Prescription Stimulants and Adverse Health Outcomes in Oregon

This report is a public health investigation and descriptive analysis on prescription stimulants and negative health outcomes

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Table of Contents

Executive Summary

Prescription stimulant dispensations in Oregon have steadily increased since the Oregon Prescription Drug Monitoring Program was created in mid-2011, with a greater increase starting in 2020. In the fourth quarter of 2012, 1.7 percent of Oregonians received a stimulant dispensation from a retail pharmacy. This percentage nearly doubled to 3.1 percent by the fourth quarter of 2022. (1) Percentages in Oregon are consistent with those nationwide, as research on the 2015 and 2016 National Surveys on Drug Use and Health reported that 4.5 percent of U.S. adults receive prescription stimulants. (2) Despite this increase in Oregon and nationwide, there is limited information on negative health outcomes associated with acute or chronic stimulant use. The purpose of this report is to investigate differences in negative health outcomes, including emergency department visits, hospitalizations, and deaths, and prescription stimulants in Oregon. A specific focus of the report is on possibly risky stimulant prescribing. These practices were identified through a literature review and previous findings from the opioid epidemic and include 1) prescribing to stimulant naïve patients, 2) high quantity stimulant prescribing, 3) long duration stimulant prescribing, 4) co-prescribing with opioids, and 5) co-prescribing with benzodiazepines. The most important findings of this report are the following:

- The death rate for Oregonians who received a benzodiazepine prescription concurrently with a stimulant prescription was 60 percent higher than the death rate for any other stimulant prescribing practice.
- The highest death rates occurred in individuals receiving modafinil compared to the death rates of those that received other prescription stimulants.

- Oregonians receiving modafinil dispensations with a greater than 30-day supply had the highest hospitalization rate of all medications and prescribing practices.
- Emergency department visit, hospitalization, and death rates for overlapping modafinil and benzodiazepine dispensations were higher than rates for other stimulants overlapping with benzodiazepines. Studies that supported the FDA approval of modafinil did not include individuals taking benzodiazepines.
- One in 10 Oregonians ages 65 years and older who received a stimulant with a greater than 30-day supply went to the emergency room from January 2018 through September 2021.
- One in 20 Oregonians ages 65 years and older who received a stimulant with a greater than 30-day supply were hospitalized from October 2017 to September 2021.
- Oregonians receiving dispensations of prescription amphetamine often had lower emergency department, hospitalization, and death rates than Oregonians receiving dispensations of other prescription stimulants.
- Males taking stimulants consistently experienced higher death rates than females.
- The emergency department, hospitalization, and death rates in cases where suicide was a contributing cause appeared marginally higher in cases where individuals were taking stimulants, compared to other contributing causes examined here. Rates calculated where the total number of events was < 20 may change with additional data.

The findings in the report should be considered by Oregon Health Authority advisory groups, including the Prescription Drug Monitoring Program Advisory Commission and Prescribing Practices Review Subcommittee. Members of the advisory groups may consider if findings raise further questions that can be investigated by analytic teams or if new educational interventions for prescribers should be introduced. Report figures may be updated as new data become available, which could change the rates and conclusions. The datasets used were administrative in nature and not ideally built for a descriptive analysis of stimulant prescribing practices and negative health outcomes. Importantly, this initial report is largely exploratory and based on known risk factors associated with prescription opioids or benzodiazepines because public health research on prescription stimulants and potential negative health outcomes is limited at the time of this writing. Hypothesis-driven research studies, especially those that assess the impact of long-term prescription stimulant use on health outcomes, are needed.

Introduction

The Oregon Health Authority has observed an increase in prescription stimulant dispensations and a corresponding increase in concern among epidemiologists about potential negative health outcomes of stimulant use. (1) Simultaneously, illicit stimulant use and overdose deaths, primarily attributed to methamphetamine, have been increasing since 2019 in Oregon. (3) These observations parallel those of the early opioid epidemic with increased prescribing, illicit use, and overdose. But it is unknown if legitimately prescribed stimulants are contributing to increased rates of emergency department visits, hospitalizations, and deaths.

There are numerous known negative health effects of stimulant (also known as psychostimulant) medication that could increase the rates of emergency department visits, hospitalizations, and deaths. Myocardial infarction and arrythmias have occurred in persons taking psychostimulants, resulting in sudden death. (4–7) Risk may be higher among people taking methylphenidate, which is often used to treat individuals with a Attention Deficit Hyperactivity Disorder (ADHD) diagnosis. (8) Sudden death, stroke, and myocardial infarction has occurred in adults and children taking methylphenidate, with a higher risk for those with structural or rhythm cardiac abnormalities. (4) The rate of sudden death in college-age persons using methylphenidate is between 1-10 per 100,000, which converts to over 146 deaths caused by methylphenidate in the United States per year among this population. (6) An increased risk of suicide attempts and new psychotic symptoms (e.g., hallucinations, delusional thinking, mania) have also been reported. (4,9) Psychostimulants also have documented cardiovascular side-effects, including increasing heart rate by 3-10 beats per minute, increasing blood pressure (systolic and diastolic) by 2-14 mm Hg, and delaying ventricular repolarization. (10) One large study of 1,224 persons under 18 years old with an ADHD diagnosis found a 1.6 times higher rate of arrythmia with the prescription stimulant methylphenidate, when compared to not taking methylphenidate. (11) Other stimulants, such as modafinil, can also result in cases of agitation, tachycardia, and hypertension. (12) However, there are no studies on different prescribing practices of psychostimulants and negative health events in a large population across multiple years.

In response, the Prescription Drug Monitoring Program, which is part of the Injury and Violence Prevention Section in the Oregon Health Authority, proposed in the “BJA FY

20 Harold Rogers Prescription Drug Monitoring Program" grant (#2020-PM-BX-0017) to further examine the public health concern by completing a public health investigation into the role of stimulants on negative health outcomes. Specifically, the Program planned to complete a descriptive analysis of stimulants and adverse outcomes by creating several new linked datasets.

Methods

A dataset of all controlled substance dispensations in Oregon, held by the Oregon Health Authority Prescription Drug Monitoring Program, was linked on the person level with identifiers and keys to emergency department visit and hospitalization data from the Oregon Health Authority Office of Health Analytics. The Link King, a SAS-based application, (13,14) was used with probabilistic and deterministic algorithms to match individuals in the dispensation and the Health Analytics datasets on first name, last name, date of birth, gender, and residence ZIP Code. Link King default probabilistic weights were used for each, with the elimination of negative weighting in cases where the Zip Code did not match. The rare name cut point was set to 0.2. Mapping certainty levels 1-3 were selected, which are described extensively in the manual. (13) The mapping levels selected did not require that records be manually reviewed after the linkage, so they were not. Keys were used to match the identified dispensation data to previously de-identified emergency department and hospitalization event data. After the match, the emergency department data included 160,312 persons receiving 3,524,142 stimulant dispensations and having a total of 445,217 emergency department encounters from December 29, 2017, to September 30, 2021. The hospitalization data included 47,969 persons receiving 976,128

stimulant dispensations with a total of 77,600 encounters from October 18, 2017, to September 29, 2021.

To examine the relationship between stimulant dispensations and death, the controlled substance dispensation data described above was linked on the person level with death data from the Oregon Health Authority Department of Vital Statistics, covering January 1, 2010 – December 31, 2020. The Link King application was used here using the same methodology described in the preceding paragraph to match individuals between the dispensation and death datasets on first name, last name, date of birth, gender, and residence ZIP Code. The resulting dataset included 6,069 deceased Oregonians receiving a total of 76,808 stimulant dispensations.

This report considered five types of stimulant prescribing practices that could plausibly increase the risk of adverse events and death, including 1) prescribing to stimulant naïve patients, 2) high quantity stimulant prescribing, 3) long duration stimulant prescribing, 4) co-prescribing with opioids, and 5) co-prescribing with benzodiazepines. Methods and rationale for defining these practices are included throughout the report in their respective sections. Persons who met the criteria for a risky dispensation and had a recorded emergency department visit, hospitalization, or death date within 180 days (or 60 days for stimulant naïve prescribing) of receiving that dispensation were compared to all persons who had received the same type of stimulant dispensation; or all persons who had an emergency department visit, were hospitalized, or deceased and had received the same International Classification of Diseases 10th Revision (ICD-10) contributing cause code. The use of comparison groups also allowed for the calculation of emergency department

visit rates, hospitalization rates, and death rates. Rates (per 10,000 people) were calculated by dividing the number of emergency department visitors, hospitalized individuals, or deceased individuals who had received a particular risky dispensation by the total number of people who received a risky dispensation and multiplying by 10,000; or dividing the number of people with stimulant prescriptions with a particular ICD-10 contributing cause code(s) tied to the emergency department visit, hospitalization, or death by the overall number of people who had the same contributing cause code(s) and multiplying by 10,000. (15) For example, in figure 1 below, the number of people who were stimulant naïve and had an emergency department cause code(s) related to a suicide (U030, X600-X849, Y870) were divided by the count of all people with one or more of the same emergency department cause codes, and the quotient was multiplied by 10,000. Only the first emergency department visit or hospitalization after a person started taking stimulants was retained in cases where a person had multiple encounters, consistent with previous investigations on this topic. (11,16) For comparison groups, only the first encounter or received stimulant was considered.

