compared with those taking both ADHD medication base stimulants and depressants.

CHAPTER 2

REVIEW OF THE LITERATURE

A paucity of data exists for legally prescribed use of combinations of central nervous system stimulant and depressant medications in the primary care setting, while information is more readily available from small patient clinical trials of patients with a history of drug abuse.[17-21] More information exists in the literature about non-medical users of these CNS medications than of those taking them as prescribed.[10-16] However, adverse outcomes such as emergency department visits, hallucinations, coma, death, may still occur for both populations. In addition, there is a concern for when one controlled substance is used to treat adverse effects of another controlled substance, as proposed by the Drug Enforcement Agency's 2015 resource guide.[4] Stimulants such as modafinil and methylphenidate can reduce sedative effects caused by opioids and other CNS depressants.[22] When used appropriately, this practice can be clinically useful for patients utilizing opioids who feel overly sedated and in the hospice or palliative care setting, but data are lacking to support this practice for adolescents or older patients in the primary care setting.[22-24] Additionally, clinical guidelines from the American Pain Society make no recommendation for the use of any stimulant or other medication for the treatment of opioid-induced sedation.[25] Sedatives/hypnotics and tranquilizers may be used to reduce the stimulant effects of nervousness, restlessness, and difficulty falling asleep or staying asleep.[4] Risk of morbidity and mortality may arise when stimulants are used in combination with central nervous system depressants because this combination can lead to adverse outcomes including hospitalizations,

coma, and death, even at properly prescribed doses.[4] Properly prescribed doses refers to a physician prescribing in the usual course of his/her practice, while staying within FDA-approved maximum daily dosages.

CHAPTER 3

METHODOLOGY

Research design:

A cross-sectional study was conducted using de-identified data from the RI Prescription Drug Monitoring Program (PDMP) for 2015. This study evaluated patterns of combined use CNS stimulant and depressant controlled substance medications in the State of Rhode Island in schedules II, III, IV, and some data on schedule V, as defined by the Controlled Substances Act Code of Federal Regulations Title 21.[26] The PDMP data includes all Schedule II to IV prescription medications, some schedule V medications, and some non-controlled medications, dispensed by RI pharmacies. All pharmacies with a RI controlled substance registration (CSR) number are required by regulation to file a report on all controlled substances filled within 72 hours of the prescription being dispensed to the patient. The data provided by the Rhode Island Department of Public Health for this project included the following information: patient de-identified number, patient age (years), patient's gender, prescriber de-identified number, dispensing pharmacy de-identified number, date dispensed, National Drug Code (NDC) for the drug, drug name, drug strength, formulation, therapeutic class code, days of supply, metric quantity dispensed, and method of payment.

General Characteristics of the study population:

Inclusion criteria:

All study participants who filled a prescription at a Rhode Island pharmacy in the calendar year of 2015 for at least one controlled substance stimulant as well as at least one controlled substance depressant in the 2015 calendar year were included. Medications included in the study were grouped into one of ten categories. These categories were defined by a variable provided within the data set which indicates the therapeutic class code, which is used to differentiate medications based on their primary therapeutic use. The medications were then placed into broader groups based upon the primary effect of the base component(s) of the medications. Stimulants consisted of medications that could generally be considered of use for weight-loss therapy, narcolepsy, or Attention Deficit Hyperactivity Disorder. Examples including, but not limited to were: phentermine, modafinil, and mixed amphetamine salts. CNS depressants consisted of medications that could generally be considered of use for pain mitigation (opioids), cough, sleep disturbance (sedative/hypnotic/tranquilizer), migraines or sedation (barbiturates), neuropathic pain, or skeletal muscle spasms/pain. Examples including, but not limited to, were: oxycodone, hydrocodone, codeine, benzodiazepines (lorazepam, alprazolam, others), zolpidem, carisoprodol, pregabalin, and butalbital. If the medication contained both stimulant and depressant effects, grouping preference was given to whichever component had characteristics which corresponded to a lower schedule (as defined by the Controlled Substances Act). Analysis was based on de-identified PDMP data collected in 2015 in the State of Rhode Island.

Exclusion criteria:

Claims for medications that are not controlled substances were excluded from analyses. Claims for medications that were for hormonal replacement were excluded. Hypothesis 2 further reduced the population by three patients based upon outliers. Hypothesis 3 further reduced the population by removal of all but two stimulant bases, and any non-oral ADHD stimulant (methylphenidate patch).

Index date:

The index date was defined as the first day of overlapping prescription fill date based on a claim beginning January 1, 2015 and ending December 31, 2015.

Dependent Variables (outcomes):

In hypothesis 1, the dependent variable was chronic concomitant therapy, which was deemed "overlap". Overlap was defined as filling one or more stimulants with one or more depressants with 60 or more consecutive days of supply with no gaps >15 days. This definition was chosen based on a previous study that suggested a minimum of 61 days, where by most instances of cross-titration were not misidentified as polypharmacy.[27] As indicated in this study's definition, the one extra day was included (60 vs. 61). In hypothesis 2, the dependent variable was average days of supply, which was binarized to either less than or equal to 30 days or more than 30 days. Thirty days was chosen based upon mean values for the cohorts, as well as a clinically significant length for days supply. Many prescriptions written for patients on chronic therapy of many diseases have their prescriptions written, and filled for, thirty-day periods. This variable was formulated by totaling each patients' days of supply for each claim and dividing it

by 365 days. In hypothesis 3, the dependent variable was average total daily dose of the ADHD stimulant medication, which was binarized to either less than or equal to 25 milligrams or more than 25 milligrams. Twenty-five milligrams was chosen as a cut-off based upon a median value from the cohorts. This variable was derived by multiplying the per unit dosage strength of each medication by the number of dosage units, and then dividing by the days supply. Dichotomous variables were created because the sample sizes were large enough to do so, while also being able to create relevant cutoffs for better interpretation with odds ratios rather than β-coefficients.

Independent variables (exposures):

Independent variables included patient's age, gender, and payment type. Age is given in whole year increments, with the first age at occurrence of claim was used. Gender is given as male or female, with the first gender at occurrence of claim was used. Payment type, using the first occurrence of the claim, included three categories: government/other, private pay, and commercial insurance. Government/other pay type was comprised of several payers including Medicaid, Medicare, Military Institution or Veterans' Administration, Workers' Compensation, Indian Nations, and 'other', as given by the data set.

Descriptive Analysis:

An analysis for individuals in the age groups of (1) younger than 12, (2) 12-17, (3) 18-25, (4) 26-64, and (5) 65 or older, which is similar to how the NSDUH survey differentiated age groups (12-17, 18-26, 26+).[1] This study also examined

the effects of gender on concomitant drug use. The patient's first gender entered into the PDMP data file was used. The patient's first age in the PDMP was used. A comparison of the different payment types (cash, private, or government/other) was also be conducted. The first payment type for each patient was used.

Statistical analysis:

Statistical analyses included chi-square test or Fisher's Exact test to compare the differences between two categorical variables and multivariate logistic regression to discover any significant predictors for overlapping or concomitant therapy, as defined in the *Methodology* section. The age comparison for hypothesis 1 was performed using simple averaging of ages of all unique patients, using the age at first claim given in the PDMP, in the overlap compared with no overlap cohort. The student t-test was used to compare the two independent cohorts, with age as a continuous variable. A frequency procedure was used to determine overall percentages for gender and pay type, using the first gender given in the PDMP for each unique patient, within the stimulants and depressants and stimulants-only patients. A 30-day cut-off period was used to dichotomize the population based on the median value of all the average days of supply for hypothesis 2. This analysis was conducted using a test in the difference of means of two independent samples using a t-test, with days' supply as a continuous variable. Similarly, hypothesis 3 was dichotomized based on median of the average daily dose of ADHD stimulants of 25 mg. Due to the unbalanced sample size in two comparison groups, we examined the variance equity for student t test. We chose

chi square test to compare the categorical variables since the sample size is large. Analysis was conducted using SAS Version 9.4 (SAS Institute, Inc., Cary, NC).

CHAPTER 4

RESULTS

The first hypothesis includes the population of patients within the RI PDMP which had claims for both a stimulant and depressant (Figure 1, N=131,476) at any point during the 2015 calendar year. This population was further narrowed to those patients with claims for both a stimulant and depressant(s) for at least one day (N=4,791). Further, the population was then defined as having concomitant stimulant and depressant use if their days of overlap was 60 days or more, with no more than a 15-day gap in claims (N=4,389), indicating a 1.1% prevalence among unique patients captured by the PDMP. The two populations ultimately compared were those with the 60 days' overlap (<15-day gap, N=4,389, Overlap Yes) to those with overlap of zero to 59 days' supply (N=127,087, Overlap No). The two cohorts' baseline characteristics are listed and compared in Table 1.

