ADVERSE OUTCOMES FOLLOWING NEW BENZODIAZEPINE AND Z-DRUG PRESCRIPTIONS AMONG ADULT OREGON MEDICAID BENEFICIARIES: 2016-2019

By

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A DISSERTATION

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ABSTRACT

Benzodiazepine receptor agonists (BZRA) medications include benzodiazepines and Z-drugs. BZRA medications are commonly prescribed to adult patients for treatment of symptoms of anxiety and panic disorder or insomnia. In 2024, 9% of U.S. adults reported past year use of benzodiazepines, and 3% of Z-drugs. Short-term use of BZRA is effective for the immediate relief of adverse symptoms, but evidence for additional therapeutic benefit of long-term use is uncertain. Long-term BZRA use is estimated to occur among 24% of adults with any BZRA use. Long-term BZRA use is associated with increased risks of dependance and other adverse outcomes, including withdrawal, seizures, cognitive decline, physical injury, automobile accidents, and overdose (OD). The severe to fatal adverse outcomes associated with BZRA use has elicited public health concerns. Annual rates of OD or emergency department (ED) visits involving the use of BZRA prescriptions have increased over time among adults in the U.S. Large U.S. health systems, expert clinical opinion, and international health authorities have issued practice guidelines to mitigate potential harms associated with BZRA prescriptions. Key recommendations in the guidelines include limiting BZRA prescriptions to 4 weeks of continuous use and implementing clinically mediated discontinuation from long-term use. However, limited findings exist about the occurrence of long-term BZRA use or subsequent discontinuation among populations of U.S. adults with new BZRA use.

Further epidemiologic research is required to support preventive measures addressing BZRA-related adverse outcomes in accordance with a population-based public health framework. To accomplish this, we constructed the three research aims, which followed the sequential order of new BZRA use and subsequent BZRA-related adverse outcomes. The research aims of this dissertation were accomplished through multiple retrospective cohort studies. In these studies, we used prescription drug and medical claims to create cohorts of Oregon Medicaid adult beneficiaries with new BZRA use in 2016-2018. New BZRA use was defined as the first BZRA prescription (index BZRA fill) preceded

by 12 months without any BZRA prescription claims. Within these cohorts, we determined the occurrence of new long-term BZRA use, incident discontinuation from new long-term BZRA use, and the rate of first BZRA-related ED visits.

In Aim 1, we determined the occurrence of first long-term BZRA use and identified the baseline demographic, clinical, and prescription characteristics independently associated with its occurrence. First long-term BZRA use was defined as a total of 60 or more BZRA pills, from one or more filled prescriptions (hereafter called fills), within a period of 45 or fewer days. Multivariable modified Poisson regression models were used to estimate adjusted risk ratios and 95% confidence intervals as the measure of association between risk of first long-term BZRA prescription and baseline characteristics. We found that 28% of beneficiaries with new BZRA use transitioned to long-term use within 12 months of new use. Most first long-term BZRA use occurred within 3 months of the index BZRA fill. Accordingly, efforts to reduce risk of first long-term BZRA use could occur at or shortly following new BZRA use. Index BZRA fills for new use with high strength relative to standard strength were strongly associated with first long-term BZRA use. Targeted educational campaigns to clinical prescribers could emphasize limiting new BZRA prescriptions with high strength when appropriate. Risk of first long-term BZRA use rose successively with age. Increased occurrence of first long-term BZRA use was observed among non-Hispanic White beneficiaries and those residing in frontier areas. Efforts to reduce risk of long-term BZRA use among older adults, non-Hispanic White beneficiaries, and patients residing in frontier areas should be prioritized.

In Aim 2, we determined incident 90-day discontinuation among beneficiaries with new long-term BZRA use and identified demographic, clinical, and prescription characteristics independently associated with its occurrence. Multivariable modified Poisson regression models were used to estimate adjusted risk ratios and 95% confidence intervals as the measure of association between occurrence of incident discontinuation and baseline characteristics. Incident discontinuation was 36%

among the cohort over 12-months of follow-up. Incident discontinuation occurred with successively lower frequency as age increased. The strongest inverse association, where incident discontinuation was less frequent in the category relative to the referent, was observed for index BZRA fills with short-to-intermediate acting onset compared to long-acting onset. Older beneficiaries could benefit from increased support during future efforts to enhance discontinuation. Targeted educational campaigns to clinical prescribers could emphasize avoiding new long-term BZRA use with prescriptions of short-to-intermediate onset when appropriate.

In Aim 3, we estimated the associations between categories of new BZRA prescription pill quantities and rates of first BZRA-related ED visits. The outcome was first ED visit with any diagnosis of a BZRA-related health condition including OD, seizure, complex sleep disorder, injurious fall or fracture, motor vehicle accident, suicide, altered mental status, or substance use disorder for BZRA misuse. Percentages in the categories of pill quantity of the index BZRA fill for new use were 10% with 1-9 pills, 18% with 10-14 pills, 24% with 15-27 pills, 26% with 28-30 pills, 15% with 31-60 pills, and 7% with >60 pills. Stratified Cox proportional hazards regression models were used to estimate common hazard ratios (HR) and 95% confidence intervals (CI) as the measure of association between pill quantity and first BZRA-related ED visits. The adjusted common HR of first BZRA-related ED visits across categories of pill quantities were 1.21 (95% CI: 1.07,1.36) for 1-9 pills, 0.99 (95% CI: 0.85, 1.05) for 10-14 pills, 0.96 (95% CI: 0.87, 1.06) for 15-27 pills, 1.43 (95% CI: 1.29, 1.59) for 31-60 pills, and 1.92 (95% CI: 1.72, 2.15) for >60 pills, compared to 28-30 pills. Large prescription pill quantities of a new BZRA prescription may be a risk factor for BZRA-related harms serious enough to necessitate treatment in an ED. Enhanced clinical or health system guidelines could prioritize strategies to identify and limit new BZRA prescriptions with pill quantities that place patients at higher risk of BZRA-related ED visits.

Overall, the findings from our studies suggest that there are specific at-risk populations for BZRA-related adverse outcomes among Oregon Medicaid beneficiaries with new BZRA use. Specific at risk-populations may include beneficiaries with increasing age. Further supportive efforts to reduce long-term BZRA use and risk of BZRA-related adverse outcomes among this patient population may be necessary. Potentially modifiable risk factors for the adverse outcomes studied in this dissertation research include the pill quantity and prescription strength of the index BZRA fill. Specifically, our findings indicate that index BZRA fills of >60 pills or prescription strengths of >20 diazepam milligram equivalents could be such risk factors. Limiting index BZRA fills with these high pill quantities or high prescription strengths could help to reduce the occurrence of either new long-term BZRA use or first BZRA-related ED visits and could potentially increase the frequency of incident discontinuation.

DEDICATIONS

To my mentor, Dr Marshall

For guiding me up this mountain every single step of the way.

To my wife, Grace

For always making sure I didn't fall off the mountain.

To my children, Auckland and Eleanor

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LIST OF ABBREVIATIONS

95% CI	95% Confidence Intervals
aRR	Adjusted Risk Ratio
BZRA	Benzodiazepine Receptor Agonists
CNS	Central Nervous System
CPT	Current Procedural Terminology billing code
DME	Diazepam Milligram Equivalents
ED	Emergency Department
FDA	Food and Drug Administration
HR	Hazard Ratio
ICD	International Classification of Diseases diagnosis code
IP	Incidence Proportion
MOUD	Medication for Opioid Use Disorder
NDC	National Drug Code
Ref.	Referent
RR	Risk Ratio
SUD	Substance Use Disorder

CHAPTER 1. INTRODUCTION AND RESEARCH AIMS

1.1 Introduction

Benzodiazepine receptor agonists (BZRA) are psychiatric prescriptions that are utilized in clinical practice for their sedative/hypnotic or anxiolytic effects.[1] These prescriptions include both benzodiazepines, such as diazepam (Valium) or alprazolam (Xanax), and non-benzodiazepine Z-drugs, such as zolpidem (Ambien). BZRA are commonly prescribed in clinical outpatient settings for the treatment of the primary indications of insomnia or anxiety/panic disorders.[1,2] The prevalence of BZRA use among adults in the United States (U.S.) has increased by 2-3 fold over the past 20 years.[3–5] From 1999-2000 to 2013-2014, the proportion of U.S. adults with a benzodiazepine prescription increased from 2.0% to 4.2%, those with a Z-drug prescription increased from 0.4% to 1.6%.[4] By 2024, 9% of U.S. adults reported past year use of benzodiazepines and 3% of Z-drugs.[6] New benzodiazepine prescriptions filled at U.S. retail pharmacies, for patients without a similar fill within the prior 12-months, have increased by an average of 2,700 new prescriptions per month from 2020 to 2022.[7]

BZRA use is associated with increased risks of adverse health outcomes including dependence,[8] severe withdrawal symptoms,[9,10] seizures,[11] serious sleep disturbances,[12] suicide,[13,14] physical injuries,[15] automobile accidents,[16] overdose (OD),[17,18] and death.[3,19,20] Additionally, BZRA use increases the risk of potentially fatal OD, especially with concurrent use of opioid, alcohol, or other central nervous system (CNS) depressants.[21] The rates of benzodiazepine-involved OD deaths in U.S. have increased 6-fold from 2000 to 2019, from 0.46 to 2.96 per 100,000 individuals per year.[19] National rates of Emergency Department (ED) visits for benzodiazepine-involved OD, with and without opioid co-involvement, have also increased by 24% from 2019 to 2020.[22] BZRA-related harms extend beyond OD to other severe adverse events that require emergency care.[23] In national surveillance of drug-related ED visits, benzodiazepines alone are among the top 10 substances

attributed to causing the need for emergency care.[24] In 2024, rates of benzodiazepine-related ED visits were 58 per 100,000 individuals in the U.S.[25] Improved prevention efforts are needed to address the risks of BZRA-related harms.[26–28]

Large U.S. health systems, clinical reviews, and international health authorities have issued practice guidelines to mitigate harms associated with the use of BZRA prescriptions.[29,30] Recommendations include limiting BZRA prescriptions to 4 weeks of continuous use and attempting clinically mediated discontinuation from long-term use.[29,30] However, there are substantial challenges for the safe and successful discontinuation from long-term BZRA use.[31,32] In 2025, the U.S. Food and Drug Administration (FDA) and multiple clinical professional societies published expanded clinical practice guidelines of patient-specific approaches to safely discontinue benzodiazepines through dose tapering.[33] The FDA has also issued multiple black box warning labels concerning the potential harms associated with benzodiazepine or Z-drug use and the risk of OD or death from their combined use with opioid prescriptions.[12,21,34] To help prevent the occurrence of BZRA-related adverse outcomes, the existing practice guidelines could utilize further support through a comprehensive public health framework. This public health framework requires further epidemiologic research to determine the frequency of BZRA-related adverse outcomes and potential risk factors.

1.2 Dissertation overview and research aims

The work of this dissertation includes multiple retrospective epidemiologic cohort studies comprised of adult Oregon Medicaid beneficiaries who became new BZRA users in the period from 2016 to 2018. These cohorts were created from deidentified Oregon Medicaid administrative and pharmacy claims data from the calendar years 2015 through 2020. In this population, we determined the occurrence of new long-term BZRA use, incident discontinuation from new long-term BZRA use, and the rate of first BZRA-related ED visits. Furthermore, we investigated potential risk factors for each of these outcomes. These characteristics included patient demographics, clinical diagnoses or

measures of utilization, calendar year of cohort entry, concurrent prescriptions, and specific classifications for BZRA prescriptions. The chapters that follow contain the background literature review, manuscripts for the three separate studies, and a synthesis of the findings and implications.

In Chapter 2. Literature Review, we present a summative review of the current literature on BZRA prescriptions. The review then introduces BZRA medications, their pharmacologic effects, primary indications, prescription characteristics, patterns of use, definitions for treatment episodes, and adverse outcomes associated with BZRA use. We review recent estimates for the prevalence of BZRA use among U.S. adults under 65 years of age. We conclude with a discussion of the evidence needed to better support a public health framework for the prevention of BZRA-related adverse outcomes.

In Chapter 3. Aim 1, we present the first study. Our objective was to determine the occurrence of first long-term BZRA use and identify the baseline demographic, clinical, and prescription characteristics independently associated with its occurrence. Beneficiaries were enrolled upon new BZRA use, defined as the first prescription (index BZRA fill) preceded by 12 months without any BZRA prescriptions. Characteristics determined at cohort entry (baseline) included demographic factors, clinical diagnoses, and concurrent prescriptions. The index BZRA fill was categorized in separate variables as high or standard prescription strength, a primary indication of anxiolytic or of sedative/hypnotic, and short-to-intermediate acting onset or long-acting onset. First long-term BZRA use was defined as a total of 60 or more BZRA pills or tablets, from one or more BZRA prescriptions filled within a period of 45 or fewer days. Risk of long-term use was assessed during the 12 months following cohort entry and reported as the 12-month incidence proportion (IP). Multivariable modified Poisson regression models were used to estimate adjusted risk ratios (aRR) and 95% confidence intervals (CI) as the measure of association between occurrence of first long-term BZRA prescription

and baseline characteristics. We conducted two sensitivity analyses with samples restricted to beneficiaries with continuous Medicaid enrollment or complete data for all characteristics.

In Chapter 4. Aim 2, we present the second study. Our objective was to determine the first occurrence of 90-day discontinuation and identify demographic, clinical, and prescription characteristics associated with its occurrence, among beneficiaries with new long-term BZRA use. Characteristics determined at cohort entry (baseline) included demographic factors, clinical diagnoses, and concurrent prescriptions. Incident discontinuation was defined as 90 consecutive days with no new BZRA prescription fills and no quantity (supply) of pills remaining and reported as the 12-month IP. Multivariable modified Poisson regression models were used to estimate aRR and 95% CI as the measure of association between occurrence of incident discontinuation and baseline characteristics.

In Chapter 5. Aim 3, we present the third study. Our objective was to assess the associations between index BZRA prescription pill quantities and rates of first ED visits for BZRA-related harms. We hypothesized that a positive association would exist between new BZRA prescription pill quantities and the rate of first BZRA-related ED visits, with the strongest associations occurring among beneficiaries prescribed more than 30 pills. We classified pill quantities into categories of “1-9”, “10-14”, “15-27”, “28-30”, “31-60”, and “>60” pills based on the distributions of index BZRA fills. We defined first BZRA-related ED visits as those including any diagnosis for a BZRA-related health condition. These conditions included OD, seizure, complex sleep disorder, injurious fall or fracture, motor vehicle accident, suicide, altered mental status, and a substance use disorder for BZRA misuse. The rate of first BZRA-related ED visits was reported as the number of ED visits per 100,000 person-days. Stratified Cox proportional hazards regression models were used to estimate the hazard ratios (HR) and 95% CI as the measure of association between first BZRA-related ED visit and pill quantities.

In Chapter 6, we provide a summary of the findings and overarching conclusions from the research. We discuss the key findings of the occurrence observed and risk factors identified for new long-term BZRA use, incident discontinuation, and rates of first BZRA-related ED visits. We consider the public health framework utilized for study design to create these findings and the importance of the new BZRA use. We conclude with a discussion of several potential objectives for future studies.

CHAPTER 2. LITERATURE REVIEW

2.1 Benzodiazepine Receptor Agonists (BZRA)

BZRA nomenclature, effects, and designations

Benzodiazepine receptor agonists (BZRA) include the prescription medications of benzodiazepines and non-benzodiazepine Z-drugs. BZRA are commonly used to treat a variety of psychiatric conditions including insomnia, anxiety/panic disorders, seizures or alcohol withdrawal.[30] Benzodiazepines are drugs with a core chemical structure comprised of the fusion of a benzene ring and a diazepine ring, hence the name 'benzodiazepine'. Benzodiazepines include specific drugs such as diazepam (Valium), lorazepam (Ativan), alprazolam (Xanax), and others (Table 2.1).[35] Z-drugs, sometimes referred to as non-benzodiazepines, include multiple chemical classes with different structures than the chemical cores present in all benzodiazepines. Z-drugs include eszopiclone (Lunesta), zolpidem (Ambien), and zaleplon (Sonata).[36] The pharmacodynamic mechanics for the effects and risks associated with the use of Z-drugs are identical to benzodiazepines, such that the clinical literature does not differentiate between the two groups and refers to them jointly as BZRA.[1] The mechanism of action for all BZRA drugs is to facilitate the passage of the neurotransmitter gamma-aminoburtyric acid (GABA), thus enhancing neuro-inhibition.[35,36] The resultant therapeutic effects are an innate calming towards environmental stimuli or internal distress (anxiolytic), muscle relaxation, seizure arresting (anti-convulsant), and sleep deepening (sedative/hypnotic).[35,36]

BZRA medications can be differentiated by specific prescription characteristics, including the primary indication, the onset of effect, and the equivalent dose strength of the prescription (Table 2.1). Primary indication reflects the intended therapeutic effect of the BZRA prescription based on their principal Food and Drug Administration (FDA) labeled indication.[37] These indications include "anxiolytic" for the treatment of anxiety and panic disorders or "sedative/hypnotic" for insomnia. While

different benzodiazepines have primary indications as either anxiolytic or sedative/hypnotic, Z-drugs are exclusively indicated as sedative/hypnotics. [37] BZRA are rapidly absorbed following their primarily oral route of administration in the form of pills or tablets, resulting in fast-acting psychoactive effects.[1] The onset of effect varies for the different BZRA, which is driven by the specific elimination half-life of each drug.[8,38,39] BZRA are therefore grouped into three classes of onsets: short-acting (median half-lives of 1-12 hours), intermediate-acting (median half-lives of 12-40 hours), and long-acting (median half-lives of 40-250 hours). Full elimination from the body typically requires 4-5 half-lives, so BZRA remain in system for significantly longer than the above times.[35,36] All Z-drugs have short elimination half-lives.[36] BZRA medications further vary by prescription unit strength of the specific BZRA drug. Across BZRA medications, they are comparable by a conversion factor for the amounts of diazepine milligram equivalents (DME).[40] Alternative conversions factors such as lorazepam milligram equivalents can also be utilized when assessing BZRA prescription strength.[3,41]

Table 2.1. Benzodiazepine and Z-Drug prescriptions: Primary Indications, Classifications for Onset of Effect, Labels, and Prescription Strength Conversion Factors

Type	Primary Indication	Onset of Effect	Brand	Generic	Conversion Factor (DME*)
Benzodiazepines	Anxiolytic	Short to Intermediate	Xanax	Alprazolam	10.00
			Klonopin	Clonazepam	10.00
			Ativan	Lorazepam	5.00
		Long	Librium	Chlordiazepoxide	0.40
			Onfi	Clobazam	0.50
			Tranxene	Clorazepate	0.67
			Valium	Diazepam	***1.00***
	Sedative/ Hypnotic	Short to Intermediate	Prosom	Estazolam	7.50
			Restoril	Temazepam	0.50
			Halcion	Triazolam	20.00
		Long	Dalmane	Flurazepam	0.33
Z-drugs	Sedative/ Hypnotic	Short to Intermediate	Lunesta	Eszopiclone	0.67
			Sonata	Zaleplon	0.50
			Ambien	Zolpidem	0.50

*DME: diazepine milligram equivalents

Assessments of patterns of BZRA prescription use among patient populations are restricted by the lack of standard definitions for long-term use, high-dose use, or discontinuation.[42–47] Standard definitions and approaches to accurately measure patterns of BZRA use have been identified as important objectives for further studies.[42–46,48]

BZRA clinical use, adverse effects, and prevalence

BZRA medications have been prescribed in clinical practice in the United States (U.S.) for decades.[49] Benzodiazepines first entered clinical practice following FDA approval of chlordiazepoxide in 1960 and diazepam in 1963.[50] Other benzodiazepines such as clonazepam, lorazepam, and alprazolam were subsequently introduced, as well as Z-drugs in the 1990s.[36] Short-term BZRA use is effective for the immediate relief of adverse symptoms but evidence for additional therapeutic benefit of longer use is uncertain.[51] Long-term BZRA use is associated with increased risks of dependance and adverse events.[23] BZRA-related harms include rapid onset of physical dependence,[8] severe withdrawal symptoms,[9,10] seizures,[11] serious sleep disturbances,[12] suicide,[13,14] physical injuries,[15] automobile accidents,[16] overdose (OD),[17,18] and death.[3,19,20] Polypharmacy risks include potentially fatal OD from the concurrent use of opioid, alcohol, or other central nervous system (CNS) depressants.[21,52] BZRA misuse and dependence are an additional concern. BZRA use in combination with opioids can potentiate the overall sedative effect, possibly incentivizing high risk poly-substance misuse.[8,53–57] Because BZRA use affects the dopamine pathway in the CNS, physiological dependence, tolerance, and addiction can occur with ongoing use of BZRA.[58,59] Tolerance and physical dependence from the pharmacological effects of BZRA medications can develop rapidly, within up to 15-days of new use.[9,58,59] The symptoms of withdrawal from the discontinuation of BZRA use can be life-threatening due to seizures or suicide and includes long-term sequelae of heightened anxiety or insomnia.[31,32]

Despite the potential risk of adverse outcomes, BZRA prescriptions in outpatient clinical settings remain a preferential therapeutic option among certain prescribers and patients.[51,60,61] Preference for BZRA could be attributed to evidence that they are well tolerated by most patients and provide rapid relief for acute symptoms of common psychiatric conditions.[51] In 2020, the total outpatient prescription fills for benzodiazepines were 91 million and for Z-drugs were 28 million.[27] Over the past 20 years, the prevalence of U.S. adults with BZRA prescriptions increased 2-3 fold.[2–4] From 1999-2000 to 2013-2014, the proportion of U.S. adults with a filled prescription for benzodiazepines increased from 2.0% to 4.2%, and from 0.4% to 1.6% for Z-drugs.[4] By 2024, 9% of U.S. adults reported past year use of benzodiazepines and 3% of Z-drugs.[6] New benzodiazepine prescription filled at U.S. retail pharmacies, for patients without a similar fill within the prior 12-months, have increased by an average of 2,700 new prescriptions per month from 2020-2022.[7]

A high proportion of any BZRA use is assumed to be for long-term periods of time. Among U.S. adults with benzodiazepine or Z-drug prescriptions from 2000 to 2014, 76% to 82% reported use of 6 months or greater.[4] The high proportion of long-term BZRA use conflicts with expert clinical opinion and practice guildelines.[23,29,30,62] The prevalence of long-term BZRA use has elicited renewed public health concern given the risks of BZRA-related harms.[27] Crucially, limited findings exist for the transition from new BZRA use to long-term BZRA use. This information gap potentially contributes to ongoing high proportions of long-term BZRA use.

Increased rates of harms associated with BZRA use have coincided with increased measures of BZRA use from 2000 through 2020.[3] Rates of emergency department (ED) visits for OD from benzodiazepine use, with and without concurrent opioid use, increased substantially by 24% from 2019 to 2020.[22] The rates of OD deaths from benzodiazepine use in the U.S. also increased 6-fold from 2000 to 2019, from 0.46 to 2.96 per 100,000 individuals.[19] In national surveillance of drug-related ED visits, benzodiazepines alone are among the top 10 substances attributed to causing the need for

emergency care.[24] In 2024, rates of benzodiazepine-related ED visits were 58 per 100,000 individuals in the U.S..[25] Certain BZRA-related harms such as falls, fractures, or reduced cognitive function are considered particularly pernicious among older adults.[63–65] However, most benzodiazepine-related ED visits or fatal and non-fatal BZRA-related OD occurred among U.S. adults ages 25-64 years.[22,25] Among adults with any BZRA use, a greater proportion of young adults reported misuse (5%) than among those over 65 years (1%).[5] Conversely, among U.S. adults under 65 years, scarce findings exist for the rates and risk-factors pertaining to BZRA-related harms beyond OD.

The increased prevalence of BZRA use and rates BZRA-related harms have been highlighted as drawing less public health attention than similar harms arising from the “opioid epidemic” of the 2000s.[66,67] However, the U.S. FDA has issued multiple black box warning labels concerning the potential harms associated with benzodiazepine or Z-drug use and the risk of OD or death from their combined use with an opioid prescription.[12,21,34] Large U.S. health systems, clinical reviews, and international health authorities have issued practice guidelines to minimize harms associated with BZRA prescriptions.[29,30] Recommendations include limiting BZRA prescriptions to 4 weeks of continuous use and attempting clinically mediated discontinuation from long durations of use.[29,30] However, there are substantial challenges for the safe and successful discontinuation from long-term BZRA use.[31,32] Discontinuation can require long durations of time for dose tapering with substantial risk for acute withdrawal symptoms and severe adverse outcomes.[31,32,68] The U.S. FDA and multiple clinical professional societies recently developed expanded practice guidelines of tapering approaches to safely discontinue benzodiazepines through dose tapering.[33] Reducing the prevalence of long-term BZRA use through individual patient-specific tapering approaches is a substantial challenge.[29,33,69,70] Distinct approaches of discontinuation are necessary to mitigate potential symptoms of withdrawal or risk of discontinuation-related adverse outcomes.[10,33,68] Population based

prevention strategies based on a public health framework could be useful in supplementing the patient-specific approaches for discontinuation.

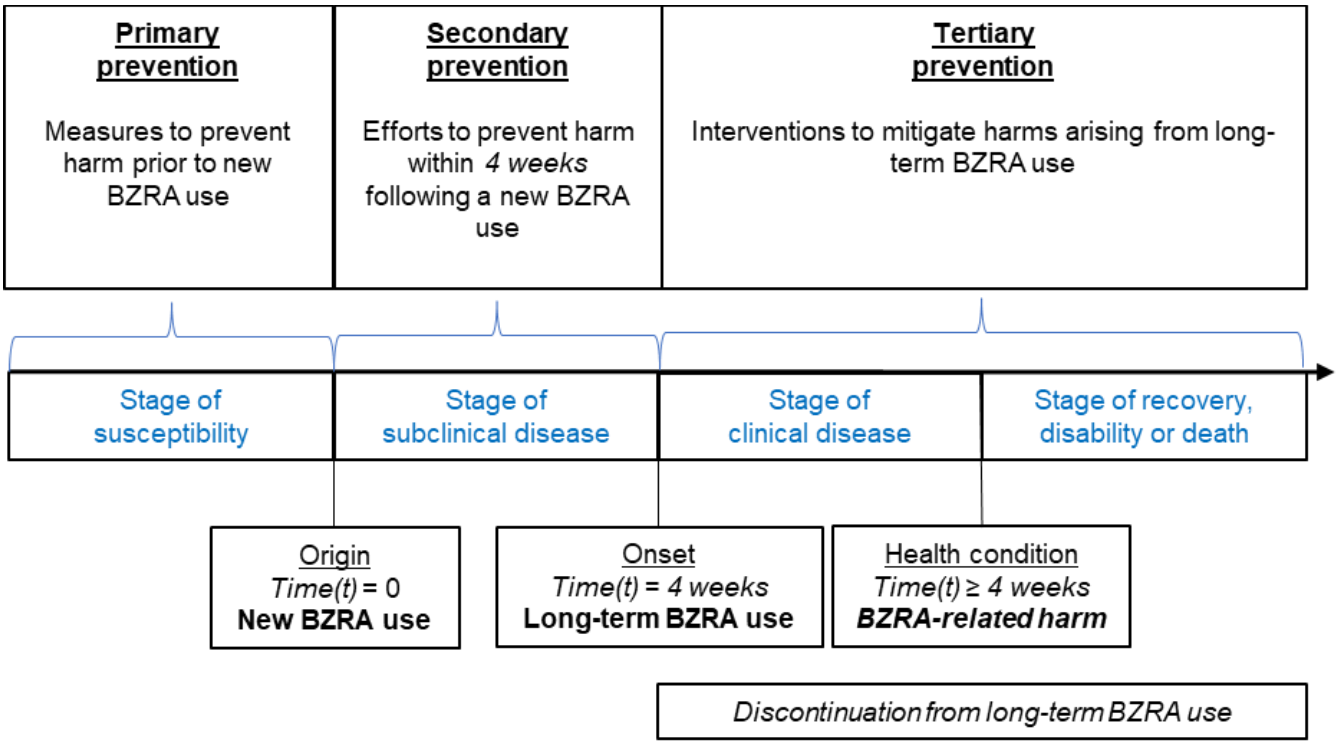
2.2 Public health approach and framework

Successful public health approaches have been utilized for effective campaigns to reduce harms that occur among the U.S. population. Public health approaches can provide a successful framework to address harms arising from complex conditions or circumstances, such as the severe to fatal injuries resulting from automobile crashes.[71] A similar conceptual model can be applied to BZRA prescriptions and BZRA-related adverse outcomes. BZRA-related adverse outcomes also include severe to fatal health outcomes, the occurrence of which may be associated with unknown risk factors. Public health approaches differ from the patient-centered medical approach used in the clinical guidelines for BZRA prescriptions or advanced practice recommendations for BZRA tapering. Patient-centered approaches are logical to guide treatment pathways while considering the risks or benefits specific to an individual patient throughout the different points in care. In contrast, comprehensive public health approaches are population-based, focused on early prevention, and seek to change specific exposures or systems first and patient behavior second.[71]

Public health approaches depend on epidemiologic research to determine the occurrence of adverse outcomes and identify independently associated risk factors among populations of interest. A similar public health framework has been proposed to reduce BZRA-related adverse outcomes among patient populations diagnosed with insomnia.[28] Given that BZRA-related adverse outcomes pertain to patient groups with other conditions, we considered this framework for a broader population of U.S. adults. Notably, this framework included potential primary, secondary, and tertiary measures of prevention for BZRA prescribers.[28] These levels of prevention were proposed according to when a specific measure could be applied: prior to a BZRA prescription, within 4-weeks of the new BZRA prescription, or subsequent to the transition to long-term use. Importantly, the differentiation of

preventions by specific stages of BZRA use provides a clear temporal sequence that begins at the origin of new BZRA use. The temporal sequence of these stages can be further distinguished through the application of the conceptual model of the natural history of disease. While BZRA use is not considered a “disease”, the natural history of disease can be applied to broader health conditions beyond infectious or chronic diseases.[9] This model is comprised of a timeline, in which the course of a “disease”, without treatment, progresses from the origin to recovery, morbidity, or mortality. We arranged the stages of the natural history of disease and the primary, secondary, and tertiary prevention measures into Figure 2.2. shown below.

Figure 2.2. The Natural History of BZRA-Related Adverse Outcomes and Primary, Secondary and Tertiary Preventions



The conceptual timeline for the natural history of BZRA-related adverse outcomes provides a useful illustration of the sequential order of key points pertaining to BZRA prescribing, use, and related adverse outcomes. These key points include the origin (new BZRA use), the onset (new long-term

use), discontinuation (from new long-term use) and the occurrence of a BZRA-related health condition. The different stages are imperfect, as BZRA-related adverse outcomes could occur at any point following new BZRA use. However, the timeline of the natural history of BZRA-related adverse outcomes remains an important conceptual framework for appropriate study designs to assess the occurrence of key points in respect to the potential measures of prevention.

Further epidemiologic research is required to support the application of preventive measures to address BZRA-related adverse outcomes according to a public health framework.[51,72] Therefore, we determined three specific research aims, which followed the sequential order of the natural history. For the first aim, we sought to determine the frequency of the onset of long-term BZRA use directly following the origin of new BZRA use. By identifying first long-term BZRA use and characteristics associated with its occurrence, our findings could help to inform secondary measures of prevention. The second aim was to estimate the occurrence of discontinuation following the onset of new long-term BZRA use. Determining characteristics associated with greater or lesser frequencies of discontinuation could provide insights to guide tertiary preventions to stop the progression of long-term BZRA use. Finally, our third aim was to determine the association between categories of pill quantities for new BZRA use and rates of first BZRA-related adverse outcomes. These findings could identify potential measures of primary prevention, through the limitation of specific pill quantities associated with higher risk of subsequent BZRA-related adverse outcomes.

CHAPTER 3. AIM 1

First Long-term Use of Benzodiazepine or Z-drug Prescriptions among Adult Oregon Medicaid Beneficiaries: 2016-2018

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3.1 Abstract

Importance

Practice guidelines from health systems, clinical reviews, and international or state health authorities recommend that benzodiazepine receptor agonist (BZRA) prescriptions should not exceed 4 weeks of continuous use. Long-term BZRA use is associated with elevated risk of dependence and adverse events. Knowledge about the first BZRA prescription indicating a transition to long-term BZRA use could help to support adherence to the clinical guidelines.