Differences in emergency department visits, hospitalizations, and death rates were also considered by reported sex (female, male), age in years (< 44, 45-64, 64+), and stimulant type [amphetamine (including dextroamphetamine), methylphenidate, phentermine, lisdexamfetamine, modafinil]. These five stimulant drugs represent over 97 percent of all stimulant dispensations collected by the Oregon Prescription Drug Monitoring Program from program inception in 2011 to September 30, 2021. Rates were also calculated for several contributing causes of injury or death identified a priori that could

plausibly be related to prescription stimulant use based on literature and findings from the opioid epidemic. These contributing causes of emergency department visits, hospitalizations, and death were identified by ICD-10 codes and included those that were cardiovascular-related (I100, I150-I160, I200 – I250, I440 – I520, I600 – I690) psychosis-related (ICD F000 – F999), drug overdose-related (T360 – T500, X400 – X449, X600 – X649, X850, Y100 – Y149, Y400 – Y599), suicide (U030, X600 – X849, Y870), and unknown causes (R000 – R999, Y100 – Y149). For analysis of the death data, cases where neoplasms were the underlying cause of death were removed for analyses of deaths since there is no known evidence that short-term prescription stimulant use can cause fatal cancer, and because stimulants are sometimes used in palliative care for terminal cancer to treat cancer fatigue. (17) Neoplasms were the most common underlying cause of death for those taking stimulants, representing approximately 70 percent of Oregonian deaths that occurred when an individual had a dispensation that met the criteria for one of the five types of possibly risky stimulant prescribing practices described in subsequent sections.

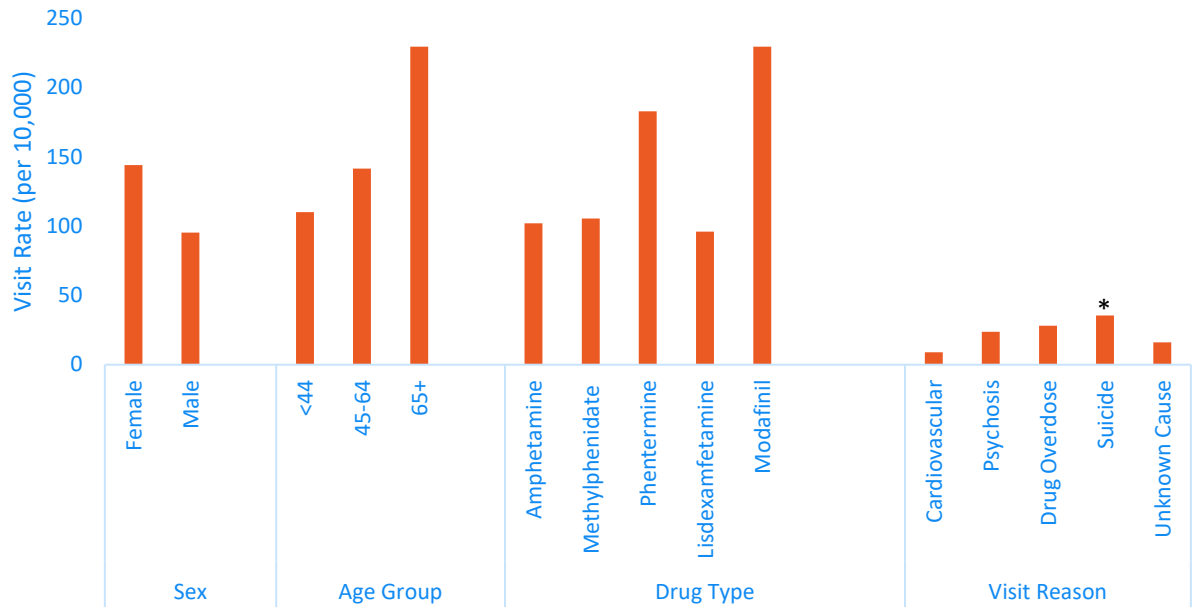
Prescribing to stimulant naïve patients

There may be an elevated risk of experiencing negative health effects when individuals first start taking stimulants. Systematic reviews and large healthcare claims studies have found myocardial infarction risk is higher and seizure risk is four-times higher in the first 56 and 30 days (respectively) after starting methylphenidate. (11,18) Risk of psychosis is also higher in the first 60 days after starting a stimulant, with studies finding that 1 in 660 patients have new-onset psychosis, and 1 in 372 patients are hospitalized for psychosis or mania. (16,19) Death is also more likely to occur in the first 80 days after

starting stimulants. But since stimulant deaths have often occurred in palliative care settings, it is unclear if stimulants caused these deaths. (9)

For this report, stimulant-naïve Oregonians were defined as individuals who received a new stimulant dispensation 60 or fewer days before an emergency department visit, hospitalization, or death. A dispensation was defined as new for a person if they were not dispensed a stimulant in the previous 360 days. The 60-day mark was chosen based on literature suggesting the risk of adverse events with psychostimulants is highest in the 60 days after initiation, although the reason is uncertain. (11,16,19) Figure 1 below shows differences in emergency department visit rates by sex, age, stimulant type taken, and reason for the visit. The highest visit rates for people who were stimulant naïve were observed for females, those ages 65 and older, and individuals taking modafinil. Stated differently, of every 10,000 Oregonians who were stimulant naïve, 144 females, 229 individuals aged 65 or older, and 229 individuals taking modafinil had an emergency department visit. Rates were not as high (< 40/10,000) for visit reasons that were anticipated to be related to stimulant use by naïve individuals (figure 1).

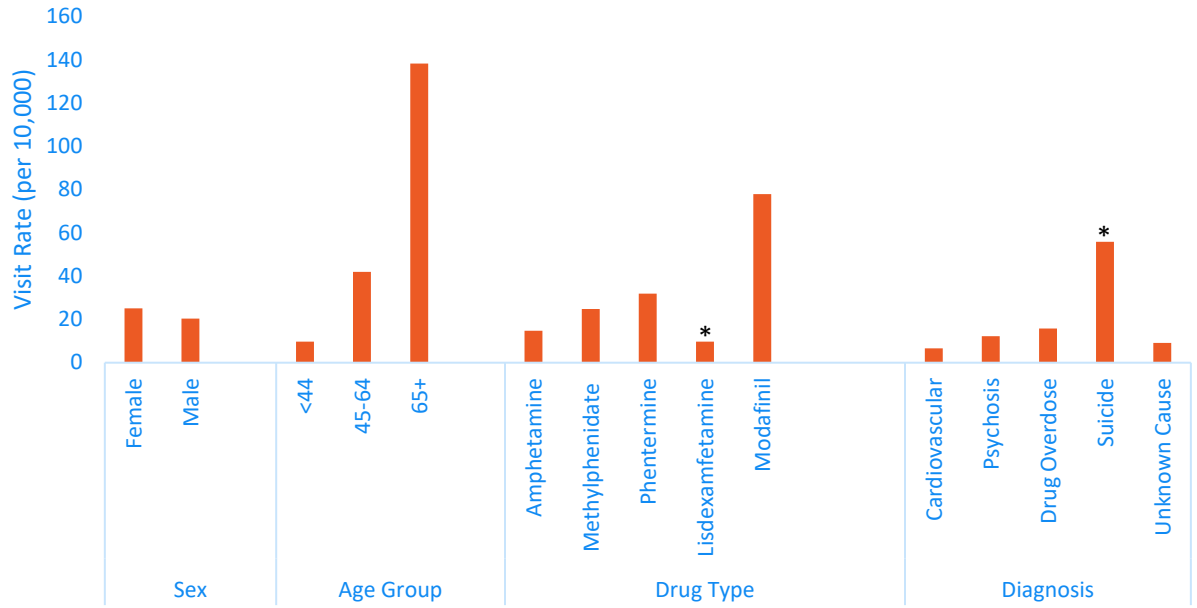
Figure 1: Emergency Department Visit Rates for Stimulant Naïve Persons



* indicates a rate numerator < 20 that may make this calculation unreliable.

The pattern of hospitalizations of stimulant naïve Oregonians (figure 2) was like that of emergency department visits. Hospitalization rates were higher for individuals ages 65 years and older and those taking modafinil. The lower rate of hospitalizations, as compared to emergency department visits, likely occurred because a hospitalization reflects a more serious visit, defined as admittance to the hospital with a 24 hour or longer stay. Individuals who initially visited the emergency department and were admitted to the hospital are recorded in only the hospitalization data and not the emergency department data. It is possible individuals ages 65 and older were considered higher risk and more likely to be hospitalized due to their age. There may be differences in comorbidities by age that influence this finding, but that data was not available here. Modafinil is often used to treat fatigue in chronic conditions (17) and the higher hospitalization rate for individuals taking modafinil may reflect other underlying health issues not captured in this analysis.