The Overlap Yes cohort had a mean age of 43.3 years with a standard deviation of 13.1 years. The Overlap No cohort had a mean age of 48.6 years with a standard deviation of 21.2 years. When compared, this resulted in a two-sided p-value of < .0001, representing a statistically significant difference between the two cohorts. The results show that patients within the Overlap Yes group tended to be younger in age from the Overlap No cohort by about five years, with a smaller standard deviation from this mean age.

Within the Overlap Yes cohort of patients, females accounted for 67.9% (N=2,979) of the patients, while men accounted for 32.1% (N=1,410). In the

Overlap No cohort, females accounted for 57.8% (N=73,401), while the men accounted for 42.2% (N=53,670). When compared using the Chi Square Test, the two-sided p-value was < .0001, representing a significant difference between females' and males' percentages between Overlap Yes and Overlap No cohorts. Females were more likely to fill both a stimulant and a depressant throughout the year, regardless whether overlap occurred.

The final variable examined in the baseline characteristics was pay type. Data entry for the pay types from the RI PDMP originally contained eight different pay codes. This study simplified the eight pay codes into three pay types: private pay (cash purchase), government payer/Other (Medicaid, Medicare, Military institution or Veterans Affairs, Indian Nations, Workers' Compensation, or Other), and Commercial insurance. The first occurrence was taken for each unique patient given by the PDMP. The Overlap Yes cohort had a higher percentage of private pay than did Overlap No. The Overlap No cohort had higher percentages of Government payer/other payer and Commercial insurance. In both cohorts, Commercial Insurance had the highest percentage of pay type used for payment of claims, followed by private pay, then government/other pay type. These differences were significant for this discrete variable, as indicated by a p-value of < .0001.

In summary, the patients in the Overlap Yes cohort tended to be younger females, which used private pay (cash) more frequently than their Overlap No counterparts, while the most frequent pay type for both cohorts was commercial insurance.

The second hypothesis was aimed at whether the percent of patients who filled for less than or equal to 30 days compared with more than 30 days differed between the stimulants and depressants cohort and that of those who only filled stimulants. In other words, are those who fill both types of medications more likely to take medication for a longer period than those who fill only stimulants? Figure 2 displays a flow chart for the cohorts. The original stimulants and depressants cohort contained 4,389 patients, as noted in hypothesis 1. However, while performing a baseline test for normality, three patients were considered outliers, identified as their average days' supply exceeded 100 days. These outliers consisted of three patients which had an average days' supply of 110, 120, or 400. Removal of the outliers reduced the population of the cohort to 4,386. The outliers more than doubled the standard deviation (outliers= 6.76 vs. no outliers= 3.3) in the average days of supply. No patients within the stimulants-only cohort were considered outliers based on the average 100 days' supply definition. The stimulants only cohort consisted of 37,982 unique patients. Table 2 shows the characteristics of the cohort with the removal of the three outliers, which was the cohort used for analysis.

Mean age in the stimulants and depressants cohort was 43.4 years with a standard deviation of 13 years. The mean age of the stimulants only cohort was 29.3 years with a standard deviation of 17 years. As compared by the t-test, the p-value for this difference between the two

cohorts was < .0001, showing a statistical significance. The patients in the stimulants only group tended to be about 14 years younger with a larger standard deviation.

The stimulants and depressants cohort contained about a 2:1 ratio of female to male patients, with females making up 67.9% of this population, reflecting the hypothesis 1 baseline characteristic. The stimulants only cohort contained almost a 1:1 ratio, with females making up a slightly higher percentage than the males. The difference between these two cohorts was tested using the Chi Square Test for Homogeneity, with a resulting p-value of < .0001, indicating a significant difference between the stimulants and depressants and stimulants only cohorts regarding gender, where women constituted a higher percentage than men in the stimulants and depressants cohort. Pay types were also significantly different between the two cohorts with a p-value of < .0001 based on the Chi Square Test for Homogeneity. Although they were not similar with their individual percentages of which pay type, the two cohorts were similar in their most commonly used pay types. The most commonly used form of payment in order of most used to least used was: commercial, private (cash), and then government/other payer. These results indicate once again, that commercial insurance is the primary payer for these two cohorts based on chronic use. In addition, two patients did not have information on pay type. Due to this loss of pay type data for two patients, there are slight differences in pay type percentages as compared

to the cohort in hypothesis 1. In comparison, the stimulants only cohort had a higher percentage of commercial payers compared with the other cohort, while also exhibiting lower percentages of government/other payer and private (cash) payers.

Determining difference in day of supply between the stimulants and depressants and stimulants only cohorts was the primary objective of this hypothesis. Figure 3 shows post-removal of outlier data including breakdown of the population. The stimulants and depressants cohort had a mean days of supply of 29.7 days and a standard deviation of 3.3 days of supply. Similarly, the stimulants only cohort had a mean days of supply of 29.6 days and a standard deviation of 3.8 days. Because both cohorts had an average days of supply of about 30 days and 30 days is a common days supply for patients filling a chronic medication on a monthly basis, this timeframe was chosen to later dichotomize the cohorts and compare using a chi-square test. The difference by percentage in average days of supply was significant, as showcased by the p-value of <.0001 shown in Figure 3. We reject the null hypothesis because the p-value (<.0001) is $\leq \alpha$ (0.05), indicating that the population variances are significantly different. Because the variances are unequal, the Satterthwaite t-value (0.2099) is used. Therefore, there is a difference in days of supply between those who take both stimulants and depressants chronically compared with those who fill only stimulants by percentage.

A multivariable logistic regression was performed on the baseline characteristics and overlap to see if there were any predictors for when the patients filled with a higher percentage to have an average days' supply less than or equal to 30 days. The average days' supply given in binary terms was the dependent variable, while the, age, gender, pay type, and whether the patient was in the overlap cohort (stimulants and depressants or stimulants only), were the independent variables. Based on the dependent variable, 42,050 patients were identified in the less than or equal to 30 days' average supply cohort, leaving the remaining 316 patients in the greater than 30 days' average supply cohort.

Age was transformed into a discrete number of categories, instead of leaving it as a continuous variable. Age was re-categorized into </= 11, 12-17, 18-25, 26-64, and > 64 years of age. These age groups are reflective of the categories in the NSDUH survey.[1] Reference values included stimulants only, age 18-25, male gender, and government/other payer. Significant patient predictors included all age categories compared to the reference age category, as well as private pay (cash) type. The patient predictors which were not significant included overlap usage, gender, and commercial pay type.

Odds ratio (OR) estimates with their corresponding confidence intervals of 95% and p-values are given in Table 5. The maximum likelihood estimates along with Akaike's information criterion (AIC) is also provided in Table 4 for both crude and adjusted models. The OR

point estimates were obtained by exponentiating each of the parameter estimates, where $e^{\wedge\beta}$.[28] The OR results show that age younger than 18-25 are over three times the risk of having filled an average days' supply of less than or equal to 30 days (</=11: OR=3.054, 95% CI= (1.412,6.603), p-value= 0.0045, 12-17: OR=3.118, 95% CI= (1.542,6.304), p-value= 0.0015), while those older than the 18-25 reference group were between 43% and 85% less likely to fill for less than an average of 30 days' supply (26-64: OR=0.57, 95% CI= (0.397,0.82), p-value= 0.0024, >64: OR=0.153, 95% CI= (0.098, 0.24), p-value= <.0001). The cohort of patients who used private (cash) pay type had lower odds of filling an average days' supply of less than or equal to 30 days' supply (vs government/other: OR=0.575, 95% CI= (0.399,0.829), p-value= 0.003), showing about a 42% decrease in odds of using this pay type when filling for less than or equal to 30 days. No difference in odds appeared in whether the two cohorts used commercial pay type compared with a government/other payer. Based on the model inputs, the Hosmer and Lemeshow Goodness-of-Fit Test p-value was 0.8222, indicating a good fit for the model.

In summary, the patients in the stimulants and depressants cohort were older women who used commercial pay type at a higher percentage than their counterparts in the stimulants only cohort. Also, there was a difference in the average of days' supply of less than or equal to 30 days compared with greater than 30 days, between those who take both

stimulants and depressants chronically compared with those who fill only stimulants. The binary logit model appears to indicate an acceptable level of fit.