Objectives

To determine the frequency of first long-term BZRA use among adults with new BZRA use and identify demographic, clinical, and prescription characteristics independently associated with the risk of first long-term BZRA use.

Design, Setting, Participants

This cohort study used administrative claims data for Oregon Medicaid beneficiaries ages 18-63 years. Beneficiaries entered the cohort upon new BZRA use during the period of January 1, 2016, to December 31, 2018. New BZRA use was defined as the first BZRA prescription preceded by 12 months without any BZRA prescription claims.

Exposures

Characteristics determined at cohort entry (baseline) included demographic factors, clinical diagnoses, and concurrent prescriptions. Additionally, the prescription for new BZRA use was categorized in separate variables as high prescription strength or standard prescription strength, primary indication as anxiolytic or sedative/hypnotic, and short-to-intermediate acting or long-acting onset.

Main Outcome

The outcome of first long-term BZRA use was defined as a total of 60 or more BZRA pills or tablets from one or more BZRA prescription fills within a period of 45 or fewer days. Risk of long-term use was assessed during the 12 months following cohort entry and is reported as 12-month incidence proportion (IP). Multivariable modified Poisson regression models were used to estimate adjusted risk ratios (aRR) and 95% confidence intervals (CI) as the measure of association between risk of first long-term BZRA prescription and baseline characteristics.

Results

Among 55,765 adult Oregon Medicaid beneficiaries with new BZRA use, the median age was 40 years, 67% were female, 60% identified as non-Hispanic White, and 58% resided in an urban county. The 12-month IP of first long-term BZRA use was 28.4% (95% CI: 28.0%, 28.8%). Risk of first long-term BZRA use rose successively with age, such that the aRR were 1.19 (95% CI: 1.12, 1.26) for ages 25-34, 1.40 (95% CI: 1.32, 1.49) for 35-44, 1.59 (95% CI: 1.50, 1.69) for 45-54, and 1.73 (95% CI: 1.63, 1.84) for 55-63, compared to ages 18-24. Frontier residence, relative to urban residence, was also associated with increased risk of first long-term BZRA use. Clinical diagnosis of anxiety/panic was positively associated with long-term BZRA use. A concurrent prescription for an antidepressant, gabapentin/pregabalin, medication for opioid use disorder, or trazodone respectively were also positively associated with long-term BZRA use. New BZRA prescriptions with high strength (aRR, 2.63, 95% CI: 2.52, 2.73) relative to standard strength, with short-to-intermediate acting (aRR 1.34, 95% CI: 1.27, 1.42) relative to long-acting onset, or with primary anxiolytic indication (aRR 1.22, 95% CI: 1.17, 1.28) relative to a sedative/hypnotic indication were positively associated with first long-term BZRA use. Lower risk of first long-term BZRA use was observed for Hispanic ethnicity, American Indian/Alaska Native, Asian/Pacific Islander, Black, or Multiracial compared to non-Hispanic

White. Cohort entry in calendar years 2017 or 2018 relative to 2016 was associated with lower occurrence of first long-term BZRA use.

Conclusions

More than a quarter of adult Oregon Medicaid beneficiaries with new BZRA use received a prescription indicating a possible transition to long-term BZRA use over 12-months of follow-up. Accordingly, potential interventions to prevent long-term BZRA use could occur at or shortly following the first prescription fill for new BZRA use. Efforts to reduce risk of long-term BZRA use among older adults, non-Hispanic White beneficiaries, and patients residing in frontier areas should be prioritized. Targeted educational campaigns to clinical prescribers could emphasize limiting new BZRA prescriptions with high strength or short-to-intermediate acting onset when appropriate.

3.2 Introduction

Benzodiazepine receptor agonists (BZRA) are medications that depress central nervous system activity to produce sedative/hypnotic or anxiolytic effects.[1] BZRA include both benzodiazepines such as diazepam (Valium) or alprazolam (Xanax) and non-benzodiazepine Z-drugs such as zolpidem (Ambien). These medications are pharmacologically similar and have been used in clinical practice worldwide for decades.[2,3] The primary indications for BZRA are anxiety/panic disorders or insomnia.[4] BZRA rapid onset of effect can relieve acute symptoms of chronic psychiatric conditions, which is one reason that these medications are frequently prescribed in outpatient settings.[1,5] In 2020, the total outpatient prescription fills for benzodiazepines were 91 million and for Z-drugs were 28 million.[6] The prevalence of BZRA use has risen 2-3 fold among adults in the United States (U.S.) over the past 20 years.[7–9] From 1999-2000 to 2013-2014, the proportion of U.S. adults with a filled prescription for benzodiazepines increased from 2.0% to 4.2%, and from 0.4% to 1.6% for Z-drugs.[8] By 2024, 9% of U.S. adults reported past year use of benzodiazepines and 3% of Z-drugs.[10]

Although BZRA can be effective when used intermittently or for a limited duration, there is scarce evidence for any therapeutic benefit of long-term BZRA use.[4,11] In contrast, BZRA have a well-established and extensive adverse effect profile that includes physical dependence and addiction, self-harm, psychomotor impairment leading to injury, cognitive decline, and death.[12,13] Additionally, BZRA are also associated with overdose, especially when used in conjunction with opioid, alcohol, and other central nervous system depressants.[14] Thus, most practice guidelines from health systems, clinical reviews, and international or state health authorities recommend that BZRA prescriptions should not exceed 4 weeks of continuous use.[4,11] However, patients and clinicians may determine that the benefits of continuing BZRA use outweigh potential risks, resulting in long-term use.[5,15] Successful and safe discontinuation from long-term BZRA use presents substantial challenges.[16] Consequently, long-term BZRA use is well documented.[17]

Existing research findings for long-term BZRA use have been challenging to interpret. For example, percentages of long-term use have ranged from 6% to 76%, with an average of 24%, among U.S. and international populations with any BZRA use.[18] The range of these estimates reflects the different definitions used, which have varied from 4 weeks to multiple years.[18–20] Furthermore, no standard definition exists to determine a prescription indicating a transition to long-term BZRA use.[18]

Determining the first occurrence of long-term BZRA use is critical to establishing a comprehensive public health framework to support the prevention of subsequent BZRA-related adverse outcomes. Existing preventative efforts have focused on averting the first transition to long-term BZRA use through prescription quantity limits or prior authorization.[11,21] Research to identify demographic or clinical characteristics that are associated with first long-term BZRA use is needed to focus preventative efforts on populations at increased risk of long-term BZRA use.

We sought to characterize the epidemiology of first long-term BZRA prescriptions among new BZRA users by conducting a cohort study within the Oregon Medicaid population. The Medicaid program is the largest healthcare payer in the U.S. and provides healthcare for low-income individuals and adults with disabilities.[22] Although the Medicaid program provides critical support for mental health and addiction care in the U.S.,[23] no studies have examined long-term BZRA use in this population. Thus, our objectives were to determine the 12-month incidence proportion of first long-term BZRA use among beneficiaries with new BZRA use and to identify factors associated with the occurrence of first long-term BZRA use.

3.3 Methods

Study design, data source, and cohort selection

We performed a retrospective cohort study using deidentified Oregon Medicaid administrative and pharmacy claims data from the calendar years 2015 through 2019. The paid pharmacy claims

indicate that a prescription was filled (dispensed) at the pharmacy, paid by Medicaid, and received by the beneficiary. We used pharmacy claims to identify and describe BZRA fills and concurrent medications, medical claims for diagnoses, and beneficiary eligibility for Medicaid enrollment and demographics. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (*STROBE*) guidelines for cohort study designs.[24] The Oregon Health & Science University Institutional Review Board determined this study to be exempt non-human subjects research.

In multiple steps, we assembled a cohort of beneficiaries with new BZRA use occurring from January 1st, 2016, to December 31st, 2018. Table.A.1 contains the National Drug Codes used to select all BZRA fills in pills or tablets form (hereafter referred to as pills) dispensed. In accord with methods used previously to establish new BZRA use,[25,26] we identified the first BZRA fill preceded by 12 months with no BZRA fills for each beneficiary, which we called the index BZRA fill. Prescription claims in 2015 were used to identify the index BZRA fill in 2016 and so on. Cohort entry was the date of the index fill. We excluded fills of liquid, gel, and injectable forms of BZRA given the difficulty of converting the prescription strength to diazepam milligram equivalents (DME).[27] Quantities of 5 or fewer benzodiazepine pills, which typically indicate procedural sedation, were also excluded.[28] Second, we restricted to beneficiaries ages 18-63 years old on the date of the index fill. The upper age limit allowed for 12 months of follow-up (see below) before beneficiaries became eligible for Medicare coverage at age 65 years. Third, we further restricted the cohort to beneficiaries who had at least 6 months of enrollment within the 12 months prior to new BZRA use. Next, we excluded beneficiaries with dual Medicaid-Medicare enrollment or with no Medicaid enrollment upon cohort entry. Finally, we excluded beneficiaries who had diagnosis codes for multiple sclerosis, epilepsy or hospice within the 12 months before the date of the index fill, because long-term BZRA prescription may be appropriate for these conditions.[4,29–31] Specific codes for exclusion criteria are listed in Table.A.2. Beneficiaries were selected into the cohort only once.

Outcome and follow-up period

The study outcome was the first fill of a BZRA prescription that met criteria for a transition to long-term use. Because there is no standard definition of when long-term use begins, we defined long-term BZRA use to start when a beneficiary received an accumulation of pills representing at least 60 days (two months) duration of continuous use. Duration of use was based on pills dispensed with the assumption that one pill per day is taken.[32] We used the period of at least 60 days because it was found to distinguish long-term benzodiazepine use from short-term use in a previous study.[32]

Follow-up for the first long-term BZRA prescription occurred from the date of cohort entry through the subsequent 12 months. To identify the first long-term BZRA prescription and the date that it occurred, we first constructed distinct treatment episodes by arranging each beneficiary's BZRA fills in chronological order starting with their index BZRA fill. The construction of treatment episodes is a standard method to document prescription use from pharmacy claims data.[33,34] Criteria were met for the first long-term BZRA prescription when at least 60 pills were accumulated, from one or more BZRA prescriptions of any type, at the earliest treatment episode comprising a period of 45 or fewer days. We used 45 days to reflect real-world settings. Specifically, continuous treatment episodes often include grace periods to accommodate gaps likely to occur between prescription fills.[21,33,35] Therefore, we included a grace period of 15 days in assessing the first identifiable point where 60 or more days of continuous use is possible. For example, a patient with a prescription for 30 pills on day 1 would need to have a second prescription by day 45 (30 days + 15-day grace period) for this treatment episode to be considered continuous. Next, we determined the date of the first long-term BZRA prescription from the treatment episodes. For beneficiaries with an index fill of ≥60 pills, the date of first long-term BZRA prescription was the index fill date. For individuals with multiple contiguous fills, we considered the fill date for the prescription where the total was 60 or more pills to

be the date when long-term BZRA use began. Specific examples of scenarios meeting criteria for first long-term BZRA prescription are included in Figure 3.S.1.

Independent variables

Independent variables included demographic, clinical, and prescription characteristics. We ascertained demographic factors of age, sex, race, or Hispanic ethnicity, and rurality from zip codes of residence at cohort entry. Sex, race, and Hispanic ethnicity were self-reported by the beneficiary. Age was categorized as 18-24, 25-34, 35-44, 45-54, 55-63 years. Age was also examined separately as a continuous variable. Categories for race and ethnicity were included as a social construct to assess possible disparities in BZRA prescribing practices.[36] Designations of rurality from the Oregon Office of Rural Health were applied to zip codes to categorize residence as urban, rural, or frontier, with frontier being an extremely rural, sparsely populated region.[37] Both variables of race/ethnicity and rurality contained a category for “missing/unknown”. For clinical characteristics, we identified medical claims for diagnoses of anxiety/panic disorders, insomnia, and substance use disorders (SUD) in the 12 months before date of cohort entry. Each of these three conditions was represented as a binary variable based on separate groups of ICD diagnostic codes (Table.A.3). Concurrent prescriptions were identified from claims using drug identifications codes for antidepressants, opioid, gabapentin/pregabalin, medication for opioid use disorder (MOUD), or trazodone in the 3 months prior to cohort entry (Table.A.4). Trazodone was not categorized as an antidepressant as it is commonly used off label as a sedative agent to treat insomnia.[38] Prescriptions for these medications are represented with five separate indicator variables.

We classified the index BZRA fill in three ways. First, we calculated the BZRA prescription strength by multiplying the index BZRA fill unit strength (e.g. 1 mg) by the DME conversion for the specific BZRA (Table.A.5), resulting in an equivalent strength independent of units dispensed. We dichotomized

BZRA prescription strength into categories of <20 DME as “Standard” and ≥20 DME as “High”, which is double the World Health Organization’s defined daily dose for BZRA prescriptions of diazepam indicated for anxiety treatment.[39] Second, we categorized BZRA with functional half-lives of >24 hours as “long-acting” and of ≤24 hours as “short-to-intermediate acting” as shown in Table.A.5.[40–42] We chose these categories because the onset for the effects of BZRA prescriptions are dependent on their half-life.[1,40–42] Finally, we categorized the primary indication of the BZRA into two groups of “sedative/hypnotic” and “anxiolytic” (Table.A.5). Primary indication reflects the intended therapeutic effect of the BZRA prescription based on their principal FDA-labeled indication.[43]

Statistical analyses

Analyses were conducted using Stata software version 19 (Stata Corp LLC, College Station TX, USA). In initial descriptive analyses, the distributions of categorical variables were examined as counts and percentages in the cohort overall and by calendar year of cohort entry. Each pair of categorical variables was examined in contingency tables, which confirmed that none were so highly correlated that they should not be fit together into a statistical model.

The measure of outcome occurrence was the 12-month incidence proportion (“risk”) of first long-term BZRA prescription. The crude incidence proportion (IP) was calculated as the number of cohort members with a long-term prescription divided by the total number of cohort members and expressed as a percentage with its 95% confidence interval (CI). A crude IP was also estimated within each category of the independent variables. Risk ratios (RR) were used as the measure of association between the independent variables and occurrence of first long-term prescriptions. We calculated the crude RR as the IP within a category of an independent variable divided by the IP in the referent category. We selected referent categories based on prior findings in the literature. For example, the youngest age group of 18-24 years was chosen because of increasing risks of adverse events by advancing age.[12] We chose female sex as a referent category because of greater prevalence of

benzodiazepine prescriptions among U.S. female adults compared to male.[9] Black and Hispanic patient groups have been observed with lower proportions of benzodiazepine prescriptions compared to white patients, potentially indicating systemic bias within prescribing practices resulting in undertreatment.[36] We therefore chose non-Hispanic White as a referent category.

We estimated the multivariable adjusted RR (aRR) and their 95% CI from a generalized linear model with modified Poisson distribution, log-link function, and robust standard errors. Modified Poisson models with robust standard errors converge more reliably than alternative approaches of log-binomial models.[44,45] To construct the multivariable models, we began with a base model that included age and sex, given their possible association with prevalent BZRA use and other clinical factors. Next, we fit a model including each remaining variable, one at a time, retaining those with an aRR ≥ 1.25 or aRR ≤ 0.80 or an p-value ≤0.10 for individual levels of categorical variables.[46] Using this planned approach, all variables except diagnosis of SUD met criteria for retention. Therefore, instead of omitting only SUD, we report the multivariable aRR for all variables.

We tested for linear trend across categories of age groups. We replaced the indicator variable for each age group category with its median value and then fit the new variable with the medians as continuous.[47] The linear trend was considered statistically significant if the p-value for the continuous age variable was < 0.05.

We conducted multiple sensitivity analyses. First, we restricted the analytic cohort to the 33,674 beneficiaries with continuous Medicaid enrollment for 12 months before and 12 months after cohort entry. The sensitivity analysis was conducted to determine the extent to which the RRs for long-term BZRA use in the main analytic cohort were robust to the inclusion of beneficiaries with non-continuous Medicaid enrollment. Second, we restricted the analytic cohort to 39,996 beneficiaries without the category of “missing/unknown” for demographic characteristics of race/ethnicity and rurality.

3.4 Results

Characteristics at cohort entry

During the period 2016-2018, 55,765 adult Medicaid beneficiaries met criteria for new BZRA use (Figure 3.1). Nearly half of the cohort (45%) had new BZRA use in 2016 (Table 3.1)**.** Most members of the cohort were in the age categories of 25-34 years (27%) or 35-44 years (24%), female (67%), non-Hispanic White (60%), and resided in an urban area (56%). Anxiety/panic disorders (69%) and SUD (46%) were the most prevalent clinical conditions. The most common concurrent prescriptions in the cohort were for an antidepressant (49%) or an opioid (36%). The majority of index BZRA prescription fills were of standard prescription strength of <20 DME (98%) or of short-to-intermediate acting onset (81%). The primary indication most often was anxiolytic (70%). The distributions of independent variables according to year of cohort entry were generally comparable to those in the entire cohort.

First long-term BZRA use

During 12 months of follow-up, 15,827 beneficiaries, representing 28.4% (95% CI: 28.0%, 28.8%) of the cohort, had a first long-term BZRA prescription (Table 3.2). Among the beneficiaries with a first long-term BZRA prescription, 54% received it at the index fill, 30% at the second fill, and 10% at the third fill (data not shown). The median time to first long-term BZRA prescription comprised of multiple fills was 38 days from cohort entry (data not shown).

The crude IP of first long-term BZRA use varied across categories of most independent variables (Table 3.2). The crude IP increased progressively with age, from 19% for ages 18-24 years to 35% for ages 55-63 years. Among the race and ethnic groups, the crude IP was greatest among non-Hispanic white beneficiaries (31%) and least among Hispanic beneficiaries (19%). The crude IP was larger among beneficiaries residing in a frontier rurality (35%) than among those residing in rural (29%) or urban (27%) locations. Across the three years of the enrollment period, the crude IP became

successively lower, ranging from 33% to 26% to 22% respectively in 2016, 2017 and 2018. For the respective clinical diagnoses, the crude IP were about 30%. When concurrent prescriptions status was considered, the crude IP varied from 36% among those with a trazadone or gabapentin/pregabalin to 29% among those with an opioid. The crude IP was substantially greater among beneficiaries with a high strength index BZRA fill (70%) compared to those with a standard strength (27%). Among beneficiaries with short-to-intermediate acting BZRA (30%), the crude IP was greater than among those with long-acting BZRA (19%). Among beneficiaries with anxiolytic BZRA (31%), the crude IP was also greater than among those with sedative/hypnotic BZRA (21%).

The crude RR and aRR for first long-term BZRA use were generally consistent in magnitude and direction (Table 3.3). Risk of first long-term BZRA use was positively associated with age and with rurality. Risk of first long-term BZRA use rose successively with age, such that the aRR were 1.19 (95% CI: 1.12, 1.26) for ages 25-34, 1.40 (95% CI: 1.32, 1.49) for 35-44, 1.59 (95% CI: 1.50, 1.69) for 45-54, and 1.73 (95% CI: 1.63, 1.84) for 55-63, compared to ages 18-24. Frontier residence (aRR 1.34, 95% CI:1.26, 1.43) relative to urban residence was also associated with increased risk of first long-term BZRA use. Inverse associations are represented by aRR below values of 1.0 and indicate lower risk of first long-term BZRA use compared to the referent. Beneficiaries of Hispanic ethnicity (aRR 0.70, 95% CI: 0.64, 0.76), American Indian/Alaska Native (aRR 0.90, 95% CI: 0.85, 0.95), Asian/Pacific Islander (aRR 0.86, 95% CI: 0.77, 0.96), Black (aRR 0.86, 95% CI: 0.77, 0.96), or of multiple, other race (aRR 0.83, 95% CI: 0.72, 0.96), had lower risks of first long-term BZRA use compared to beneficiaries who were non-Hispanic White. Risk of long-term BZRA use decreased progressively with year of cohort entry, such that the aRR were 0.79 (95% CI: 0.76, 0.81) in 2017 and 0.66 (95% CI: 0.64, 0.96) in 2018, relative to 2016. A diagnosis of anxiety/panic disorder was weakly associated with risk of first long-term BZRA use, whereas associations with diagnoses of insomnia or of SUD were null. A concurrent prescription for an antidepressant, trazodone, MOUD, and gabapentin/pregabalin were positively associated with risk of first long-term BZRA use, whereas the

association of a concurrent prescription for an opioid was null. The strongest positive association observed was the aRR of 2.63 (95% CI: 2.52, 2.73) for index BZRA fills with high strength compared with standard strength. Short-to-intermediate acting BZRA (aRR 1.34, 95% CI: 1.27, 1.42) relative to long-acting BZRA was also positively associated with first long-term BZRA use. Likewise, anxiolytic indication for the index BZRA fill (aRR 1.22, 95% CI: 1.17, 1.28) relative to a sedative/hypnotic indication was also associated with greater risk of long-term BZRA use.

There was evidence of a statistically significant linear trend in the aRR across age ($p<0.001$) *(data not shown)*.

In the first sensitivity analysis, we first restricted the cohort to 33,674 beneficiaries who had continuous Medicaid enrollment for 12 months before and after their date of cohort entry (Table 3.S.1). The aRR in the cohort with continuous enrollment were comparable to those obtained from the entire cohort. Second, we restricted the cohort to 39,996 beneficiaries with complete data consisting of no missing or unknown variables for demographic characteristics. The aRR in the cohort with complete data also were comparable to those estimated in the entire cohort. The inference of the study results was not materially affected by the sensitivity analyses. Therefore, we present findings from the entire cohort as the primary results.

3.5 Discussion

This study examined 55,765 Oregon Medicaid beneficiaries aged 18-63 years with new BZRA use. Within a year, more than one quarter of this cohort received a prescription indicating a possible transition to long-term BZRA use. For half of these beneficiaries, long-term use first began with the initial BZRA fill, and for about a third, it occurred upon their second fill. These findings suggest that a substantial proportion of long-term BZRA use may begin at or shortly following the first BZRA prescription fill. Characteristics independently associated with elevated risk of long-term BZRA use

were older age, residence in a frontier area, anxiety/panic diagnosis, a concurrent prescription for an antidepressant, gabapentin/ pregabalin, MOUD, or trazodone and a new BZRA fill of either a high dose strength, short-to-intermediate onset, or a BZRA with a primary anxiolytic indication. Factors independently associated with lower occurrence of first long-term BZRA use were race and ethnicity other than non-Hispanic White and cohort entry in 2017 or 2018.

Our estimate of 28% for long-term BZRA use is consistent with other cohort studies with follow-up from new BZRA use.[25,48–50] Among French adults with new BZRA use, 20% to 30% received prescriptions for long-term use.[49] Our findings were slightly lower than the 36% long-term use of 3 months of continuous use among Japanese adults with new BZRA use.[48] The findings from our study were greater than the 8% long-term benzodiazepine use of 6 months or more, observed for individuals ages 13-64 years with commercial insurance.[25] Our study's findings also align with those from a cohort of Pennsylvania Medicare beneficiaries, ages 65 years and older, in which 30% had long-term use of 3 months or more in the subsequent year after new benzodiazepine use.[50] Together these findings indicate that a substantial proportion of new BZRA users progress to long-term use within a relatively short time. This suggests that interventions to reduce long-term BZRA could be implemented at new BZRA use. Specific interventions could include interactive educational outreach to clinicians within large health systems, a strategy known as academic detailing.[51,52] Academic detailing has been successful in reducing the frequency of benzodiazepine prescriptions to patient populations determined to be at greater risks of BZRA-related adverse health outcomes.[53] The outreach strategies derived from academic detailing specifically advise against BZRA prescription fills with large quantities that may represent a transition to long-term use. For example, clinical guidelines for at least one large U.S. health system includes recommendations limiting new BZRA prescriptions to a less than 30-day supply.[54]

Overall, substantial differences were observed for the occurrence of new long-term BZRA use according to differing demographic characteristics in our findings and in other reports. In particular, age and extremely rural frontier residence may be characteristics important for identifying new BZRA users who are at elevated risk for long-term BZRA use. Other studies have reported greater associations of long-term use with increasingly older age, including individuals over 65 years compared to younger individuals.[49,55–57] The pattern we observed of successively larger adjusted risk ratios with each age category was consistent with these prior findings. The magnitude of the association for the three oldest age groups of, ages 35-44, 45-55 and 55-63 years, relative to ages 18-24 years, were among the largest observed in this study. Reasons for the successive increased risk of first long-term BZRA use by beneficiary age, observed across multiple populations, are likely to be complex. One possible consideration is that total healthcare utilization increases proportionally with successive age among U.S. adults.[58] BZRA prescriptions and use originate from outpatient care visits.[59] The proportion of outpatient visits among U.S. adults resulting in a benzodiazepine prescription increased from 3.8% in 2003 to 7.4% in 2015, coinciding with increases in the prevalence of benzodiazepine use.[7,8,59] Increased healthcare utilization could therefore potentially result in a greater likelihood of first long-term BZRA use. The single study that examined residential location in relation to long-term BZRA use also reported higher risk among rural compared with urban residence.[60] Greater risk of first long-term BZRA use among beneficiaries with frontier residence could result from prescribers attempting to mitigate the long distance for travel required for prescription refills. Efforts to reduce the risk of first long-term BZRA use could prioritize appropriate preventative strategies for older age beneficiaries or those who reside in frontier areas.

We observed a lower risk of first long-term BZRA use among cohort members identifying as American Indian/Native Alaskan, Asian/Pacific Islander, Black, Hispanic (any race), and Multiple or other race, than among non-Hispanic White members. While lower percentages of long-term BZRA use among these racial and ethnic groups could be interpreted as better adherence to clinical guidelines, these

findings merit further scrutiny. Differences in BZRA prescription fills have suggested potential unconscious biases of prescribers towards the presentation and treatment of acute symptoms from members of minoritized populations.[36] For U.S. emergency department visits from 2009-2018, Black or Hispanic patients were 36% and 19% less likely to receive a benzodiazepine prescription compared to White patients, despite the same percentages with diagnoses of anxiety disorder.[36] Difference in the occurrence of long-term BZRA use therefore could also reflect possible unconscious biases of prescribers.

Increased risk of long-term BZRA use by characteristics of index BZRA fill were observed in one other study. Among Japanese adults, Takeshima et al., reported a positive association was also observed between 3-months of continuous BZRA use and an index BZRA fill for a high dose strength compared to a fill for standard dose strength.[48] Within the same cohort, new BZRA use with a short-acting BZRA compared to a long-acting BZRA was positively associated with continuous BZRA use. In our study, the characteristics of the index BZRA fill that were most strongly associated with first long-term BZRA were for a high strength or short-to-intermediate acting onset. Given the consistency of the findings from our study and Takeshima et al., new BZRA use with high dose strengths or short-to-intermediate onset could be considered to be risk factors for first long-term BZRA use. However, additional cohort studies of index BZRA fill characteristics in relation to risk of long-term BZRA use are needed to corroborate these findings. The possibility that high strength BZRA prescriptions may be associated with risk of long-term BZRA use is also supported by clinical guidelines from a large U.S. healthcare system.[54] Specifically, those guidelines advise prescribing the lowest possible BZRA prescription strength when patients are starting new BZRA use.

We also note the association between different concurrent prescriptions and long-term BZRA use. The positive associations observed for all concurrent prescriptions compared to no prescriptions could indicate the presence of complex patient symptoms. As a result, physicians may prescribe

BZRA, not in accordance with clinical guidelines, in attempt to successfully treat these symptoms.[11] Patients are often prescribed gabapentin/pregabalin for chronic pain, which can be associated with subsequent symptoms of anxiety and depression, potentially leading to extended pharmacotherapeutic interventions including BZRA use.[61] However, the treatment of complex indications should be carefully balanced against the increases in risk of long-term BZRA use.

The successively lower risks of first long-term BZRA prescription associated with the calendar years of 2017 and 2018 likely resulted from changes in prescribing practices compared to the calendar year of 2016. Specifically, in 2016 Oregon Medicaid adopted a prior authorization policy targeting long-term benzodiazepine use from continued fills,[56] which could have changed prescribing practices over time. Given the reduction in first long BZRA prescriptions during the next two years of our study period, further examination of the effect of factors such as Medicaid prior authorization policies or secular changes in clinical practice due to FDA warnings are warranted. Despite implementation of the Oregon Medicaid prior authorization policy, the IP for first long-term BZRA prescriptions in 2018 remained over 20%. The continued occurrence of first long-term BZRA prescriptions suggests that additional supporting interventions may be necessary to complement policy changes. For example, qualitative feedback from patients attempting discontinuation from long-term BZRA use supports expanded earlier communication regarding the risks of long-term use.[62] Additional interventions could include patient accessible material concerning long-term BZRA use, made available by Oregon Medicaid upon a fill for a new BZRA prescription.

3.5.1 Limitations

This study has several limitations. First, we defined new BZRA use as a prescription fill preceded by 12 months with no BZRA fill but acknowledge that cohort members could have used BZRA medications prior to the 12-months before cohort entry. For individuals with unmeasured prior BZRA use, an increased occurrence of long-term BZRA could be expected. However, this definition is in

accordance with other studies determining new BZRA use from prescription fills.[25,26] Furthermore, we chose a stricter definition than other benzodiazepine studies and selected a method commonly utilized to define any new prescription use from claims data.[25,26,63] Second, to construct treatment episodes, we made assumptions about daily pill consumption. If cohort members consumed more than one BZRA pill per day “as needed” or “as prescribed” [64] for a shorter duration than assumed, this would overestimate the IP of first long-term BZRA use. However, other studies of benzodiazepine use have made similar assumptions for utilization of available pills and found no differences between electronic health record prescriptions listed “as needed” versus “daily”.[65] Therefore, we believe our assumptions for consumption to be a valid approach for defining long-term BZRA use. Third, as we assessed BZRA prescriptions paid for by Medicaid, the total number of BZRA prescriptions received by cohort members may be undercounted. Additional cash purchases of BZRA prescriptions were possible, because several BZRA were available as relatively low-cost generic products. Studies show that 15% of opioid prescriptions dispensed to Oregon Medicaid beneficiaries were paid out-of-pocket without a reimbursed Medicaid claim.[54,55] If cohort members did obtain additional BZRA fills paid out-of-pocket, then the risk of a first long-term BZRA prescription may be underestimated. Alternatively, given the prevalence of misuse among patients with BZRA use,[9] it is possible that risk of first long-term BZRA use would be greater than what we observed as a result of purchases of illicit or diverted BZRA. Another possible limitation was non-continuous Medicaid enrollment among cohort members. We assumed continuous 12-months of follow-up after cohort enrollment regardless of their actual Medicaid enrollment status. To address whether our results were affected by this assumption, we conducted a sensitivity analysis restricted to beneficiaries with continuous enrollment and found no substantial difference in results. Thus, we are confident that our main findings for characteristics associated with long-term BZRA prescriptions are robust with regard to loss of Medicaid enrollment in the year following new BZRA use. Given that enrollment in Medicaid can be intermittent,[66] we explored various eligibility criteria for Medicare enrollment. Use of a larger cohort with less restrictive

enrollment criteria was advantageous because of the greater sample size and the greater representation of Medicaid beneficiaries with non-continuous periods of enrollment.

This study was comprised of adult Oregon Medicaid beneficiaries, and the findings are primarily generalizable to other U.S. Medicaid populations with comparable demographic characteristics to Oregon. Whether our results pertain to Medicaid populations with differing demographic characteristics or to populations with private insurance is less certain. Nevertheless, the 12-month incidence proportion of first long-term BZRA use was comparable to other observed proportions of long-term BZRA use,[25,48–50] suggesting the potential applicability of our approach in other populations.

Conclusion

We found that more than 1 in 4 beneficiaries with new BZRA use transitioned to potentially problematic first long-term use. Most first long-term BZRA use occurred within 3 months of the index BZRA fill, indicating an almost immediate transition from new BZRA to long-term BZRA use. Accordingly, potential interventions to prevent long-term BZRA use could occur at or shortly following the first prescription fill for new BZRA use. These interventions could include academic detailing of targeted educational material provided to Medicaid prescribers. Targeted educational campaigns to clinical prescribers could emphasize limiting new BZRA prescriptions with high strength or short-to-intermediate acting onset when appropriate. Efforts to reduce risk of long-term BZRA use among older adults, non-Hispanic White beneficiaries, and frontier patients should be prioritized.