Figure 2: Hospitalization Rates for Stimulant Naïve Persons

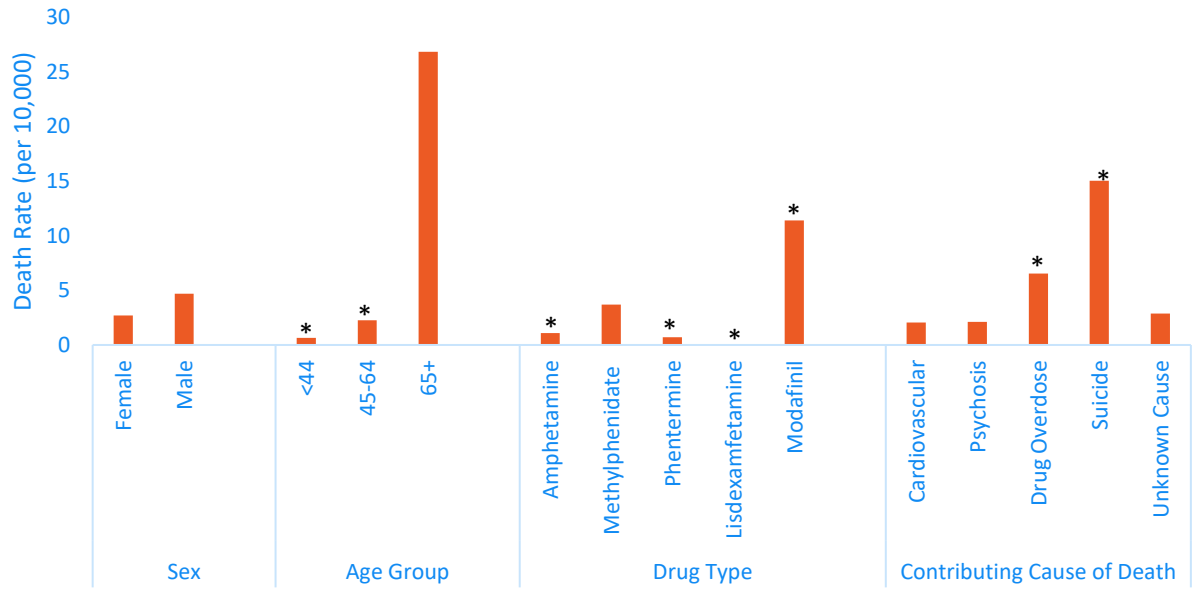


* indicates a rate numerator < 20 which may be unreliable.

Differences in death rates by sex, age, stimulant type taken, and contributing cause of death were considered. As shown in figure 3 below, the death rate for stimulant naïve males was higher than for females. The death rate was especially high for those ages 65 years and older taking stimulants. Finally, the death rate for those who were stimulant naïve and taking modafinil appeared to be higher than those taking methylphenidate or amphetamine. The small difference in rates by sex was not expected, but differences in age and drug type may be due to how stimulants are prescribed. Specifically, those in palliative care may be receiving stimulants for fatigue associated with chronic illnesses, such as multiple sclerosis and stroke. (20,21) Although this is speculative as reliable diagnosis code information is not available, the differences in risk by age should be explored further.

When considering select contributing causes of death, suicide and drug overdose rates were higher than other contributing causes that were considered. This data in Oregon is consistent with reports that risk of suicide attempts is increased when starting methylphenidate. (9) The high death rate from drug overdose may have occurred because individuals diagnosed with ADHD are more likely to develop substance use disorders, and stimulants are often used to treat ADHD. (22) Age may also be a factor for further exploration regarding the drug overdose rate, as risk of drug overdose is higher nationally for those under age 65. (23) Finally, the number of individuals being considered in these groups is < 20 for some rates, so these rates should be interpreted with caution.

Figure 3: Death Rates for Stimulant Naïve Persons



* indicates a rate numerator < 20, which may make this calculation unreliable.

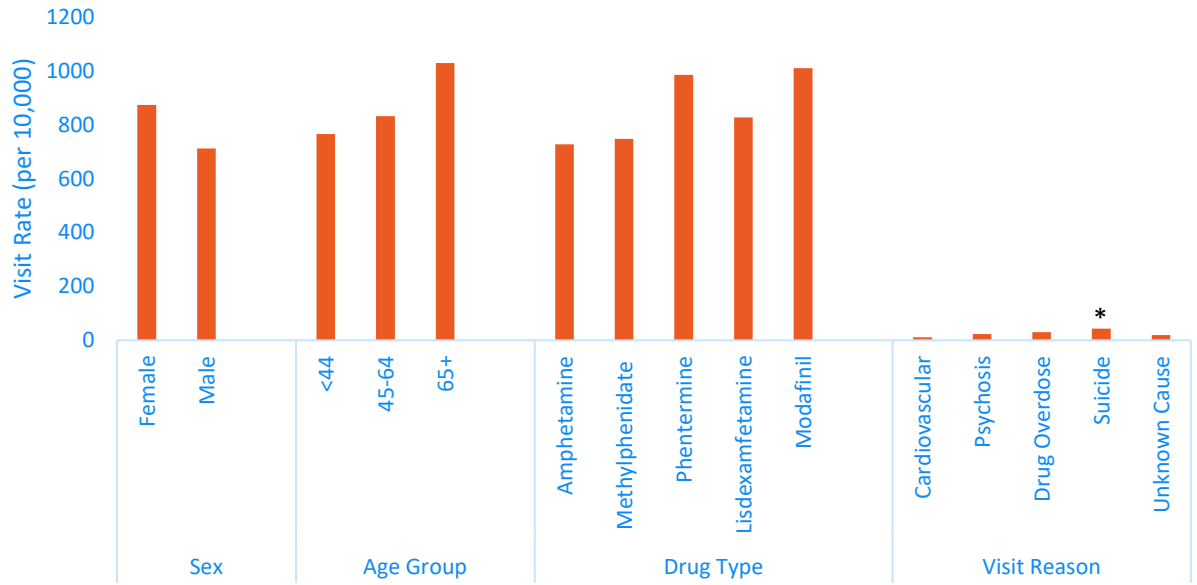
High quantity stimulant prescribing

Overall, there has been very little investigation of stimulant medication strength, quantity, or duration on negative health events across different stimulant medications. Opioid research in this area is extensive because of the development of morphine milligram equivalents, which allow opioids differing in quantity, strength, and duration to be directly compared. Morphine milligram equivalents have allowed researchers and the Centers for Disease Control and Prevention to make minimally effective dose recommendations for opioids, and document that risk of misuse, unintentional overdose, and death increase at higher morphine milligram equivalents. (24) Without a direct equivalency method for stimulants, high quantity stimulants were defined by the number of days that a single prescription could be taken according to provider instructions (i.e., day supply). In this report, a high quantity stimulant dispensation is defined as one with a >30-day supply. This cut-point was chosen because 96 percent of all stimulant dispensations in this Oregon dataset had a supply of 30 days or less. Only dispensations received ≤ 180 days of a negative health event were included.

Figure 4 below shows differences in emergency department visit rates by sex, age, stimulant type taken, and reason for the visit in individuals who had high quantity stimulant dispensations. Emergency department visit rates are highest for individuals ages 65 and older and those taking modafinil or phentermine. As a percentage, over 10 percent of Oregonians with a high quantity stimulant dispensation either aged 65 years or older and/or taking modafinil visited the emergency department during the study period. These are the same categories with the highest rates among individuals who were stimulant naïve and

went to the emergency department, although the rates are nearly four times higher for people in this group who received a high quantity stimulant dispensation. The visit rates were slightly higher for females than males (874 vs. 713 per 10,000). In some stimulants, such as methylphenidate, plasma concentrations of the primary metabolite are higher in females than males, indicating a slower metabolism which could allow medications to build up over time and result in more negative health events. (4)

Figure 4: Emergency Department Visit Rates for Persons With >30-Day Stimulant Prescription

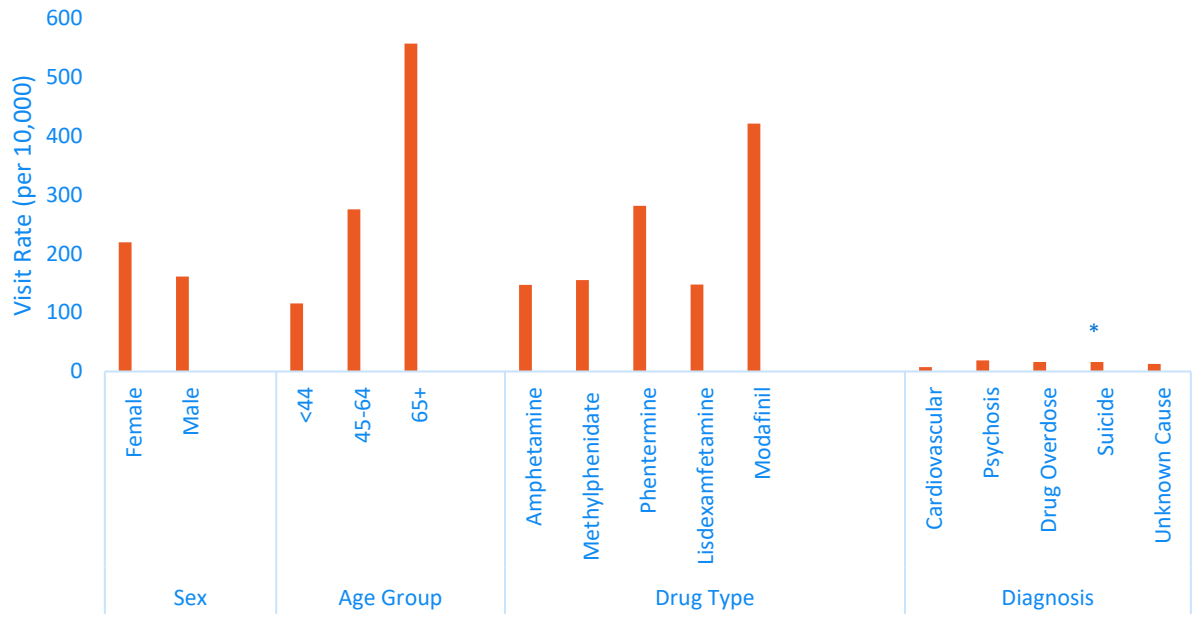


* indicates a rate numerator < 20 which may be unreliable.