The study population within hypothesis 3 was a smaller cohort derived from the stimulants only cohort in hypothesis 2, as indicated in Figure 4. The baseline characteristics are given in Table 4. The mean age for the ADHD-stims cohort was 27 with a standard deviation of 16 years, while the mean age and standard deviation for stimulants and depressants was 42 and 13, respectively. The ADHD stimulants cohort consisted of a significantly higher percent of males (52%) compared with the stimulants and depressants cohort (32.5%), as measured by chi square p-value of < .0001. Pay types were also significantly different between the two cohorts. Commercial insurance was used 70% of the time in the ADHD-stimulants cohort compared to 48% with the stimulants and depressants cohort, also measured by p-value <.0001.

The seven most commonly prescribed ADHD stimulants based on total claims from the RI PDMP in 2015 are shown in Figure 5. The two main medication groups studied were stimulants and CNS depressants (Table 6). However, only mixed amphetamine salts-based and methylphenidate-based medications were included in this hypothesis as a subpopulation of interest, deemed ADHD-stimulants. These medication bases were chosen because the 2015 NSDUH stated that they were the two most commonly prescribed stimulant bases for ADHD in 2015[1]. Bases refers to the underlying active ingredient, disregarding any corresponding brand names. The population breakdown and

average daily dose in milligrams(mg) is given in Figure 6, comparing the ADHD-stims cohort with the stimulants and depressants cohort. The ADHD-stimulants cohort had an average daily dose of 29 mg, while the cohort averaged 39 mg.

The multivariate logistic regression compared the ADHD-stimulants cohort to that of stimulants and depressants cohort in a similar manner as in hypothesis 2. As such, odds ratios (OR) were measured upon the same variables of sex, age by group, and pay type. However, because this hypothesis was based on average daily dose, the dependent variable was dichotomized based on an average daily dose; less than or equal to 25 mg or greater than 25 mg. This dichotomization reflected the median average daily dose for the ADHD-stims cohort (24.5 mg). Reference values included ADHD-stims, age 18-25, male gender, and government/other payer. Significant patient predictors cohort, sex, ages less than 18 or age 26 to 64, and private pay type. The patient predictors which were not significant included age greater than 64 and commercial pay type.

Odds ratio estimates with their corresponding confidence intervals of 95% and p-values are given in Table 6. The maximum likelihood estimates along with Akaike's information criterion (AIC) is also provided in Table 6 for both crude and adjusted models. The OR results show that females had a 24% increase in odds (vs. males: OR= 1.244, 95% CI= (1.185,1.305), p-value= <.0001). Patients aged </=11 compared with age 18-25 had four times greater odds or three times increased risk

(OR=4.109, 95% CI= (3.747,4.505, p-value= <.0001), and those aged 12-17 compared with 18-15 had a 32% increase in odds (OR=1.326, 95% CI= (1.229,1.43), p-value= <.0001) of filling less than 25 mg average daily dose of stimulants. The OR results show that the S&D cohort had 44% decreased odds of filling less than 25 mg for their average daily dose (vs. ADHD-stims: OR=0.561, 05% CI= (0.518,0.608), p-value= <.0001). Private (cash) payers compared with government/other payers had 25% decreased odds (OR=0.752, 95% CI= (0.691,0.819), p-value= <.0001) of filling 25 mg average daily dose. Patients aged 26-64 compared with 18-25-year-old patients had a 35% decrease in odds (OR=0.647, 95% CI= (0.608,0.688), p-value= <.0001) of filling for 25 mg average daily dose. The Hosmer and Lemeshow Goodness-of-Fit Test p-value was 0.0111, indicating a less than acceptable level of fit for the model.

In summary, the ADHD-stimulants cohort was younger, had a lower average daily dose of stimulant, more likely to be of male sex, and use commercial insurance as the primary pay type compared to the stimulants and depressants cohort. However, the Goodness-of-Fit Test showed a less than acceptable level of fit for the model.

CHAPTER 5

DISCUSSION

Over 400,000 patients filled more than 2.5 million prescriptions, captured by the RI PDMP for calendar year 2015. In all hypotheses, the number of patients falling under the overlap definition was far fewer than the comparative cohorts. The patients in the overlap cohort in hypothesis 1 tended to be younger women, who used commercial insurance more frequently than their counterparts. Patients in hypothesis 2 in the stimulants and depressants cohort were mostly older women (mean age 43.4 years old +/- 13 years) who used commercial pay type at a higher percentage than their counterparts in the stimulants-only cohort. A difference existed in the percent of patients who filled for an average of days' supply of less than or equal to 30 days compared with greater than 30 days between those who filled both stimulants and depressants chronically compared with those who filled only stimulants. The stimulants only cohort was younger, on average, possibly because ADHD stimulants are primarily prescribed to younger patients. The average age at onset of ADHD is seven years old, while ADHD symptoms often improve for many people with increasing age.[29] However, this hypothesis also contained stimulants for diagnoses other than ADHD, including weight loss and narcolepsy.

Hypothesis 3 was based on a subpopulation of hypothesis 2. The ADHD-stimulants cohort was younger with a lower average daily dose of stimulant, more likely to be males, and use commercial insurance as the primary pay type compared to the usage of stimulants in the S&D cohort. Research supports the

finding that the ADHD stimulants cohort should be comprised of mostly younger males as reported by Merikangas et al.[30] This study reported that males 13-18 years of age have a lifetime prevalence of 12.9% compared with females 13-18 years of age of 4.9%, with children 13-18 having an overall lifetime prevalence higher than adults.[31] In the State of Rhode Island, children aged 4-17 having ever been diagnosed with ADHD rose steadily from year 2003 to 2007 to 2011, with corresponding percentages of 9.8, 11.1 and 13.4%, respectively.[31] Children in Rhode Island in a similar age group (4-17 years old) which were reported by a parent as currently diagnosed with ADHD, also revealed that these children had a higher than average current diagnosis percentage (2011: RI 11.1% vs. U.S. 8.8%) and a higher percentage of children taking ADHD medication (2011: RI 6.3% vs. U.S. 6.1%) as compared to the average of all children in the United States.[32]

By focusing on the two most commonly prescribed stimulants, which were also estimated to be the two most prescribed medications for ADHD[1] in 2015, we sought whether patients using these two medications differed from those filling a combination of ADHD stimulants and depressants. The results showed that those in the stimulants only cohort had a lower percent for their average daily dose below 25 mg. This could have been for several reasons. One reason may be that younger patients may not require as high a dose as older patients based on severity of disorder or disease. Research indicates ADHD symptoms only persist in about half of patients into adulthood.[33,34] This 50% could be the more severe cases of patients, who then may require higher doses of the ADHD stimulants later in life. In addition, a study by Merikangas et al reported that children 13-18

years old have a 1.8% lifetime prevalence of severe ADHD, while Kessler et al reported that adults have a 1.7% lifetime prevalence of severe ADHD.[30,35] Another possibility is that older patients may develop greater tolerance over the course of their lifetime or therapy and require higher doses over time. Tolerance is defined by the National Institute on Drug Abuse as "when the person no longer responds to the drug in the way that person initially responded".[36] Another reason may be that those patients filling depressants may need higher doses of stimulants to counteract the sedating effects of the depressants, hypothesized once again, due to tolerance. In this situation, a concern can be raised that as patients require higher doses of CNS depressants, they may also treat the worsening of adverse effects with stimulants. For example, a patient may become tolerant to their opioid and begin to escalate their dose to cover their increase in pain. As the patient does this, they may also experience more sedating effects from the opioid. To counter those effects the patient may begin taking more of a (prescribed) stimulant, which helps keep them awake, alert, and/or capable of performing their usual daily tasks. Unfortunately, the patient may reach a tipping point where the self-medicating titration of the combination exposes the patient to a toxic level of one, either, or both medications. In the case of an opioid, this may result in respiratory depression, coma, or death, as referenced above.[3,4]

A limitation of this study is lack of certain patient health information, primarily diagnosis codes. Initial diagnosis(es) of patients' health conditions were not recorded, nor were pertinent other medications which may lead to a better understanding of severity of the patients' disorders. A difference in percent of

average daily dose could simply be due to severity of mental illness or learning disability. A differential diagnosis should rule out major depression, bipolar disorder, generalized anxiety, substance abuse or dependence, or personality disorders.[37] For example, a patient with a more debilitating form of ADHD may require higher doses of their stimulant to reduce the symptoms of their disease. Additionally, data within the PDMP did not differentiate human from animal claims data. As such, it is believed that a small portion of the claims may have included animal patients, which may have influenced the number of private pay claims.