3.6 Figures, Tables

Figure 3.1. Study Cohort Enrollment of Oregon Medicaid Beneficiaries with New BZRA use: 2016-2018

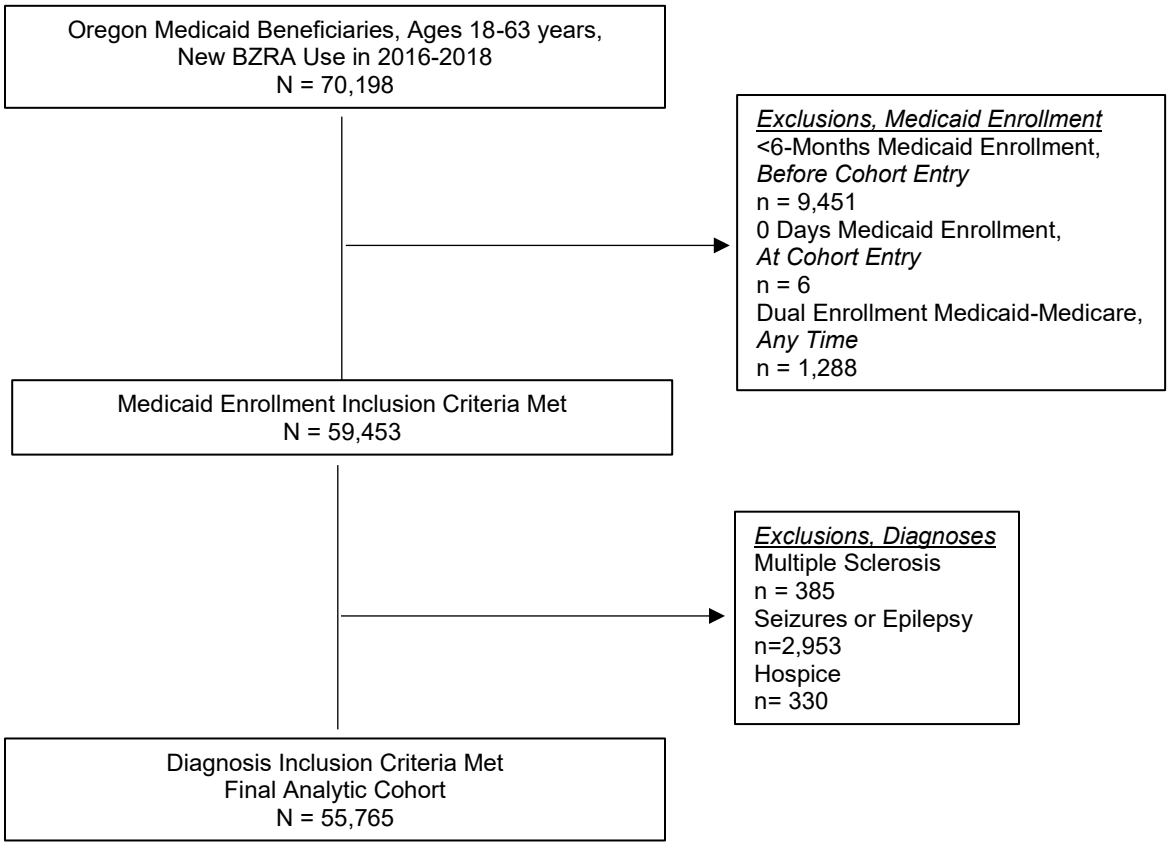

Table 3.1. Distributions of Characteristics of Adult Oregon Medicaid Beneficiaries with New BZRA Use: 2016-2018

		Study Cohort	2016	2017	2018
Characteristics (n, %)		55,765	25,290 (45.4)	17,670 (31.7)	12,805 (23.0)
Demographic Factors					
Age (years)	18-24	5,181 (9.3)	2,288 (9.0)	1,649 (9.3)	1,244 (9.7)
	25-34	14,899 (26.7)	6,734 (26.6)	4,620 (26.1)	3,545 (27.7)
	35-44	13,323 (23.9)	5,998 (23.7)	4,185 (23.7)	3,140 (24.5)
	45-54	12,445 (22.3)	5,779 (22.9)	4,017 (22.7)	2,649 (20.7)
	55-63	9,917 (17.8)	4,491 (17.8)	3,199 (18.1)	2,227 (17.4)
Sex	Female	37,440 (67.1)	8,326 (32.9)	11,948 (67.6)	8,528 (66.6)
	Male	18,325 (32.9)	16,964 (67.1)	5,722 (32.4)	4,277 (33.4)
Race, Ethnicity	American Indian/Native Alaskan	3,418 (6.1)	1,620 (6.4)	1,050 (5.9)	748 (5.8)
	Asian/Pacific Islander	681 (1.2)	298 (1.2)	221 (1.3)	162 (1.3)
	Black	959 (1.7)	416 (1.6)	291 (1.6)	252 (2.0)
	Hispanic	2,333 (4.2)	1,031 (4.1)	762 (4.3)	540 (4.2)
	Multiple, Other Race	611 (1.1)	262 (1.0)	184 (1.0)	165 (1.3)
	White	33,245 (59.6)	15,373 (60.8)	10,589 (59.9)	7,283 (56.9)
	Missing, Unknown	14,518 (26.0)	6,290 (24.9)	4,573 (25.9)	3,655 (28.5)
Rurality	Urban	31,209 (56.0)	14,162 (56.0)	9,914 (56.1)	7,133 (55.7)
	Rural	20,924 (37.5)	9,584 (37.9)	6,558 (37.1)	4,782 (37.3)
	Frontier	1,657 (3.0)	748 (3.0)	572 (3.2)	337 (2.6)
	Missing, Unknown	1,975 (3.5)	796 (3.1)	626 (3.5)	553 (4.3)
Clinical Diagnoses					
Anxiety/Panic	Yes	38,339 (68.8)	16,983 (67.2)	12,189 (69.0)	9,167 (71.6)
	No	17,426 (31.2)	8,307 (32.8)	5,481 (31.0)	3,638 (28.4)
Insomnia	Yes	16,255 (29.1)	7,184 (28.4)	5,204 (29.5)	3,867 (30.2)
	No	39,510 (70.9)	18,106 (71.6)	12,466 (70.5)	8,938 (69.8)
Substance Use Disorder	Yes	25,688 (46.1)	11,601 (45.9)	8,032 (45.5)	6,055 (47.3)
	No	30,077 (53.9)	13,689 (54.1)	9,638 (54.5)	6,750 (52.7)
Concurrent Prescriptions					
Antidepressant*	Yes	27,041 (48.5)	12,250 (48.4)	8,601 (48.7)	6,190 (48.3)
	No	28,724 (51.5)	13,040 (51.6)	9,069 (51.3)	6,615 (51.7)
Trazodone	Yes	5,890 (10.6)	2,606 (10.3)	1,868 (10.6)	1,416 (11.1)
	No	49,875 (89.4)	22,684 (89.7)	15,802 (89.4)	11,389 (88.9)
Opioid	Yes	20,037 (35.9)	10,096 (39.9)	6,186 (35.0)	3,755 (29.3)
	No	35,728 (64.1)	15,194 (60.1)	11,484 (65.0)	9,050 (70.7)
Medication for Opioid Use Disorder	Yes	791 (1.4)	255 (1.0)	283 (1.6)	253 (2.0)
	No	54,974 (98.6)	25,035 (99.0)	17,387 (98.4)	12,552 (98.0)
Gabapentin/ Pregabalin	Yes	7,966 (14.3)	3,584 (14.2)	2,514 (14.2)	1,868 (14.6)
	No	54,398 (97.5)	24,632 (97.4)	17,194 (97.3)	12,572 (98.2)

(*Table 3.1* continues next page)

Index BZRA Fill					
Prescription Strength†	Standard (<20 DME)	54,398 (97.5)	24,632 (97.4)	17,194 (97.3)	12,572 (98.2)
	High Strength (≥20 DME)	1,367 (2.5)	658 (2.6)	476 (2.7)	233 (1.8)
Onset of Effects	Long	10,637 (19.1)	4,723 (18.7)	3,405 (19.3)	2,509 (19.6)
	Short to Intermediate	45,128 (80.9)	20,567 (81.3)	14,265 (80.7)	10,296 (80.4)
Primary Indication	Sedative/Hypnotic	16,66(30.0)	7,558 (29.9)	5,304 (30.0)	3,804 (29.7)
	Anxiolytic	39,099 (70.0)	17,732 (70.1)	12,366 (70.0)	9,001 (70.3)

†Diazepam Milligram Equivalents (DME)
*Antidepressants do not include trazodone

Table 3.2. Incidence Proportion (IP) of First Long-Term BZRA Use among 55,765 Adult Oregon Medicaid Beneficiaries with New BZRA Use: 2016-2018

		First Long-Term BZRA Use	
Characteristics (n, %)		n	IP(%) (95% CI)
Study Cohort		15,827	28.4 (28.0,28.8)
Demographic Factors			
Age (years)	18-24	4,176	19.4 (18.3,20.5)
	25-34	11,364	23.7 (23.1,24.4)
	35-44	9,570	28.2 (27.4,28.9)
	45-55	8,380	32.7 (31.9,33.5)
	55-63	6,448	35.0 (34.1,35.9)
Sex	Female	10,460	27.9 (27.5,28.4)
	Male	5,367	29.3 (28.6,29.9)
Race, Ethnicity	American Indian/Native Alaskan	897	26.2 (24.8,27.8)
	Asian/Pacific Islander	154	22.6 (19.5,25.9)
	Black	225	23.5 (20.8,26.3)
	Hispanic	450	19.3 (17.7,21.0)
	Multiple, Other Race	135	22.1 (18.9,25.6)
	White	10,245	30.8 (30.3,31.3)
	Missing, Unknown	3,721	25.6 (24.9,26.4)
Rurality (residence)	Urban	8,420	27.0 (26.5,27.5)
	Rural	6,236	29.2 (29.2,30.4)
	Frontier	612	34.6 (34.6,39.3)
	Missing, Unknown	559	28.3 (26.3,30.4)
Year, Cohort Entry	2016	8,432	33.3 (32.8,33.9)
	2017	4,622	26.2 (25.5,26.8)
	2018	2,773	21.7 (20.9,22.4)

(*Table 3.2.* continues next page)

		First Long-Term BZRA Use	
Characteristics (n, %)		n	IP(%) (95% CI)
Clinical Diagnosis			
Anxiety/Panic	Yes	11,665	30.4 (30.0,30.9)
	No	4,162	23.9 (23.3,24.5)
Insomnia	Yes	5,067	31.2 (30.5,31.9)
	No	10,760	27.2 (26.8,27.7)
Substance Use Disorder	Yes	7,528	29.3 (28.8,29.9)
	No	8,299	27.6 (27.1,28.1)
Concurrent Prescription			
Antidepressant‡	Yes	8,988	33.2 (32.7,33.8)
	No	6,839	23.8 (23.3,24.3)
Trazodone	Yes	13,699	27.5 (27.1,27.9)
	No	2,128	36.1 (34.9,37.4)
Opioid	Yes	5,957	29.7 (29.1,30.4)
	No	9,870	27.6 (27.2,28.1)
Medication for Opioid Use Disorder	Yes	267	33.4 (30.1,36.8)
	No	15,563	28.3 (27.9,28.7)
Gabapentin/ Pregabalin	Yes	2,940	36.9 (35.9,38.0)
	No	12,887	27.0 (26.6,27.4)
Index BZRA Prescription Fill			
Prescription Strength†	Standard (<20 DME)	14,869	27.3 (27.0,27.7)
	High (≥20 DME)	958	70.1 (67.6,72.5)
Onset of Effect	Long	2,037	19.2 (18.4,19.9)
	Short to Intermediate	13,790	30.6 (30.1,31.0)
Primary Indication	Sedative/Hypnotic	3,583	21.5 (22.1,27.5)
	Anxiolytic	12,244	31.3 (31.8,30.4)

*Definitions: Incidence Proportion (IP), 95% Confidence Interval (CI)
‡Antidepressants do not include trazodone
†Diazepam Milligram Equivalents (DME)

Table 3.3. Risk ratios (RR) for First Long-Term BZRA Use among Adult Oregon Medicaid beneficiaries with New BZRA Use: 2016-2018

		First Long-Term BZRA Use		
Characteristics (n, %)		Crude RR	aRR (95% CI)	P-value
Demographic Factors				
Age (years)	18-24	Ref.	Ref.	
	25-34	1.22	1.19 (1.12,1.26)	<0.01
	35-44	1.45	1.40 (1.32,1.49)	<0.01
	45-55	1.68	1.59 (1.50,1.69)	<0.01
	55-63	1.80	1.73 (1.63,1.84)	<0.01
Sex	Female	Ref.	Ref.	
	Male	1.05	1.10 (1.07,1.13)	<0.01
Race, Ethnicity	American Indian/Native Alaskan	0.85	0.90 (0.85,0.95)	<0.01
	Asian/Pacific Islander	0.73	0.82 (0.72,0.94)	0.01
	Black	0.76	0.86 (0.77,0.96)	<0.01
	Hispanic	0.63	0.70 (0.64,0.76)	<0.01
	Multiple, Other Race	0.72	0.83 (0.72,0.96)	0.01
	White	Ref.	Ref.	
	Missing, Unknown	0.83	0.89 (0.86,0.91)	<0.01
Rurality (residence)	Urban	Ref.	Ref.	
	Rural	1.11	1.08 (1.05,1.11)	<0.01
	Frontier	1.37	1.34 (1.26,1.43)	<0.01
	Missing, Unknown	1.05	1.08 (1.01,1.16)	0.03
Year, Cohort Entry	2016	Ref.	Ref.	
	2017	0.79	0.79 (0.76,0.81)	<0.01
	2018	0.66	0.66 (0.64,0.69)	<0.01

(*Table 3.3.* continues next page)

Characteristics (n, %)		First Long-Term BZRA Prescription		
		Crude RR	aRR (95% CI)	P-value
Clinical Diagnoses				
Anxiety/Panic	No	Ref.	Ref.	
	Yes	1.27	1.15 (1.12,1.19)	<0.01
Insomnia	No	Ref.	Ref.	
	Yes	1.15	1.03 (1.01,1.07)	0.02
Substance Use Disorder	No	Ref.	Ref.	Ref.
	Yes	1.06	0.99 (0.97, 1.02)	0.56
Concurrent Prescription				
Antidepressant	No	Ref.	Ref.	
	Yes	1.40	1.23 (1.12,1.36)	<0.01
Trazodone‡	No	Ref.	Ref.	
	Yes	1.32	1.13 (1.09,1.18)	<0.01
Opioid	No	Ref.	Ref.	
	Yes	1.08	1.03 (1.00,1.06)	<0.01
Medication for Opioid Use Disorder	No	Ref.	Ref.	
	Yes	1.18	1.23 (1.12,1.36)	<0.01
Gabapentin/ Pregabalin	No	Ref.	Ref.	
	Yes	1.18	1.23 (1.12,1.36)	<0.01
Index BZRA Prescription Fill				
Prescription Strength†	Standard (<20 DME)	Ref.	Ref.	
	High (≥20 DME)	2.56	2.63 (2.52,2.73)	<0.01
Onset of Effect	Long	Ref.	Ref.	
	Short to Intermediate	1.6	1.34 (1.27,1.42)	<0.01
Primary Indication	Sedative/Hypnotic	Ref.	Ref.	
	Anxiolytic	1.46	1.22 (1.17,1.28)	<0.01

*Definitions: Adjusted Risk Ratio (aRR), Risk Ratio (RR), 95% Confidence Interval (CI)
‡Antidepressants do not include trazodone
†Diazepam Milligram Equivalents (DME)

Supplemental (S) Figures, Tables

See **Appendix 2** for Tables A.1. - A.5.

Figure 3.S.1. Examples of Criteria for First Long-Term BZRA Use

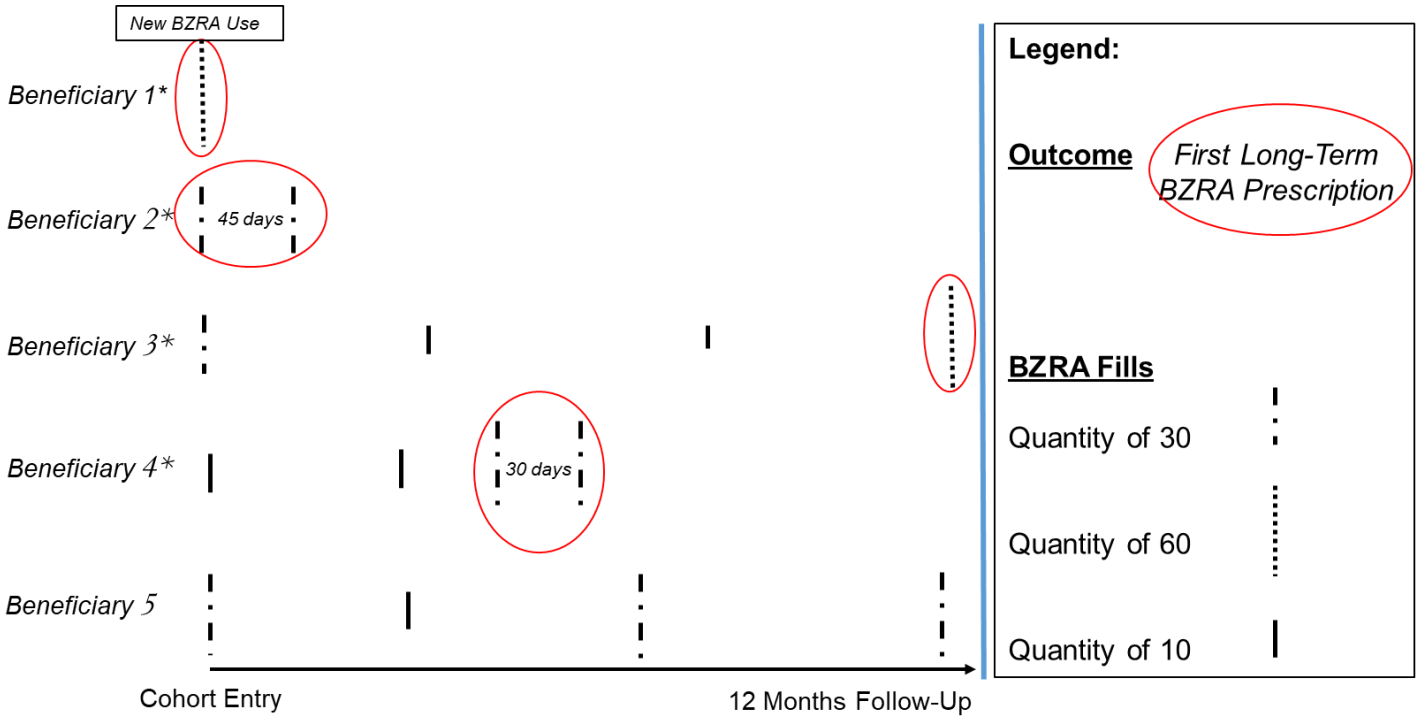

Table 3.S.1. Risk ratios (RR) for First Long-Term BZRA Use Among Adult Oregon Medicaid Beneficiaries with New BZRA Use from Full Study Cohort, with Continuous Medicaid Enrollment, or with Complete Data: 2016-2018

		Study Cohort	Continuous Medicaid Enrollment‡	Complete Data†
Characteristics		aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
Demographic Factors				
Age (years)	18-24	Ref.	Ref.	Ref.
	25-34	1.19 (1.12,1.26)	1.15 (1.06,1.24)	1.15 (1.07,1.24)
	35-44	1.40 (1.32,1.49)	1.34 (1.24,1.44)	1.35 (1.26,1.44)
	45-55	1.59 (1.50,1.69)	1.48 (1.37,1.59)	1.54 (1.44,1.65)
	55-63	1.73 (1.63,1.84)	1.59 (1.47,1.71)	1.65 (1.54,1.77)
Sex	Female	Ref.	Ref.	Ref.
	Male	1.10 (1.07,1.13)	1.12 (1.09,1.16)	1.11 (1.07,1.14)
Race, Ethnicity	American Indian/Native Alaskan	0.90 (0.85,0.95)	0.90 (0.84,0.96)	0.89 (0.84,0.94)
	Asian/Pacific Islander	0.82 (0.72,0.94)	0.74 (0.63,0.87)	0.81 (0.71,0.93)
	Black	0.86 (0.77,0.96)	0.97 (0.86,1.09)	0.86 (0.77,0.96)
	Hispanic	0.70 (0.64,0.76)	0.65 (0.59,0.73)	0.68 (0.63,0.74)
	Multiple, Other Race	0.83 (0.72,0.96)	0.86 (0.73,1.02)	0.83 (0.72,0.96)
	White	Ref.	Ref.	Ref.
	Missing, Unknown	0.89 (0.86,0.91)	0.87 (0.84,0.91)	--
Rurality	Urban	Ref.	Ref.	Ref.
	Rural	1.08 (1.05,1.11)	1.06 (1.03,1.10)	1.07 (1.04,1.10)
	Frontier	1.34 (1.26,1.43)	1.34 (1.24,1.44)	1.33 (1.24,1.43)
	Missing, Unknown	1.08 (1.01,1.16)	1.02 (0.93,1.12)	--
Year, Cohort Entry	2016	Ref.	Ref.	Ref.
	2017	0.79 (0.76,0.81)	0.77 (0.74,0.79)	0.78 (0.75,0.81)
	2018	0.66 (0.64,0.69)	0.60 (0.58,0.63)	0.66 (0.63,0.68)

(*Table 3.S.1* continues next page)

Characteristics		Study Cohort aRR (95% CI)	Continuous Medicaid Enrollment aRR (95% CI)	Complete Data aRR (95% CI)
Demographic Factors				
Anxiety/ Panic	No	Ref.	Ref.	Ref.
	Yes	1.15 (1.12,1.19)	1.14 (1.10,1.18)	1.15 (1.11,1.19)
Insomnia	No	Ref.	Ref.	Ref.
	Yes	1.03 (1.01,1.07)	1.00 (0.97,1.04)	1.04 (1.00,1.07)
Substance Use Disorder	No	Ref.	Ref.	Ref.
	Yes	0.99 (0.97,1.02)	1.00 (0.97,1.03)	0.98 (0.95,1.01)
Concurrent Prescription				
Antidepressant	No	Ref.	Ref.	Ref.
	Yes	1.23 (1.12,1.36)	1.27 (1.23,1.32)	1.24 (1.21,1.28)
Trazodone	No	Ref.	Ref.	Ref.
	Yes	1.13 (1.09,1.18)	1.13 (1.08,1.18)	1.12 (1.07,1.17)
Opioid	No	Ref.	Ref.	Ref.
	Yes	1.03 (1.00,1.06)	1.01 (0.98,1.04)	1.03 (1.00,1.06)
Medication for Opioid Use Disorder	No	Ref.	Ref.	Ref.
	Yes	1.23 (1.12,1.36)	1.23 (1.10,1.38)	1.20 (1.07,1.35)
Gabapentin/ Pregabalin	No	Ref.	Ref.	Ref.
	Yes	1.20 (1.16,1.24)	1.17 (1.13,1.22)	1.19 (1.14,1.23)
Index BZRA Prescription Fill				
Prescription Strength*	Standard (<20 DME)	Ref.	Ref.	Ref.
	High Strength (≥20 DME)	2.63 (2.52,2.73)	2.37 (2.27,2.49)	2.55 (2.44,2.67)
Onset of Effect	Long	Ref.	Ref.	Ref.
	Short to Intermediate	1.34 (1.27,1.42)	1.41 (1.32,1.51)	1.36 (1.27,1.45)
Primary Indication	Sedative/Hypnotic	Ref.	Ref.	Ref.
	Anxiolytic	1.22 (1.17,1.28)	1.17 (1.11,1.24)	1.21 (1.15,1.28)

*Definitions: Adjusted Risk Ratio (aRR), Risk Ratio (RR), 95% Confidence Interval (CI)
‡Continuous Medicaid enrollment for 12 months prior to new BZRA use and for 12 months following.
†No missing/unknown for category of race/ethnicity or rurality.
*Diazepam Milligram Equivalents (DME)

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CHAPTER 4. AIM 2

Incident Discontinuation from New Long-term Use of Benzodiazepine or Z-drug Prescriptions among Adult Oregon Medicaid Beneficiaries: 2016-2019

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4.1 Abstract

Importance

Clinical practice guidelines recommend discontinuation from long-term benzodiazepine receptor agonist (BZRA) use to prevent subsequent adverse health outcomes. However, no standard definition of discontinuation exists. A period of 90 days without a new BZRA prescription claim has been shown to be indicative of discontinuation. Determining the clinical or demographic factors related to occurrence of incident 90-day discontinuation could help identify groups who may benefit from efforts to reduce ongoing new long-term BZRA use.

Objective

To estimate the occurrence of 90-day discontinuation among adults with new long-term BZRA use and determine demographic, clinical, and prescription characteristics independently associated with its occurrence.

Design, Setting, Participants

This cohort study was comprised of adult Oregon Medicaid beneficiaries with new long-term BZRA use occurring in the period January 1, 2016, to December 31, 2019. We used administrative claims data to create a cohort of adult beneficiaries ages 18-64 years and with continuous enrollment. Cohort entry (baseline) was the date of the first fill for a BZRA prescription which met criteria for new long-term use, which was defined as the receipt of 60 or more BZRA pills or tablets within a period of 45 or fewer days.

Exposures

Characteristics determined at cohort entry included demographic factors, clinical diagnoses, and concurrent prescriptions. Additionally, the baseline prescription for new long-term BZRA use was

categorized in two separate variables representing indication as anxiolytic or sedative/hypnotic and speed of effect as short-to-intermediate acting or long-acting.

Main Outcome

The primary outcome was incident discontinuation, defined as 90 consecutive days with no additional BZRA prescription fills and no quantity (supply) of pills remaining. The occurrence of discontinuation was reported as 12-month incidence proportion (IP) (risk) expressed as a percentage. Multivariable modified Poisson regression models were used to estimate adjusted risk ratios (aRR) and 95% confidence intervals (CI) as the measure of association between occurrence of incident discontinuation and baseline characteristics. Associations with a P-value of < 0.05 were considered statistically significant.

Results

The study cohort included 10,902 adult Oregon Medicaid beneficiaries with new long-term BZRA use. Most beneficiaries were over 45-64 years old, female, non-Hispanic white and resided in an urban area. The 12-month crude IP for incident discontinuation was 36.0% (95% CI: 35.1%, 36.9%). Inverse associations of aRR < 1.0 indicate that incident 90-day discontinuation was less frequent in the category relative to the referent. Incident discontinuation occurred with successively lower frequency as age increased, such that the aRR were 0.84 (95% CI: 0.76, 0.92) for ages 25-34, 0.70 (95% CI: 0.64, 0.77) for 35-44, 0.64 (95% CI: 0.58, 0.70) for 45-54, and 0.65 (95% CI: 0.59, 0.71) for 55-64, compared to ages 18-24 years. The strongest inverse association was observed for index BZRA fills with short-to-intermediate acting (aRR 0.62, 95% CI: 0.59, 0.66) compared to long-acting onset. Weak inverse associations were also observed for index BZRA fills with a primary anxiolytic indication (aRR 0.91, 95% CI: 0.85, 0.97), compared to sedative/hypnotic. A concurrent prescription for an antidepressant (aRR 0.94, 95% CI: 0.89, 0.99), an opioid (aRR 0.91, 95% CI: 0.87, 0.96), or

gabapentin/pregabalin (aRR 0.93 95% CI: 0.87, 1.00), respectively were also weakly inversely associated with incident discontinuation. Rural (aRR 1.13, 95% CI: 1.10,1.19) and frontier residence (aRR 1.23, 95% CI: 1.09, 1.39) compared to urban residence were positively associated with incident discontinuation. Substance use disorder diagnosis also had a weak positive association with incident discontinuation, compared to no diagnosis. No significant associations were observed for sex, race/ethnicity, diagnosis of anxiety/panic, diagnosis of insomnia, or a concurrent trazodone prescription.

Conclusions

Incident discontinuation was 36% among adult Medicaid beneficiaries with new long-term BZRA use. Older beneficiaries could benefit from increased support during future efforts to enhance discontinuation. Targeted educational campaigns to clinical prescribers could emphasize avoiding new long-term BZRA use with prescriptions of short-to-intermediate onset when appropriate. Additional research is needed to assess the applicability of 90-day incident discontinuation among other patient cohorts with new long-term BZRA use.

4.2 Introduction

Benzodiazepine receptor agonists (BZRA) include both benzodiazepines and non-benzodiazepine Z-drugs. BZRA depress central nervous system activity to produce anxiolytic or sedative hypnotic effects.[1] BZRA are most commonly prescribed to treat the primary indications of insomnia or anxiety/panic disorders in clinical outpatient settings.[1,2] In 2024, 9% of adults in the United States (U.S.) reported past year use of benzodiazepines and 3% of Z-drugs.[3] Short-term BZRA use is effective for the immediate relief of adverse symptoms but evidence for additional therapeutic benefit of longer use is uncertain.[4] Long-term BZRA use is associated with increased risks of dependance and other adverse events, including withdrawal, seizures, cognitive decline, physical injury, automobile accidents, and fatal overdose.[5–8] Long-term BZRA use is prevalent despite the risk of adverse events.[6] A systemic review found long-term BZRA use occurred among 24% of adults with any BZRA use.[9]

Reducing the prevalence of long-term BZRA use through individual patient-specific tapering approaches is a substantial challenge.[1,5,10–16] Clinically mediated discontinuation from long-term BZRA use is supported by clinical practice guidelines, but requires distinct approaches over varying periods of time.[16] Distinct approaches of discontinuation from long-term BZRA use are necessary to mitigate potential symptoms of withdrawal or risk of discontinuation-related adverse outcomes.[16–18] Withdrawal from BZRA use can include mortality, seizures, rebound symptoms of the treated conditions, or the potential for seeking illicit BZRA replacements.[16,19] Discontinuation from persistent long-term BZRA use may require longer periods of time given high risk of withdrawal symptoms.[16] Longer times to discontinue from BZRA use are understood to be challenging for both patients and clinicians alike.[20,21] Population based prevention strategies based on a public health framework could be useful in supplementing the patient-specific approaches for discontinuation.

Transition to new long-term BZRA use may be an important point on which to focus population-based approaches to enhance discontinuation. Discontinuation from long-term BZRA use is the result of many complex factors including clinically directed, patient choice, or prescription regulations, all which lead to a period where BZRA are not used. The complexities surrounding the outcome of discontinuation present a substantial challenge towards the study of its occurrence.[22] The definitions utilized to assess discontinuation from long-term BZRA use have varied in epidemiologic studies, resulting in estimates for its occurrence that range from 13% - 33%.[19,23–25] Recent studies have used the first ≥90-day period of BZRA discontinuation as the incident outcome ascertained from prescription claims data with linked electronic health records.[24,26] When this definition was used in a cohort of older adults across multiple health systems, incident discontinuation was estimated as 29%.[24] Furthermore, a ≥90-period demonstrated increased accuracy for correctly identifying clinically mediated and sustained discontinuation, compared to shorter periods.[24,26] Thus, based on these studies,[24,26] a 90-day period provides a reasonable definition of incident discontinuation from long-term BZRA use. However, the applicability of this definition of discontinuation has not been assessed in any study with follow-up starting at new long-term BZRA use.

Population based approaches also depend on identifying demographic, clinical, or other characteristics associated with incident discontinuation from new long-term BZRA. In cohort studies among U.S. adults with long-term benzodiazepine use, multiple characteristics were associated with decreased frequency of incident discontinuation. Characteristics identified included a diagnosis of anxiety, a concurrent opioid prescription, and long-term use of a benzodiazepines with short-to-intermediate acting onset.[23,25] Characteristics associated with increased occurrence of discontinuation from long-term benzodiazepine included a diagnosis for substance use disorders (SUD), insomnia, or location of patient residence.[23,25] These results indicate that similar demographic, clinical or other characteristics could be associated with incident discontinuation from new long-term BZRA use.

The objective of our study was to estimate the 12-month incidence proportion of incident discontinuation among adults with new long-term BZRA use and determine demographic, clinical, and prescription characteristics associated with its occurrence. We conducted this study within cohort of adult Oregon Medicaid beneficiaries.

4.3 Methods

Study design, data source, and cohort selection

We performed a retrospective cohort study using deidentified Oregon Medicaid claims and enrollment data from adult beneficiaries during the calendar years 2015 through 2020. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (*STROBE*) guidelines for cohort study designs.[27] The Oregon Health & Science University Institutional Review Board determined this was exempt non-human subjects research.