The pattern of hospitalization rates, shown in figure 5 below, is like the pattern of emergency department visit rates for high quantity stimulant prescribing described above. Hospitalization rates are highest for individuals ages 65 and older (5.5 percent) and those taking phentermine (2.8 percent) or modafinil (4.2 percent). However, the magnitude by which those groups have the highest hospitalization is nearly double that of other age

groups or stimulants considered. Differences of this magnitude are not in the emergency department data for high quantity stimulants. It is possible that individuals ages 65 and older are generally higher risk patients and more likely to be admitted to the hospital (and recorded in the hospitalization data) rather than treated only in the emergency department and released. Similarly, the use of modafinil may be indicative of a person taking the stimulant to treat fatigue related to a medical condition with higher risk of complication, rather than for ADHD, which may be treated with different stimulants. (25–27) Suicide had the highest rate of contributing causes that were specifically examined, but the rate numerator is under 20 for suicide, which means that the rate may change with more data.

Figure 5: Hospitalization Rates for Persons With >30-Day Stimulant Prescription

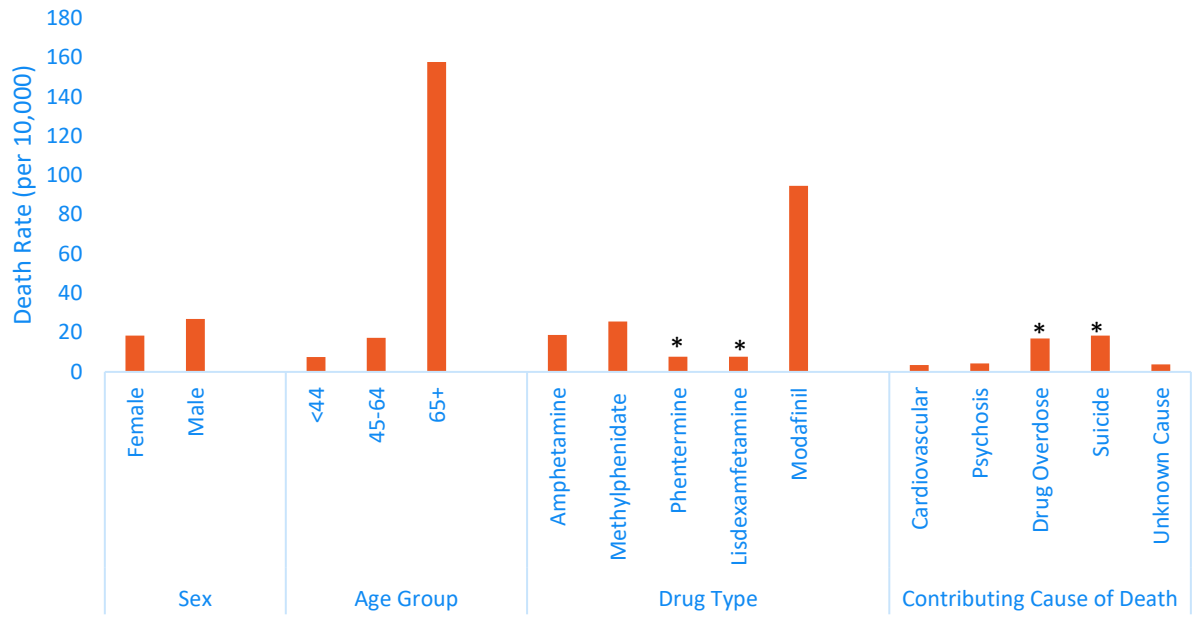


* indicates a rate numerator < 20 which may be unreliable.

In reviewing the death data (figure 6) below, the pattern of death rates for individuals receiving a >30-day supply of stimulant medication prior to death is very similar to those who were stimulant naïve prior to death. Death rates for individuals ages 65 and older

appear to be much higher than death rates of younger persons (157 per 10,000 vs. < 20 per 10,000). Death rates for individuals taking modafinil (94 per 10,000) also appear higher than those taking other stimulants examined (< 30 per 10,000). The death rates are about 4 times smaller than the hospitalization rates for those receiving a >30-day supply of stimulants. When reviewing contributing causes of death, suicide and drug overdose also appear to be higher than other reviewed causes. Suicide and drug overdose rates for high quantity stimulant cases are not noticeably higher than stimulant naïve cases. However, there were a small number (< 20) of suicide and drug overdose deaths among individuals with a >30-day supply of stimulant medication which may affect the reliability of the reported rate.

Figure 6: Death Rates for Persons With >30-Day Stimulant Prescription



* indicates a rate numerator < 20 which may be unreliable.

Long duration stimulant prescribing

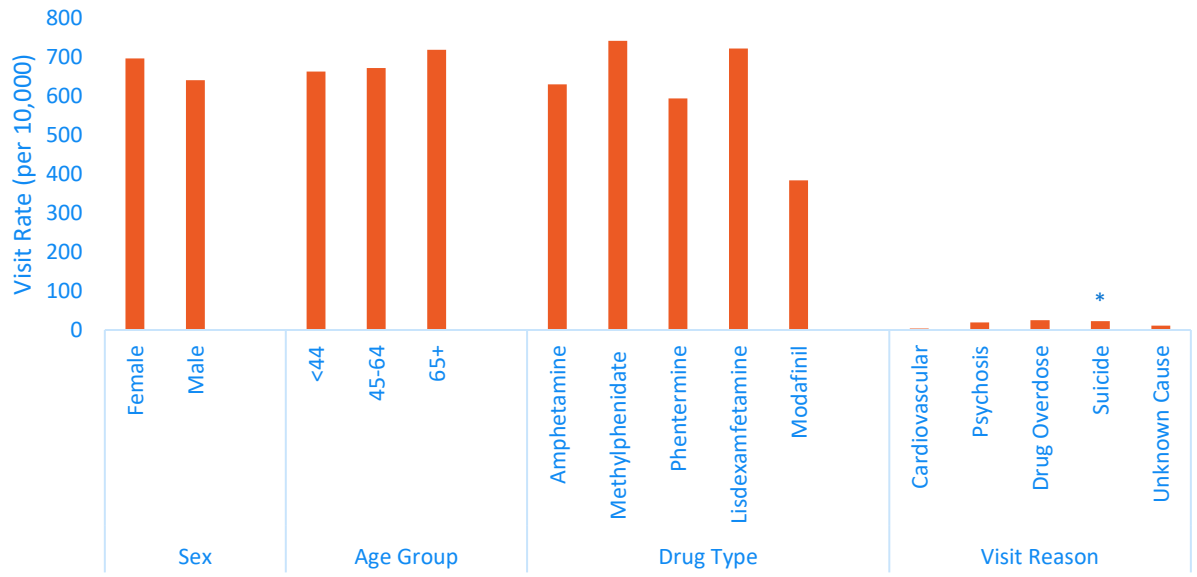
There are no known long-term (i.e., 26 or more weeks), well controlled (i.e., randomized, placebo-controlled) studies of stimulants, possibly because of ethical issues and costs associated with conducting blinded, longer duration trials. (28) However, cohort studies, patient-control studies, case investigations, and studies using medical records have been able to examine risks and adverse health events associated with longer duration stimulant use. (8) A cohort study from Sweden using drug and patient registers (n=23,898) found no increase in psychotic events in persons aged 12-30 when looking specifically at a 12-week period that occurred one year after starting methylphenidate. (29)

However, a systematic review of non-randomized methylphenidate studies that often had longer follow up periods than randomized controlled trials found that 1 percent of patients taking methylphenidate suffered a serious adverse health event, and more than 50 percent of patients experienced one or more adverse health events. (8)

In consideration of Oregon data, a period of long duration stimulant use was defined as more than 12 stimulant dispensations in a calendar year. This cut-point was chosen because 90 percent of all individuals who received stimulants in the dataset filled 12 or fewer dispensations per year. Only dispensations received ≤ 180 days of negative health events were considered. In the emergency department data below in figure 7, individuals who were female, ages 65 years and older, and/or taking long duration prescriptions of methylphenidate or lisdexamfetamine experienced the highest rate of emergency department visits. Rates were similar for each of these elevated groups, with about 7 percent of individuals in these groups who received a long-duration stimulant visiting the

emergency department in the sample timeframe. Long duration modafinil resulted in the lowest rate of emergency department visits of examined stimulants. Drug overdose was the contributing cause with the highest rate of those examined. About 0.2 percent of those with a listed cause of drug overdose in the emergency department had recently taken a long-duration stimulant.