By choosing the first claim for each patient to specify age, gender, and paytype, there is a possibility of misrepresenting the patients' true demographics. For instance, if a pharmacy placed a claim for a female as male for the first claim, but later corrected it for the other fills, the corrected gender would not be represented. By choosing the patients' first age, there may have also been a tendency to have an overall younger population. Following gender and age, paytype may have also been biased towards one payment type over the others and may account for the large percentage of cash payers. One explanation for this is if the claims tended to be earlier in the year when patients did not have insurance coverage, they may have paid the cash price for their medication(s). Another possibility regarding pay type is that patients may be in and out of the work force throughout the year, gaining and losing insurance coverage for a certain period. This may have also increased the percentage of cash payers in the population.

Another limitation involves lack of distinction of different CNS depressants classes. This study first started by creating depressant groups based on therapeutic class code, but did not differentiate by class or by the drug itself. Conducting a study based upon individual drugs was beyond the scope of this research, but could be considered for future investigation.

This study has several strengths, primarily that it was the first study based on the RI PDMP which sought to discover relationships between chronic concomitant therapy of controlled substance CNS stimulants with CNS depressants and underlying demographics. One relationship was the average days' supply, comparing the overlap cohort with that of those who only take stimulants. The other relationship was whether there was a difference in average daily dose for patients who had claims for both stimulants and depressants compared with those who had claims only for ADHD stimulants. By researching these two relationships, forward-looking hypotheses of interest can be developed.

One potential hypothesis would question the importance of time to diagnosis for a health condition regarding another health condition. The patient could be followed in time to see if doses increase (or decrease) on average over time. For example, if a patient begins taking a CNS depressant, such as an opioid for a pain syndrome, do they also begin taking a stimulant? How long after initiation does this concomitant therapy begin? If so, was this due to (1) excessive sedation from the opioid or (2) was this for an entirely separate and new diagnosis, for example, ADHD? Conversely, if a patient begins with a diagnosis of ADHD, and then develops insomnia, are the two health conditions related?

Was the added therapy part of treatment for an underlying sleep disorder, or was it to alter the effects of the ADHD stimulant? These relationships can add insight into whether patients are being treated for underlying diseases or to "medicate a medication".

This study was designed to help describe a subset of the RI population which chronically fills both stimulants and CNS depressants. The value of this study comes from its ability to lay groundwork for future research into combined utilization of stimulants and depressants. Future work could include researching specific medication combinations, i.e., methylphenidate with oxycodone, or zolpidem with mixed amphetamine salts. Future work may also include a data set which is more robust, and includes other patient demographics such as socioeconomic status, race/ethnicity, and comorbid conditions.

APPENDIX 1: TABLES

Table 1. Baseline characteristics for Hypothesis 1. Comparison of patients with claims for both stimulants and depressants for 60 or more days (<15 days gap) "overlap yes" compared with patients with less than 60 days overlap (<15 days gap) "overlap no".

Characteristics	Overlap Yes N=4,389	Overlap No N=127,087	P Value
Recipient Age, Years, Mean ± SD	43.4 ± 13.1	48.6 ± 21.1	< .0001
Recipient Female Gender, N (%)	2,979 (67.9)	73,401 (57.8)	< .0001
Male Gender, N (%)	1,410 (32.1)	53,670 (42.2)	
Paytype, N (%)			< .0001
Govt. Payer/Other	787 (18.0)	25,929 (20.4)	
Private pay	1,440 (32.8)	30,662 (24.1)	
Commercial Ins.	2,160 (49.2)	70,494 (55.5)	

Note: SD: standard deviation. N: number of patients. Govt.: government or other payer. Ins.: insurance.

Table 2. Baseline characteristics for Hypothesis 2 (excluding outliers). Comparison of patients with claims for both stimulants and depressants for 60 or more days (<15 days gap) compared to patients who filled only stimulants for 60 or more days (<15 days gap).

Characteristics	Stimulants and Depressants[‡] N=4,386[†]	Stimulants-only N= 37,982	P-Value
Recipient Age, Years, Mean ± SD	43.4 ± 13	29.3 ± 17	<.0001
Recipient Female Gender, N (%)	2,978 (67.9)	19,254 (50.7)	<.0001
Male Gender, N (%)	1,408 (32.1)	18,728 (49.3)	
Paytype[‡], N (%)			<.0001
Govt. Payer/Other	787 (17.9)	5,857 (15.4)	
Private Pay	1,437 (32.8)	6,049 (15.9)	
Commercial Ins.	2,160 (49.3)	26,076 (68.7)	

Note: [‡]N= Two 'paytype' missing from missing data. [†]N= Three outliers removed. SD: standard deviation. N: number of patients. Govt.: government or other payer. Ins.: insurance.

Table 3. Model results for average days of supply more than 30 days versus less than and equal to 30 days. Comparison of patients with claims for both stimulants and depressants for 60 or more days (<15 days gap) compared with patients who filled only stimulants for 60 or more days (<15 days gap).

Models for Crude Average Days of Supply (</= or > 30 days)							
Model	**Independent variables(s)**	**MLE β**	**AIC**	**OR**	**Confidence Interval**		**p-value**
1	*Overlap yes or no*	-0.6728	3711.082	0.510	0.383	0.680	<.0001
2	*Overlap yes or no + age*		3543.408				<.0001
	overlap yes	-0.2405		0.786	0.587	1.052	0.1061
	age <=11	1.1541		3.171	1.473	6.829	0.0032
	age 12-17	1.1751		3.238	1.606	6.532	0.001
	age 26-64	-0.6695		0.512	0.358	0.732	0.0002
	age 65+	-2.0584		0.128	0.083	0.197	<.0001
3	*Overlap yes or no + sex: female*		3704.254				<.0001
	overlap yes	-0.616		0.540	0.405	0.721	<.0001
	sex: female	-0.3447		0.708	0.563	0.892	0.0033
4	*Overlap yes or no + paytype*		3658.767				<.0001
	overlap yes	-0.4815		0.618	0.461	0.827	0.0012
	paytype commercial	0.0365		1.037	0.732	1.469	0.8369
	paytype private	-0.914		0.401	0.279	0.576	<.0001
5	*Overlap yes or no + age + sex: female*		3545.284				<.0001
	overlap yes	-0.2388		0.788	0.588	1.055	0.1088
	sex: female	-0.0419		0.959	0.760	1.210	0.7244
	age <=11	1.1439		3.139	1.455	6.774	0.0036
	age 12-17	1.1668		3.212	1.590	6.488	0.0011
	age 26-64	-0.6641		0.515	0.360	0.737	0.0003
	age 65+	-2.0542		0.128	0.083	0.198	<.0001
6	*Overlap yes or no + age + paytype*		3527.796				<.0001
	overlap yes	-0.1939		0.824	0.614	1.104	0.1949
	paytype commercial	-0.00135		0.999	0.701	1.423	0.994
	paytype private	-0.5539		0.575	0.399	0.829	0.003
	age <=11	1.1187		3.061	1.419	6.605	0.0044
	age 12-17	1.1392		3.124	1.548	6.307	0.0015
	age 26-64	-0.5625		0.570	0.397	0.818	0.0023
	age 65+	-1.876		0.153	0.098	0.240	<.0001
7	*Overlap yes or no + sex: female + paytype*		3656.187				<.0001
	overlap yes	-0.4536		0.635	0.474	0.851	0.0024
	sex: female	-0.2507		0.778	0.617	0.981	0.0338
	paytype commercial	0.0402		1.041	0.735	1.474	0.8211
	paytype private	-0.8772		0.416	0.289	0.598	<.0001
	Model for Adjusted Average Days of Supply (</= or > 30 days)						
	Independent variables(s)	**MLE β**	**AIC**	**OR**	**Confidence Interval**		**p-value**
	Overlap yes or no + age + sex: female + paytype		3529.789				<.0001
	overlap yes	-0.1937		0.824	0.614	1.105	0.1956
	sex: female	-0.00959		0.990	0.784	1.251	0.9358
	paytype commercial	-0.00154		0.998	0.701	1.423	0.9932
	paytype private	-0.5534		0.575	0.399	0.829	0.0030
	age <=11	1.1164		3.054	1.412	6.603	0.0045
	age 12-17	1.1373		3.118	1.542	6.304	0.0015
	age 26-64	-0.5614		0.570	0.397	0.820	0.0024
	age 65+	-1.8751		0.153	0.098	0.240	<.0001
	Note: MLE: Maximum Likelihood Estimate; AIC: Akaike's information criterion; OR: Odds ratio						

Table 4. Baseline Characteristics of Hypothesis 3. Comparison of patients with claims for both ADHD stimulants and CNS depressants for 60 or more days (<15 days gap) compared with patients who filled only ADHD stimulants for 60 or more days (<15 days gap).