The study cohort was comprised of beneficiaries with new long-term BZRA use beginning within the period January 1st, 2016, up to December 31st, 2019, to allow for 12-months of follow-up. This study cohort was created in multiple steps. First, we assembled a preliminary cohort of beneficiaries with new BZRA use, identified from paid claims as the first BZRA fill (dispensed) that had been preceded by 12 months without a BZRA fill.[28] Second, we excluded those with diagnosis codes for multiple sclerosis, epilepsy or hospice within the 12-months before new BZRA use, given long-term use may be appropriate for these conditions.[15,29–31] Specific codes for exclusion criteria are listed in Table A.2. Third, we identified beneficiaries with new long-term use from the criteria of single or contiguous BZRA fills totaling 60 pills, received over 45 or fewer days.[32] Thus, the definition here is presumed to be new long-term BZRA use. Cohort entry was the date the beneficiary first received a BZRA prescription (index BZRA fill) which met the criteria for new long-term use. Beneficiaries could enter the cohort only once during the study period. Finally, we selected beneficiaries with continuous

Medicaid enrollment for the 12-months both before and after cohort entry. Those with dual Medicaid-Medicare enrollment were excluded.

Outcome and follow-up period

The primary outcome was incident discontinuation from new long-term BZRA use. To define discontinuation, we selected a 90-day period without a new BZRA fill or remaining pill quantities. This definition has been validated against both chart review and medication orders in multiple studies with linked electronic health records and claims data.[24,26,33] To identify discontinuation in this study, we arranged each beneficiary's BZRA fills in chronological order starting with the index fill. Next, we constructed treatment episodes from pill quantities and determined gaps between prescriptions.[24,26,33,34] When a cohort member was first observed with no new BZRA fills and no remaining quantity of pills for 90 consecutive days, discontinuation was defined as occurring on the 91st day. Figure 4.S.1. shows specific examples of scenarios in which a beneficiary could meet criteria for discontinuation. Follow-up for incident discontinuation began on the date of cohort entry and continued through the subsequent 12 months.

Independent variables

Independent variables determined at cohort entry (baseline) included demographic factors, clinical encounters or diagnoses, and concurrent prescriptions. We ascertained the demographic factors of age, sex, race, or Hispanic ethnicity, and rurality from zip code of residence at cohort entry. Sex, race, and Hispanic ethnicity are self-reported by the beneficiary. Age was categorized as 18-24, 25-34, 35-44, 45-54, 55-64 years. Age was also examined separately as a continuous variable. Categories of race and ethnicity were included as a social construct to assess possible disparities in discontinuation from new long-term BZRA use.[35] Designations of rurality from the Oregon Office of Rural Health were applied to zip codes to categorize residence as urban, rural, or frontier, with frontier being an

extremely rural, sparsely populated region.[36] The clinical characteristics we identified from medical claims were diagnoses of anxiety/panic disorders, insomnia, and SUD in the 12 months before date of cohort entry. Each of these three conditions was represented as a binary variable based on separate groups of diagnostic codes (Table A.3). Concurrent prescriptions were identified prescriptions claims using drug identifications codes for antidepressants, opioid, gabapentin/ pregabalin, or trazodone in the 3 months prior to cohort entry (Table A.4). Trazodone was not categorized as an antidepressant because it is commonly used off-label as a sedative agent to treat insomnia.[37] Concurrent prescriptions for these medications are represented with four separate indicator variables. We classified the index BZRA fill in two ways (Table A.5). First, we categorized BZRA with functional half-lives of >24 hours as “long-acting” and of ≤24 hours as “short-to-intermediate acting” as shown in Table.A.5.[38–40] We chose these categories because the onset for the effects of BZRA prescriptions are dependent on their half-life.[1,38–40] Second, we categorized the primary indication of the BZRA into two groups of “sedative/hypnotic” and “anxiolytic” (Table.A.5). Primary indication reflects the intended therapeutic effect of the BZRA prescription based on their principal FDA-labeled indication.[41]

Statistical analyses

Analyses were conducted using Stata software version 19 (Stata Corp LLC, College Station TX, USA). For the initial descriptive analyses, the distributions of categorical variables were examined as counts and percentages. Each pair of categorical variables was examined in contingency tables, which confirmed that none were so highly correlated that they should not be fit together into a statistical model.

The measure of outcome occurrence was the 12-month incidence proportion (“risk”) of incident discontinuation. The crude incidence proportion (IP) was calculated as the number of cohort members with discontinuation divided by the total number of cohort members and expressed as a

percentage with a 95% confidence interval (CI). A crude IP was also estimated within each category of the independent variables. Risk ratios (RR) were used as the measure of association between the independent variables and incident discontinuation. We calculated the crude RR as the IP within a category of an independent variable divided by the IP in the referent category.

We estimated the multivariable adjusted RR (aRR) and their 95% CI from a generalized linear model with modified Poisson distribution, log-link function, and robust standard errors. Modified Poisson models with robust standard errors converge more reliably than alternative approaches of log-binomial models.[43,44] Robust standard errors are recommended for these models, to better estimate RR with greater consistency and efficiency.[89] All independent variables were included into the model and thus are mutually adjusted for one another. Associations were considered statistically significant if the p-value for aRR was < 0.05.

We tested for linear trend across categories of age groups. We replaced the indicator variable for each age group category with its median value and then fit the new variable with the medians as continuous.[45] The linear trend was considered statistically significant if the p-value for the continuous age variable was < 0.05.

4.4 Results

Characteristics at cohort entry

During the period of 2016-2019, 10,902 adult Oregon Medicaid beneficiaries met criteria for new long-term BZRA use (Figure 4.1). Most beneficiaries were over 45 years old (27% ages 45-54, 24% ages 55-64), female (68%), non-Hispanic white (66%), and resided in an urban area (54%) (Table 4.1). The majority of index BZRA fills were of anxiolytic primary indication (88%) or of short-to-intermediate acting onset (88%). Anxiety/panic disorders (76%) and SUD (48%) were the most prevalent clinical

conditions. Concurrent prescriptions in the cohort were for an antidepressant (59%), an opioid (38%), gabapentin/pregabalin (20%), or trazadone (14%).

Incident discontinuation

Over the 12 months following new long-term BZRA use, 3,921 beneficiaries, representing 36.0% (95% CI: 35.1%, 36.9%) of the cohort, had incident discontinuation (Table 4.2). The crude IP for incident discontinuation varied across categories of the independent variables and was most notable for age, race and ethnicity, and the index BZRA prescription fill. The crude IP decreased with age, from 50% for ages 18-24 years to 33% for ages 55-64 years. Among the race and ethnic groups, the crude IP was greatest among Hispanic (41%) and American Indian/Alaska Native (38%) beneficiaries, least among non-Hispanic Black (31%) beneficiaries, and similar among Asian/Pacific Islander (36%), Multiracial (36%) and White (35%) beneficiaries. The crude IP was substantially greater among beneficiaries with a short-to-intermediate acting BZRA (54%) compared to those with a long-acting BZRA (34%).

The crude RR and aRR for incident discontinuation were generally consistent in magnitude and direction (Table 4.3). Most of the statistically significant associations were inverse (aRR < 1.0), indicating that incident discontinuation was significantly less frequent in a category relative to the referent. Incident discontinuation occurred with successively lower frequency as age increased, such that the aRR were 0.84 (95% CI: 0.76, 0.92) for ages 25-34, 0.70 (95% CI: 0.64, 0.77) for 35-44, 0.64 (95% CI: 0.58, 0.70) for 45-54, and 0.65 (95% CI: 0.59, 0.71) for 55-64, compared to ages 18-24 years. The strongest inverse association was observed for index BZRA fills with short-to-intermediate acting (aRR 0.62, 95% CI: 0.59, 0.66) compared to long-acting onset. Weak inverse associations were also observed for index BZRA fills with a anxiolytic primary indication (aRR 0.91, 95% CI: 0.85, 0.97) compared to sedative/hypnotic indication. A concurrent prescription for an antidepressant (aRR 0.94, 95% CI: 0.89, 0.99), an opioid (aRR 0.91, 95% CI 0.87, 0.96), or gabapentin/pregabalin (aRR

0.93 95% CI: 0.87, 1.00), respectively, were also weakly inversely associated with incident discontinuation. A few statistically significant positive associations were observed, indicating that the incident discontinuation was significantly more frequent in the group compared with the referent. Rural (aRR 1.13, 95% CI: 1.10,1.19) and frontier residence (aRR 1.23, 95% CI: 1.09, 1.39) compared to urban residence were positively associated with incident discontinuation. A SUD diagnosis also was weakly positively associated with incident discontinuation compared to no SUD diagnosis. Associations with sex, diagnosis of anxiety/panic, diagnosis of insomnia, and concurrent trazodone were null. Associations in the categories of race and ethnicity were not significantly associated with incident discontinuation.

There was evidence of a statistically significant inverse linear trend in the aRR across age ($p<0.001$) *(data not shown)*.

4.5 Discussion

In this retrospective cohort study among adult Oregon Medicaid beneficiaries, 36% had incident 90-day discontinuation within 12 months following new long-term BZRA use. Factors associated with a decreased likelihood of incident discontinuation included older age, an index BZRA fill with a anxiolytic primary indication or of a short-to-intermediate acting onset, or a concurrent prescription of an antidepressant or of an opioid. Characteristics associated with an increased likelihood of incident discontinuation included residence in a rural or frontier zip code area or a SUD diagnosis.

Several cohort studies have estimated discontinuation from long-term BZRA use among other populations of U.S. adults.[19,23–25] These studies used varying definitions both of long-term BZRA use and of durations for subsequent discontinuation. Percentages of discontinuation in the 12 months from long-term BZRA use were 29% for a 90-day discontinuation,[24] 33% for a 120-day discontinuation,[25] and 13% for a 185-day discontinuation.[23] When follow-up was limited to 6 months,

20% of patients had a 31-day discontinuation.[19] Our findings of 36% with incident 90-day discontinuation from new long-term BZRA use exceed the range of 13% to 33% observed in other studies of U.S. adults.[19,23–25] Our estimate for incident discontinuation may be higher than in other studies because our follow-up period started at new long-term BZRA use. Other studies used selection criteria for long-term benzodiazepine use with minimum thresholds, resulting in substantial variation in the duration of benzodiazepine use prior to cohort entry.[19,23,25] Moreover, other studies focused only on long-term benzodiazepine use and did not include long-term Z-drug use.[19,23,25] Clinical guidelines for discontinuation from benzodiazepine use suggest that discontinuation following persistent use may require extended durations to mitigate symptoms of withdrawal.[16] Given that our study began follow-up at new long-term BZRA use, additional cohort studies are needed to document the frequency of incident 90-day discontinuation in the year following the transition to long-term use.

Variation in incident discontinuation according to demographic, clinical, and other characteristics were observed in our study and in others. In our study, progressively older age was associated with decreased occurrence of incident discontinuation. Other studies observed similar associations of older age and incident discontinuation from long-term benzodiazepine use.[23,25] In cohorts of Veterans Health Administration patients or beneficiaries with commercial insurance, discontinuation was more likely among those ages <45 years compared to those 45 – 65 years.[23,25] Given the decreasing frequency of discontinuation from long-term BZRA use observed with progressively older age, populations of older patients may benefit from enhanced efforts to support discontinuation.

The strongest inverse association for incident discontinuation was observed for index BZRA fills with short-to-intermediate acting compared to long-acting onset. Gerlach et al., examined the relation of index benzodiazepine fill with incidence of discontinuation among a cohort of commercially insured U.S. adults.[23] These authors defined high potency as binary variable and observed lower adjusted odds of discontinuation among those with high potency index benzodiazepine fills.[23] The implication

of this finding is important because high potency benzodiazepines corresponds to short-to-intermediate onset of effect.[23,46] Thus, our findings and those of Gerlach et al., suggest that characteristics of the index BZRA fill may be a modifiable risk factor for discontinuation. However, additional cohort studies among those with new long-term BZRA use would be beneficial to corroborate these findings.

Only two cohort studies have examined demographic or other factors in relations to discontinuation from long-term benzodiazepine use. [23,25n] Numerous factors were examined, but those in common across the two studies were sex, race/ethnicity, and respective diagnosis of anxiety or insomnia. In our study, we observed null or non-significant associations for these characteristics. Our findings conflicted with those from the two other cohort studies. Individual factors identified as inversely associated with discontinuation from long-term benzodiazepine use included a diagnosis for anxiety/panic, no diagnosis for insomnia, white non-Hispanic race ethnicity and female sex. [23,25] The reasons for conflicting findings are unclear but potentially could be attributed to dissimilarities between the cohorts. Our cohort consisted of Oregon Medicaid beneficiaries ages 18 to 64 years compared to those 18 to >65 years.[23,25] The study inclusion criteria of new long-term BZRA use differed from that of new or continuing long-term benzodiazepine use.[23,25 46]

Limitations

This study has several limitations. Primarily, we could not determine the specific reason for incident discontinuation following new long-term use. Discontinuation is an outcome which can occur as the result of different complex pathways. These pathways range from clinically supervised tapering to the involuntary abrupt cessation of further prescription fills. Similar pathways can vary substantially, as the suggested approaches for tapering include flexible, gradual, patient-centered, symptom-driven reductions of BZRA dose strength over varying durations of time.[16] No criteria currently exist to identify tapering, abrupt discontinuation, or other specific approaches in claims data that precede

discontinuation. If documentation of these specific approaches to discontinuation are necessary to accurately assess discontinuation, then our definition of incident discontinuation would be incomplete. Thus, misclassification of discontinuation could have potentially occurred in this study. If the misclassification of discontinuation did occur, then the true frequency of discontinuation could have been higher than what we observed in this study. Despite the inability to identify specific forms of discontinuation, the 90-day incident discontinuation definition has shown to be valid for claims data.[26] The accuracy of the outcome of 90-day discontinuation was supported through additional research which included linked electronic health records.[26] Another important limitation was that we could not assess BZRA prescriptions not paid for by Medicaid. It is possible that beneficiaries with additional BZRA prescriptions could have been misclassified as discontinued. During the study period, all BZRA prescriptions were available as low-cost generic medications which beneficiaries could have purchased out-of-pocket with cash. Other studies during the same period found that Oregon Medicaid beneficiaries filled substantial amounts of similarly controlled prescriptions with out-of-pocket payments.[47] Prescription cash purchases were associated with a SUD diagnosis and concurrent benzodiazepine/opioid prescriptions.[47] If similar amounts of cash-purchased BZRA existed within our study, the true IP of incident discontinuation would be smaller than what was observed for cohort members with a SUD or an opioid prescription.

The findings of this study are primarily generalizable to other U.S. Medicaid populations with similar demographic, clinical, and other characteristics to our cohort of Oregon Medicaid beneficiaries. The pertinence of the study findings to other U.S. Medicaid populations with differing characteristics or to populations with private insurance is not certain. However, we believe the population-based framework for our approach and the validated definition for incident discontinuation to be suitable for further assessment in other populations.

Conclusion

We found that 36% of adult Medicaid beneficiaries had incident 90-day discontinuation within the 12-months following new long-term BZRA use. This percentage of incident discontinuation could provide a suitable comparison for population-based efforts to enhance discontinuation undertaken in other populations newly transitioned to long-term BZRA use. Progressively older age and new long-term BZRA use with short-to-intermediate onset were associated with the lowest occurrence of discontinuation. Accordingly, future efforts to enhance discontinuation should prioritize support for older beneficiaries. Targeted educational campaigns to clinical prescribers could emphasize avoiding new long-term BZRA use with prescriptions of short-to-intermediate onset when appropriate. Additional research is needed to assess the applicability of 90-day incident discontinuation among other patient cohorts with new long-term BZRA use.

4.6 Figures, Tables

Figure 4.1. Enrollment into Study Cohort for Oregon Medicaid Beneficiaries with a New Long-Term BZRA Use: 2016-2019

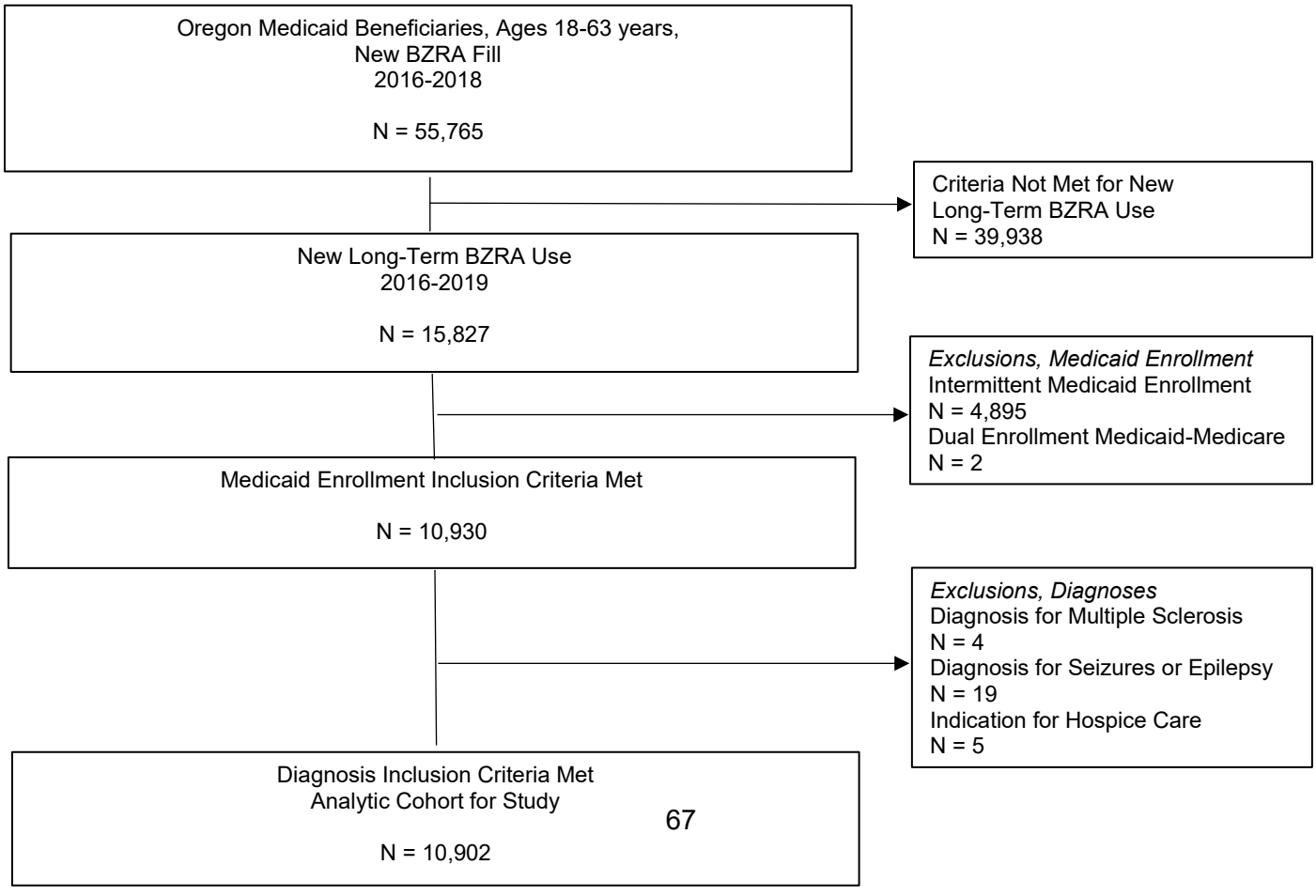


Table 4.1. Distributions of Characteristics of Adult Oregon Medicaid Beneficiaries with New Long-Term BZRA Use: 2016-2019

		Study Cohort
Characteristics		10,902
Demographic Factors		(n, %)
Age (years)	18-24	595 (5.5)
	25-34	2,198 (20.2)
	35-44	2,531 (23.2)
	45-54	2,930 (26.9)
	55-64	2,648 (24.3)
Sex	Male	3,526 (32.3)
	Female	7,376 (67.7)
Race, Ethnicity	American Indian/Native Alaskan	650 (6.0)
	Asian/Pacific Islander	110 (1.0)
	Black	174 (1.6)
	Hispanic	263 (2.4)
	Multiple, Other Race	100 (0.9)
	White	7,205 (66.1)
	Missing, Unknown	2,400 (22.0)
Rurality (residence)	Urban	5,855 (53.7)
	Rural	4,304 (39.5)
	Frontier	426 (3.9)
	Missing, Unknown	317 (2.9)
Index BZRA Fill		
Primary Indication	Sedative/Hypnotic	1,327 (12.2)
	Anxiolytic	9,575 (87.8)
Onset of Effect	Long	1,349 (12.4)
	Short to Intermediate	9,553 (87.6)

(*Table 4.1.* continues next page)

Clinical Diagnoses		
Anxiety / Panic	Yes	8,240 (75.6)
	No	2,662 (24.4)
Insomnia	Yes	3,737 (34.3)
	No	7,165 (65.7)
Substance Use Disorder	Yes	5,236 (48.0)
	No	5,666 (52.0)
Concurrent Prescriptions		
Antidepressant*	Yes	6,385 (58.6)
	No	4,517 (41.4)
Trazodone	Yes	1,528 (14.0)
	No	9,374 (86.0)
Opioid	Yes	4,138 (38.0)
	No	6,764 (62.0)
Gabapentin / Pregabalin	Yes	2,173 (19.9)
	No	8,729 (80.1)

*Antidepressants do not include trazodone

Table 4.2. Incidence Proportion (IP) of Incident 90-day Discontinuation from New Long-Term BZRA Use among Adult Oregon Medicaid Beneficiaries: 2016-2019

		Incident Discontinuation	
Characteristics		n	IP(%) (95% CI)
Study Cohort		3,921	36.0 (35.1,36.9)
Demographic Factors			
Age (years)	18-24	299	50.3 (46.2,54.3)
	25-34	929	42.3 (40.2,44.4)
	35-44	891	35.2 (33.3,37.1)
	45-54	942	32.2 (30.5,33.9)
	55-64	860	32.5 (30.7,34.3)
Sex	Female	1,292	36.6 (35.1,38.3)
	Male	2,629	35.6 (34.6,36.8)
Race, Ethnicity	American Indian/Native Alaskan	248	38.2 (34.4,42.0)
	Asian/Pacific Islander	40	36.4 (27.4,46.1)
	Black	53	30.5 (23.7,37.9)
	Hispanic	107	40.7 (34.7,46.9)
	Multiple, Other Race	36	36.0 (26.6,46.2)
	White	2,544	35.3 (34.2,36.4)
	Missing, Unknown	893	37.2 (35.3,39.2)
Rurality (residence)	Urban	1,987	33.9 (32.7,35.2)
	Rural	1,631	37.9 (36.4,39.4)
	Frontier	175	41.1 (36.4,45.9)
	Missing, Unknown	128	40.4 (34.9,46.0)
Index BZRA Fill			
Primary Indication	Sedative/Hypnotic	554	41.8 (39.1,44.5)
	Anxiolytic	3,367	35.2 (34.2,36.1)
Onset of Effect	Long	725	53.7 (51.0,56.4)
	Short to Intermediate	3,196	33.5 (32.5,34.4)

(*Table 4.2.* continues next page)

		Incident Discontinuation	
Characteristics (n, %)		n	IP(%) (95% CI)
Clinical Diagnosis			
Anxiety/Panic	No	977	36.7 (34.9,38.6)
	Yes	2,944	35.7 (34.7,36.8)
Insomnia	No	2,605	36.4 (35.2,37.5)
	Yes	1,316	35.2 (33.7,36.8)
Substance Use Disorder	No	1,931	34.1 (32.9,35.3)
	Yes	1,990	38.0 (36.7,39.3)
Concurrent Prescription			
Antidepressant†	No	1,725	38.2 (36.8,39.6)
	Yes	2,196	34.4 (33.2,35.6)
Trazodone	No	3,364	35.9 (34.9,36.9)
	Yes	557	36.5 (34.0,38.9)
Opioid	No	2,523	37.3 (36.2,38.5)
	Yes	1,398	33.8 (32.3,35.3)
Gabapentin/ Pregabalin	No	3,206	36.7 (35.7,37.8)
	Yes	715	32.9 (30.9,34.9)

*Definitions: Incidence Proportion (IP), 95% Confidence Interval (CI)
†Antidepressants do not include trazodone

Table 4.3. Risk ratios (RR) for Incident 90-day Discontinuation from New Long-Term BZRA Use among Adult Oregon Medicaid Beneficiaries: 2016-2019

		Incident Discontinuation		
Characteristics		Crude RR	aRR (95% CI)	P-Value
Demographic Factors				
Age (years)	18-24	Ref.	Ref.	
	25-34	0.84	0.84 (0.76,0.92)	<0.01
	35-44	0.70	0.70 (0.64,0.77)	<0.01
	45-54	0.64	0.64 (0.58,0.70)	<0.01
	55-64	0.65	0.65 (0.59,0.71)	<0.01
Sex	Female	Ref.	Ref.	
	Male	1.03	0.98 (0.93,1.03)	0.12
Race, Ethnicity	American Indian/Native Alaskan	1.08	1.05 (0.95,1.17)	0.41
	Asian/Pacific Islander	1.03	1.10 (0.85,1.41)	0.44
	Black	0.86	0.89 (0.71,1.12)	0.33
	Hispanic	1.15	1.11 (0.96,1.29)	0.15
	Multiple, Other Race	1.02	0.97 (0.74,1.25)	0.82
	White	Ref.	Ref.	
	Missing, Unknown	1.05	1.04 (0.98,1.11)	0.20
Rurality (residence)	Urban	Ref.	Ref.	
	Rural	1.12	1.13 (1.07,1.19)	<0.01
	Frontier	1.21	1.23 (1.09,1.39)	<0.01
	Missing, Unknown	1.19	1.18 (1.03,1.35)	0.01
Index BZRA Fill				
Primary Indication	Sedative/Hypnotic	Ref.	Ref.	
	Anxiolytic	0.84	0.91 (0.85,0.97)	0.01
Onset of Effect	Long	Ref.	Ref.	
	Short to Intermediate	0.62	0.62 (0.59,0.66)	<0.01

(*Table 4.3.* continues next page)

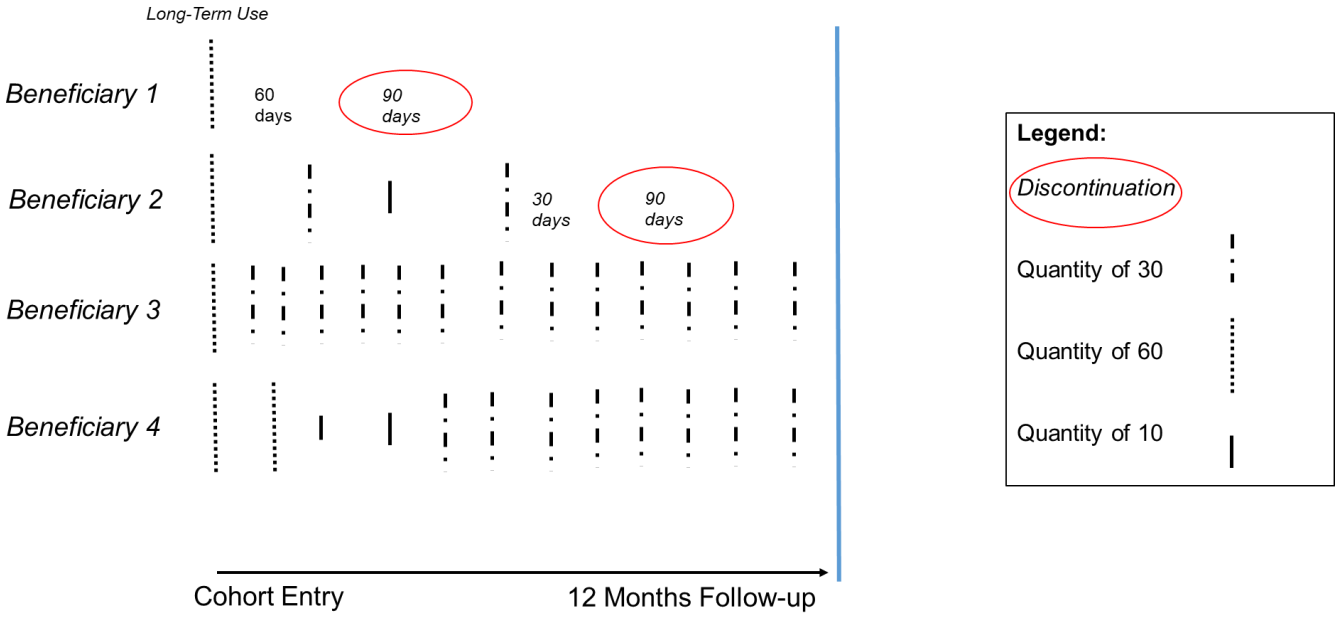
		Incident Discontinuation		
Characteristics		Crude RR	aRR (95% CI)	P-Value
Clinical Diagnosis				
Anxiety/Panic	No	Ref.	Ref.	
	Yes	0.97	1.00 (0.95,1.07)	0.91
Insomnia	No	Ref.	Ref.	
	Yes	0.97	1.01 (0.95,1.07)	0.77
Substance Use Disorder	No	Ref.	Ref.	
	Yes	1.12	1.10 (1.05,1.16)	<0.01
Concurrent Prescription				
Antidepressant	No	Ref.	Ref.	
	Yes	0.90	0.94 (0.89,0.99)	0.02
Trazodone	No	Ref.	Ref.	
	Yes	1.02	1.00 (0.94,1.08)	0.91
Opioid	No	Ref.	Ref.	
	Yes	0.91	0.91 (0.87,0.96)	0.02
Gabapentin/ Pregabalin	No	Ref.	Ref.	
	Yes	0.90	0.93 (0.87,1.00)	0.04

*Definitions: Risk Ratio (RR), adjusted Risk Ratio (aRR), 95% Confidence Interval (CI)

Supplemental (S) Figures, Tables

See **Appendix 2** for Tables A.1. - A.5.

Figure 4.S.1. Examples of Criteria for Incident 90-day Discontinuation from New Long-Term BZRA Use



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CHAPTER 5. AIM 3

Pill Quantities of New Benzodiazepine and Z-Drug Prescriptions in Relation to Rates of First Emergency Department Visits among Adult Oregon Beneficiaries: 2016-2018

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5.1 Abstract

Importance

Benzodiazepine receptor agonists (BZRA) are commonly prescribed medications, but use can be associated with the onset of serious health conditions requiring emergency department (ED) treatment. Pill quantities of BZRA medications prescribed are not standardized and can vary considerably. Whether the quantity of BZRA medication in a new prescription is related to the risk of subsequent ED visits for BZRA-related health conditions remains unclear.

Objective

To determine the association between new BZRA prescription pill quantities and rates of first BZRA-related ED visits.

Hypothesis

There will be a positive association between new BZRA prescription pill quantities and the rate of first BZRA-related ED visits, with the strongest associations occurring for prescriptions of more than 30 pills.

Design, Setting, Participants

This cohort study used administrative claims data for Oregon Medicaid beneficiaries ages 18-63 years. Beneficiaries entered the cohort upon new BZRA use during the period January 1, 2016, to December 31, 2018. New use was defined as the first (index) BZRA prescription fill that was preceded by 12 months without any BZRA prescription fills.

Exposure

The primary exposure was the pill quantity of the index BZRA fill. Based on the distribution of pill quantities within the cohort, we classified this exposure into categories of “1-9”, “10-14”, “15-27”, “28-30”, “31-60”, and “>60” pills.

Main Outcome

The outcome was a first ED visit with any diagnosis of a BZRA-related health condition. These conditions were overdose (toxicity/poisoning), seizure, complex sleep disorder, injurious fall or fracture, motor vehicle accident, suicide, altered mental status, or a benzodiazepine or Z-drug substance use disorder (including symptoms of misuse, dependance, or withdrawal). Follow-up began on the date of new BZRA prescription fill. The rate of first BZRA-related ED visits was reported as the number of ED visits per 100,000 person-days. Crude cumulative incidence and 95% confidence intervals (95% CI) were calculated at 30, 60, 90, 180, and 365 days of follow-up. Stratified Cox proportional hazards regression models were used to estimate the hazard ratios (HR) and 95% CI as the measure of association between pill quantity and first BZRA-related ED visits. Common HR for prescription pill categories were estimated by allowing for each stratum of prior ED visits to have its own baseline hazard function.