Figure 7: Emergency Department Visit Rates for Persons Receiving >12 Stimulant Prescriptions in 1 Year

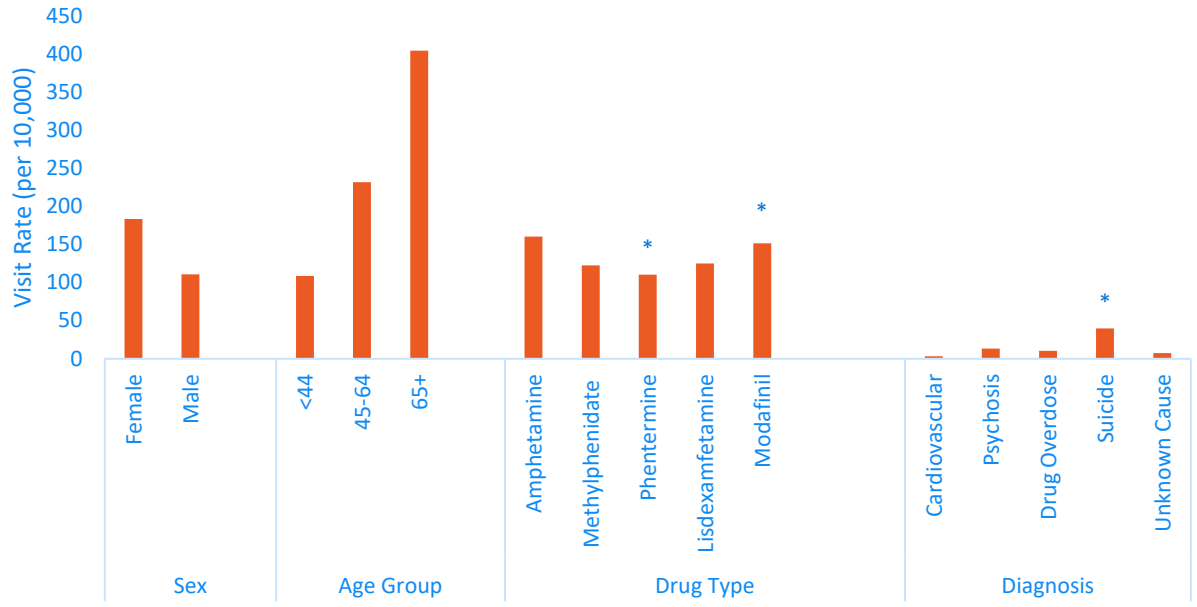


* indicates a rate numerator < 20 which may be unreliable.

Hospitalization rates for Oregonians who received long duration stimulant prescriptions are presented below in figure 8. Females and persons ages 65 and older taking long duration stimulants experienced the highest rates of hospitalization. Individuals taking any of the long duration stimulants examined had similar hospitalization rates, with those taking amphetamine experiencing the highest hospitalization rate at 160 per 10,000. Said another way, 1.6 percent of those taking amphetamine for a long duration were hospitalized. The number of hospitalizations for individuals taking phentermine or modafinil

was less than 20, which is sufficiently low that the rate may change over time with additional data. Suicide was the highest contributing cause of hospitalization, but there were also a small number of total hospitalizations among individuals taking long duration stimulants.

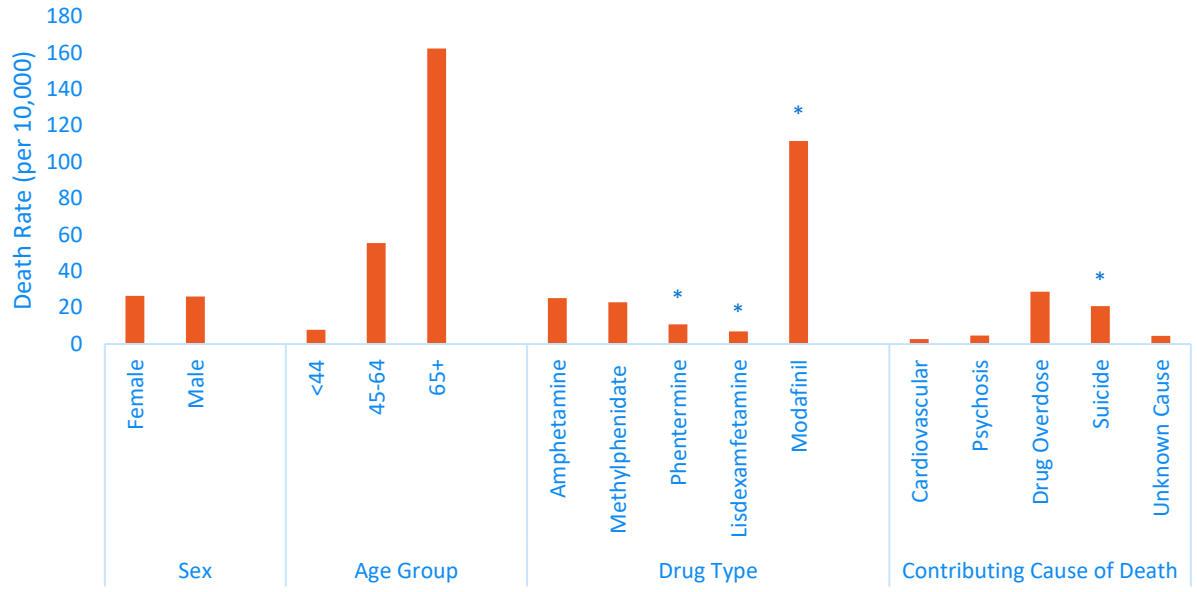
Figure 8: Hospitalization Rates for Persons Receiving >12 Stimulant Prescriptions in 1 Year



* indicates a rate numerator < 20 which may be unreliable.

For the death data (figure 9), there were similar patterns and rates observed for individuals who received high quantity stimulant prescriptions. The highest death rate was for those ages 65 years and older at 162 per 10,000 or 1.6 percent. Death rates are also higher for individuals taking modafinil, and cases where drug overdose or suicide was a contributing factor. The similarity with Figure 6 (death rates and high quantity dispensations) above could be due to the underlying reason for the stimulant prescription, or individual factors. It was not possible here to account for diagnosis code, which would allow for further exploration of this possibility.

Figure 9: Death Rates for Persons Receiving >12 Stimulant Prescriptions in 1 Year



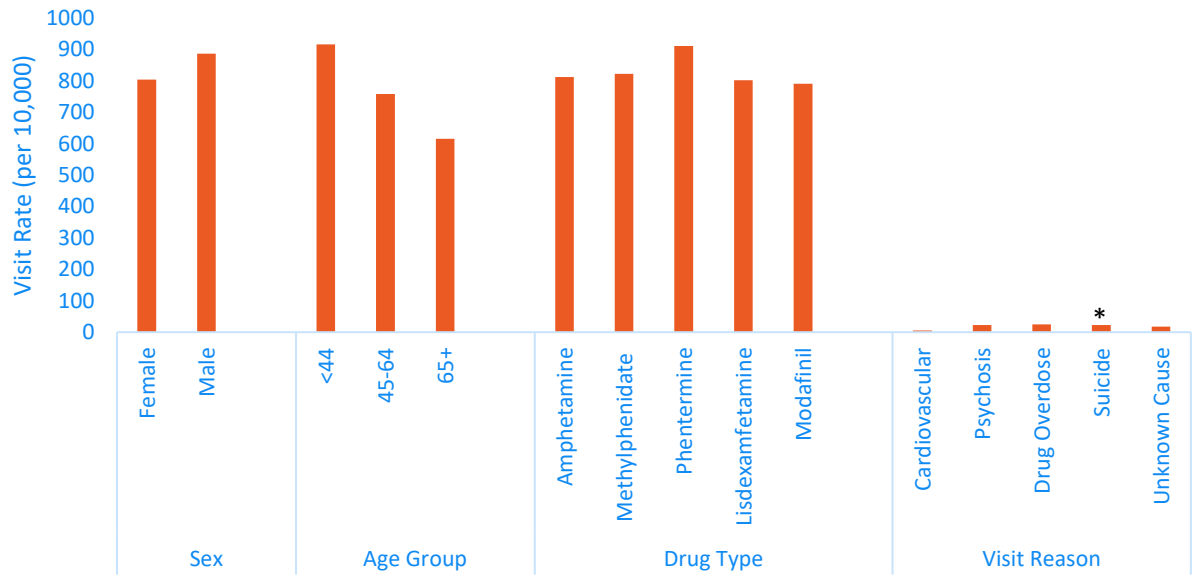
* indicates a rate numerator < 20 which may be unreliable.

Co-prescribing with opioids

Opioids and stimulants taken concurrently may result in negative health events, especially given that adverse events can occur from opioids alone. (3) Although there have been reports on health consequences of concurrent illicit stimulants and opioids, (30) investigations have not been conducted on negative health events experienced by individuals concurrently taking prescribed stimulants and opioids. Oregon data has also never been examined. For the analysis described here, stimulant and opioid (excluding buprenorphine) prescriptions were considered concurrent if the date dispensed of the second prescription overlapped with the date dispensed plus the day supply of the first prescription. Only stimulant and opioid prescriptions that were concurrent ≤ 180 days of negative health events were considered, and only the most recent prescriptions were considered if there were multiple concurrent cases in the 180-day period.