Characteristics	Stimulants and Depressants N=3,493	ADHD-stimulants N= 28,589	P-Value
Recipient Age, Years, Mean ± SD	42.2 ± 13	27.4 ± 16	<.0001
Recipient Female Gender, N (%)	2,358 (67.5)	13,717 (48)	<.0001
Male Gender, N (%)	1,135 (32.5)	14,872 (52)	
Paytype, N (%)			<.0001
Govt. Payer/Other	679 (19.4)	5,086 (17.8)	
Private Pay	1,142 (32.7)	3,426 (12.0)	
Commercial Ins.	1,672 (47.9)	20,077 (70.2)	

Note: SD: standard deviation. N: number of patients. Govt.: government or other payer. Ins.: insurance.

Table 5. Model results for average daily dose above 25 mg versus less or equal to 25 mg. Comparison of patients with claims for both ADHD stimulants and CNS depressants for 60 or more days (<15 days gap) compared with patients who filled only ADHD stimulants for 60 or more days (<15 days gap).

Models for Crude Average Daily Dose (</= or > 25 mg)							
Model	**Independent variable(s)**	**MLE β**	**AIC**	**OR**	**Confidence Interval**		**p-value**
1	*Overlap yes or no*	-1.0198	43726.624	0.361	0.334	0.389	<.0001
2	*Overlap yes or no + age*		41388.635				<.0001
	overlap yes	-0.603		0.547	0.505	0.593	<.0001
	age <=11	1.362		3.904	3.566	4.274	<.0001
	age 12-17	0.2485		1.282	1.190	1.381	<.0001
	age 26-64	-0.4508		0.637	0.599	0.677	<.0001
	age 65+	-0.072		0.931	0.802	1.079	0.341
3	*Overlap yes or no + sex: female*		43719.212				<.0001
	overlap yes	-1.0065		0.366	0.338	0.395	<.0001
	sex: female	-0.0697		0.933	0.892	0.975	0.0022
4	*Overlap yes or no + paytype*		43445.003				<.0001
	overlap yes	-0.9262		0.396	0.366	0.428	<.0001
	paytype commercial	-0.0986		0.906	0.854	0.961	0.001
	paytype private	-0.632		0.532	0.490	0.576	<.0001
5	*Overlap yes or no + age + sex: female*		41311.573				0.791
	overlap yes	-0.6222		0.537	0.496	0.581	<.0001
	sex: female	0.2176		1.243	1.185	1.304	<.0001
	age <=11	1.4171		4.125	3.765	4.52	<.0001
	age 12-17	0.2909		1.338	1.241	1.442	<.0001
	age 26-64	-0.4718		0.624	0.587	0.664	<.0001
	age 65+	-0.0851		0.918	0.792	1.065	0.2613
6	*Overlap yes or no + age + paytype*		41305.782				0.0151
	overlap yes	-0.5584		0.572	0.528	0.620	<.0001
	paytype commercial	0.0428		1.044	0.981	1.111	0.1777
	paytype private	-0.2885		0.749	0.689	0.816	<.0001
	age <=11	1.3571		3.885	3.547	4.255	<.0001
	age 12-17	0.239		1.270	1.178	1.369	<.0001
	age 26-64	-0.4149		0.660	0.621	0.703	<.0001
	age 65+	0.0254		1.026	0.883	1.192	0.7403
7	*Overlap yes or no+ sex: female + paytype*		43441.831				<.0001
	overlap yes	-0.9166		0.400	0.370	0.432	<.0001
	sex: female	-0.052		0.949	0.908	0.993	0.0229
	paytype commercial	-0.098		0.907	0.855	0.962	0.0011
	paytype private	-0.628		0.534	0.492	0.579	<.0001
	Model for Adjusted Average Daily Dose (</= or > 25 mg)						
	Independent variable(s)	**MLE β**	**AIC**	**OR**	**Confidence Interval**		**p-value**
	Overlap yes or no + age + sex: female + paytype		41228.605				0.5624
	overlap yes	-0.5774		0.561	0.518	0.608	<.0001
	sex: female	0.2181		1.244	1.185	1.305	<.0001
	paytype commercial	0.0476		1.049	0.985	1.116	0.1343
	paytype private	-0.2846		0.752	0.691	0.819	<.0001
	age <=11	1.4131		4.109	3.747	4.505	<.0001
	age 12-17	0.2821		1.326	1.229	1.43	<.0001
	age 26-64	-0.4357		0.647	0.608	0.688	<.0001
	age 65+	0.0134		1.013	0.872	1.178	0.862
	Note: MLE: Maximum Likelihood Estimate; AIC: Akaike's information criterion; OR: Odds ratio						

Table 6. List of stimulant and CNS depressant medications filled, with frequency (count) and percent, by those who chronically fill stimulants and/or depressants.

Stimulant Medications	Frequency	Percent
MIXED AMPHETAMINE (all dosage forms)	188,455	25.07
METHYLPHENIDATE	76624	19.33
VYVANSE	33952	8.56
DEXTROAMPHETAMINE	27294	6.88
PHENTERMINE	14405	3.63
DEXTROAMPHETAMINE	11761	2.97
DEXMETHYLPHENIDATE	9034	2.28
PHENDIMETRAZINE	5269	1.33
FOCALIN XR	3942	0.99
MODAFINIL	3727	0.94
CONCERTA	2757	0.7
NUVIGIL	2640	0.67
DEXTROAMPHETAMINE SPANSULE	2406	0.61
QUILLIVANT	1217	0.31
DAYTRANA	936	0.24
ADIPEX-P	849	0.21
RITALIN LA	578	0.15
BELVIQ	555	0.14
XYREM	542	0.14
METADATE ER	422	0.11
METADATE CD	387	0.1
QSYMIA	343	0.09
RITALIN	330	0.08
PROVIGIL	216	0.05
DEXEDRINE SPANSULE	157	0.04
DIETHYLPROPION	145	0.04
FOCALIN	131	0.03
EVEKEO	51	0.01
BENZPHETAMINE	36	0.01
METHAMPHETAMINE	33	0.01
METHYLIN	25	0.01
MORPHINE SUL	21	0.01

DESOXYN	16	0
ZENZEDI	14	0
APTENSIO XR	9	0
RITALIN-SR	8	0
BONTRIL PDM	6	0
METHYLIN ER	5	0
PROCENTRA	5	0
SUPRENZA	3	0

CNS Depressant Medications	Frequency	Percent
CLONAZEPAM	188451	14.93
OXYCODONE	173206	13.72
ALPRAZOLAM	157466	12.48
HYDROCODONE	152217	12.06
ZOLPIDEM	134382	10.65
LORAZEPAM	129990	10.3
DIAZEPAM	53940	4.27
MORPHINE SUL	34015	2.7
OXYCONTIN	30497	2.42
SUBOXONE	25514	2.02
TEMAZEPAM	24499	1.94
BUTALBITAL-COMBO	22183	1.76
BUPRENORPHINE	18534	1.47
APAP W/ CODEINE	13609	1.08
PHENOBARBITAL	13275	1.05
CARISOPRODOL	12546	0.99
FENTANYL	10104	0.8
METHADONE H	8386	0.66
HYDROMORPHONE	8228	0.65
FENTANYL TRANSDERMAL	6946	0.55
ESZOPICLONE	6939	0.55
ZALEPLON	3285	0.26
TRIAZOLAM	3110	0.25
CLORAZEPATE	2942	0.23
LORAZEPAM I	2257	0.18
LYRICA	1808	0.14
ZUBSOLV	1569	0.12
ENDOCET	1534	0.12
BUTRANS	1397	0.11
DRONABINOL	1338	0.11
CHLORDIAZEPOXIDE	1283	0.1
OPANA ER	1104	0.09
OXYMORPHONE	1071	0.08
BELSOMRA	981	0.08
ONFI	895	0.07
OXAZEPAM	827	0.07