Results

Among the cohort of 55,292 adult Oregon Medicaid beneficiaries with new BZRA use, the median age was 40 years and 67% were female. Percentages in the categories of pill quantity of the index BZRA fill were 10% with 1-9 pills, 18% with 10-14 pills, 24% with 15-27 pills, 26% with 28-30 pills, 15% with 31-60 pills, and 7% with >60 pills. The crude cumulative incidence estimates of first BZRA-related ED visit were 0.8% (95% CI: 0.9%, 1.6%) at 30 days, 2.8% (95% CI: 3.2%, 4.9%) at 90 days, and 4.9% (95% CI: 5.8% ,8.2%) at 365 days. The rate of first BZRA-related ED visits was 10.7 per 100,000 person-days. The adjusted common HR of first BZRA-related ED visits across categories of

pill quantities were 1.21 (95% CI: 1.07,1.36) for 1-9 pills, 0.99 (95% CI: 0.85, 1.05) for 10-14 pills, 0.96 (95% CI: 0.87, 1.06) for 15-27 pills, 1.43 (95% CI: 1.29, 1.59) for 31-60 pills, and 1.92 (95% CI: 1.72, 2.15) for >60 pills, compared to 28-30 pills.

Conclusion

New BZRA prescription quantities of over 30 pills were associated with increased rates of first BZRA-related ED visits. Large prescription pill quantities of a new BZRA prescription may be a risk factor for BZRA-related harms serious enough to necessitate treatment in an ED. Enhanced clinical or health system guidelines could prioritize strategies to identify and limit new BZRA prescriptions with pill quantities that place patients at higher risk of BZRA-related ED visits.

5.2 Introduction

Benzodiazepine receptor agonists (BZRA) prescriptions have been commonly prescribed in outpatient settings as anxiolytics or sedative/hypnotics for over 60 years.[1–3] BZRA include benzodiazepines, such as diazepam (Valium), alprazolam (Xanax), lorazepam (Ativan), and non-benzodiazepine Z-drugs like zolpidem (Ambien). BZRA use is prevalent in United States (U.S.), with 9% of adults reporting past year use of benzodiazepines and 3% of Z-drugs in 2024.[4] The frequency of BZRA prescriptions from clinical practice has elicited renewed public health concern given the adverse health conditions associated with BZRA use.[3,5,6] The U.S. Food and Drug Administration (FDA) has issued multiple black box warning labels concerning the potential harms associated with benzodiazepine or Z-drug use and the risk of overdose (OD) or death from their combined use with an opioid prescription.[7–9] BZRA-related harms include several other serious health conditions besides OD, including dependence,[10] protracted or acute withdrawal symptoms,[11,12] seizures,[13] severe sleep disturbances,[8] suicide,[14,15] physical injuries,[16] automobile accidents,[17] and death.[18–20]

Patients who experience a BZRA-related harm may require immediate care in an emergency department (ED) setting.[21,22] Over 20% of ED visits for BZRA-related harms concluded with a hospital admission, patient transfer, or death.[23] ED visits for OD from benzodiazepine use, with and without concurrent opioid use, increased by 24% from 2019 to 2020.[24] The rates of OD deaths from benzodiazepine use in the U.S. have increased 6-fold from 2000 to 2019, from 0.46 to 2.96 per 100,000 individuals.[18] Recent increases in rates of BZRA-related harms observed in national surveillance of ED visits and OD are a critical public health concern. To address this concern, clinical practice groups have suggested interventions in patient populations who are beginning new BZRA prescription use.[25–29] From a population-based public health framework, new BZRA use is considered the appropriate starting point for the prevention of subsequent BZRA-related adverse outcomes.[25–29]

Guidelines from one large U.S. health systems suggest limiting some BZRA prescription quantities to minimize subsequent harms, particularly for patients with new BZRA prescriptions.[30] However, these guidelines provide fragmented suggestions which include restricting new benzodiazepine prescriptions to ≤15 pills, no pill limits for Z-drugs, and ≤30-day supply for all BZRA prescriptions.[30] The possibility that benzodiazepine pill quantity or medication supply could be associated with OD occurrence has been explored in one study among Medicare beneficiaries.[31] This study demonstrated that prescriptions with supply of 14 days or less were associated with higher OD rates compared to those with supply of 15-30 days.[31] Thus, characteristics of the new (or index) benzodiazepine prescription could be a factor in subsequent risk of harm. Whether specific pill quantities at new BZRA use are related to increased risk of subsequent BZRA-related harm remains unclear.

The objective of this study was to determine the association between categories of pill quantities of the index BZRA fill and the subsequent rates of BZRA-related harms manifesting in ED visits. We utilized a composite outcome comprised of health conditions previously identified as BZRA-related harms.[21] We hypothesized that there would be a positive association between the quantity of pills prescribed at the index BZRA fill and the rate of ED visits, with the strongest associations occurring among beneficiaries prescribed more than 30 pills. We tested this hypothesis using claims data from adult Oregon Medicaid beneficiaries.

5.3 Methods

Study design, data source, and cohort selection

We performed a retrospective cohort study using deidentified Oregon Medicaid administrative and pharmacy claims data from the calendar years 2015 through 2019. The paid pharmacy claims indicate that a prescription was filled (dispensed) at the pharmacy, paid by Medicaid, and received by the beneficiary. We used pharmacy claims to identify and describe BZRA fills and concurrent

medications, medical claims for diagnoses, and beneficiary eligibility for Medicaid enrollment and demographics. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (*STROBE*) guidelines for cohort study designs.[32] The Oregon Health & Science University Institutional Review Board determined this was exempt non-human subjects research.

In multiple steps, we assembled a cohort of beneficiaries with new BZRA use occurring from January 1st, 2016, to December 31st, 2018. Table A.1. contains the National Drug Codes used to select all BZRA fills in pills or tablets form (hereafter referred to as pills) dispensed. In accord with methods used previously to establish new BZRA use,[33,34] we identified the index BZRA fill as the first BZRA prescription preceded by 12 months with no BZRA fills for each beneficiary. Prescription claims in 2015 were used to identify the index BZRA fill in 2016 and so on. Cohort entry (baseline) was the date of the index fill. We excluded fills of liquid, gel, and injectable forms of BZRA given the difficulty of converting the prescription strength to diazepam milligram equivalents (DME).[35] Second, we restricted to beneficiaries ages 18-63 years on the date of the index fill. The upper age limit allowed for 12 months of follow-up (*see below*) before beneficiaries became eligible for Medicare coverage at age 65 years. Third, we further restricted the cohort to beneficiaries who had at least 6 months of enrollment within the 12 months prior to new BZRA use. Next, we excluded beneficiaries with dual Medicaid-Medicare enrollment and with no Medicaid enrollment upon cohort entry. Fourth, we excluded beneficiaries who had diagnosis codes for multiple sclerosis, epilepsy or hospice within the 12 months before the date of the index fill, because BZRA prescription use may be differ for these conditions.35–38 Specific codes for exclusion criteria are listed in Table A.2. Finally, we excluded beneficiaries with an ED visit on the same date as their index BZRA fill. Billing codes for ED visits are contained in Table 4.S.1. Beneficiaries were selected into the cohort only once.

Exposure

The primary exposure was the pill quantity of the index BZRA fill. Pill quantities ranged from 1 to >120 pills with quantities of 30 (24%), 10 (12%), 15 (11%), 20 (10%), or 60 (9%) being the most frequent. We created categories of pill quantities based on several factors. We considered the frequency and distribution of distinct pill quantities observed. We also determined categories based on a reference for chronic benzodiazepine day-supply amounts of 0-14, 15-30, and >30 days.[31] We then classified this exposure into categories of “1-9“, “10-14”, “15-27”, “28-30”, “31-60” and “>60” pills. The category of “28-30” pills was chosen as the referent, with the assumption that one pill per day is to be taken.[40] The referent category was consistent with the two other cohort studies of benzodiazepine use and OD.[31,41]

We quantified a secondary exposure variable according to the prescription strength of the index BZRA fill through use of the standard diazepam milligram equivalents (DME) algorithm.[35] We calculated this variable for index BZRA fill by multiplying the initial prescription unit strength (e.g. 1 mg) by its DME conversion (Table A.5), resulting in an equivalent strength independent of pills dispensed. We categorized BZRA equivalent unit strengths into categories of ≥20 DME, ≥10 to <20 DME, >2.5 to <10 DME, and ≤2.5 DME based on the World Health Organization’s defined daily dose of 10 DME for BZRA prescriptions of diazepam indicated for anxiety treatment.[42]

Independent variables

Multiple characteristics were selected based on their potential to confound the association between pill quantities and the rate of first BZRA-related ED visits. Independent variables determined at cohort entry included demographic factors, clinical encounters or diagnoses, and concurrent prescriptions. We ascertained the demographic factors of beneficiary age and sex. Sex is self-reported by the beneficiary. Age was categorized as 18-24, 25-34, 35-44, 45-54, 55-63 years. Clinical encounters included assessment of prior ED use. Prior ED use included any ED visits identified by billing codes, regardless of diagnosis, in the 12 months before to cohort entry (Table 4.S.1). Clinical diagnoses

were identified with medical claims indicating anxiety/panic disorders, insomnia, or substance use disorders (SUD) in the 12 months before date of cohort entry. Each of these three conditions was represented as a binary variable based on separate groups of ICD diagnostic codes (Table A.3). Concurrent prescriptions were identified from prescriptions claims using drug identification codes for antidepressants, opioid, gabapentin/pregabalin, or trazodone in the 3 months prior to cohort entry (Table A.4). Trazodone was not categorized as an antidepressant as it is commonly used off-label as a sedative agent to treat insomnia.[43] Prescriptions for these medications are represented with four separate binary variables.

We classified the index BZRA prescription fill in two ways. First, we categorized BZRA with functional half-lives of >24 hours as “long-acting” and of ≤24 hours as “short-to-intermediate acting” as shown in Table A.5.[10,44,45] We chose these categories because the onset for the effects of BZRA prescriptions are dependent on their half-life.[3,10,44,45] Next, we categorized the primary indication of the BZRA into two groups as “sedative/hypnotic” or “anxiolytic” (Table A.5). Primary indication reflects the intended therapeutic effect of the BZRA prescription based on their principal FDA-labeled indication.[46]

Outcome and follow-up period

The primary outcome was a first ED visit with any diagnosis for a BZRA-related harm. We assessed BZRA-related harms using a composite of adverse outcomes potentially associated with BZRA use or withdrawal.[21] Using medical claims for encounters, the first ED visit was identified through specific billing codes for ED services (Table 5.S.1). ED visits were then selected as encounters that included one or more diagnosis codes for BZRA-related harms. (Table 5.S.1). We selected the composite group of BZRA-related diagnoses from published findings on adverse events or conditions associated with BZRA use. BZRA-related diagnoses included codes for BZRA substance use disorders,[10] seizures or convulsions,[13] poisonings or overdose,[18,19] injurious falls,[16] complex sleep disorders,[8]

suicide,[14] motor vehicle accidents,[17] and altered mental status.[47] The first BZRA-related ED visit was determined by selecting the earliest encounter date.

Cohort members were followed from cohort entry until occurrence of a first BZRA-related ED-visit, loss of Medicaid enrollment, age 65 years when of the participant would be eligibility for Medicare coverage, or the end of the study period on December 31st, 2019, whichever occurred first.

Statistical analyses

Analyses were conducted using Stata software version 19 (Stata Corp LLC, College Station TX, USA). For the initial descriptive analyses, the distributions of categorical variables were examined as counts and percentages in the cohort overall and by the categories for pill quantities. Each pair of categorical variables was examined in contingency tables, which confirmed that none were so highly correlated that they should not be fit together into a statistical model.

The rate of first BZRA-related ED visits was computed as the total count of first ED visits divided by the total person-days at risk then scaled to 100,000 person-days. To estimate the crude cumulative incidence of first BZRA-related ED-visits across categories of pill quantities, we first calculated the Product-Limit survivorship function, denoted as $S(t)$, using a Kaplan-Meier estimator.[48,49] The crude cumulative incidences were then calculated as the failure, denoted as $F(t)$, at time (t), through the equation: $F(t) = 1 - S(t)$.[48] Follow up times of 30, 60, 90, 180, and 365-days were chosen. The 95% confidence intervals (CI) for the crude cumulative incidences were obtained using the Greenwood method.[48]

Stratified Cox proportional hazards (CPH) regression models were used to estimate the hazard ratios (HR) and 95% CI as the measure of association between prescription pill quantities and rates of first BZRA-related ED visits.[50] We first calculated the crude HR and then modeled the HR adjusted for age and sex. To assess characteristics as potential confounders, we utilized purposeful manual selection

and applied a change-in-estimate approach.[51,52] The minimum change required for retention, was defined by a 10% change in the adjusted HR in any category of pill quantity.[53] We added each variable, one by one to the model containing age and sex. We retained the variable that produced the greatest amount of change in the HR that exceeded 10%. We then repeated the process for the remaining variables. Following this approach, the only variable retained was prior ED visits. Variables assessed as potential confounders but not retained included clinical diagnoses, concurrent prescriptions, and characteristics of the new BZRA prescription.

We next assessed all CPH regression models for potential violations of the proportional-hazards assumption through examination of plots of Schoenfeld residuals for each characteristic included in the model.[54] The inclusion of prior ED visits in the model was assessed to violate the proportional-hazards assumption. To further explore the possibility of interaction between prior ED visits and BZRA pill quantities on the rates of first BZRA-related ED visit, we ran separate CPH models by strata of prior ED visits. We observed that estimates of HR did not differ substantially between models and determined that use of a common HR to be appropriate. Therefore, we created a final stratified CPH model, allowing for each stratum of prior ED visits to have its own baseline hazard function while estimating common HR for prescription pill categories. This approach assumes that estimates of HR did not differ substantially by strata.[54]

In a separate analysis, we fit categories of BZRA prescription strength in place of prescription pill quantities into the stratified CPH regression model. We conducted this separate analysis because categories of higher prescription strength were highly concordant with large pill quantities. The category of <2.5 DME, the lowest prescription strength, was selected as the referent.

5.4 Results

During the period 2016-2018, 55,292 adult Medicaid beneficiaries met criteria for new BZRA use (Figure 5.1). Among the cohort, percentages of beneficiaries in the pill quantity categories were 7%

with >60 pills, 15% with 31-60 pills, 26% with 28-30 pills, 24% with 15-27 pills, 18% with 10-14 pills, and 10% with 1-9 pills (Table 5.1). The median age was 40 years and 67% were female. The proportion of the cohort with prior ED visits varied, 43% had 0 visits, 23% had 1-2 visits, and 34% had ≥3 visits. Most of the index BZRA fills were of a short-to-intermediate acting onset (81%) or of a anxiolytic primary indication (85%). Anxiety/panic disorders (69%) and SUD (46%) were the most prevalent clinical conditions. The most common concurrent prescriptions in the cohort were for an antidepressant (49%) or an opioid (36%). Distributions of characteristics varied somewhat across categories of prescription pill quantities. For example, a higher proportion of beneficiaries receiving >60 pills (21%) were ages 55-63 years compared to 1-9 pills (14%). The reverse was observed for those ages 25-34 years with comprising 29% for 1-9 pills and 24% for >60 pills.

The crude cumulative incidence of first BZRA-related ED visits was 0.8% (95% CI: 0.9%, 1.6%) at 30 days, 2.8% (95% CI: 3.2%, 4.9%) at 90-days, and 4.9% (95% CI: 5.8%, 8.2%) at 365-days (Table 5.2). The steepest increases in crude cumulative incidence over 365 days was observed in the category of >60 pills (Figure 5.2).

During 35,733,547 person-days of follow-up, there were 3,828 first BZRA-related ED-visits. The rate of first BZRA-related ED visits was 10.7 per 100,000 person-days. The unadjusted rates of first BZRA-related ED visits followed a U-shaped pattern across the categories of prescription pill quantities (Table 5.3). The U-shaped pattern was also observed in the HR before and after adjustment for age and sex as well as in the common HR from the stratified CPH model. The common HR across categories of pill quantities were 1.92 (95% CI: 1.72, 2.15) for >60 pills, 1.43 (95% CI: 1.29, 1.59) for 31-60 pills, 0.96 (95% CI: 0.87, 1.06) for 15-27 pills, 0.99 (95% CI: 0.85, 1.05) for 10-14 pills, and 1.21 (95% CI: 1.07,1.36) for 1-9 pills, compared to 28-30 pills.

In a separate analysis, we examined categories of BZRA prescription strength of the new BZRA prescription fill (Table 5.S.4). We treated categories of prescription strength as a separate exposure

from pill quantities, because counts of higher prescription dose strength were mostly concentrated among cohort members with prescription pill counts of >30 pills (*data not shown*). Most index BZRA fills were for prescription strengths of <10 to 2.5 DME (51%) and <2.5 DME (29%). Risk of first BZRA-related ED visits rose successively with prescription strength, such that the adjusted common HR were 1.15 (95% CI: 1.06,1.25) for <10 to 2.5 DME, 1.74 (95% CI: 1.58,1.91) for <20 to 10 DME, and 2.75 (95% CI: 2.36,3.20) for ≥20 DME, compared to prescription strengths of <2.5 DME.

We also examined proportions of the different diagnoses for BZRA-related ED-visits by exposure categories and found comparable proportions within each category. (Table 5.S.2). To assess the potential of informative censoring, we also report the counts of first BZRA-related ED visits and censoring outcomes by prescription pill quantities (Table 5.S.3). A large proportion of the cohort (40%) were censored due to a loss of Medicaid enrollment. The proportion with a loss of Medicaid enrollment was not uniform across prescription pill quantities.

5.5 Discussion

In this cohort study of 55,292 adult Oregon Medicaid beneficiaries with new BZRA use, the rate of first BZRA-related ED visits was 10.7 per 100,000 person-days. Across categories of pill quantities of the index BZRA fill, we observed a U-shaped pattern for associations of first BZRA-related ED visits. The rate of first BZRA-related visits among those prescribed >60 pills was twice the rate among those prescribed 28-30 pills. Our hypothesis was supported in part, as the crude cumulative incidence and the adjusted rates of first BZRA-related ED visits were highest among beneficiaries with prescription pill quantities of >60 pills. The categories of 31-60 and 1-9 pills were also weakly associated with increased adjusted rates of first BZRA-related ED visits, compared to the referent category of 28-30 pills. In a separate analysis, without the inclusion of pill quantity, progressively greater prescription strength of the index BZRA fill was associated with increasing rates of first BZRA-related ED visits. The findings indicate that characteristics of index BZRA fills, specifically high pill quantities of >60 or

prescription strength ≥20 DME, may be related to the risk of subsequent BZRA-related health conditions manifesting in ED visits.

There is a paucity of findings for composite measures of BZRA-related harms manifesting in ED visits following new long-term BZRA use. Prior studies have primarily examined OD following new or continuing benzodiazepine use.[31,41,55] Our finding of crude cumulative incidence of 2.8% at 180 days was comparable to the crude 6-month cumulative incidence of 2.1% of OD determined among Medicaid beneficiaries ages 18-29 years with new benzodiazepine use.[55] However, first ED visits with a diagnosis of OD accounted for only 23% of all cases observed over follow-up in our study. Potential differences for the occurrence of other non-OD BZRA-related harms are difficult to compare, as our cohort was comprised of multiple age groups with potentially distinct susceptibilities to different harms. Maust et al., determined in a cohort study of Medicare beneficiaries ages 65 and older with new benzodiazepine use, an index fill with less than 14-day supply was associated with 20% higher OD rate compared to a supply of 15-30 days.[31] These findings align with the weak positive associations we observed for increased first BZRA-related ED visits with the smallest prescription pill quantities of 1-9 pills compared to the referent of 28-30 pills. Additionally, for Medicare beneficiaries, a day supply of over 30 days was also strongly associated with 44% lower OD rate which contrasts with our findings of a 2-fold greater rate of BZRA-related ED visits among those with quantities of >60 pills. Possible differences could arise from the comparison of amounts of day supply versus prescription pill quantities. The proportion Medicare beneficiaries with >30 day-supply (8.7%) did differ from our larger categories of prescription pill quantities of >60 (7.8%) and 31-60 (14.6%). Additionally, the adjusted associations observed by Maust et al., controlled for higher prescription dose strength.[31] For cohort studies across different populations, higher dose-strengths of benzodiazepines were associated with increased rates of OD.[31,41] In our study, higher prescription dose strengths were mostly concordant with greater prescription pill quantities. Further examination of the frequency and concordance of the BZRA prescription characteristics of day-supply, prescription

pill quantity, and prescription dose strength would be helpful in determining which is most meaningful as a risk factor.

Our findings hold potentially important implications for enhanced clinical guidelines to support BZRA prescribing practices. Existing practice guidelines, expert clinical opinion, and FDA warnings focus on limiting the durations of BZRA use to under 4 weeks.[56] Updated clinical guidelines could suggest avoiding new BZRA prescription fills for higher pill quantities, when appropriate. Expanded clinician education could emphasize alternative therapeutic or treatment options in place of the smallest quantities of pills for BZRA prescriptions, which were still associated the increased risk of a first ED visits. These options could include other anxiolytic or sedative/hypnotic treatments, as opposed to higher BZRA pill quantities.[30]

Limitations

The findings from this study should be considered in the context of several possible limitations. A potential threat to validity was selection bias resulting from differential losses to follow-up. In our study, 40% of the cohort was censored due to a loss of Medicaid enrollment. A loss of enrollment may have precluded our ability to observe a first BZRA visit as follow-up time elapsed. We observed that the proportions of cohort members with a loss of enrollment were lower for the two largest categories of prescription pill quantities. With more frequent loss of enrollment among beneficiaries with lower pill quantities, including the referent category, the observed rates for these categories may have been spuriously lower. The result of a lowered rate for the referent category would have been overestimation of the HR in the categories of larger pill quantities. However, the actual differences in proportions with a loss of enrollment across categories of pill quantities were not large (≤10%). We observed strong to moderate positive associations of first BZRA-related ED visits for the two largest pill quantities, in comparison to the referent category. Therefore, we do not believe these differences in a loss of enrollment could completely account for the associations observed. Further limitations

include the potential for unmeasured confounding. Potential confounders were limited to variables which could be ascertained from the Medicaid claims data. Specifically, if clinicians were aware of heightened risks for BZRA-related adverse events among cohort members and accordingly prescribed lower pill quantities, then this circumstance could account for the positive association of 1-9 pills with increased rates of first BZRA-related ED visits. However, our findings for increased rates with the lowest quantities are concordant with another cohort study of Medicare beneficiaries.[31] A further limitation is that our definition of first BZRA-related ED visits could have omitted BZRA-related health conditions, specifically those unlikely to present in an emergency care setting. Our outcomes did not include care received psychiatric inpatient or non-ED ambulatory settings for BZRA-related health conditions. However, it is also likely that such BZRA-related health conditions could be of lesser severity given their treatment outside an emergency setting. Therefore, we believe our outcome to accurately represent rates of first BZRA-related harms with such severity as to require care in an ED.

Our study was comprised of Oregon Medicaid beneficiaries, a population with distinct demographic, clinical, or other characteristics. However, the therapeutic effects of new BZRA use and the risks of BZRA-related adverse health conditions are presumed to be similar within other populations of U.S. adults. Therefore, we believe our findings to be generalizable to other U.S. populations of adults 18-63 years with new BZRA use. Whether our findings pertain to U.S. adult populations of 65 years or older is less certain. Possible differences for both the therapeutic effects of BZRA use and specific BZRA-related adverse outcomes have been observed for older adults, compared to among adults younger than 65 years.[21]

Conclusion

New BZRA prescription pill quantities of over 60 pills may be an important risk factor for substantially greater rates of BZRA-related harms manifesting as ED visits. These findings suggest that enhanced

clinical guidelines for different prescription quantities of new BZRA fills could help to support improved BZRA prescribing practices. Clinical guidelines specifically could caution against fill quantities of over 60 pills for new BZRA use. Targeted education for BZRA prescribers could suggest alterative non-BZRA therapeutic treatments rather than new BZRA use with prescription quantities of less than 10 pills. Enhanced health system guidelines could prioritize strategies to identify and limit new BZRA prescriptions with pill quantities that place patients at higher risk of BZRA-related ED visits.

5.6 Figures, Tables

Figure 5.1. Enrollment into Study Cohort for Oregon Medicaid Beneficiaries with a New BZRA Use: 2016-2018

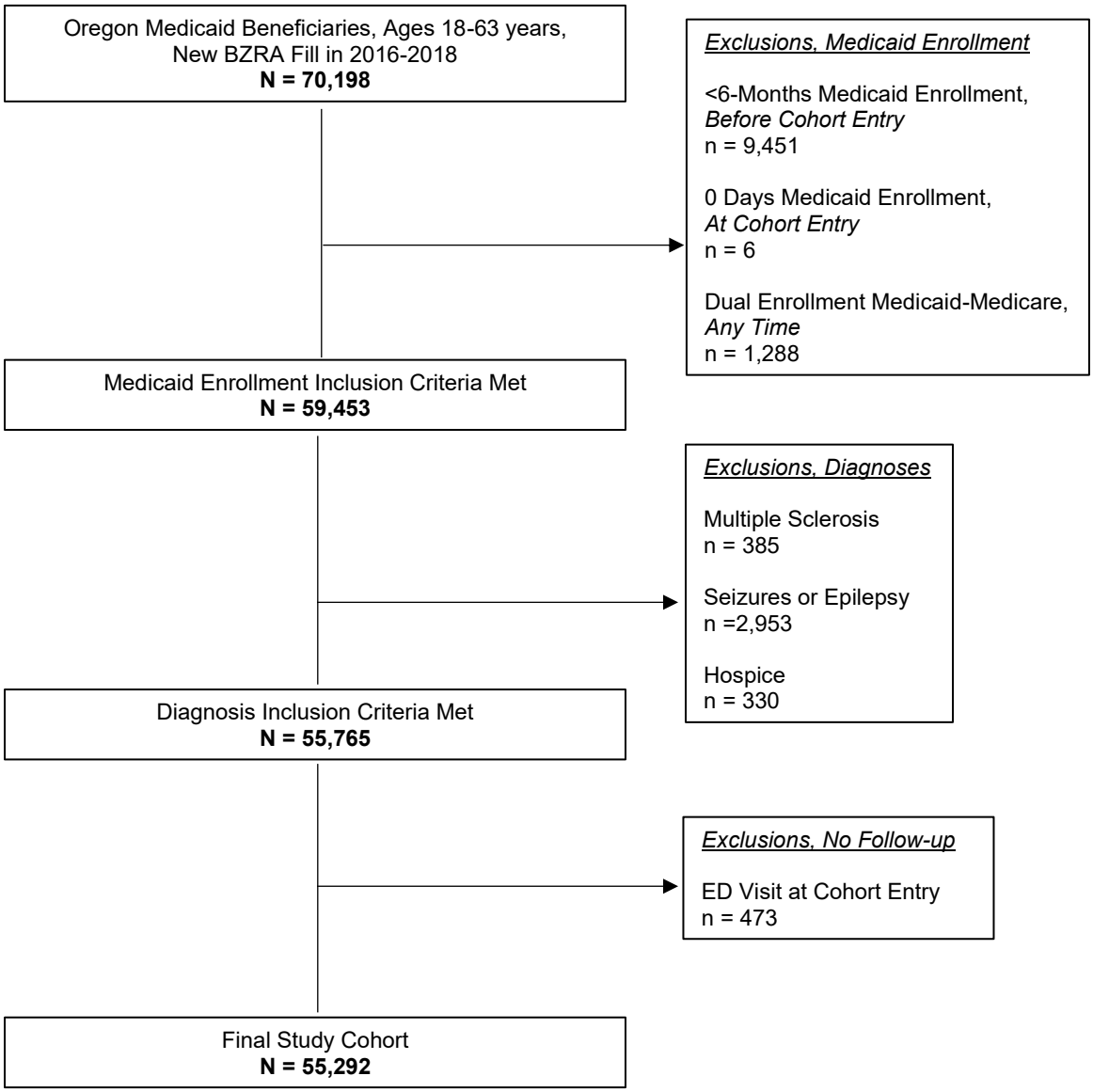

Table 5.1. Distributions of Characteristics of Adult Oregon Medicaid Beneficiaries by New BZRA Prescription Pill Quantity: 2016-2018

		Study Cohort	Prescription Pill Quantity					
			>60	31-60	28-30	15-27	10-14	1-9
Characteristics (n, %) †		55,292	4,327 (7.8)	8,096 (14.6)	14,201 (25.7)	13,362 (24.2)	9,933 (18.0)	5,373 (9.7)
Demographic Factors								
Age (years)	18-24	5,141 (9.3)	307 (7.1)	575 (7.1)	1,159 (8.2)	1,332 (10.0)	1,198 (12.1)	570 (10.6)
	25-34	14,753 (26.7)	988 (22.8)	1,936 (23.9)	3,441 (24.2)	3,791 (28.4)	3,019 (30.4)	1,578 (29.4)
	35-44	13,218 (23.9)	1,043 (24.1)	1,952 (24.1)	3,268 (23.0)	3,230 (24.2)	2,397 (24.1)	1,328 (24.7)
	45-54	12,355 (22.3)	1,088 (25.1)	1,987 (24.5)	3,326 (23.4)	2,839 (21.2)	1,963 (19.8)	1,152 (21.4)
	55-63	9,825 (17.8)	901 (20.8)	1,646 (20.3)	3,007 (21.2)	2,170 (16.2)	1,356 (13.7)	745 (13.9)
Sex	Male	18,057 (32.7)	1,653 (38.2)	2,772 (34.2)	4,466 (31.4)	4,343 (32.5)	3,076 (31.0)	1,747 (32.5)
	Female	37,235 (67.3)	2,674 (61.8)	5,324 (65.8)	9,735 (68.6)	9,019 (67.5)	6,857 (69.0)	3,626 (67.5)
Emergency Department Use								
Visits Prior to Cohort Entry	0	23,800 (43.1)	1,937 (44.8)	3,757 (46.4)	7,079 (49.9)	5,410 (40.5)	3,684 (37.1)	1,933 (36.0)
	1 - 2	12,710 (23.0)	930 (21.5)	1,817 (22.4)	3,187 (22.4)	3,157 (23.6)	2,434 (24.5)	2,434 (24.5)
	≥ 3	18,782 (33.0)	1,460 (33.7)	2,522 (31.2)	3,935 (27.7)	4,795 (35.9)	3,815 (38.4)	3,815 (38.4)
Index BZRA Fill								
Onset of Effect	Long	10,520 (19.0)	913 (21.1)	1,278 (15.8)	1,737 (12.2)	2,997 (22.4)	2,339 (23.5)	1,256 (23.4)
	Short to Interm.	44,772 (81.0)	3,414 (78.9)	6,818 (84.2)	12,464 (87.8)	10,365 (77.6)	7,594 (76.5)	4,117 (76.6)
Primary Indication	Sedative/Hyp.	8,206 (14.8)	824 (19.0)	650 (8.0)	2,228 (15.7)	2,412 (18.1)	983 (9.9)	1,109 (20.6)
	Anxiolytic	47,086 (85.2)	3,503 (81.0)	7,446 (92.0)	11,973 (84.3)	10,950 (81.9)	8,950 (90.1)	4,264 (79.4)
Clinical Conditions								
Diagnoses	Anxiety/Panic	38,025 (68.8)	3,147 (72.7)	5,970 (73.7)	9,570 (67.4)	8,900 (66.6)	6,894 (69.4)	3,544 (66.0)
	Insomnia	16,098 (29.1)	1,193 (27.6)	2,275 (28.1)	4,518 (31.8)	3,864 (28.9)	2,567 (25.8)	1,681 (31.3)
	SUD	25,339 (45.8)	2,364 (54.6)	3,921 (48.4)	5,720 (40.3)	6,116 (45.8)	4,498 (45.3)	2,720 (50.6)
Concurrent Prescriptions	Opioid	19,874 (35.9)	1,556 (36.0)	3,006 (37.1)	5,031 (35.4)	4,804 (36.0)	3,417 (34.4)	2,060 (38.3)
	Antidepressant*	26,871 (48.6)	2,341 (54.1)	4,422 (54.6)	7,249 (51.0)	6,099 (45.6)	4,490 (45.2)	2,270 (42.2)
	Trazodone	5,844 (10.6)	758 (17.5)	979 (12.1)	1,389 (9.8)	1,273 (9.5)	923 (9.3)	522 (9.7)
	Gaba/Preg.	7,907 (14.3)	847 (19.6)	1,399 (17.3)	1,974 (13.9)	1,630 (12.2)	1,230 (12.4)	827 (15.4)

†*Abbreviations*: Short to Intermediate, Sedative/Hypnotic, Substance Use Disorder, Gabapentin/Pregabalin
*Antidepressants do not include trazadone