Visit rates to the emergency department among individuals who received opioids and stimulants concurrently are displayed below in figure 10. The highest visit rates below are for individuals who are male and ages 44 or younger at 886 and 916 persons per 10,000. Said another way, about 9 percent of individuals who were either male or age 44 and younger and concurrently taking a stimulant and an opioid visited the emergency department during the sample period. Individuals taking phentermine also had higher visit rates (911 per 10,000), although the visit rates of all examined stimulants are similar.

Figure 10: Emergency Department Visit Rates for Persons Co-Prescribed Stimulants and Opioids

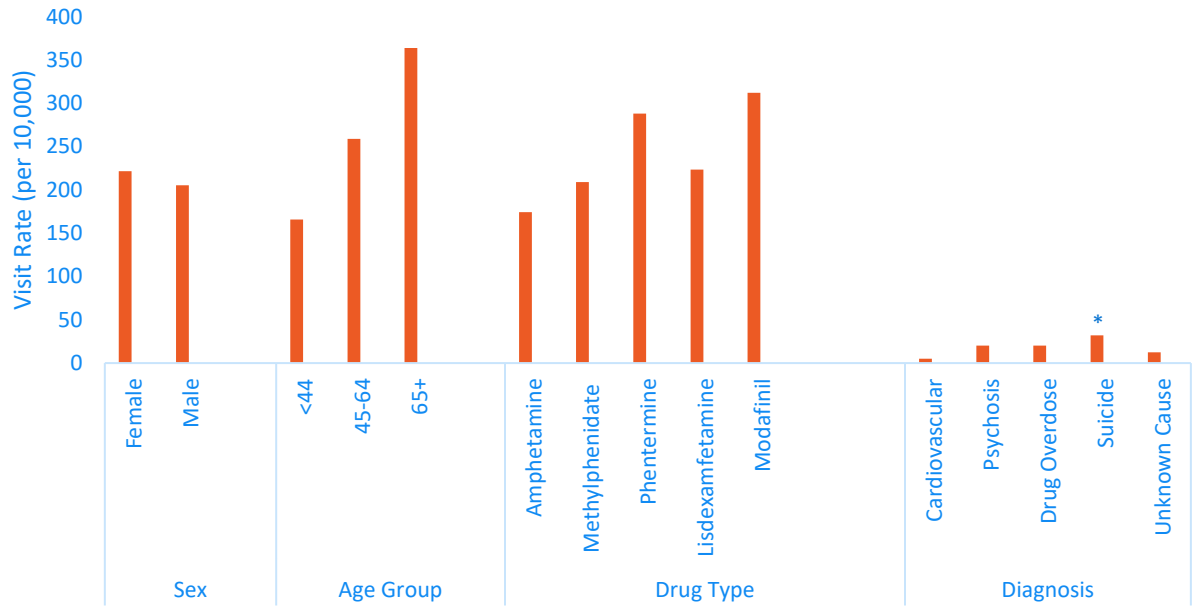


* indicates a rate numerator < 20 which may be unreliable.

Figure 11 below shows hospitalization rates for Oregonians taking opioids and stimulants concurrently, and a pattern like other prescribing practices examined in this report is evident. Individuals ages 65 and older and individuals taking modafinil had higher hospitalization rates. The rates in the figure are 364 and 312 per 10,000 people respectively, or about 3 percent of individuals taking a stimulant and opioid concurrently.

Modafinil may be prescribed alongside opioids for purposes of reducing the sedative side-effects of opioids in patients suffering from pain. (31,32) As with other prescribing practices, it is unclear whether the higher hospitalization rates reflect underlying health conditions more likely to result in hospitalization, or a true risk of taking opioids with modafinil, especially in individuals ages 65 and older. The hospitalization rate for individuals who received opioids and phentermine also appears higher than the hospitalization rate for lisdexamfetamine, methylphenidate, or amphetamine. Differences in hospitalization rates by sex or contributing cause codes are small.

Figure 11: Hospitalization Rates for Persons Co-Prescribed Stimulants and Opioids

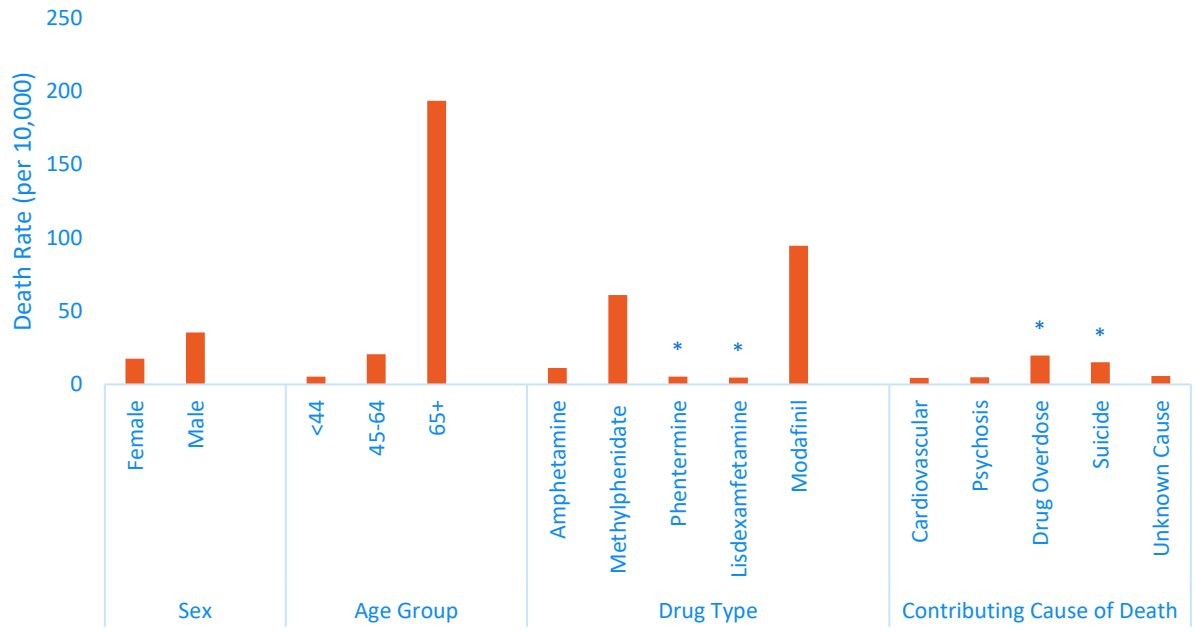


* indicates a rate numerator < 20 which may be unreliable.

In viewing the death rates in Figure 12 below, there is a similar pattern with other stimulant prescribing practices examined in the report, but the death rates are higher here. Death rates are especially high for individuals ages 65 and older and taking modafinil. Nearly 2 percent of individuals ages 65 and older taking any stimulant with an opioid, and

about 1 percent of those taking modafinil with an opioid passed away during the sample period. Higher death rates could be attributable to the use of prescription opioids, an additive risk of taking opioids with stimulants, or underlying health factors that necessitated the use of both opioids and stimulants (e.g., palliative care). The Rhode Island Prescription Drug Monitoring Program has noted that individuals ages 65 and older received overlapping opioids and stimulants at a rate nearly 10 times that of persons ages 18 and under, suggesting a need to focus specifically on this age group with concurrent stimulant and opioid prescribing. (33)

Figure 12: Death Rates for Persons Co-Prescribed Stimulants and Opioids



* indicates a rate numerator < 20 which may be unreliable.

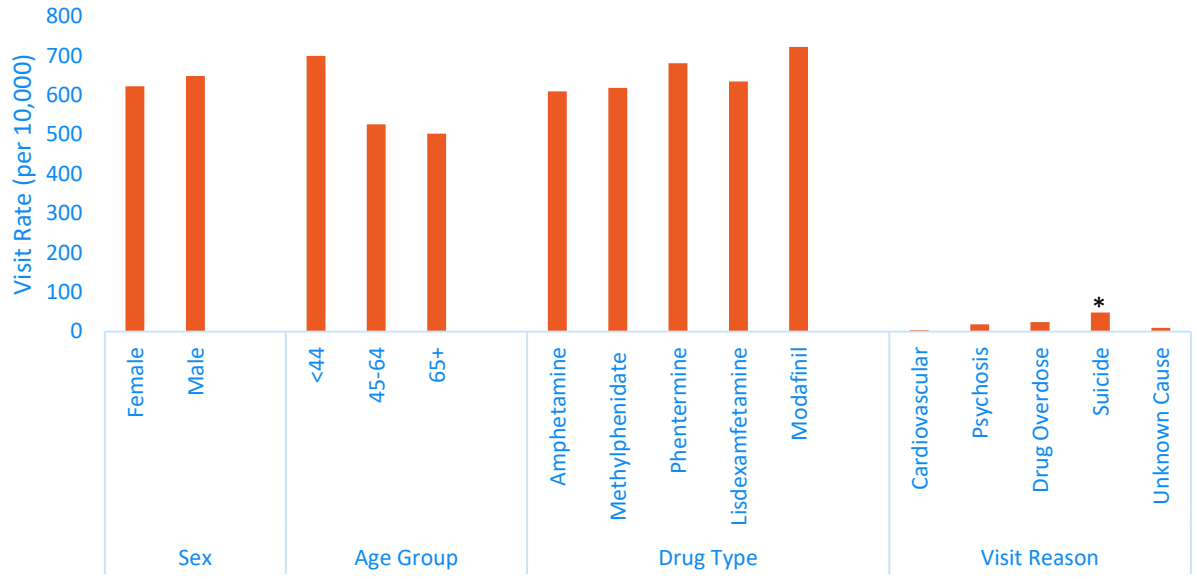
Co-prescribing with benzodiazepines

There is documented increased risk of overdose while taking benzodiazepines (e.g., lorazepam, zolpidem, clonazepam) either alone, or with opioids. (34,35) Less is known about concurrent use of benzodiazepines and stimulants. One cohort study of persons

diagnosed with amphetamine use disorder found that concurrent benzodiazepine use increased risk of any hospitalization or death. (36) But further increased risk of overdose in Oregon when receiving benzodiazepines and stimulants at the same time use is unknown. Concurrent use of stimulants and benzodiazepines was defined here using the same methodology for defining concurrent use of stimulants and opioids, as described in the section above.