NUCYNTA	592	0.05
FLURAZEPAM	560	0.04
XANAX	526	0.04
NUCYNTA ER	506	0.04
ASCOMP W/CODEINE	476	0.04
VICODIN	450	0.04
DIAZEPAM RECTAL	449	0.04
VICODIN ES	443	0.04
AMBIEN	440	0.03
BUTORPHANOL	394	0.03
OPIUM	387	0.03
CODEINE SUL	359	0.03
KLONOPIN	341	0.03
PENTAZOCINE	321	0.03
LUNESTA	279	0.02
PERCOCET	279	0.02
VALIUM	262	0.02
BUTALBITAL/COMBO	260	0.02
FYCOMPA	235	0.02
GUAIFENESIN	234	0.02
HYSINGLA ER	218	0.02
DURAGESIC	207	0.02
MEPROBAMATE	204	0.02
PROMETHAZINE	199	0.02
AMBIEN CR	196	0.02
ATIVAN	194	0.02
MEPERIDINE	191	0.02
VIMPAT	190	0.02
CHERATUSSIN	161	0.01
EMBEDA	160	0.01
XARTEMIS XR	158	0.01
VICODIN HP	153	0.01
HYDROMET	137	0.01
EXALGO	101	0.01
FIORICET	98	0.01
NORCO	95	0.01
ESTAZOLAM	75	0.01
FIORINAL	60	0
KADIAN	59	0

FENTANYL CITRATE	54	0
BUNAVAIL	52	0
NOVAPLUS FE	50	0
INTERMEZZO	45	0
MS CONTIN	43	0
ROXICODONE	43	0
DONNATAL	42	0
MIDAZOLAM H	41	0
ZOHYDRO ER	41	0
FIORICET W CODEINE	39	0
BUTISOL SOD	37	0
CAPACET	36	0
AVINZA	34	0
DILAUDID	33	0
SUBSYS	31	0
ESGIC	30	0
TYLENOL W/ CODEINE	29	0
LAZANDA	28	0
ORAL TRANSMUCOSAL FENTANYL	28	0
BELLADONNA/COMBO	27	0
KETAMINE	27	0
XANAX XR	26	0
DIASTAT ACUDIAL	23	0
FENTORA	21	0
LORTAB ELIXIR	21	0
ISOMETHEPTENE, APAP, DICHLORALPHENAZONE	20	0
SOMA	19	0
DIAZEPAM IN	18	0
LORTAB 10/3	17	0
TRANXENE T	16	0
XODOL 7.5/3	16	0
BUPRENEX	14	0
HALCION	14	0
OXAYDO	14	0
ROXICET	13	0
SECONAL SOD	13	0

FIORINAL W/ CODEINE	9	0
LEVORPHANOL	9	0
CODEINE-GUAIFENESIN	8	0
MARGESIC	8	0
DEMEROL HYD	7	0
METHADOSE	5	0
MIDAZOLAM	5	0
RESTORIL	5	0
SONATA	5	0
LORTAB 5/325	4	0
GUAIATUSSIN	3	0
EDLUAR	2	0
INFUMORPH	2	0
VIRTUSSIN A	2	0
DEMEROL	1	0
DOLOPHINE	1	0
NODOLOR	1	0

APPENDIX 2: FIGURES

Figure 1. Flow chart design for Overlap Yes vs. Overlap no cohorts.

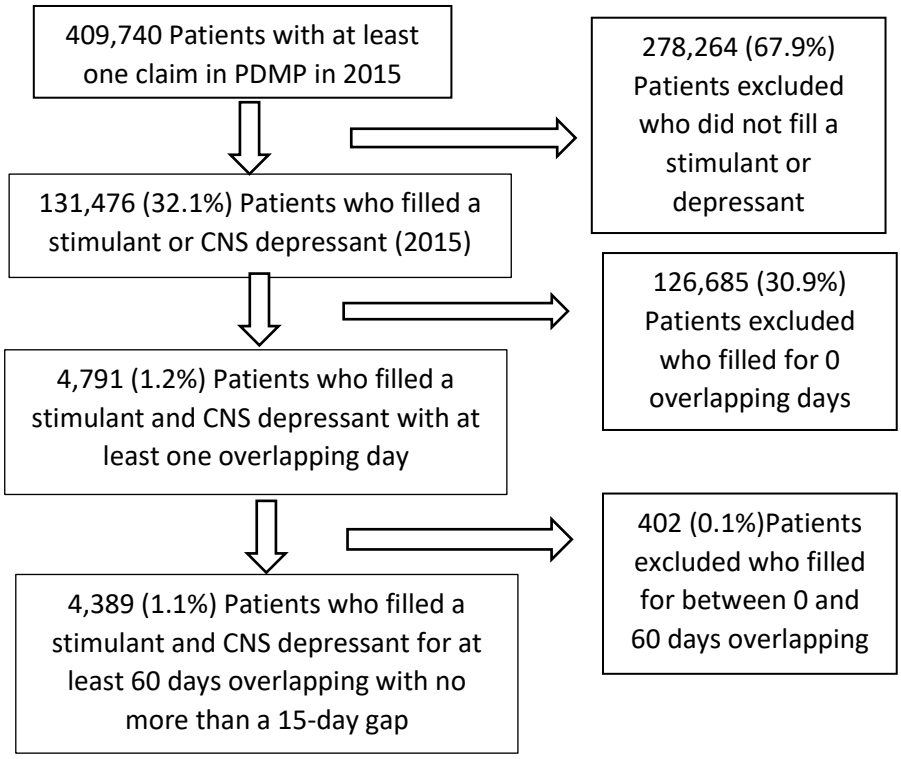


Figure 2. Flow chart design for comparison between stimulants and depressants cohort and stimulants only cohort.

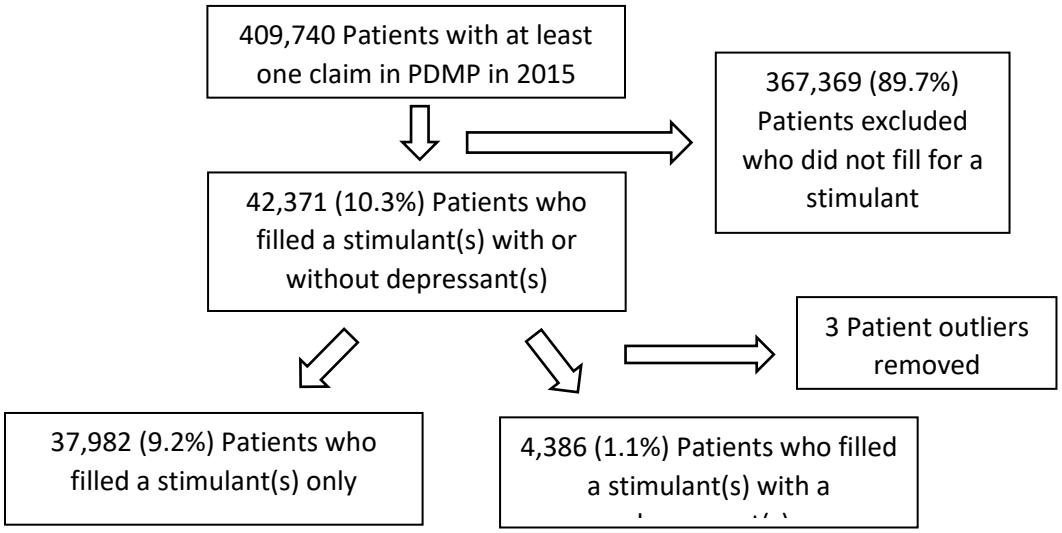
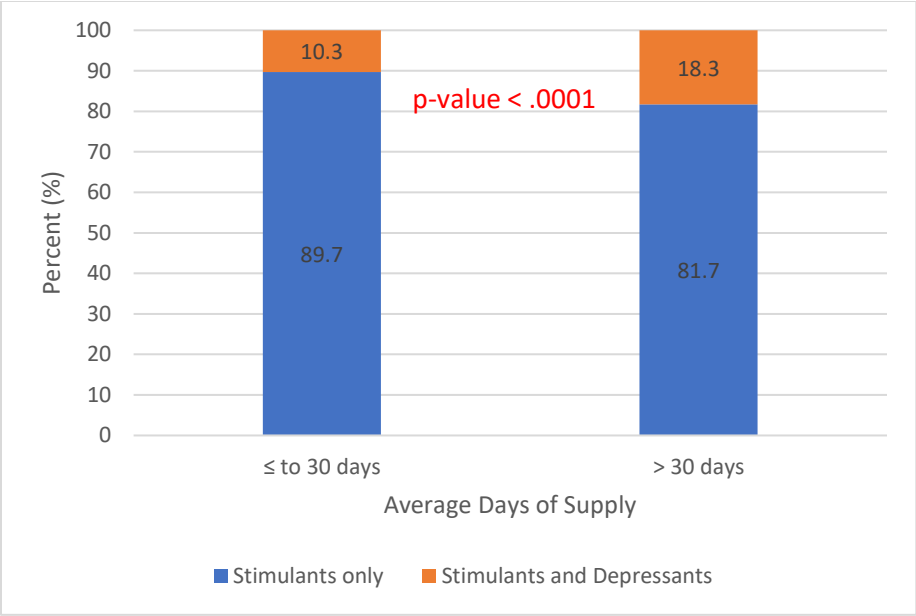


Figure 3. Percent of patients who filled for an average of ≤ 30 days or > 30 days. Comparison between those who filled both stimulants and depressants or stimulants only. An accompanying
table of number of patients in each cohort is listed below.