Table 5.2. Cumulative incidence of first BZRA-related ED visit at 30, 60, 90, 180, and 365 days of follow-up by prescription pill quantities among Medicaid beneficiaries: 2016-2018

	Study	Prescription Pill Quantity					
	Cohort	>60	31-60	28-30	28-30	10-14	1-9
Day	Cumulative Incidence (%) (95% CI) of First BZRA-Related ED Visit						
30	0.8 (0.9,1.6)	1.6 (1.3,2.0)	0.9 (0.7,1.1)	0.5 (0.4,0.6)	0.9 (0.7,1.0)	0.8 (0.7,1.0)	1.0 (0.8,1.3)
60	1.3 (1.5,2.4)	2.4 (2.0,2.9)	1.5 (1.2,1.8)	0.7 (0.6,0.9)	1.3 (1.1,1.5)	1.2 (1.0,1.5)	1.5 (1.2,1.9)
90	1.7 (2.0,3.2)	3.2 (2.7,3.8)	2 (1.7,2.4)	1.1 (0.9,1.2)	1.6 (1.4,1.8)	1.5 (1.3,1.8)	2.1 (1.8,2.6)
180	2.8 (3.2,4.9)	4.9 (4.3,5.6)	3.2 (2.8,3.6)	2 (1.8,2.3)	2.6 (2.3,2.9)	2.4 (2.1,2.7)	3.4 (2.9,3.9)
365	4.9 (5.8,8.2)	8.2 (7.4,9.1)	5.8 (5.3,6.4)	3.8 (3.5,4.1)	4.1 (3.8,4.5)	4.2 (3.8,4.6)	5.9 (5.2,6.6)

Figure 5.2. Cumulative incidence of first BZRA-related ED visit during 365-days of follow-up by prescription pill quantities among Medicaid beneficiaries: 2016-2018

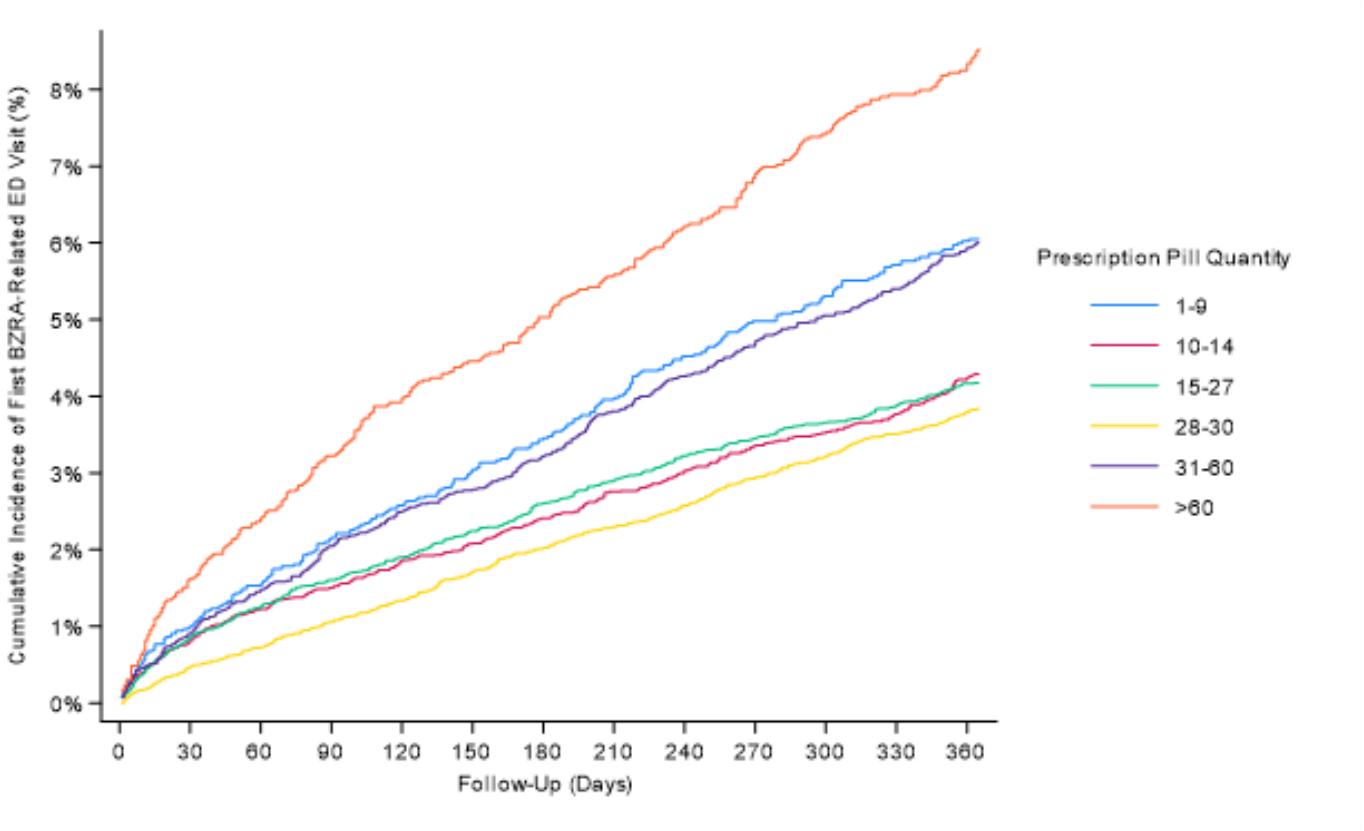

Table 5.3. Associations of prescription pill quantities with rates of first BZRA-related ED visits among Medicaid beneficiaries: 2016-2018

	Prescription Pill Quantity					
	>60	31-60	28-30	15-27	10-14	1-9
No. Cases (First BZRA-related ED visit)	512	688	791	802	604	431
No. Person Days	3,008,422	5,437,096	9,184,025	8,464,315	6,206,398	3,433,297
First ED Visit Rate / 100,000 Person Days	17.0	12.7	8.6	9.5	9.7	12.6
Model	Hazard Ratio (HR) (95% CI)					
Unadjusted Estimates	2.08 (1.86,2.33)	1.51 (1.36,1.67)	Ref.	1.10 (1.00,1.22)	1.13 (1.01,1.25)	1.48 (1.32,1.66)
Adjusted for Age, Sex	2.05 (1.84,2.30)	1.50 (1.35,1.66)	Ref.	1.09 (0.98,1.20)	1.10 (0.99,1.23)	1.45 (1.29,1.63)
Stratified by Prior Emergency Department Use	1.92 (1.72,2.15)	1.43 (1.29,1.59)	Ref.	0.96 (0.87,1.06)	0.99 (0.85,1.05)	1.21 (1.07,1.36)

Supplemental (S) Figures, Tables

See **Appendix 2** for Tables A.1. - A.5.

Table 5.S.1. Billing and diagnosis codes utilized to identify first BZRA-related ED visits

Current Procedural Terminology (CPT) Code for Any ED Visit	
ED Visit	99281, 99282, 99283, 99284, 99285
ICD10 Diagnoses Codes for BZRA-related harms	
BZRA Substance Use Disorder	
F13	Sedative, hypnotic, or anxiolytic related disorders
F19	Other psychoactive substance related disorders (includes polysubstance)
Seizures	
G40.X	Epilepsy and seizures
R56.9	Convulsions of unspecified causes
F44.5	Conversion disorder with seizures or convulsions
BZRA Poisoning	
T50.901A	Poisoning by unspecified drugs, medicaments and biological substances, accidental (unintentional), initial encounter
T50.911A	Poisoning by multiple drugs, medicaments and biological substances, accidental (unintentional), initial encounter
T42.4X1A	Poisoning by benzodiazepines, accidental (unintentional), initial encounter
T42.4X1D	Poisoning by benzodiazepines, accidental (unintentional), subsequent encounter
T42.4X1S	Poisoning by benzodiazepines, accidental (unintentional), sequela
T42.4X2A	Poisoning by benzodiazepines, intentional self-harm, initial encounter
T42.4X2D	Poisoning by benzodiazepines, intentional self-harm, subsequent encounter
T42.4X2S	Poisoning by benzodiazepines, intentional self-harm, sequela
T42.4X4A	Poisoning by benzodiazepines, undetermined, initial encounter
T42.4X4D	Poisoning by benzodiazepines, undetermined, subsequent encounter
T42.4X4S	Poisoning by benzodiazepines, undetermined, sequela
T42.4X5A	Adverse effect of benzodiazepines, initial encounter
T42.4X5D	Adverse effect of benzodiazepines, subsequent encounter
T42.4X5S	Adverse effect of benzodiazepines, sequela
T42.4X6A	Underdosing of benzodiazepines, initial encounter
T42.4X6D	Underdosing of benzodiazepines, subsequent encounter
T42.4X6S	Underdosing of benzodiazepines, sequela
T42.6X1A	Poisoning by other antiepileptic and sedative-hypnotic drugs, accidental (unintentional), initial encounter
T42.6X1D	Poisoning by other antiepileptic and sedative-hypnotic drugs, accidental (unintentional), subsequent encounter
T42.6X1S	Poisoning by other antiepileptic and sedative-hypnotic drugs, accidental (unintentional), sequela
T42.6X2A	Poisoning by other antiepileptic and sedative-hypnotic drugs, intentional self-harm initial encounter
T42.6X2D	Poisoning by other antiepileptic and sedative-hypnotic drugs, intentional self-harm subsequent encounter
T42.6X2S	Poisoning by other antiepileptic and sedative-hypnotic drugs, intentional self-harm sequela
T42.6X4A	Poisoning by other antiepileptic and sedative-hypnotic drugs, undetermined, initial encounter

(*Table 5.S.1.* continues next page)

BZRA Poisoning (continued)	
T42.6X4D	Poisoning by other antiepileptic and sedative-hypnotic drugs, undetermined, subsequent encounter
T42.6X4S	Poisoning by other antiepileptic and sedative-hypnotic drugs, undetermined, sequela
T42.6X5A	Adverse effect of other antiepileptic and sedative-hypnotic drugs, intentional self-harm initial encounter
T42.6X5D	Adverse effect of other antiepileptic and sedative-hypnotic drugs, intentional self-harm subsequent encounter
T42.6X5S	Adverse effect of other antiepileptic and sedative-hypnotic drugs, intentional self-harm sequela
T42.6X6A	Underdosing of other antiepileptic and sedative-hypnotic drugs, initial encounter
T42.6X6D	Underdosing of other antiepileptic and sedative-hypnotic drugs, subsequent encounter
T42.6X6S	Underdosing of other antiepileptic and sedative-hypnotic drugs, sequela
T42.7X1A	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, accidental (unintentional), initial encounter
T42.7X1D	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, accidental (unintentional), subsequent encounter
T42.7X1S	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, accidental (unintentional), sequela
T42.7X2A	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, intentional self-harm initial encounter
T42.7X2D	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, intentional self-harm subsequent encounter
T42.7X2S	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, intentional self-harm sequela
T42.7X4A	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, undetermined, initial encounter
T42.7X4D	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, undetermined, subsequent encounter
T42.7X4S	Poisoning by unspecified antiepileptic and sedative-hypnotic drugs, undetermined, sequela
T42.7X5A	Adverse effect of unspecified antiepileptic and sedative-hypnotic drugs, intentional self-harm initial encounter
T42.7X5D	Adverse effect of unspecified antiepileptic and sedative-hypnotic drugs, intentional self-harm subsequent encounter
T42.7X5S	Adverse effect of unspecified antiepileptic and sedative-hypnotic drugs, intentional self-harm sequela
T42.7X6A	Underdosing of unspecified antiepileptic and sedative-hypnotic drugs, initial encounter
T42.7X6D	Underdosing of unspecified antiepileptic and sedative-hypnotic drugs, subsequent encounter
T42.7X6S	Underdosing of unspecified antiepileptic and sedative-hypnotic drugs, sequela
Falls	
Z91.81	History of a fall
R29.6	Repeated falling
Complex Sleep Disorders	
F51	sleep disorders
G47.8	other sleep disorders
G47.9	sleep disorder, unspecified
G47.5	Parasomnia

(*Table 5.S.1.* continues next page)

Self-Harm	
X71	Intentional self-harm by drowning and submersion
X72	Intentional self-harm by handgun discharge
X73	Intentional self-harm by rifle, shotgun and larger firearm discharge
X74	Intentional self-harm by other and unspecified firearm and gun discharge
X75	Intentional self-harm by explosive material
X76	Intentional self-harm by smoke, fire and flames
X77	Intentional self-harm by steam, hot vapors and hot objects
X78	Intentional self-harm by sharp object
X79	Intentional self-harm by blunt object
X80	Intentional self-harm by jumping from a high place
X81	Intentional self-harm by jumping or lying in front of moving object
X82	Intentional self-harm by crashing of motor vehicle
X83	Intentional self-harm by other specified means
T14.91XA	Suicide attempt, initial encounter
T14.91XD	Suicide attempt, subsequent encounter
T14.91XS	Suicide attempt, sequela
R45.851	Suicidal ideations
Motor Vehicle Accident	
V89	Motor- or nonmotor-vehicle accident, type of vehicle unspecified
Altered Mental Status	
R41. 82	Altered Mental Status
Opioid Overdoses	
T40.0X1A	Poisoning by opium, accidental (unintentional), initial encounter
T40.0X1D	Poisoning by opium, accidental (unintentional), subsequent encounter
T40.0X1S	Poisoning by opium, accidental (unintentional), sequela
T40.0X2A	Poisoning by opium, intentional self-harm, initial encounter
T40.0X2D	Poisoning by opium, intentional self-harm, subsequent encounter
T40.0X2S	Poisoning by opium, intentional self-harm, sequela
T40.0X4A	Poisoning by opium, undetermined, initial encounter
T40.0X4D	Poisoning by opium, undetermined, subsequent encounter
T40.0X4S	Poisoning by opium, undetermined, sequela
T40.0X5A	Adverse effect of opium, initial encounter
T40.0X5D	Adverse effect of opium, subsequent encounter
T40.0X5S	Adverse effect of opium, sequela
T40.1X1A	Poisoning by heroin, accidental (unintentional), initial encounter
T40.1X1D	Poisoning by heroin, accidental (unintentional), subsequent encounter
T40.1X1S	Poisoning by heroin, accidental (unintentional), sequela
T40.1X2A	Poisoning by heroin, intentional self-harm, initial encounter
T40.1X2D	Poisoning by heroin, intentional self-harm, subsequent encounter
T40.1X2S	Poisoning by heroin, intentional self-harm, sequela
T40.1X4A	Poisoning by heroin, undetermined, initial encounter

(*Table 5.S.1.* continues next page)

Opioid Overdoses (continued)	
T40.1X4D	Poisoning by heroin, undetermined, subsequent encounter
T40.1X4S	Poisoning by heroin, undetermined, sequela
T40.1X5A	Adverse effect of heroin, initial encounter
T40.1X5D	Adverse effect of heroin, subsequent encounter
T40.1X5S	Adverse effect of heroin, sequela
T40.2X1A	Poisoning by other Opioid, accidental (unintentional), initial encounter
T40.2X1D	Poisoning by other Opioid, accidental (unintentional), subsequent encounter
T40.2X1S	Poisoning by other Opioid, accidental (unintentional), sequela
T40.2X2A	Poisoning by other Opioid, intentional self-harm, initial encounter
T40.2X2D	Poisoning by other Opioid, intentional self-harm, subsequent encounter
T40.2X2S	Poisoning by other Opioid, intentional self-harm, sequela
T40.2X4A	Poisoning by other Opioid, undetermined, initial encounter
T40.2X4D	Poisoning by other Opioid, undetermined, subsequent encounter
T40.2X4S	Poisoning by other Opioid, undetermined, sequela
T40.2X5A	Adverse effect of other Opioid, initial encounter
T40.2X5D	Adverse effect of other Opioid, subsequent encounter
T40.2X5S	Adverse effect of other Opioid, sequela
T40.3X1A	Poisoning by methadone, accidental (unintentional), initial encounter
T40.3X1D	Poisoning by methadone, accidental (unintentional), subsequent encounter
T40.3X1S	Poisoning by methadone, accidental (unintentional), sequela
T40.3X2A	Poisoning by methadone, intentional self-harm, initial encounter
T40.3X2D	Poisoning by methadone, intentional self-harm, subsequent encounter
T40.3X2S	Poisoning by methadone, intentional self-harm, sequela
T40.3X4A	Poisoning by methadone, undetermined, initial encounter
T40.3X4D	Poisoning by methadone, undetermined, subsequent encounter
T40.3X4S	Poisoning by methadone, undetermined, sequela
T40.3X5A	Adverse effect of methadone, initial encounter
T40.3X5D	Adverse effect of methadone, subsequent encounter
T40.3X5S	Adverse effect of methadone, sequela
T40.4X1A	Poisoning by fentanyl or fentanyl analogs, accidental (unintentional), initial encounter
T40.4X1D	Poisoning by fentanyl or fentanyl analogs, accidental (unintentional), subsequent encounter
T40.4X1S	Poisoning by fentanyl or fentanyl analogs, accidental (unintentional), sequela
T40.4X2A	Poisoning by fentanyl or fentanyl analogs, intentional self-harm, initial encounter
T40.4X2D	Poisoning by fentanyl or fentanyl analogs, intentional self-harm, subsequent encounter
T40.4X2S	Poisoning by fentanyl or fentanyl analogs, intentional self-harm, sequela
T40.4X4A	Poisoning by fentanyl or fentanyl analogs, undetermined, initial encounter
T40.4X4D	Poisoning by fentanyl or fentanyl analogs, undetermined, subsequent encounter

(*Table 5.S.1.* continues next page)

Opioid Overdoses (continued)	
T40.4X4S	Poisoning by fentanyl or fentanyl analogs, undetermined, sequela
T40.4X5A	Adverse effect of fentanyl or fentanyl analogs, initial encounter
T40.4X5D	Adverse effect of fentanyl or fentanyl analogs, subsequent encounter
T40.4X5S	Adverse effect of fentanyl or fentanyl analogs, sequela
Codes below were replaced in 2020, but are still relevant for study period 2016-2019	
T40.411A	Poisoning by fentanyl or fentanyl analogs, accidental (unintentional), initial encounter
T40.411D	Poisoning by fentanyl or fentanyl analogs, accidental (unintentional), subsequent encounter
T40.411S	Poisoning by fentanyl or fentanyl analogs, accidental (unintentional), sequela
T40.412A	Poisoning by fentanyl or fentanyl analogs, intentional self-harm, initial encounter
T40.412D	Poisoning by fentanyl or fentanyl analogs, intentional self-harm, subsequent encounter
T40.412S	Poisoning by fentanyl or fentanyl analogs, intentional self-harm, sequela
T40.414A	Poisoning by fentanyl or fentanyl analogs, undetermined, initial encounter
T40.414D	Poisoning by fentanyl or fentanyl analogs, undetermined, subsequent encounter
T40.414S	Poisoning by fentanyl or fentanyl analogs, undetermined, sequela
T40.415A	Adverse effect of fentanyl or fentanyl analogs, initial encounter
T40.415D	Adverse effect of fentanyl or fentanyl analogs, subsequent encounter
T40.415S	Adverse effect of fentanyl or fentanyl analogs, sequela
T40.421A	Poisoning by tramadol, accidental (unintentional), initial encounter
T40.421D	Poisoning by tramadol, accidental (unintentional), subsequent encounter
T40.421S	Poisoning by tramadol, accidental (unintentional), sequela
T40.422A	Poisoning by tramadol, intentional self-harm, initial encounter
T40.422D	Poisoning by tramadol, intentional self-harm, subsequent encounter
T40.422S	Poisoning by tramadol, intentional self-harm, sequela
T40.424A	Poisoning by tramadol, undetermined, initial encounter
T40.424D	Poisoning by tramadol, undetermined, subsequent encounter
T40.424S	Poisoning by tramadol, undetermined, sequela
T40.425A	Adverse effect of tramadol, initial encounter
T40.425D	Adverse effect of tramadol, subsequent encounter
T40.425S	Adverse effect of tramadol, sequela
T40.491A	Poisoning by other synthetic narcotics, accidental (unintentional), initial encounter
T40.491D	Poisoning by other synthetic narcotics, accidental (unintentional), subsequent encounter
T40.491S	Poisoning by other synthetic narcotics, accidental (unintentional), sequela
T40.492A	Poisoning by other synthetic narcotics, intentional self-harm, initial encounter
T40.492D	Poisoning by other synthetic narcotics, intentional self-harm, subsequent encounter
T40.492S	Poisoning by other synthetic narcotics, intentional self-harm, sequela
T40.494A	Poisoning by other synthetic narcotics, undetermined, initial encounter
T40.494D	Poisoning by other synthetic narcotics, undetermined, subsequent encounter
T40.494S	Poisoning by other synthetic narcotics, undetermined, sequela
T40.495A	Adverse effect of other synthetic narcotics, initial encounter
T40.495D	Adverse effect of other synthetic narcotics, subsequent encounter

(*Table 5.S.1.* continues next page)

Opioid Overdoses (continued)	
T40.495S	Adverse effect of other synthetic narcotics, sequela
T40.601A	Poisoning by unspecified narcotics, accidental (unintentional), initial encounter
T40.601D	Poisoning by unspecified narcotics, accidental (unintentional), subsequent encounter
T40.601S	Poisoning by unspecified narcotics, accidental (unintentional), sequela
T40.602A	Poisoning by unspecified narcotics, intentional self-harm, initial encounter
T40.602D	Poisoning by unspecified narcotics, intentional self-harm, subsequent encounter
T40.602S	Poisoning by unspecified narcotics, intentional self-harm, sequela
T40.604A	Poisoning by unspecified narcotics, undetermined, initial encounter
T40.604D	Poisoning by unspecified narcotics, undetermined, subsequent encounter
T40.604S	Poisoning by unspecified narcotics, undetermined, sequela
T40.605A	Adverse effect of unspecified narcotics, initial encounter
T40.605D	Adverse effect of unspecified narcotics, subsequent encounter
T40.605S	Adverse effect of unspecified narcotics, sequela

Table 5.S.2. Counts of diagnoses for first BZRA-related ED visits by prescription pill quantities among Medicaid beneficiaries: 2016-2018

	Study Cohort	Prescription Pill Quantity					
		>60	31-60	28-30	28-30	10-14	1-9
All First ED Visits n (%)	3,828	512	688	791	802	604	4,321
First ED Visits, by Diagnosis							
BZRA Poisoning	436 (11.4)	63 (12.3)	76 (11)	92 (13.4)	86 (12.5)	83 (12.1)	36 (5.2)
Opioid Poisoning	296 (7.7)	29 (5.7)	55 (10.7)	56 (10.9)	64 (12.5)	49 (9.6)	43 (8.4)
Seizures	769 (20.1)	115 (22.5)	146 (28.5)	169 (33)	151 (29.5)	112 (21.9)	76 (14.8)
Falls	432 (11.3)	49 (9.6)	81 (15.8)	88 (17.2)	102 (19.9)	68 (13.3)	44 (8.6)
Complex Sleep Disorders	326 (8.5)	40 (7.8)	53 (10.4)	70 (13.7)	74 (14.5)	54 (10.5)	35 (6.8)
Self-Harm	211 (5.5)	18 (3.5)	42 (8.2)	45 (8.8)	44 (8.6)	44 (8.6)	18 (3.5)
Motor Vehicle Accident	85 (2.2)	5 (1.0)	4 (0.8)	22 (4.3)	24 (4.7)	20 (3.9)	10 (2.0)
BZRA SUD	1,053 (27.5)	148 (28.9)	192 (37.5)	201 (39.3)	220 (43)	151 (29.5)	141 (27.5)
Multiple Diagnoses*	217 (5.7)	45 (8.8)	39 (7.6)	47 (9.2)	37 (7.2)	23 (4.5)	26 (5.1)

*Includes Altered Mental Status and all other BZRA-related diagnoses

Table 5.S.3. Study outcomes by new BZRA prescription pill quantities among Medicaid beneficiaries: 2016-2018

	Study	Prescription Pill Quantity					
	Cohort	>60	31-60	28-30	28-30	10-14	1-9
(n, column %)	55,597	4,327	8,096	14,201	13,362	9,933	5,373
First BZRA-Related ED visit	3,828 (6.9)	512 (11.8)	688 (8.5)	791 (5.6)	802 (6.0)	604 (6.1)	431 (8.0)
Censoring							
Loss of Medicaid Enrollment	22,438 (40.4)	1,431 (33.1)	2,964 (36.6)	5,863 (41.3)	5,804 (43.4)	4,228 (42.6)	2,148 (40)
Medicare Eligible	415 (0.7)	42 (1)	64 (0.8)	153 (1.1)	88 (0.7)	36 (0.4)	32 (0.6)
End of Study (12/31/2019)	28,611 (51.5)	2,342 (54.1)	4,380 (54.1)	7,394 (52.1)	6,668 (49.9)	5,065 (51)	2,762 (51.4)

Table 5.S.4. Associations of BZRA prescription dose strengths with rates of first BZRA-related ED visits among Medicaid beneficiaries: 2016-2018

	Prescription Dose Strength (DME‡)			
	≥20	≥10, <20	>2.5, <10	≤2.5
Study Cohort (n, % of total)	1,343 (2.4)	9,527 (17.2)	28,412 (51.4)	16,010 (29.0)
Model	Hazard Ratio (HR) (95% CI)			
Unadjusted Estimates	3.11 (2.55,3.46)	1.87 (1.67,2.01)	1.23 (1.11,1.31)	Ref.
Adjusted for Age, Sex	2.97 (2.55,3.46)	1.83 (1.67,2.01)	1.21 (1.11,1.31)	Ref.
Stratified by Prior ED Use	2.75 (2.36,3.20)	1.74 (1.58,1.91)	1.15 (1.06,1.25)	Ref.

‡Diazepam Milligram Equivalents

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CHAPTER 6. SYNTHESIS OF RESEARCH

Summary

In this dissertation, we presented a series of epidemiologic studies to estimate measures of occurrence for new long-term benzodiazepine receptor agonist (BZRA) use, incident discontinuation from a long-term BZRA prescription, and first BZRA-related adverse outcomes presenting in an emergency department (ED) visit. To support a public health framework for prevention, our objective was to determine frequencies of occurrence and to identify risk factors associated with outcomes pertaining to BZRA-related harms. For this research, we used prescription drug and medical claims for Oregon Medicaid adult beneficiaries with new BZRA use in 2016-2018. We were able to meet our objectives with estimates of new long-term BZRA use, incident discontinuation, and rates of first BZRA-related ED visits among this population. Furthermore, we identified specific demographic, clinical, and other characteristics associated with these specific outcomes.

Our research objectives were determined according to a framework that emphasized comprehensive population-based public health approaches to address adverse outcomes related to BZRA use. According to this framework, we estimated measures of occurrence in a period directly following new BZRA use. We aligned our findings with the stages of the natural history of BZRA-related adverse outcomes, progressing over time from the origin of new BZRA use (Figure 2.2). By determining different measures of occurrence at the beginning or early stages of this conceptual model, we presumed that the risk factors identified could serve as points for interventions to prevent subsequent BZRA-related harms. Overall, the public health framework overlaying our study designs was successful. Our findings included specific characteristics associated with greater or lesser frequencies of occurrence of new long-term BZRA use or incident discontinuation. These characteristics could be utilized to prioritize supportive interventions within a population-based public health framework. However, our assumption for potential limitations of the conceptual model of the

natural history of BZRA-related adverse outcomes were also correct. In Aim 3, we observed BZRA-related harms occurring at all timepoint points subsequent to the origin of new BZRA use, including before the onset of first long-term use. The crude cumulative incidences estimated for all pill quantities began at day 1 of follow-up and continued to increase throughout follow-up. These results suggest that an updated timeline for the natural history of BZRA-related adverse outcomes would show the stage of recovery, disability, or death directly proceeding the onset of new BZRA use.

For our research findings in Aim 1, we identified the outcome of first long-term BZRA use among beneficiaries with new BZRA use and determined demographic, clinical, and prescription characteristics independently associated with the risk of first long-term BZRA use. We found more than one in four beneficiaries with new BZRA use received a prescription that met criteria for new long-term use in the subsequent 12 months. For half of these beneficiaries, long-term use first began with the initial BZRA fill, and for about a third, it occurred upon their second fill. Demographic factors associated with new long-term BZRA use were older age and residence in frontier area. Concurrent prescriptions associated with new long-term use were an antidepressant, gabapentin/pregabalin, medication for opioid use disorder, or trazodone. Characteristics of the index BZRA fill associated with new long-term use were a high prescription strength, short-to-intermediate acting onset, or a anxiolytic primary indication. Factors independently associated with lower occurrence of first long-term BZRA use were race and ethnicity other than non-Hispanic White and cohort entry in 2017 or 2018.

In Aim 2, we measured incident 90-day discontinuation among new long-term BZRA recipients and identified the demographic, clinical, and prescription characteristics independently associated with its occurrence. In the 12-months following new long-term BZRA use, incident 90-day discontinuation occurred for 36% of the cohort. Factors associated with a decreased likelihood of incident discontinuation included progressively older age, an index BZRA fill of an anxiolytic primary indication or of a short-to-intermediate acting onset, or a concurrent prescription of an antidepressant or of an

opioid. Characteristics associated with an increased likelihood of incident discontinuation included residence in a rural or frontier zip code area or a SUD diagnosis.

In Aim 3, we determined the association between new BZRA prescription pill quantities and rates of first BZRA-related ED visits. Across categories of pill quantities of the index BZRA fill, we observed a U-shaped pattern for associations of first BZRA-related ED visits. Our hypothesis was supported in part, as the crude cumulative incidence and the adjusted rates of first BZRA-related ED visits were highest among beneficiaries with prescription pill quantities of >60 pills. The categories of 31-60 and 1-9 pills were also weakly associated with increased adjusted rates of first BZRA-related ED visits, compared to the referent category of 28-30 pills.

For the findings in Aims 1 and 2, the differences in the frequency of occurrence of the outcomes of interest between multiple categories suggest both potentially modifiable risk factors and specific at-risk populations. Populations with greater occurrence of new long-term BZRA use or lesser occurrence of incident discontinuation require additional consideration. The clinical guidelines for BZRA prescribing do allow for modifications based on patient needs and clinician judgement, factors which cannot be comprehensively measured through claims data.[62] However, potential differences in prescribing practices warrant further exploration. Research to assess specific clinical or other rationale for differences in BZRA prescribing could yield valuable insights to improve adherence to the existing guidelines. Possible variation in BZRA prescribing does suggest an ongoing need for expanded clinical guidelines, which aligns with requests for updated evidence-based recommendations regarding intermittent or as-needed BZRA use.[51,72] Better understanding of how clinicians determine the appropriateness of new BZRA prescriptions is also needed. Justifications for new use differentiated by the BZRA prescription characteristics of primary indication, onset of effect, dose strength, or by pill quantity are highly important to discern.

Guidelines from large healthcare systems in the United States (U.S.), such as Kaiser or the Veterans Health Administration (VA), specifically recommend rigorous safety measures for new BZRA use. These recommendations include quantities of 15 pills or less, short-term use comprising no longer than 2 weeks, and not for patients with current opioid prescriptions.[29] Among our study cohorts of adult Medicaid beneficiaries for Aims 1 and 3, we noted high proportions of new BZRA use counter to these stricter recommendations. In Aim 1, over 30% of beneficiaries begin new BZRA use within 3 months or less of receiving an opioid prescription. In Aim 3, over 70% of beneficiaries began new use with pill quantities of 15 pills or more. These expanded safety measures were further supported by our findings in Aim 3. We observed increased rates of BZRA-related ED visits associated with larger quantities of pills. Our observation of increased risk for the smallest quantities of pills is more difficult to interpret. It is possible that lowered quantities of BZRA use and the resulting infrequent use could be associated with more pronounced effects of sedation, thus leading to greater amounts of BZRA-related adverse events.[41] However, the possibility that clinicians were aware of heightened risks for BZRA-related adverse events among cohort members and accordingly prescribed lower pill quantities is also plausible. Given the increased rates of first ED visits for patients with the 1-9 pills, further consideration towards the appropriateness of any new BZRA use versus alternative non-BZRA therapies is merited.