Emergency department visit rates for Oregonians receiving overlapping stimulant and benzodiazepine prescriptions are shown below in figure 13. Males (648 per 10,000), persons ages 44 and under (700 per 10,000), and individuals taking modafinil (722 per 10,000) experienced the highest emergency department visit rates. This pattern is similar to that in figure 10 of individuals receiving both stimulants and opioids, although the visit rates for stimulants and benzodiazepines are lower. Contributing cause visit rates are highest for suicide-related codes (48 per 10,000). However, only select contributing cause visit reasons were examined and a small number of individuals (less than 20) both visited the emergency room with suicide-related codes and had received both a stimulant and a benzodiazepine.

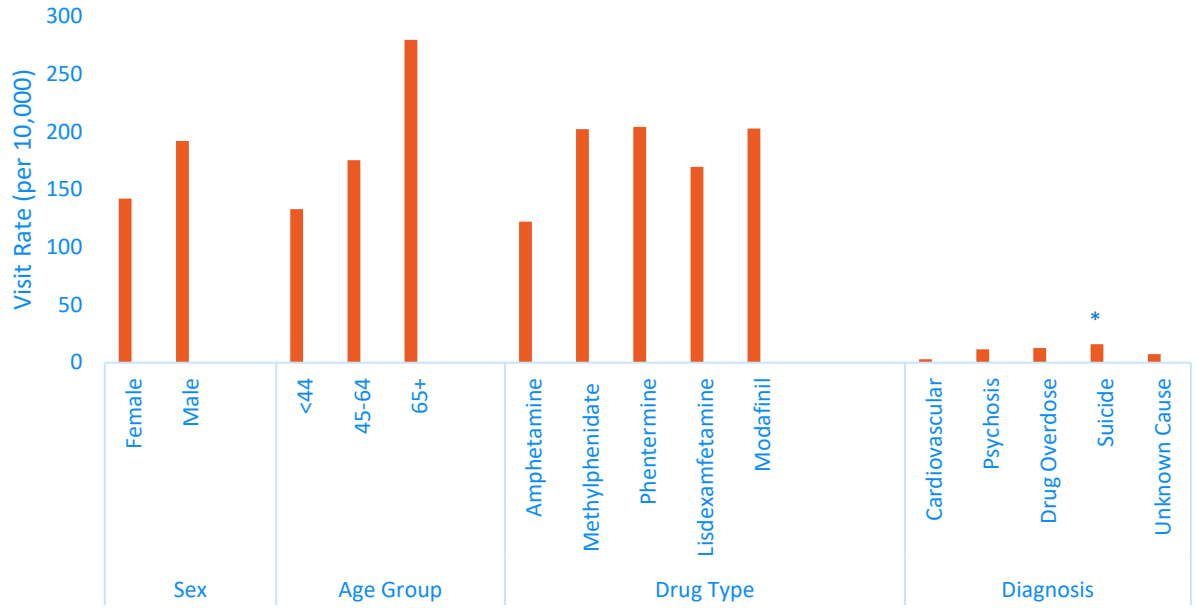
Figure 13: Emergency Department Visit Rates for Persons Co-Prescribed Stimulants and Benzodiazepines



* indicates a rate numerator < 20 which may be unreliable.

Hospitalization rates in figure 14 below show a different pattern than emergency department visit rates for individuals concurrently receiving a stimulant and benzodiazepine. Individuals ages 65 and older experienced a much higher hospitalization rate (279 per 10,000) than individuals ages 44 and younger. Males also had a higher hospitalization rate (191 per 10,000), although the difference in rates by sex is not as large as differences by age. Individuals receiving methylphenidate, phentermine, or modafinil along with a benzodiazepine also had higher hospitalization rates (over 200 per 10,000), while the hospitalization rate for individuals taking amphetamine was notably lower (122 per 10,000). Suicide was the diagnosis with the highest hospitalization rate of the diagnoses examined, which is a consistent finding with other stimulant prescribing characteristics examined in this report.

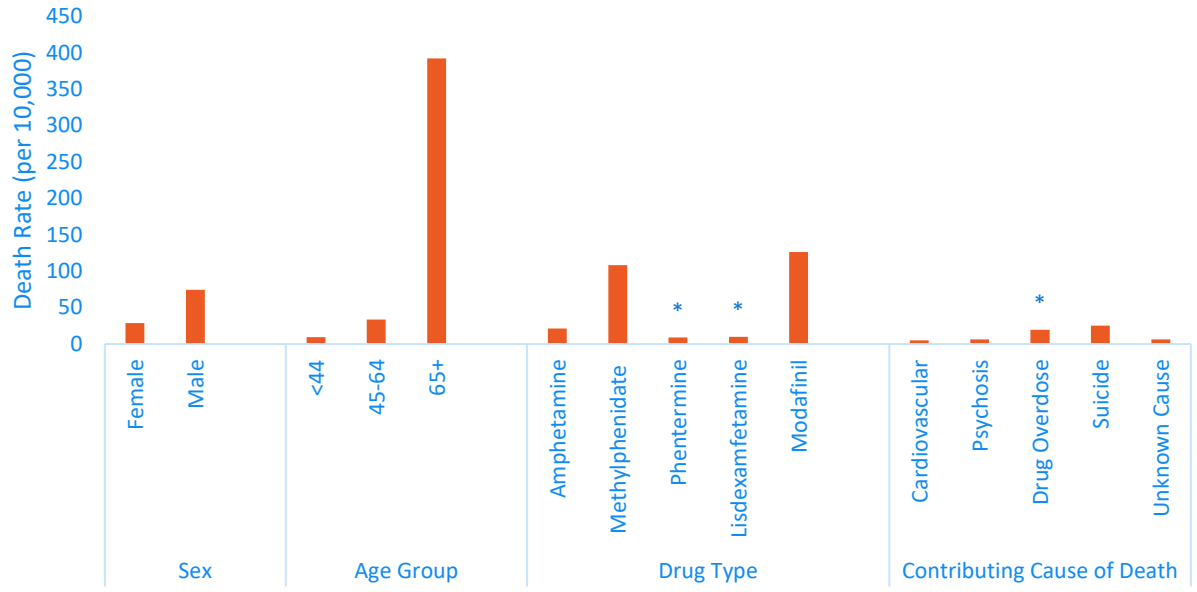
Figure 14: Hospitalization Rates for Persons Co-Prescribed Stimulants and Benzodiazepines



* indicates a rate numerator < 20 which may be unreliable.

Death rates shown in figure 15 below also have a similar pattern of rates occurring with co-prescribed opioids and stimulants. However, the death rate for individuals 65 years and older taking benzodiazepines is roughly double that of those taking concurrently taking opioids, at 392 per 10,000. The death rate for individuals taking modafinil is nearly 1.5 times higher at 126 per 10,000. These death rates are higher than death rates for any other stimulant prescribing practice considered in this report. Further investigation is needed to better understand these cases, particularly to determine if there is any causal relationship between concurrent use of stimulants and benzodiazepines and death.

Figure 15: Death Rates for Persons Co-Prescribed Stimulants and Benzodiazepines



* indicates a rate numerator < 20 wich may be unrelaible.

Discussion

Prescription stimulant dispensations have increased 2.6 times from 2012-2023 in Oregon (1), with the increase mirroring the surge in opioid dispensations that contributed to the first wave of the opioid overdose epidemic. (37) But it has been unclear whether Oregon residents taking stimulant medications are suffering negative health outcomes at higher rates. The purpose of this public health report was to investigate differences in stimulant prescription dispensations and rates of negative health outcomes. Future investigations are needed to begin to understand causal factors beyond the descriptive differences described in this report. Findings from this report could inform the direction of future investigations.