Average Days of Supply	Stimulants only N= 37,982	Stimulants and Depressants N= 4,386	Total
≤ 30, N (%)	37,724 (89.7)	4,328 (10.3)	42052
> 30, N (%)	258 (81.7)	58 (18.3%)	316

Figure 4. Flow chart design comparison between ADHD stimulants only cohort and ADHD stimulants with depressants cohort.

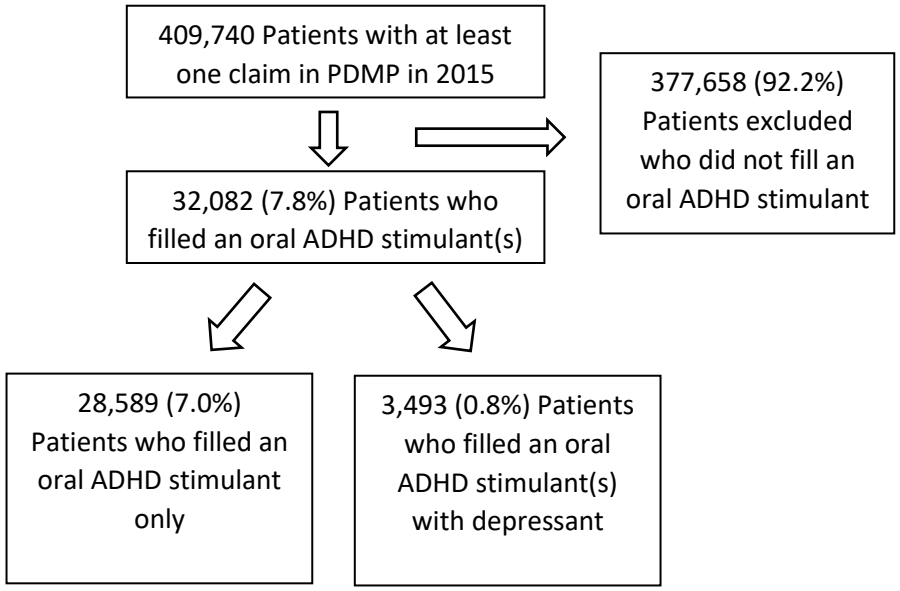


Figure 5. Seven most commonly prescribed ADHD stimulant medications by base drug in Rhode Island in 2015.

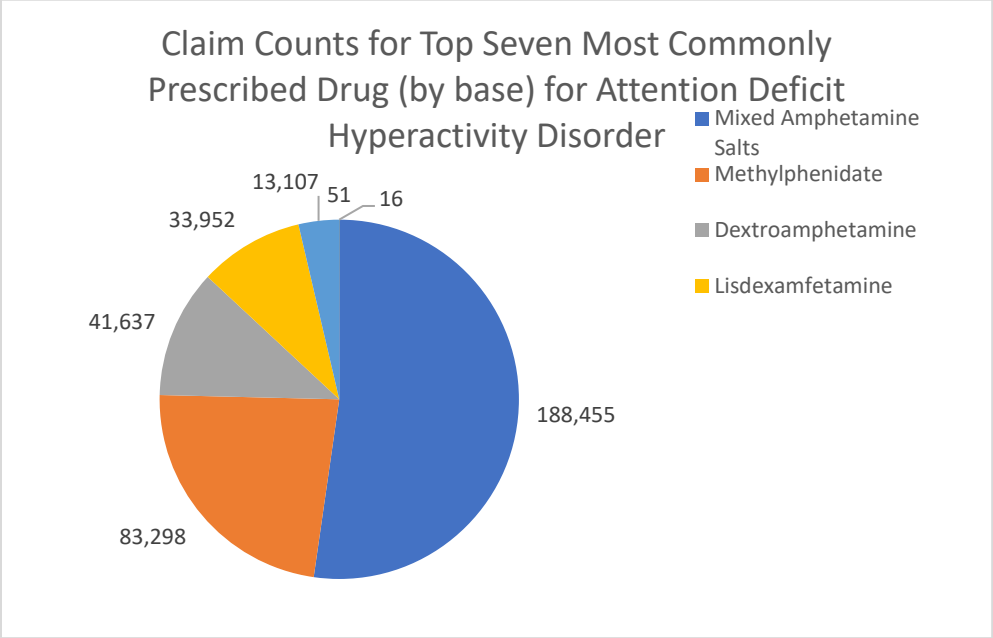
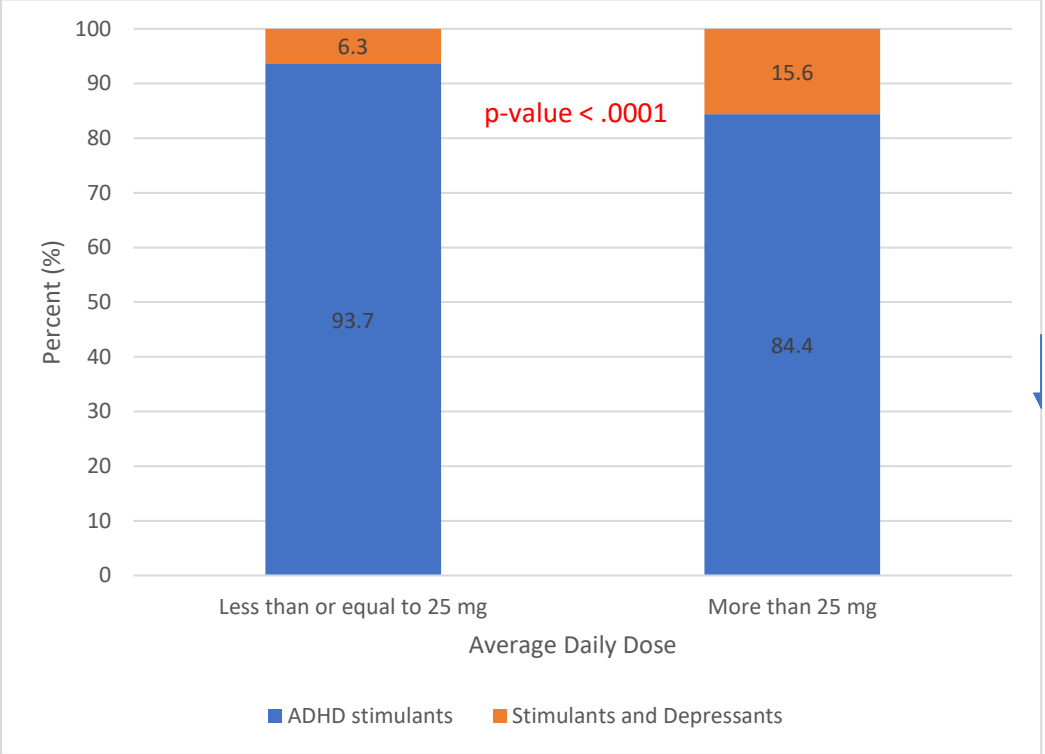


Figure 6. Comparison of the percent of patients who filled for an average daily dose of less than or equal to 25 mg compared to those who filled for more than 25 mg average daily dose, between those who filled both ADHD stimulants with depressants or ADHD stimulants only.