The majority of the new BZRA use and first long-term BZRA use were observed as multiple prior authorization policies for new benzodiazepine and Z-drug prescriptions were enacted by the Oregon Health Authority from 2016 through 2017.[73] However, the comprehensiveness of these policies and their effect upon new BZRA prescriptions remains to be determined. It is noteworthy that these policies focused on the prevention of new long-term BZRA use,[73] in alignment with the public health framework utilized for this research. Also noteworthy was the use of the prescription day-supply field to trigger prior authorization, which differs from the prescription pill quantities utilized for this research and within a large U.S. healthcare system.[74] Further distinctions between these prescription fields are

worth exploring, given potential differences in the assessment of new or long-term BZRA use. Furthermore, the findings from Aims 1 and 3 emphasize the need for additional measures to mitigate the risk of BZRA use beyond the current prior authority policies and clinical guidelines. Among this cohort of Medicaid beneficiaries with new BZRA, 7% had index BZRA fills with quantities of over 60 pills, indicating potential new long-term use without a period of transition. These larger prescriptions quantities were also associated with increased rates of first BZRA-related ED visits. Enhanced clinical or health system guidelines could prioritize strategies to identify and limit new BZRA prescriptions with these higher pill quantities.

In summary, we believe the findings from this dissertation support the importance of new BZRA use for a public health framework to mitigate BZRA-related adverse outcomes. Expanded policies to reduce the occurrence of BZRA-related harms, new long-term BZRA use, or to enhance the frequency of incident discontinuation could justifiably focus additional preventive efforts at the time of new BZRA use. Additional measures of prevention appear to be necessary given the differences observed for the occurrence of long-term use or incident discontinuation based on demographic, clinical, or prescription factors.

Strengths

This dissertation has several strengths. These include the assessment of new BZRA use within a population of U.S. adults under the age 65 years. Specifically, within a population of Medicaid beneficiaries, for which limited findings exist regarding BZRA prescription use. BZRA-related harms are most recognized as pertaining to older adults, despite the potential risks for patients of all ages. For adults over 65 years, clinical and health system guidelines are more direct in recommending against any BZRA use.[75] However, most benzodiazepine-related ED visits or fatal and non-fatal BZRA-related OD occurred among U.S. adults ages 25-64 years.[22,25] Among adults with any BZRA use, a greater proportion of young adults reported misuse (5%) than among those over 65 years

(1%).[5] The Medicaid population represents a key component for equitable public health policies to address BZRA-related harms or misuse.[76] A further strength was the careful construction of treatment episodes to measure new BZRA use, long-term BZRA use, and incident discontinuation from long-term BZRA use. We precisely defined treatment episodes using standard pharmacoepidemiologic approaches to estimate remaining prescriptions quantities over follow-up.[48,77] Finally, our use of a composite outcome to determine rates of BZRA-related harms was a strength. Assessments of BZRA-related harms have primarily focused on benzodiazepine-related OD, ED visits involving the use of BZRA prescriptions, or singular BZRA-related adverse outcomes.[11,13] Our composite outcome measure was comprehensive in the inclusion of multiple potential adverse health conditions related to BZRA prescription use. As a result, our findings for rates of first BZRA-related harms are a novel and robust assessment of the risks associated with BZRA use.

Limitations

Beyond the limitations discussed in Chapters 3-5 (Aims 1-3), several overarching limitations could apply to this dissertation. First is the possibility that patients had additional unmeasured forms of BZRA use. Cohorts for all studies were created by first selecting patients with new BZRA use. We defined new BZRA use using similar criteria as have other studies of prescription claims data.[7] However, we cannot exclude that cohort members could have had other forms of BZRA use prior to this determination. Intermittent or prior long-term BZRA use could potentially exist as a source of unmeasured confounding for our estimates. Similarly, illicit use of BZRA prescriptions could have impacted the findings for all cohorts. Examples could include unmeasured misuse of BZRA prescriptions in Aim 3 resulting first BZRA-related ED visits, which could have then led to spurious estimates for risks associated with specific pill quantities. Similarly in Aim 1, existing misuse of BZRA prescriptions among certain beneficiaries could have been observed by clinicians and remained unmeasured in the claims data. Among beneficiaries with observed but unmeasured BZRA misuse,

clinicians may have been hesitant to prescribe additional BZRA prescriptions, which could have resulted in lesser occurrence of new long-term BZRA use. Conversely in Aim 2, perceived BZRA misuse among beneficiaries could also have prompted clinicians to initiate clinical mediated discontinuation. While these concerns for unmeasured forms of BZRA use do merit consideration, we do not have substantial reasons to suspect that they would be sufficient to undermine the validity of our findings.

A further limitation was the potential for changes in clinical BZRA prescribing patterns over time. Differences in the frequency of occurrence by year of cohort entry were assessed for new long-term BZRA use in Aim 1. Cohort entry in 2017 or 2018 relative to 2016 was associated with lower occurrence of first long-term BZRA use. These findings suggest improved clinical guidelines for BZRA prescribing practices or expanded policy interventions could positively affect patterns of high-risk BZRA use over time.

Directions for Future Research

An important direction for future research pertains to classification of distinct forms of BZRA prescriptions and their use. Specifically, distinct forms of BZRA use which fit within the comprehensive public health framework, subsequent to the onset of new BZRA use. Expanded classifications for BZRA prescriptions could include dose strength, onset of effect, primary indication, as well as defined daily dose, day-supply, specific BZRA prescriptions (e.g. alprazolam), or even the estimated drug clearance following use.[77] Expanded classifications are important for the development of further public health prevention strategies. For example, our findings suggest lesser occurrence of discontinuation following new long-term use with BZRA of short-to-intermediate acting onset. Clinical tapering guidelines has suggested the possible benefit of conversion to BZRA of long-acting onset prior to discontinuation attempts.[1] Further exploration could provide supporting evidence for safer BZRA prescribing practices. Use of expanded datasets with linkage beyond Medicaid claims are also

important. Enhanced public health preventions could be developed through the use of a linked dataset such as the Prescription Drug Monitoring Program (PDMP), that contains all prescriptions including those purchased with cash out-of-pocket. Prior studies utilizing Oregon Medicaid claims linked with PDMP data have identified increased proportions of prescription use.[54,55] More comprehensive estimates of BZRA use could better address the limitations raised in this research and further identify characteristics associated with patterns BZRA use.

Further research is also needed to determine the impact of policy interventions or clinical guidelines within distinct populations with BZRA use. Comprehensive public health approaches for prevention necessitate consistent and current assessments of preventative interventions. Determining changing prescribing practices attributable to new policies is critical for several reasons. First is to support or modify preventative efforts to reduce BZRA-related harms in accordance with the success of the interventions. Second is to monitor for unintended consequences resulting in inadvertent harms among the effected population. The risk of adverse health conditions related to BZRA use remains complex, because adverse outcomes can result from both BZRA use and discontinuation. Therefore, the public health approaches for reducing BZRA-related adverse outcomes require updated findings that also monitor the inadvertent occurrence of harms attributed to interventions. Finally, future studies could include qualitative research directed by the specific findings from Aims 1-3. Conducting interviews or focus groups among clinical BZRA prescribers could provide important insights beyond quantitative measurements. Clinician feedback could illustrate the rationale for new BZRA use compared to alternative non-BZRA therapies or how specific pill quantities are chosen. These insights could help modify targeted educational material for clinicians that better supports both safer BZRA prescribing practices and the decreased occurrence of BZRA-related adverse outcomes.

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Appendix 1: Institutional Review Board Documentation

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

NOT HUMAN RESEARCH

October 18, 2022

Dear Investigator:

On 10/18/2022, the IRB reviewed the following submission:

Title of Study:	Long-term Benzodiazepine & Z-drug Use and Discontinuation
Investigator:	Daniel Hartung
IRB ID:	STUDY00025025
Funding:	None

The IRB determined that the proposed activity is not research involving human subjects. IRB review and approval is not required.

Certain changes to the research plan may affect this determination. Contact the IRB Office if your project changes and you have questions regarding the need for IRB oversight.

If this project involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

Sincerely,

The OHSU IRB Office

Appendix 2: Supplemental Tables and Figures for Chapters 3, 4, and 5.

Table A.1. BZRA Medications by NDC Codes

Generic Name	NDC
alprazolam	00009002901
alprazolam	00009005501
alprazolam	00009009001
alprazolam	00228202710
alprazolam	00228202750
alprazolam	00228202796
alprazolam	00228202910
alprazolam	00228202950
alprazolam	00228202996
alprazolam	00228203110
alprazolam	00228203150
alprazolam	00228203196
alprazolam	00228203910
alprazolam	00228308306
alprazolam	00228308406
alprazolam	00228308606
alprazolam	00228308706
alprazolam	00228401911
alprazolam	00228402211
alprazolam	00228402411
alprazolam	00228402511
alprazolam	00378400305
alprazolam	00378400501
alprazolam	00378400505
alprazolam	00378400701
alprazolam	00378502191
alprazolam	00378502291
alprazolam	00603212721
alprazolam	00603212728
alprazolam	00603212732
alprazolam	00603212821
alprazolam	00603212828
alprazolam	00603212832
alprazolam	00603212921
alprazolam	00603212928
alprazolam	00603212932
alprazolam	00781106101
alprazolam	00781106105

Generic Name	NDC
alprazolam	00781106110
alprazolam	00781107701
alprazolam	00781107705
alprazolam	00781107710
alprazolam	00781107901
alprazolam	00781107905
alprazolam	00781107910
alprazolam	00781108901
alprazolam	00781108905
alprazolam	00904585961
alprazolam	47335060313
alprazolam	47335060318
alprazolam	47335060388
alprazolam	47335060413
alprazolam	47335060418
alprazolam	47335060488
alprazolam	47335060513
alprazolam	47335060518
alprazolam	47335060588
alprazolam	47335060688
alprazolam	49884011074
alprazolam	49884011174
alprazolam	49884021374
alprazolam	49884021474
alprazolam	51079078920
alprazolam	51991070401
alprazolam	51991070405
alprazolam	51991070501
alprazolam	51991070505
alprazolam	51991070510
alprazolam	51991070601
alprazolam	51991070605
alprazolam	51991070610
alprazolam	51991070701
alprazolam	51991070705
alprazolam	59762005701
alprazolam	59762005901
alprazolam	59762006601
alprazolam	59762006801
alprazolam	59762371901
alprazolam	59762371903
alprazolam	59762371904
alprazolam	59762372001
alprazolam	59762372003
alprazolam	59762372004

Generic Name	NDC
alprazolam	59762372101
alprazolam	59762372103
alprazolam	59762372104
alprazolam	59762372201
alprazolam	59762372203
alprazolam	63739066910
alprazolam	64376063001
alprazolam	64376063005
alprazolam	64376063010
alprazolam	64376063101
alprazolam	64376063105
alprazolam	64376063110
alprazolam	64376063201
alprazolam	64376063205
alprazolam	64376063210
alprazolam	64376063301
alprazolam	64376063305
alprazolam	65162081006
alprazolam	65162081206
alprazolam	65862045460
alprazolam	65862045560
alprazolam	65862045660
alprazolam	65862045760
alprazolam	65862067699
alprazolam	65862067799
alprazolam	65862067899
alprazolam	67253090009
alprazolam	67253090010
alprazolam	67253090011
alprazolam	67253090050
alprazolam	67253090110
alprazolam	67253090111
alprazolam	67253090150
alprazolam	67253090210
alprazolam	67253090211
alprazolam	67253090250
alprazolam	67253090310
alprazolam	67253090350
alprazolam	68084064701
alprazolam	69452011030
alprazolam	69452011032
alprazolam	69452011130
alprazolam	69452011132
alprazolam	69452011230
alprazolam	69452011232

Generic Name	NDC
alprazolam	69452011320
alprazolam	69452011330
chlordiazepoxide	00555003302
chlordiazepoxide	00555003305
chlordiazepoxide	00555015802
chlordiazepoxide	00555015902
chlordiazepoxide	00555015904
chlordiazepoxide	43547025110
chlordiazepoxide	43547025210
chlordiazepoxide	43547025310
chlordiazepoxide	51079014101
chlordiazepoxide	51079014120
chlordiazepoxide	51079037420
chlordiazepoxide	51079037501
chlordiazepoxide	51079037520
clobazam	00054052625
clobazam	00054052725
clobazam	00832058011
clobazam	00832058111
clobazam	16714088701
clobazam	16714088801
clobazam	31722063901
clobazam	31722064001
clobazam	42571031501
clobazam	42571031601
clobazam	51672420201
clobazam	51672420301
clobazam	51991090001
clobazam	51991090101
clobazam	67386031101
clobazam	67386031401
clobazam	67386031501
clobazam	68180015701
clobazam	68180015801
clobazam	69238130501
clobazam	69238130601
clobazam	69452011420
clobazam	69452011520
clobazam	70710132501
clobazam	70710132601
clonazepam	00004005801
clonazepam	00004006801
clonazepam	00093083201
clonazepam	00093083205
clonazepam	00093083210

Generic Name	NDC
clonazepam	00093083301
clonazepam	00093083305
clonazepam	00093083310
clonazepam	00093083401
clonazepam	00093083405
clonazepam	00093321201
clonazepam	00093321205
clonazepam	00093321305
clonazepam	00185006301
clonazepam	00185006305
clonazepam	00185006310
clonazepam	00185006401
clonazepam	00185006405
clonazepam	00185006410
clonazepam	00185006501
clonazepam	00185006505
clonazepam	00185006510
clonazepam	00228300311
clonazepam	00228300350
clonazepam	00228300411
clonazepam	00228300450
clonazepam	00228300511
clonazepam	00228300550
clonazepam	00378191001
clonazepam	00378191010
clonazepam	00378191077
clonazepam	00378191201
clonazepam	00378191210
clonazepam	00378191401
clonazepam	00378191405
clonazepam	00555009496
clonazepam	00555009596
clonazepam	00555009696
clonazepam	00555009796
clonazepam	00555009896
clonazepam	00603294802
clonazepam	00603294820
clonazepam	00603294821
clonazepam	00603294822
clonazepam	00603294828
clonazepam	00603294832
clonazepam	00603294916
clonazepam	00603294920
clonazepam	00603294921
clonazepam	00603294928

Generic Name	NDC
clonazepam	00603294932
clonazepam	00603295002
clonazepam	00603295021
clonazepam	00603295028
clonazepam	00781556701
clonazepam	00781556705
clonazepam	00781556710
clonazepam	00781556901
clonazepam	00781556905
clonazepam	00781556910
clonazepam	00781801801
clonazepam	00781801805
clonazepam	00781801810
clonazepam	00904610161
clonazepam	16714046901
clonazepam	16714046902
clonazepam	16714047001
clonazepam	16714047002
clonazepam	16714047101
clonazepam	16714047102
clonazepam	16714075001
clonazepam	16714075002
clonazepam	16714075101
clonazepam	16714075102
clonazepam	16714075201
clonazepam	16714075202
clonazepam	16729013600
clonazepam	16729013616
clonazepam	16729013700
clonazepam	16729013716
clonazepam	16729013800
clonazepam	16729013816
clonazepam	43547040610
clonazepam	43547040611
clonazepam	43547040650
clonazepam	43547040710
clonazepam	43547040711
clonazepam	43547040750
clonazepam	43547040810
clonazepam	43547040850
clonazepam	49884030602
clonazepam	49884030702
clonazepam	49884030802
clonazepam	49884030902
clonazepam	49884031002

Generic Name	NDC
clonazepam	51079088120
clonazepam	51079088220
clonazepam	57664027318
clonazepam	57664078386
clonazepam	57664078486
clonazepam	57664078586
clonazepam	57664078686
clonazepam	57664078786
clonazepam	60429052430
clonazepam	60429052490
clonazepam	60429052530
clonazepam	60429052590
clonazepam	63739026310
clonazepam	63739026410
clorazepate dipotassium	00378003001
clorazepate dipotassium	00378003005
clorazepate dipotassium	00378004001
clorazepate dipotassium	00378004005
clorazepate dipotassium	00378007001
clorazepate dipotassium	51672404201
clorazepate dipotassium	51672404301
clorazepate dipotassium	51672404302
clorazepate dipotassium	51672404401
clorazepate dipotassium	55292030201
clorazepate dipotassium	63304055201
clorazepate dipotassium	63304055305
diazepam	00172392560
diazepam	00172392570
diazepam	00172392660
diazepam	00172392670
diazepam	00172392680
diazepam	00172392760
diazepam	00172392770
diazepam	00172392780
diazepam	00378027101
diazepam	00378027105
diazepam	00378034501
diazepam	00378034505
diazepam	00378047701
diazepam	00378047705
diazepam	00591561901
diazepam	00591561905
diazepam	00591561910
diazepam	00591562001
diazepam	00591562005

Generic Name	NDC
diazepam	00591562010
diazepam	00591562101
diazepam	00591562105
diazepam	00603321320
diazepam	00603321321
diazepam	00603321328
diazepam	00603321416
diazepam	00603321420
diazepam	00603321421
diazepam	00603321428
diazepam	00603321432
diazepam	00603321516
diazepam	00603321521
diazepam	00603321528
diazepam	00603321532
diazepam	51079028420
diazepam	51079028520
diazepam	51079028620
diazepam	51862006201
diazepam	51862006205
diazepam	51862006301
diazepam	51862006305
diazepam	51862006310
diazepam	51862006401
diazepam	51862006405
diazepam	51862006410
diazepam	63739007310
estazolam	00591074401
estazolam	00591074501
estazolam	75907002801
estazolam	75907002901
estazolam	70954048010
estazolam	70954048110
eszopiclone	00054029125
eszopiclone	00054029225
eszopiclone	00093553756
eszopiclone	00093553801
eszopiclone	00093553901
eszopiclone	00378527001
eszopiclone	00378527101
eszopiclone	00378527201
eszopiclone	33342029907
eszopiclone	33342030011
eszopiclone	33342030111
eszopiclone	42043032003

Generic Name	NDC
eszopiclone	42043032101
eszopiclone	42043032201
eszopiclone	47335058683
eszopiclone	47335058788
eszopiclone	47335058888
eszopiclone	51079034903
eszopiclone	51079041403
eszopiclone	55111061701
eszopiclone	55111061901
eszopiclone	55111062930
eszopiclone	63402019110
eszopiclone	63402019310
eszopiclone	65862096701
eszopiclone	65862096801
eszopiclone	65862096901
eszopiclone	68180032201
eszopiclone	68180032301
eszopiclone	68180032401
eszopiclone	68462038201
eszopiclone	68462038301
eszopiclone	68462038401
flurazepam	00378441501
flurazepam	00378443001
Lorazepam	00187006301
lorazepam	00187006401
lorazepam	00187006501
lorazepam	00378232101
lorazepam	00378232105
lorazepam	00378245701
lorazepam	00378245710
lorazepam	00378277701
lorazepam	00378277705
lorazepam	00591024001
lorazepam	00591024005
lorazepam	00591024010
lorazepam	00591024101
lorazepam	00591024105
lorazepam	00591024110
lorazepam	00591024201
lorazepam	00591024205
lorazepam	00591024210
lorazepam	00603424621
lorazepam	00603424628
lorazepam	00603424632
lorazepam	00603424721

Generic Name	NDC
lorazepam	00603424728
lorazepam	00603424732
lorazepam	00603424821
lorazepam	00603424828
lorazepam	00603424832
lorazepam	00781537101
lorazepam	00781537105
lorazepam	00781537701
lorazepam	00781537705
lorazepam	00781537901
lorazepam	00781537905
lorazepam	00781540401
lorazepam	00781540405
lorazepam	00781540601
lorazepam	00781540605
lorazepam	00781540801
lorazepam	00832091015
lorazepam	00832091115
lorazepam	00832091215
lorazepam	00904598161
lorazepam	00904600760
lorazepam	00904600761
lorazepam	00904600860
lorazepam	00904600861
lorazepam	00904600960
lorazepam	00904600961
lorazepam	13107008305
lorazepam	13107008405
lorazepam	13107008501
lorazepam	51079038620
lorazepam	51079038720
lorazepam	51079041720
lorazepam	51079041721
lorazepam	63304077201
lorazepam	63304077205
lorazepam	63304077301
lorazepam	63304077305
lorazepam	63304077310
lorazepam	63304077401
lorazepam	63739049910
lorazepam	63739050010
lorazepam	63739050110
lorazepam	64125090401
lorazepam	64125090405
lorazepam	64125090410

Generic Name	NDC
lorazepam	64125090501
lorazepam	64125090505
lorazepam	64125090510
lorazepam	64125090601
lorazepam	64125090605
lorazepam	64125090610
lorazepam	68084073601
lorazepam	68084074201
lorazepam	69315090401
lorazepam	69315090405
lorazepam	69315090410
lorazepam	69315090501
lorazepam	69315090505
lorazepam	69315090510
lorazepam	69315090601
lorazepam	69315090605
lorazepam	69315090610
oxazepam	00228206710
oxazepam	00228206910
oxazepam	00228207310
oxazepam	00781280901
oxazepam	00781281001
oxazepam	00781281101
oxazepam	62584081301
temazepam	00228207610
temazepam	00228207650
temazepam	00228207710
temazepam	00228207750
temazepam	00378311001
temazepam	00378312093
temazepam	00378401001
temazepam	00378401005
temazepam	00378505001
temazepam	00378505005
temazepam	00406991701
temazepam	00406995903
temazepam	00406996001
temazepam	00603589121
temazepam	00603589221
temazepam	00603589421
temazepam	00781220101
temazepam	00781220105
temazepam	00781220201
temazepam	00781220205
temazepam	51079041820

Generic Name	NDC
temazepam	53489064801
temazepam	53489065007
temazepam	63739023110
temazepam	65162055610
temazepam	65162055710
temazepam	65162058310
temazepam	67877014601
temazepam	67877014605
temazepam	67877014701
temazepam	67877014705
temazepam	67877014801
temazepam	67877014930
temazepam	68084054921
triazolam	00009001758
triazolam	00054485825
triazolam	00054485851
triazolam	00054485925
triazolam	00054485929
triazolam	00054485951
triazolam	00054885825
triazolam	00054885925
triazolam	59762371704
triazolam	59762371709
triazolam	59762371803
triazolam	59762371804
triazolam	59762371809
zaleplon	00054008425
zaleplon	00054008525
zaleplon	00093526801
zaleplon	00093526901
zaleplon	00378680501
zaleplon	16714055102
zaleplon	16714056102
zaleplon	29300013101
zaleplon	29300013201
zaleplon	42043021101
zaleplon	57237023901
zaleplon	57237024001
zaleplon	65862021401
zaleplon	65862021501
zolpidem	00024540131
zolpidem	00024542131
zolpidem	00024550131
zolpidem	00024552131
zolpidem	00093007301

Generic Name	NDC
zolpidem	00093007401
zolpidem	00228348111
zolpidem	00228348211
zolpidem	00378530501
zolpidem	00378530505
zolpidem	00378531001
zolpidem	00378531005
zolpidem	00603646821
zolpidem	00603646828
zolpidem	00603646832
zolpidem	00603646916
zolpidem	00603646921
zolpidem	00603646928
zolpidem	00603646932
zolpidem	00781531501
zolpidem	00781531601
zolpidem	00781531701
zolpidem	00781531710
zolpidem	00781531801
zolpidem	00781531810
zolpidem	00904608261
zolpidem	00955170210
zolpidem	00955170310
zolpidem	10370011610
zolpidem	10370011710
zolpidem	13668000701
zolpidem	13668000705
zolpidem	13668000710
zolpidem	13668000790
zolpidem	13668000801
zolpidem	13668000805
zolpidem	13668000810
zolpidem	16714062101
zolpidem	16714062102
zolpidem	16714062201
zolpidem	16714062202
zolpidem	47335030788
zolpidem	47335030888
zolpidem	51079072420
zolpidem	51079072501
zolpidem	51079072520
zolpidem	55111047901
zolpidem	60505260401
zolpidem	60505260508
zolpidem	64679071501

Generic Name	NDC
zolpidem	64679071504
zolpidem	65862015901
zolpidem	65862015905
zolpidem	65862016001
zolpidem	65862016005
zolpidem	68180077901
zolpidem	68180078001

Table A.2. ICD Diagnoses for Cohort Exclusions

Exclusions	Code Type	Codes
Seizures	ICD-9	345.XX
Seizures	ICD-9	300.11
Seizures	ICD-10	G40.XX
Seizures	ICD-10	F44.5
Multiple Sclerosis	ICD-9	340.XX
Multiple Sclerosis	ICD-10	G35.XX
Hospice Care	ICD-9	V66.7
Hospice Care	ICD-10	Z51.5

Table A.3. ICD Diagnosis Codes for Clinical Conditions

Clinical Condition	Code Type	Code
Anxiety/Panic	ICD-9	300.1
Anxiety/Panic	ICD-9	300.2
Anxiety/Panic	ICD-9	300.3
Anxiety/Panic	ICD-9	309.8
Anxiety/Panic	ICD-10	F40.XX
Anxiety/Panic	ICD-10	F41.XX
Anxiety/Panic	ICD-10	F42.XX
Anxiety/Panic	ICD-10	F43.XX
Anxiety/Panic	ICD-10	F93.0
Anxiety/Panic	ICD-10	F93.1
Anxiety/Panic	ICD-10	F93.3
Insomnia	ICD-9	307.4
Insomnia	ICD-9	327.X
Insomnia	ICD-9	292.85
Insomnia	ICD-10	F51.XX
Insomnia	ICD-10	G47.XX
Insomnia	ICD-10	G51.XX
Substance Use Disorder	ICD-9	291.XX
Substance Use Disorder	ICD-9	292.XX
Substance Use Disorder	ICD-9	303.XX
Substance Use Disorder	ICD-9	304.XX
Substance Use Disorder	ICD-9	305.XX
Substance Use Disorder	ICD-10	F10.XX
Substance Use Disorder	ICD-10	F11.XX
Substance Use Disorder	ICD-10	F12.XX
Substance Use Disorder	ICD-10	F13.XX
Substance Use Disorder	ICD-10	F14.XX
Substance Use Disorder	ICD-10	F15.XX
Substance Use Disorder	ICD-10	F16.XX
Substance Use Disorder	ICD-10	F17.XX
Substance Use Disorder	ICD-10	F18.XX
Substance Use Disorder	ICD-10	F19.XX

Table A.4. NDC Codes for Concurrent Prescriptions

Concurrent Prescription	Generic Name	NDC
Medication for opioid use disorder	buprenorphine HCl	00054017613
Medication for opioid use disorder	buprenorphine HCl	00054017713
Medication for opioid use disorder	buprenorphine HCl	00228315303
Medication for opioid use disorder	buprenorphine HCl	00228315603
Medication for opioid use disorder	buprenorphine HCl	00378092393
Medication for opioid use disorder	buprenorphine HCl	00378092493
Medication for opioid use disorder	buprenorphine HCl	42858050103
Medication for opioid use disorder	buprenorphine HCl	42858050203
Medication for opioid use disorder	buprenorphine HCl	50383092493
Medication for opioid use disorder	buprenorphine HCl	50383093093
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00054018813
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00054018913
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00093572056
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00093572156
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00228315403
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00228315473
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00228315503
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00228315573
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	00406802003
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	12496120203
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	12496120403
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	12496120801
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	12496120803
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	12496121203
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	43598058230
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	50383028793
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	50383029493
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	54123095730
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	59385001430
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	62175045832
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	62756096983
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	62756097083
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	65162041503
Medication for opioid use disorder	buprenorphine HCl/naloxone HCl	65162041603
Gabapentin/Pregabalin	gabapentin	00093444301
Gabapentin/Pregabalin	gabapentin	00093444305
Gabapentin/Pregabalin	gabapentin	00093444401
Gabapentin/Pregabalin	gabapentin	00093444405
Gabapentin/Pregabalin	gabapentin	00228263650
Gabapentin/Pregabalin	gabapentin	00228263711
Gabapentin/Pregabalin	gabapentin	00228266511
Gabapentin/Pregabalin	gabapentin	00228266550

Concurrent Prescription	Generic Name	NDC
Gabapentin/Pregabalin	gabapentin	00228266611
Gabapentin/Pregabalin	gabapentin	00228266650
Gabapentin/Pregabalin	gabapentin	00228266711
Gabapentin/Pregabalin	gabapentin	00228266750
Gabapentin/Pregabalin	gabapentin	00904563261
Gabapentin/Pregabalin	gabapentin	13913000519
Gabapentin/Pregabalin	gabapentin	16714033001
Gabapentin/Pregabalin	gabapentin	16714033002
Gabapentin/Pregabalin	gabapentin	16714033201
Gabapentin/Pregabalin	gabapentin	16714033202
Gabapentin/Pregabalin	gabapentin	16714050301
Gabapentin/Pregabalin	gabapentin	16714050302
Gabapentin/Pregabalin	gabapentin	16714050401
Gabapentin/Pregabalin	gabapentin	16714050402
Gabapentin/Pregabalin	gabapentin	16714050501
Gabapentin/Pregabalin	gabapentin	16714050502
Gabapentin/Pregabalin	gabapentin	16714066101
Gabapentin/Pregabalin	gabapentin	16714066102
Gabapentin/Pregabalin	gabapentin	16714066201
Gabapentin/Pregabalin	gabapentin	16714066202
Gabapentin/Pregabalin	gabapentin	16714066301
Gabapentin/Pregabalin	gabapentin	16714066302
Gabapentin/Pregabalin	gabapentin	31722022101
Gabapentin/Pregabalin	gabapentin	31722022105
Gabapentin/Pregabalin	gabapentin	31722022201
Gabapentin/Pregabalin	gabapentin	31722022205
Gabapentin/Pregabalin	gabapentin	31722022301
Gabapentin/Pregabalin	gabapentin	31722022305
Gabapentin/Pregabalin	gabapentin	31722040501
Gabapentin/Pregabalin	gabapentin	31722040505
Gabapentin/Pregabalin	gabapentin	31722040601
Gabapentin/Pregabalin	gabapentin	31722040605
Gabapentin/Pregabalin	gabapentin	42192060816
Gabapentin/Pregabalin	gabapentin	42582011418
Gabapentin/Pregabalin	gabapentin	42582011518
Gabapentin/Pregabalin	gabapentin	42582011618
Gabapentin/Pregabalin	gabapentin	43547026550
Gabapentin/Pregabalin	gabapentin	43547026650
Gabapentin/Pregabalin	gabapentin	43547026750
Gabapentin/Pregabalin	gabapentin	43547033210
Gabapentin/Pregabalin	gabapentin	43547033250
Gabapentin/Pregabalin	gabapentin	43547033310
Gabapentin/Pregabalin	gabapentin	43547033350
Gabapentin/Pregabalin	gabapentin	43547038350
Gabapentin/Pregabalin	gabapentin	43547038410

Concurrent Prescription	Generic Name	NDC
Gabapentin/Pregabalin	gabapentin	43547038450
Gabapentin/Pregabalin	gabapentin	43547038910
Gabapentin/Pregabalin	gabapentin	43547038950
Gabapentin/Pregabalin	gabapentin	45963055511
Gabapentin/Pregabalin	gabapentin	45963055550
Gabapentin/Pregabalin	gabapentin	45963055611
Gabapentin/Pregabalin	gabapentin	45963055650
Gabapentin/Pregabalin	gabapentin	45963055711
Gabapentin/Pregabalin	gabapentin	45963055750
Gabapentin/Pregabalin	gabapentin	49483060550
Gabapentin/Pregabalin	gabapentin	49483060650
Gabapentin/Pregabalin	gabapentin	49483060750
Gabapentin/Pregabalin	gabapentin	50228018005
Gabapentin/Pregabalin	gabapentin	50383031109
Gabapentin/Pregabalin	gabapentin	50383031147
Gabapentin/Pregabalin	gabapentin	52343003101
Gabapentin/Pregabalin	gabapentin	52343003199
Gabapentin/Pregabalin	gabapentin	52343003290
Gabapentin/Pregabalin	gabapentin	53746010105
Gabapentin/Pregabalin	gabapentin	53746010201
Gabapentin/Pregabalin	gabapentin	53746010205
Gabapentin/Pregabalin	gabapentin	53746010210
Gabapentin/Pregabalin	gabapentin	53746010301
Gabapentin/Pregabalin	gabapentin	53746010305
Gabapentin/Pregabalin	gabapentin	58657062050
Gabapentin/Pregabalin	gabapentin	58657062101
Gabapentin/Pregabalin	gabapentin	58657062201
Gabapentin/Pregabalin	gabapentin	58657062250
Gabapentin/Pregabalin	gabapentin	58657062301
Gabapentin/Pregabalin	gabapentin	58657062350
Gabapentin/Pregabalin	gabapentin	58657062401
Gabapentin/Pregabalin	gabapentin	59762502501
Gabapentin/Pregabalin	gabapentin	60505011200
Gabapentin/Pregabalin	gabapentin	60505011201
Gabapentin/Pregabalin	gabapentin	60505011208
Gabapentin/Pregabalin	gabapentin	60505011300
Gabapentin/Pregabalin	gabapentin	60505011301
Gabapentin/Pregabalin	gabapentin	60505011308
Gabapentin/Pregabalin	gabapentin	60505011401
Gabapentin/Pregabalin	gabapentin	60505011405
Gabapentin/Pregabalin	gabapentin	60505255101
Gabapentin/Pregabalin	gabapentin	60505255105
Gabapentin/Pregabalin	gabapentin	60505255201
Gabapentin/Pregabalin	gabapentin	60505255205
Gabapentin/Pregabalin	gabapentin	62756013702