The highest emergency department visit rates were among Oregonians who received a stimulant dispensation with a >30-day supply. Over 10 percent of Oregonians ages 65 and older who received such a dispensation (1,030 for every 10,000) or

specifically received a >30-day supply of modafinil (1,010 for every 10,000) visited the emergency room. There was a similar pattern for hospitalizations, even though the rates were slightly smaller. Over 5 percent of Oregonians ages 65 and older who received a >30-day supply of a stimulant were hospitalized (557 for every 10,000), and over 4 percent of Oregonians who received a >30-day supply of modafinil were hospitalized (421 per 10,000). The high emergency department visit and hospitalization rates occurring with higher quantity stimulant dispensations were surprising. It was not possible for this report to examine dosage across stimulants because an equivalency calculation, such as morphine milligram equivalents for opioids, has not been established. (24) Instead, a >30-day supply was chosen to measure outlying high quantity stimulant dispensations because 96 percent of Oregon stimulant dispensations had a shorter day supply. Although the health effects of a >30-day supply for a stimulant have not previously been examined on the population level, repeated use of a stimulant without a washout period may allow the stimulant, or any drug, to reach unsafe levels which could occur more often in older individuals. (38) Modafinil may also present increased risk when taken for a prolonged period of time because the half-life (the time it takes for half of one dose to be metabolized) is 13-15 hours. (39,40) Methylphenidate, by contrast, has a half-life of 3 hours for short-acting formulations and 12 or fewer hours for long-acting formulations. (41,42) Future reports should continue to investigate negative health outcomes and high quantity stimulant prescriptions, paying particular attention to moderating effects of age and stimulant half-life.

In Oregon the highest death rates occurred when stimulants were received concurrently with benzodiazepines, whereas the lowest death rates were seen among

individuals who were stimulant naïve at the time of death. This was somewhat surprising given that much of the literature suggested individuals taking stimulants were most at risk of adverse health events in the first 30-90 days after first starting stimulants. (11,16,18,19,43) However, several national epidemiological studies have documented the rise of benzodiazepine prescriptions and associated risks of negative health events. (44–47) About 0.5 percent of individuals taking a stimulant and benzodiazepine died within 180 days of the concurrent dispensations. The number of persons in Oregon who had overlapping dispensations of stimulants and benzodiazepines was also quite small (41,767) whereas the number of individuals who were stimulant naïve was much higher (208,437), because anyone who takes a stimulant is naïve initially. Cases where an individual is concurrently prescribed a stimulant and benzodiazepine should be further explored to determine if there are factors not measured here that increase risk of adverse health events. Possible unique interactions between stimulants and benzodiazepines taken concurrently could also be examined.

There was also an observation of higher death rates within sub-categories of Oregonians who received stimulants. Death rates were noticeably higher for individuals ages 65 and older compared to younger age groups and death rates were somewhat higher for individuals who were identified as male or taking modafinil, regardless of other prescription characteristics. Although rates in this report are not age-adjusted, the higher rates for individuals ages 65 and older are not only due to age, because the rate denominator is calculated using death data of individuals in the same age group that did not receive a possibly risky stimulant dispensation. The higher death rates for individuals

ages 65 and older could have occurred due to health conditions that resulted in the individuals receiving the stimulant dispensation, which would confound any relationship between death rate and age. This report was not able to examine the diagnosis associated with the stimulant dispensation, but other research has found adults ages 65 and older most often receive stimulant dispensations after a diagnosis of narcolepsy or major depressive disorder. (48) Taken together, there is strong reason to continue to observe the health consequences of individuals ages 65 and older who receive stimulants.

The interacting effect of modafinil with age was not examined for this report, but modafinil is metabolized at a lower rate in older patients, resulting in higher plasma levels of modafinil in older patients over time. (40) Older adults may be more likely to receive modafinil as it is often used for palliative care. (20,21) Modafinil is also used off-label even though a manufacturer, Cephalon Inc., entered a criminal plea and paid $425 million for marketing Provigil (a brand name for modafinil) for clinical uses beyond those approved by the United States Food and Drug Administration. (27,49) Additionally, early randomized controlled trials assessing efficacy and safety of modafinil excluded individuals taking additional centrally-acting medications, including benzodiazepines. (27,50,51) Oregonians who received overlapping modafinil and benzodiazepine dispensations experienced higher rates of emergency department visits, hospitalizations, and deaths than any other stimulant and benzodiazepine combination. It is unknown how these past practices influence individual prescribing decisions and safety assessments by providers that occur today. The appropriateness of prescribing or dispensing overlapping modafinil and benzodiazepine medications could possibly be further explored and considered.

Oregonians taking amphetamine tended to experience lower rates of emergency department visits, hospitalizations, or deaths of all specific stimulants examined among the five prescribing practices. Amphetamine had the highest hospitalizations rates for stimulant medications in cases where individuals received a long duration stimulant (i.e., > 12 dispensations in one year). A possible explanation for the lower rates is that amphetamine is used more often to treat ADHD (28) whereas other stimulants are often used for chronic conditions tied to more serious health problems, including fatigue in neurological conditions (52), sleep disorders (25,50,51), obesity (53), post-stroke care (21), and cancer fatigue. (17) Therefore, the lower rates of negative health events for individuals taking amphetamine could have occurred because other stimulants are more often used to treat those already at higher risk of emergency department visits, hospitalization, or death. Another possibility is that the shorter half-life (the time it takes for half of one dose to be metabolized) of amphetamine, relative to other stimulants prescribed in Oregon, prevented drug levels from increasing beyond the point they could be metabolized. The most common amphetamine dispensed was Adderall, which accounted for over 75 percent of amphetamine dispensations. Adderall has a half-life of 9-13 hours (7), which is comparable to long-acting methylphenidate, but less than modafinil at 13-15 hours. (39,40,42) But this reasoning is also speculative and differences in negative health event rates by stimulant medication should be monitored in the future and may inform prescribing decisions as additional data become available.

Emergency department, hospitalization, and death rates were slightly higher for individuals where a contributing cause was suicide, although the number of total cases was

often less than 20. This was expected given that higher suicide rates have been reported with some stimulants. (4,9) However, research studies note that it remains unclear if individuals who receive stimulants are already at higher risk of suicide, or if higher suicide rates are caused by stimulants themselves. (9) The report only considered contributing causes that were considered ahead of the analysis to possibly be related to prescription stimulant medication use. Given the limited research in the area it is possible that prescription stimulant use is associated with other contributing causes that were not examined in the report. The low case numbers overall also mean that calculated rates and, and any possible interpretation, could readily change with a relatively small change in the number of cases. However, suicide rates among individuals dispensed prescription stimulants should continue to be monitored given the past research and report findings.

Many Oregonians may be prescribed stimulants as part of palliative care for terminal cancer, and in this data approximately 70 percent of individuals who were deceased within 180 days of receiving a stimulant prescription had cancer listed as their underlying cause of death. A strength of this analysis is electing to not consider those who had cancer as an underlying cause of death in the death analysis. However, it is possible that many Oregonians who received stimulants were under palliative care for another terminal condition that was not dropped from descriptive analysis. Although diagnosis code is included within Prescription Drug Monitoring Program data, it is not a required field and is often missing or inaccurate. Improvement in the completeness and accuracy of the diagnosis code field may improve the ability of public health officials to better understand death rates for Oregonians dispensed prescription stimulants.

There are several limitations of this public health analysis. Although prescription stimulant dispensations are increasing in Oregon, there is little academic research on negative health outcomes of stimulants or risky stimulant prescribing practices, compared to that of opioids or benzodiazepines. The limited literature meant that examination of stimulant prescribing practices, individual characteristics, and contributing causes of death were largely exploratory or based on known risk factors of the opioid epidemic, rather than data driven. Second, the datasets used were administrative in nature and not ideally built for a descriptive analysis of stimulant prescribing practices and negative health outcomes. Probabilistic linkage procedures may have erroneously matched dispensation and hospital or death records while failing to link other true matches. Another limitation of the analyses is the lack of information on how stimulants were taken by patients. As many as 60 percent of individuals who receive stimulant dispensations, especially college-aged persons, report giving away or selling stimulant medication at some point in their lifetime. (54,55) Only 45 months of emergency department and hospitalization data, and 10 years of death data were available, meaning the number of negative health events considered for some analyses was small. This can lead to uncertain rate calculations that may change when more data become available. Information on the severity of health events that resulted in emergency department visits or hospitalizations was not available and it is possible event severity varies by factors considered here, such as sex, age, and the stimulant taken.

Finally, the five different stimulant prescribing practices discussed here should not be directly compared to each other for several reasons. First, the practices are not independent because a single person can plausibly fall into multiple categories

simultaneously. For example, a person may be stimulant naïve on a high quantity stimulant prescription and receiving a benzodiazepine, which would place them in three of the categories of practices examined here. The observation times of the practices, while chosen based on a combination of previous literature and data distributions, are also not equal. For the stimulant naïve measure, only stimulants dispensed within 60 days of a negative health event were considered because of research suggesting that risk was highest in the first 60 days. (11,16,19) But rate calculations of other prescribing practices included stimulants dispensed within the much longer time period of 180 days. This was done based on a review of data distributions before analysis began, which was necessary given the limited literature on possible risk associated with other possibly risky stimulant prescribing practices. For these reasons, prescribing practices and associated risk should be reviewed separately and not be directly compared.

This initial investigative report describing the observed negative health outcomes that occurred among Oregonians who received prescription stimulants dispensed from Oregon pharmacies has identified several individual and prescription characteristics with elevated rates of adverse events. Tracking and monitoring of these characteristics should continue. As the research literature on prescription stimulants progresses in the future, characteristics and tracking metrics may need to be modified to best understand prescription stimulants and their impact on the health of Oregonians.

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