Average Daily Dose (mg)	ADHD-Stimulants	Stimulants and depressants	Total
≤ 25, N (%)	13,327 (46.6)	2,472 (70.8)	15,799
> 25, N (%)	15,262 (53.3)	1,021 (29.2)	16,283
Total	28,589	3,493	32,082

BIBLIOGRAPHY

1. Hughes, A., Williams, M. R., Lipari, R. N., Bose, J., Copello, E. A. P., & Kroutil, L. A. (2016, September). Prescription drug use and misuse in the United States: Results from the 2015 National Survey on Drug Use and Health. NSDUH Data Review. Retrieved from https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm#topofpage [accessed Oct 22, 2016]
2. Stein MA, Waldman ID, Charney E, Aryal S, Sable C, Gruber R, Newcorn JH. Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts. *J Child Adolesc Psychopharmacol*. 2011 Dec;21(6):581-8. PubMed PMID: 22136094
3. Spiller HA, Hays HL, Aleguas Jr., A. Overdose of drugs for attention-deficit hyperactivity disorder: clinical presentation mechanisms of toxicity, and management. *CNS Drugs* 2013 Jul;27(7):531-543. PubMed PMID: 23757186
4. Drugs of Abuse 2015 Edition: A DEA resource guide. Drug Enforcement Administration. U.S. Department of Justice. pp1-88. www.dea.gov [accessed Oct 27, 2016]
5. Overutilization further guidance 2013 [PDF]. Center for Medicare and Medicare Services. Jul 5, 2013. CMS.gov. Retrieved from https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/HPMS-memo-Medicare-Part-D-Overutilization-Monitoring-System-07-05-13-.pdf [accessed Oct 22, 2016]
6. Paulozzi LJ, Strickler GK, Kreiner PW, Koris CM. Controlled Substance Prescribing Patterns — Prescription Behavior Surveillance System, Eight States,

2013. *Surveillance Summaries.* Oct 16, 2015;64(SS09);1-14**.** Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6409a1.htm [accessed Oct 22, 2016]

7. Mher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Ipin Drug Saf.* 2014 Jan;13(1):57-65. PubMed PMID: 24073682.
8. Tjia J, Velten SJ, Parsons C, et al. Studies to reduce unnecessary medication use in frail older adults: a systematic review. *Drugs Aging* 2013;30:285–307. PubMed PMID: 23475597
9. Rambhade S, Chakarboty A, Shrivastava A, Patil U, Rambahde A. A survey on polypharmacy and use of inappropriate medications. *Toxicol Int.* 2012 19(1):68-73. PubMed PMID: 3339249
10. Brandt S, Taverna E, Hallock R. A survey of nonmedical use of tranquilizers, stimulants, and pain relievers among college students: patterns of use among users and factors related to abstinence in non-users. *Drug Alcohol Dependence* 2014;143:272-276
11. Chen L, Curm R, Martins S, Kaufmann C, Strain E, Mojtabal. Patterns of concurrent substance use among nonmedical ADHD stimulant users: results from a national survey on drug use and health. *Drug Alcohol Depend* 2014;0:86-90
12. McCabe S, West B. Medical and nonmedical use of prescription stimulants: results from a national multicohort study. *J Am Acad Child Adolesc Psychiatry* 2013;52(12):1272-1280

13. Cassidy T, Varughese S, Russo L, Budman S, Eaton T, Butler S. Nonmedical use and diversion of ADHD stimulants among U.S. adults ages 18-49: a national internet survey. *J Attention Disorders* 2015;19(7):630-640
14. Whiteside L, Cunningham R, Bonar E, Blow F, Ehrlich P, Walton M. Nonmedical prescription stimulant use among youth in the emergency department: prevalence, severity, and correlates. *J Subst Abuse Treat* 2015 48(1):21-27
15. Kaloyanides K, McCabe S, Cranford J, Teter C. Prevalence of illicit use and abuse of prescription stimulants, alcohol, and other drugs among college students: relationship with age at initiation of prescription stimulants. *Pharmacotherapy* 2007;27(5):666-674
16. Kroutil LA, Van Brunt DL, Herman-Stahl MA, Heller DC, Bray RM, Penne MA. Non-medical use of prescription stimulants in the United States. *Drug Alcohol Depend* 2006;84(2):135-43
17. Marks KR, Lile JA, Stoops WW, Rush CR. Separate and combined impact of acute naltrexone and alprazolam on subjective and physiological effects of oral d-amphetamine in stimulant users. *Psychopharmacology (Berl).* 2014 Jul;231(14):2741-50. PubMed PMID 24464531.
18. Rush CR, Stoops WW, Wagner FP, Hays LR, Glaser PE. Alprazolam attenuates the behavioral effects of d-amphetamine in humans. *J Clin Psychopharmacol*. 2004 Aug;24(4):410-20. PubMed PMID 15232333.
19. Lile JA, Stoops WW, Glaser PE, Hays LR, Rush CR. Physiological and subjective effects of acute intranasal methamphetamine during extended-release

alprazolam maintenance. *Drug Alcohol Depend*. 2011 Dec 15;119(3):187-93. PubMed PMID 21737214.

20. Lile JA, Stoops WW, Wagner FP, Glaser PE, Rush CR. Oxazepam does not modulate the behavioral effects of d-amphetamine in humans. *Pharmacol Biochem Behav*. 2005 Oct;82(2):270-9. PubMed PMID 16182353.
21. Mintzer MZ, Griffiths RR. Triazolam-amphetamine interaction: dissociation of effects on memory versus arousal. *J Psychopharmacol.* 2003 Mar;17(1):17-29. PubMed PMID 12680736.
22. Rogers E, Metha S, Shengalia R, Reid MC. Four strategies for managing opioid-induced side effects in older adults. *Clin Geriartr*. 2013 April;21(4). PubMed PMID: 25949094
23. Stone P, Minton O. European Palliative Care Research collaborative pain guidelines. Central side-effects management: what is the evidence to support best practice in the management of sedation, cognitive impairment and myoclonus? *Palliat Med*. 2011;25(5):431-441. PubMed PMID: 20870687.
24. Yee JD, Berde CB. Dextroamphetmine or methylphenidate as adjuvants to opioid analgesia for adolescents with cancer. *J Pain Symptom Manage* 1994;9:122-5.
25. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel.Clinical guidelines for the use of chronic opioid therapy

in chronic noncancer pain. *J Pain.* 2009 Feb;10(2):113-30. PubMed PMID 19187889.

26. Code of Federal Regulations Title 21. Sec. 1308.12-1308.15. Revised Apr 1, 2016.
27. Constantine RJ, Boaz TB, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. *Clin Ther.* 2010;32:949-959.
28. Kleinbaum DG, Klein M. (2010). *Logistic Regression: Statistics for Biology and Health*. Spinger.
29. NIDA. Stimulant ADHD Medications: Methylphenidate and Amphetamines. National Institute on Drug Abuse website. https://www.drugabuse.gov/publications/drugfacts/stimulant-adhd-medications-methylphenidate-amphetamines. January 21, 2014. Accessed June 11, 2017.
30. Merikangas KR, He J, Burstein M, Swanson SA, Avenevoli S, Cui L, Benjet C, Georgiades K, Swendsen J. Lifetime prevalence of mental disorders in U.S. adolescents: Results from the National Comorbidity Study Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010 Oct;49(10):980-989.
31. Centers for Disease Control. State Profiles- Diagnosis and Medication Treatment Among Children Ages 4-17 (Survey Data). https://www.cdc.gov/ncbddd/adhd/stateprofiles/index.html. Accessed June 11, 2017.

32. Centers for Disease Control. Parent-Reported Diagnosis of ADHD by a Health Care Provider and Medication Treatment Among Children 4-17 Years: National Survey of Children's Health* – 2003 to 2011. State Profile: Rhode Island. https://www.cdc.gov/ncbddd/adhd/stateprofiles/stateprofile_rhodeisland.pdf. Accessed June 11, 2017.
33. Vollmer S. AD/HD: it's not just in children. *Family Pract Recertif.* 1998;20:45–6.
34. Wender PH. Attention-deficit hyperactivity disorder in adults. New York: Oxford University Press, 1995
35. Kessler RC, Berglund PA, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Archives of General Psychiatry. 2005 Jun;62(6):593-602.
36. NIDA. The Neurobiology of Drug Addiction. National Institute on Drug Addiction website. https://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/. January 2, 2007. Accessed June 11, 2007.
37. Searight HR, Burke JM, Rottnek R. Adult ADHD: evaluation and treatment in family medicine. Am Fam Physician. 2000 Nov 1;62(9):2077-86, 2091-2. PMID 11087189. http://www.aafp.org/afp/2000/1101/p2077.html#ref-list-1. Accessed June 11, 2017.