Concurrent Prescription	Generic Name	NDC
Gabapentin/Pregabalin	gabapentin	62756013705
Gabapentin/Pregabalin	gabapentin	62756013802
Gabapentin/Pregabalin	gabapentin	62756013805
Gabapentin/Pregabalin	gabapentin	62756020201
Gabapentin/Pregabalin	gabapentin	62756020203
Gabapentin/Pregabalin	gabapentin	62756020401
Gabapentin/Pregabalin	gabapentin	63739023610
Gabapentin/Pregabalin	gabapentin	63739068910
Gabapentin/Pregabalin	gabapentin	65162010110
Gabapentin/Pregabalin	gabapentin	65162010111
Gabapentin/Pregabalin	gabapentin	65162010150
Gabapentin/Pregabalin	gabapentin	65162010210
Gabapentin/Pregabalin	gabapentin	65162010211
Gabapentin/Pregabalin	gabapentin	65162010250
Gabapentin/Pregabalin	gabapentin	65162010310
Gabapentin/Pregabalin	gabapentin	65162010350
Gabapentin/Pregabalin	gabapentin	65162069890
Gabapentin/Pregabalin	gabapentin	65862019801
Gabapentin/Pregabalin	gabapentin	65862019805
Gabapentin/Pregabalin	gabapentin	65862019899
Gabapentin/Pregabalin	gabapentin	65862019901
Gabapentin/Pregabalin	gabapentin	65862019999
Gabapentin/Pregabalin	gabapentin	65862020001
Gabapentin/Pregabalin	gabapentin	65862020005
Gabapentin/Pregabalin	gabapentin	65862052301
Gabapentin/Pregabalin	gabapentin	65862052305
Gabapentin/Pregabalin	gabapentin	65862052401
Gabapentin/Pregabalin	gabapentin	65862052405
Gabapentin/Pregabalin	gabapentin	67877022201
Gabapentin/Pregabalin	gabapentin	67877022205
Gabapentin/Pregabalin	gabapentin	67877022210
Gabapentin/Pregabalin	gabapentin	67877022301
Gabapentin/Pregabalin	gabapentin	67877022305
Gabapentin/Pregabalin	gabapentin	67877022310
Gabapentin/Pregabalin	gabapentin	67877022401
Gabapentin/Pregabalin	gabapentin	67877022405
Gabapentin/Pregabalin	gabapentin	67877022410
Gabapentin/Pregabalin	gabapentin	67877042805
Gabapentin/Pregabalin	gabapentin	67877042905
Gabapentin/Pregabalin	gabapentin	68001000600
Gabapentin/Pregabalin	gabapentin	68001000603
Gabapentin/Pregabalin	gabapentin	68001000700
Gabapentin/Pregabalin	gabapentin	68001000703
Gabapentin/Pregabalin	gabapentin	68084077401
Gabapentin/Pregabalin	gabapentin	68382020401

Concurrent Prescription	Generic Name	NDC
Gabapentin/Pregabalin	gabapentin	68382020405
Gabapentin/Pregabalin	gabapentin	68382020505
Gabapentin/Pregabalin	gabapentin	68462012601
Gabapentin/Pregabalin	gabapentin	68462012605
Gabapentin/Pregabalin	gabapentin	68462012701
Gabapentin/Pregabalin	gabapentin	68462012705
Gabapentin/Pregabalin	gabapentin	69097081107
Gabapentin/Pregabalin	gabapentin	69097081112
Gabapentin/Pregabalin	gabapentin	69097081207
Gabapentin/Pregabalin	gabapentin	69097081212
Gabapentin/Pregabalin	gabapentin	69097081307
Gabapentin/Pregabalin	gabapentin	69097081312
Gabapentin/Pregabalin	gabapentin	69097081407
Gabapentin/Pregabalin	gabapentin	69097081412
Gabapentin/Pregabalin	gabapentin	69097081507
Gabapentin/Pregabalin	gabapentin	69097081512
Gabapentin/Pregabalin	gabapentin	69097094312
Gabapentin/Pregabalin	gabapentin	69367013306
Gabapentin/Pregabalin	gabapentin	69367013406
Gabapentin/Pregabalin	gabapentin	69367013506
Gabapentin/Pregabalin	gabapentin	71093011104
Gabapentin/Pregabalin	gabapentin	71093011105
Gabapentin/Pregabalin	gabapentin	71093011204
Gabapentin/Pregabalin	gabapentin	71093011205
Gabapentin/Pregabalin	gabapentin	71093012005
Gabapentin/Pregabalin	gabapentin	71093012105
Gabapentin/Pregabalin	gabapentin	71399055105
Gabapentin/Pregabalin	gabapentin	71399055305
Gabapentin/Pregabalin	gabapentin	76282040501
Gabapentin/Pregabalin	gabapentin	76282040505
Gabapentin/Pregabalin	gabapentin	76282040690
Gabapentin/Pregabalin	pregabalin	00071101268
Gabapentin/Pregabalin	pregabalin	00071101368
Gabapentin/Pregabalin	pregabalin	00071101468
Gabapentin/Pregabalin	pregabalin	00071101541
Gabapentin/Pregabalin	pregabalin	00071101568
Gabapentin/Pregabalin	pregabalin	00071101668
Gabapentin/Pregabalin	pregabalin	00071101768
Gabapentin/Pregabalin	pregabalin	00071101868
Gabapentin/Pregabalin	pregabalin	00071101968
Opioid	acetaminophen with codeine	00093005001
Opioid	acetaminophen with codeine	00093015001
Opioid	acetaminophen with codeine	00093015010
Opioid	acetaminophen with codeine	00093035001
Opioid	acetaminophen with codeine	00093035005

Concurrent Prescription	Generic Name	NDC
Opioid	acetaminophen with codeine	00121050404
Opioid	acetaminophen with codeine	00121050416
Opioid	acetaminophen with codeine	00406048401
Opioid	acetaminophen with codeine	00406048410
Opioid	acetaminophen with codeine	00406048462
Opioid	acetaminophen with codeine	00406048501
Opioid	acetaminophen with codeine	00406048505
Opioid	acetaminophen with codeine	00603233721
Opioid	acetaminophen with codeine	00603233804
Opioid	acetaminophen with codeine	00603233821
Opioid	acetaminophen with codeine	00603233822
Opioid	acetaminophen with codeine	00603233832
Opioid	acetaminophen with codeine	00603233921
Opioid	acetaminophen with codeine	00603233928
Opioid	acetaminophen with codeine	13107005801
Opioid	acetaminophen with codeine	13107005901
Opioid	acetaminophen with codeine	13107005999
Opioid	acetaminophen with codeine	13107006001
Opioid	acetaminophen with codeine	50383007916
Opioid	acetaminophen with codeine	60432024516
Opioid	acetaminophen with codeine	65162003310
Opioid	acetaminophen with codeine	65162003311
Opioid	buprenorphine	00093360040
Opioid	buprenorphine	00093360140
Opioid	buprenorphine	00093360340
Opioid	buprenorphine	42858049340
Opioid	buprenorphine	42858058640
Opioid	buprenorphine	42858083940
Opioid	buprenorphine	59011075004
Opioid	buprenorphine	59011075104
Opioid	buprenorphine	59011075204
Opioid	buprenorphine	59011075704
Opioid	buprenorphine	59011075804
Opioid	buprenorphine HCl	63481051960
Opioid	butalbit/acetamin/caff/codeine	00591264101
Opioid	butalbit/acetamin/caff/codeine	00591322001
Opioid	butalbit/acetamin/caff/codeine	00603255321
Opioid	butalbit/acetamin/caff/codeine	51991007301
Opioid	butorphanol tartrate	00054309036
Opioid	butorphanol tartrate	00378963943
Opioid	butorphanol tartrate	60505081301
Opioid	codeine sulfate	00054024324
Opioid	codeine sulfate	00054024424
Opioid	codeine sulfate	00054024425
Opioid	codeine sulfate	00054024525

Concurrent Prescription	Generic Name	NDC
Opioid	codeine sulfate	00527169801
Opioid	codeine/butalbital/ASA/caffein	00527131201
Opioid	codeine/butalbital/ASA/caffein	00591354601
Opioid	codeine/butalbital/ASA/caffein	51991007401
Opioid	fentanyl	00378911998
Opioid	fentanyl	00378912198
Opioid	fentanyl	00378912298
Opioid	fentanyl	00378912398
Opioid	fentanyl	00378912498
Opioid	fentanyl	00378912598
Opioid	fentanyl	00378912698
Opioid	fentanyl	00406900076
Opioid	fentanyl	00406901276
Opioid	fentanyl	00406902576
Opioid	fentanyl	00406905076
Opioid	fentanyl	00406907576
Opioid	fentanyl	00591319872
Opioid	fentanyl	00591321272
Opioid	fentanyl	00591321372
Opioid	fentanyl	00591321472
Opioid	fentanyl	00781724055
Opioid	fentanyl	00781724155
Opioid	fentanyl	00781724255
Opioid	fentanyl	00781724355
Opioid	fentanyl	00781724455
Opioid	fentanyl	47781042347
Opioid	fentanyl	47781042447
Opioid	fentanyl	47781042647
Opioid	fentanyl	47781042747
Opioid	fentanyl	47781042847
Opioid	fentanyl	49884076178
Opioid	fentanyl	49884076278
Opioid	fentanyl	49884076378
Opioid	fentanyl	49884076478
Opioid	fentanyl	60505700602
Opioid	fentanyl	60505700702
Opioid	fentanyl	60505700802
Opioid	fentanyl	60505700902
Opioid	fentanyl	60505701002
Opioid	hydrocodone bitartrate	65224031560
Opioid	hydrocodone bitartrate	65224033060
Opioid	hydrocodone bitartrate	65224034060
Opioid	hydrocodone/acetaminophen	00074304113
Opioid	hydrocodone/acetaminophen	00074304153
Opioid	hydrocodone/acetaminophen	00074304313

Concurrent Prescription	Generic Name	NDC
Opioid	hydrocodone/acetaminophen	00074305413
Opioid	hydrocodone/acetaminophen	00074305453
Opioid	hydrocodone/acetaminophen	00121077204
Opioid	hydrocodone/acetaminophen	00121077216
Opioid	hydrocodone/acetaminophen	00406012301
Opioid	hydrocodone/acetaminophen	00406012305
Opioid	hydrocodone/acetaminophen	00406012310
Opioid	hydrocodone/acetaminophen	00406012401
Opioid	hydrocodone/acetaminophen	00406012405
Opioid	hydrocodone/acetaminophen	00406012410
Opioid	hydrocodone/acetaminophen	00406012501
Opioid	hydrocodone/acetaminophen	00406012505
Opioid	hydrocodone/acetaminophen	00406012510
Opioid	hydrocodone/acetaminophen	00406012562
Opioid	hydrocodone/acetaminophen	00406036501
Opioid	hydrocodone/acetaminophen	00406036562
Opioid	hydrocodone/acetaminophen	00406036601
Opioid	hydrocodone/acetaminophen	00406036762
Opioid	hydrocodone/acetaminophen	00406037605
Opioid	hydrocodone/acetaminophen	00591217201
Opioid	hydrocodone/acetaminophen	00591217205
Opioid	hydrocodone/acetaminophen	00591217401
Opioid	hydrocodone/acetaminophen	00591217601
Opioid	hydrocodone/acetaminophen	00591260501
Opioid	hydrocodone/acetaminophen	00591260505
Opioid	hydrocodone/acetaminophen	00591261201
Opioid	hydrocodone/acetaminophen	00591261205
Opioid	hydrocodone/acetaminophen	00591320201
Opioid	hydrocodone/acetaminophen	00591320205
Opioid	hydrocodone/acetaminophen	00603360921
Opioid	hydrocodone/acetaminophen	00603388702
Opioid	hydrocodone/acetaminophen	00603388704
Opioid	hydrocodone/acetaminophen	00603388721
Opioid	hydrocodone/acetaminophen	00603388722
Opioid	hydrocodone/acetaminophen	00603388728
Opioid	hydrocodone/acetaminophen	00603388732
Opioid	hydrocodone/acetaminophen	00603389004
Opioid	hydrocodone/acetaminophen	00603389021
Opioid	hydrocodone/acetaminophen	00603389028
Opioid	hydrocodone/acetaminophen	00603389032
Opioid	hydrocodone/acetaminophen	00603389121
Opioid	hydrocodone/acetaminophen	00603389128
Opioid	hydrocodone/acetaminophen	00603389132
Opioid	hydrocodone/acetaminophen	00713070489
Opioid	hydrocodone/acetaminophen	00904656761

Concurrent Prescription	Generic Name	NDC
Opioid	hydrocodone/acetaminophen	10702018950
Opioid	hydrocodone/acetaminophen	10702019110
Opioid	hydrocodone/acetaminophen	13107001901
Opioid	hydrocodone/acetaminophen	13107001905
Opioid	hydrocodone/acetaminophen	13107002001
Opioid	hydrocodone/acetaminophen	13107002005
Opioid	hydrocodone/acetaminophen	13107002101
Opioid	hydrocodone/acetaminophen	13107002105
Opioid	hydrocodone/acetaminophen	13107002199
Opioid	hydrocodone/acetaminophen	17478045016
Opioid	hydrocodone/acetaminophen	27808003501
Opioid	hydrocodone/acetaminophen	27808003502
Opioid	hydrocodone/acetaminophen	27808003503
Opioid	hydrocodone/acetaminophen	27808003601
Opioid	hydrocodone/acetaminophen	27808003602
Opioid	hydrocodone/acetaminophen	27808003603
Opioid	hydrocodone/acetaminophen	27808003701
Opioid	hydrocodone/acetaminophen	27808003703
Opioid	hydrocodone/acetaminophen	27808011401
Opioid	hydrocodone/acetaminophen	27808011501
Opioid	hydrocodone/acetaminophen	27808011601
Opioid	hydrocodone/acetaminophen	42291033201
Opioid	hydrocodone/acetaminophen	42858020101
Opioid	hydrocodone/acetaminophen	42858020150
Opioid	hydrocodone/acetaminophen	42858020201
Opioid	hydrocodone/acetaminophen	42858020301
Opioid	hydrocodone/acetaminophen	42858020350
Opioid	hydrocodone/acetaminophen	43386035601
Opioid	hydrocodone/acetaminophen	43386035610
Opioid	hydrocodone/acetaminophen	43386035701
Opioid	hydrocodone/acetaminophen	43386035801
Opioid	hydrocodone/acetaminophen	43386035810
Opioid	hydrocodone/acetaminophen	51862022701
Opioid	hydrocodone/acetaminophen	51862022705
Opioid	hydrocodone/acetaminophen	51862022801
Opioid	hydrocodone/acetaminophen	51862022805
Opioid	hydrocodone/acetaminophen	51862022901
Opioid	hydrocodone/acetaminophen	51862022905
Opioid	hydrocodone/acetaminophen	51862058701
Opioid	hydrocodone/acetaminophen	53746010901
Opioid	hydrocodone/acetaminophen	53746010905
Opioid	hydrocodone/acetaminophen	53746011001
Opioid	hydrocodone/acetaminophen	53746011005
Opioid	hydrocodone/acetaminophen	54569552301
Opioid	hydrocodone/acetaminophen	57664012688

Concurrent Prescription	Generic Name	NDC
Opioid	hydrocodone/acetaminophen	57664017013
Opioid	hydrocodone/acetaminophen	57664017088
Opioid	hydrocodone/acetaminophen	57664017688
Opioid	hydrocodone/acetaminophen	63739070410
Opioid	hydrocodone/acetaminophen	64376064016
Opioid	hydrocodone/acetaminophen	64376064040
Opioid	hydrocodone/acetaminophen	64376064301
Opioid	hydrocodone/acetaminophen	64376064801
Opioid	hydrocodone/acetaminophen	64376064805
Opioid	hydrocodone/acetaminophen	64376064901
Opioid	hydrocodone/acetaminophen	64950034047
Opioid	hydrocodone/acetaminophen	65162011510
Opioid	hydrocodone/acetaminophen	65162011511
Opioid	hydrocodone/acetaminophen	65162011550
Opioid	hydrocodone/acetaminophen	65162067510
Opioid	hydrocodone/acetaminophen	66689002316
Opioid	hydrocodone/acetaminophen	68084010001
Opioid	hydrocodone/acetaminophen	68084036801
Opioid	hydrocodone/acetaminophen	68084089501
Opioid	hydrocodone/acetaminophen	68084089509
Opioid	hydrocodone/ibuprofen	00603358421
Opioid	hydrocodone/ibuprofen	00603389721
Opioid	hydrocodone/ibuprofen	00603389728
Opioid	hydrocodone/ibuprofen	13107000401
Opioid	hydrocodone/ibuprofen	53746011701
Opioid	hydrocodone/ibuprofen	53746014501
Opioid	hydrocodone/ibuprofen	53746014601
Opioid	hydrocodone/ibuprofen	62037052401
Opioid	hydromorphone HCl	00054026425
Opioid	hydromorphone HCl	00054026525
Opioid	hydromorphone HCl	00054038663
Opioid	hydromorphone HCl	00406324301
Opioid	hydromorphone HCl	00406324401
Opioid	hydromorphone HCl	00406324901
Opioid	hydromorphone HCl	00406330801
Opioid	hydromorphone HCl	00406331601
Opioid	hydromorphone HCl	00527135301
Opioid	hydromorphone HCl	00527135401
Opioid	hydromorphone HCl	00527135501
Opioid	hydromorphone HCl	00574029301
Opioid	hydromorphone HCl	00574722406
Opioid	hydromorphone HCl	13107010701
Opioid	hydromorphone HCl	13107010801
Opioid	hydromorphone HCl	13107010901
Opioid	hydromorphone HCl	42858030101

Concurrent Prescription	Generic Name	NDC
Opioid	hydromorphone HCl	42858030125
Opioid	hydromorphone HCl	42858030201
Opioid	hydromorphone HCl	42858030225
Opioid	hydromorphone HCl	42858030250
Opioid	hydromorphone HCl	42858030301
Opioid	hydromorphone HCl	42858030416
Opioid	hydromorphone HCl	68084042301
Opioid	meperidine HCl	00054459525
Opioid	meperidine HCl	00054459625
Opioid	meperidine HCl	00555038102
Opioid	meperidine HCl	00555039202
Opioid	meperidine HCl	00603441521
Opioid	methadone HCl	00054355344
Opioid	methadone HCl	00054355663
Opioid	methadone HCl	00054457025
Opioid	methadone HCl	00054457125
Opioid	methadone HCl	00054855324
Opioid	methadone HCl	00406052710
Opioid	methadone HCl	00406575501
Opioid	methadone HCl	00406575562
Opioid	methadone HCl	00406577101
Opioid	methadone HCl	00406577162
Opioid	methadone HCl	13107008801
Opioid	methadone HCl	13107008901
Opioid	methadone HCl	66689069479
Opioid	methadone HCl	67877011601
Opioid	morphine sulfate	00054023524
Opioid	morphine sulfate	00054023525
Opioid	morphine sulfate	00054023625
Opioid	morphine sulfate	00054023749
Opioid	morphine sulfate	00054023763
Opioid	morphine sulfate	00054023863
Opioid	morphine sulfate	00054040444
Opioid	morphine sulfate	00054040450
Opioid	morphine sulfate	00054051741
Opioid	morphine sulfate	00054051744
Opioid	morphine sulfate	00054051750
Opioid	morphine sulfate	00228309211
Opioid	morphine sulfate	00228311611
Opioid	morphine sulfate	00228311711
Opioid	morphine sulfate	00228350106
Opioid	morphine sulfate	00228350206
Opioid	morphine sulfate	00228427011
Opioid	morphine sulfate	00228427111
Opioid	morphine sulfate	00228431111

Concurrent Prescription	Generic Name	NDC
Opioid	morphine sulfate	00228432311
Opioid	morphine sulfate	00378265801
Opioid	morphine sulfate	00378265901
Opioid	morphine sulfate	00378266001
Opioid	morphine sulfate	00378266101
Opioid	morphine sulfate	00406800315
Opioid	morphine sulfate	00406800324
Opioid	morphine sulfate	00406800330
Opioid	morphine sulfate	00406831501
Opioid	morphine sulfate	00406831562
Opioid	morphine sulfate	00406833001
Opioid	morphine sulfate	00406838001
Opioid	morphine sulfate	00406839001
Opioid	morphine sulfate	00527142536
Opioid	morphine sulfate	00527142562
Opioid	morphine sulfate	00527190636
Opioid	morphine sulfate	00574711212
Opioid	morphine sulfate	00832022500
Opioid	morphine sulfate	00832022600
Opioid	morphine sulfate	00832022900
Opioid	morphine sulfate	27808008201
Opioid	morphine sulfate	27808008202
Opioid	morphine sulfate	42858080101
Opioid	morphine sulfate	42858080201
Opioid	morphine sulfate	42858080301
Opioid	morphine sulfate	42858080401
Opioid	morphine sulfate	49884083301
Opioid	morphine sulfate	49884083601
Opioid	morphine sulfate	50383096504
Opioid	morphine sulfate	51862018501
Opioid	morphine sulfate	51862018601
Opioid	morphine sulfate	60951065270
Opioid	morphine sulfate	60951065370
Opioid	morphine sulfate	60951065570
Opioid	morphine sulfate	60951065870
Opioid	morphine sulfate	63304045001
Opioid	morphine sulfate	63304045101
Opioid	morphine sulfate	63304045201
Opioid	morphine sulfate	63304075801
Opioid	morphine sulfate	68382090301
Opioid	morphine sulfate	68382090401
Opioid	morphine sulfate	68382090501
Opioid	opium/belladonna alkaloids	00574704012
Opioid	opium/belladonna alkaloids	00574704512
Opioid	oxycodone HCl	00054039063

Concurrent Prescription	Generic Name	NDC
Opioid	oxycodone HCl	00054052363
Opioid	oxycodone HCl	00093573101
Opioid	oxycodone HCl	00093573201
Opioid	oxycodone HCl	00093573301
Opioid	oxycodone HCl	00093573401
Opioid	oxycodone HCl	00115155601
Opioid	oxycodone HCl	00115155901
Opioid	oxycodone HCl	00228287611
Opioid	oxycodone HCl	00228287811
Opioid	oxycodone HCl	00228287911
Opioid	oxycodone HCl	00378611201
Opioid	oxycodone HCl	00378611301
Opioid	oxycodone HCl	00406055201
Opioid	oxycodone HCl	00406055262
Opioid	oxycodone HCl	00406851501
Opioid	oxycodone HCl	00406851562
Opioid	oxycodone HCl	00406853001
Opioid	oxycodone HCl	00527142636
Opioid	oxycodone HCl	00527177401
Opioid	oxycodone HCl	00591269301
Opioid	oxycodone HCl	00591270801
Opioid	oxycodone HCl	00603499021
Opioid	oxycodone HCl	00603499028
Opioid	oxycodone HCl	00603499121
Opioid	oxycodone HCl	00603499128
Opioid	oxycodone HCl	00603499221
Opioid	oxycodone HCl	00603499228
Opioid	oxycodone HCl	00603499321
Opioid	oxycodone HCl	00603499421
Opioid	oxycodone HCl	00781570301
Opioid	oxycodone HCl	00781572601
Opioid	oxycodone HCl	00781576701
Opioid	oxycodone HCl	00781578501
Opioid	oxycodone HCl	00904644461
Opioid	oxycodone HCl	00904667840
Opioid	oxycodone HCl	10702000801
Opioid	oxycodone HCl	10702000850
Opioid	oxycodone HCl	10702000901
Opioid	oxycodone HCl	10702001801
Opioid	oxycodone HCl	10702001850
Opioid	oxycodone HCl	10702002301
Opioid	oxycodone HCl	10702005601
Opioid	oxycodone HCl	10702005650
Opioid	oxycodone HCl	10702005701
Opioid	oxycodone HCl	10702005750

Concurrent Prescription	Generic Name	NDC
Opioid	oxycodone HCl	13107005501
Opioid	oxycodone HCl	13107005601
Opioid	oxycodone HCl	31722091701
Opioid	oxycodone HCl	42806000501
Opioid	oxycodone HCl	42806000601
Opioid	oxycodone HCl	42806000701
Opioid	oxycodone HCl	42806000801
Opioid	oxycodone HCl	42858000101
Opioid	oxycodone HCl	42858000110
Opioid	oxycodone HCl	42858000201
Opioid	oxycodone HCl	42858000301
Opioid	oxycodone HCl	42858000401
Opioid	oxycodone HCl	42858000501
Opioid	oxycodone HCl	43386092060
Opioid	oxycodone HCl	47781026301
Opioid	oxycodone HCl	47781026305
Opioid	oxycodone HCl	47781026405
Opioid	oxycodone HCl	47781026505
Opioid	oxycodone HCl	49884013601
Opioid	oxycodone HCl	49884013701
Opioid	oxycodone HCl	49884013801
Opioid	oxycodone HCl	49884019701
Opioid	oxycodone HCl	49999089901
Opioid	oxycodone HCl	50383096134
Opioid	oxycodone HCl	57664018788
Opioid	oxycodone HCl	57664022388
Opioid	oxycodone HCl	57664022488
Opioid	oxycodone HCl	57664037088
Opioid	oxycodone HCl	57664037188
Opioid	oxycodone HCl	59011041010
Opioid	oxycodone HCl	59011041510
Opioid	oxycodone HCl	59011042010
Opioid	oxycodone HCl	59011043010
Opioid	oxycodone HCl	59011044010
Opioid	oxycodone HCl	59011046010
Opioid	oxycodone HCl	59011048010
Opioid	oxycodone HCl	60432070605
Opioid	oxycodone HCl	62559015116
Opioid	oxycodone HCl	62559016701
Opioid	oxycodone HCl	63304068301
Opioid	oxycodone HCl	63304068401
Opioid	oxycodone HCl	64720022410
Opioid	oxycodone HCl	64950035450
Opioid	oxycodone HCl	65162004710
Opioid	oxycodone HCl	65162004810

Concurrent Prescription	Generic Name	NDC
Opioid	oxycodone HCl	65162004910
Opioid	oxycodone HCl	65162004950
Opioid	oxycodone HCl	65162005010
Opioid	oxycodone HCl	65162005110
Opioid	oxycodone HCl	65162005150
Opioid	oxycodone HCl	66689040316
Opioid	oxycodone HCl	68084004801
Opioid	oxycodone HCl	68084035401
Opioid	oxycodone HCl	68308002003
Opioid	oxycodone HCl	68308010801
Opioid	oxycodone HCl	68308011101
Opioid	oxycodone HCl	68308011201
Opioid	oxycodone HCl	68308014501
Opioid	oxycodone HCl	68382079301
Opioid	oxycodone HCl	68382079401
Opioid	oxycodone HCl	68382079501
Opioid	oxycodone HCl	68382079601
Opioid	oxycodone HCl	68382079701
Opioid	oxycodone HCl	68462020401
Opioid	oxycodone HCl	68462034737
Opioid	oxycodone HCl/acetaminophen	00054055125
Opioid	oxycodone HCl/acetaminophen	00228298111
Opioid	oxycodone HCl/acetaminophen	00228298150
Opioid	oxycodone HCl/acetaminophen	00228298211
Opioid	oxycodone HCl/acetaminophen	00228298311
Opioid	oxycodone HCl/acetaminophen	00378710501
Opioid	oxycodone HCl/acetaminophen	00406051201
Opioid	oxycodone HCl/acetaminophen	00406051205
Opioid	oxycodone HCl/acetaminophen	00406051262
Opioid	oxycodone HCl/acetaminophen	00406052201
Opioid	oxycodone HCl/acetaminophen	00406052205
Opioid	oxycodone HCl/acetaminophen	00406052301
Opioid	oxycodone HCl/acetaminophen	00406052305
Opioid	oxycodone HCl/acetaminophen	00603497821
Opioid	oxycodone HCl/acetaminophen	00603497921
Opioid	oxycodone HCl/acetaminophen	00603498221
Opioid	oxycodone HCl/acetaminophen	00603499821
Opioid	oxycodone HCl/acetaminophen	00603499828
Opioid	oxycodone HCl/acetaminophen	00904643761
Opioid	oxycodone HCl/acetaminophen	13107004401
Opioid	oxycodone HCl/acetaminophen	13107004405
Opioid	oxycodone HCl/acetaminophen	13107004501
Opioid	oxycodone HCl/acetaminophen	13107004601
Opioid	oxycodone HCl/acetaminophen	13107004605
Opioid	oxycodone HCl/acetaminophen	31722019201

Concurrent Prescription	Generic Name	NDC
Opioid	oxycodone HCl/acetaminophen	31722019205
Opioid	oxycodone HCl/acetaminophen	31722019301
Opioid	oxycodone HCl/acetaminophen	31722019401
Opioid	oxycodone HCl/acetaminophen	42858010201
Opioid	oxycodone HCl/acetaminophen	42858010250
Opioid	oxycodone HCl/acetaminophen	42858010301
Opioid	oxycodone HCl/acetaminophen	42858010350
Opioid	oxycodone HCl/acetaminophen	42858010401
Opioid	oxycodone HCl/acetaminophen	42858010450
Opioid	oxycodone HCl/acetaminophen	47781019601
Opioid	oxycodone HCl/acetaminophen	47781019605
Opioid	oxycodone HCl/acetaminophen	47781022901
Opioid	oxycodone HCl/acetaminophen	47781022905
Opioid	oxycodone HCl/acetaminophen	47781023001
Opioid	oxycodone HCl/acetaminophen	47781023005
Opioid	oxycodone HCl/acetaminophen	47781023063
Opioid	oxycodone HCl/acetaminophen	53746020301
Opioid	oxycodone HCl/acetaminophen	53746020305
Opioid	oxycodone HCl/acetaminophen	53746020401
Opioid	oxycodone HCl/acetaminophen	53746020405
Opioid	oxycodone HCl/acetaminophen	57664015513
Opioid	oxycodone HCl/acetaminophen	57664015588
Opioid	oxycodone HCl/acetaminophen	57664016088
Opioid	oxycodone HCl/acetaminophen	60951060270
Opioid	oxycodone HCl/acetaminophen	60951060285
Opioid	oxycodone HCl/acetaminophen	60951070070
Opioid	oxycodone HCl/acetaminophen	60951071270
Opioid	oxycodone HCl/acetaminophen	65162020710
Opioid	oxycodone HCl/acetaminophen	65162020750
Opioid	oxycodone HCl/acetaminophen	68084035501
Opioid	oxycodone HCl/acetaminophen	68084069901
Opioid	oxycodone HCl/acetaminophen	68308084001
Opioid	oxycodone HCl/acetaminophen	68308084101
Opioid	oxycodone HCl/acetaminophen	68308084201
Opioid	oxycodone HCl/acetaminophen	68308084301
Opioid	oxycodone HCl/aspirin	00591355101
Opioid	oxycodone HCl/aspirin	68308084501
Opioid	oxymorphone HCl	00054028325
Opioid	oxymorphone HCl	00115123201
Opioid	oxymorphone HCl	00115123213
Opioid	oxymorphone HCl	00115123313
Opioid	oxymorphone HCl	00115131701
Opioid	oxymorphone HCl	00228326311
Opioid	oxymorphone HCl	00406101001
Opioid	oxymorphone HCl	13107010401

Concurrent Prescription	Generic Name	NDC
Opioid	oxymorphone HCl	60951079470
Opioid	oxymorphone HCl	60951079570
Opioid	oxymorphone HCl	63481081260
Opioid	oxymorphone HCl	63481081460
Opioid	oxymorphone HCl	63481081560
Opioid	oxymorphone HCl	63481081660
Opioid	oxymorphone HCl	63481081760
Opioid	oxymorphone HCl	64720025810
Opioid	oxymorphone HCl	64720025910
Opioid	pentazocine HCl/naloxone HCl	00591039501
Opioid	tapentadol HCl	50458082004
Opioid	tapentadol HCl	50458084004
Opioid	tapentadol HCl	50458086201
Opioid	tapentadol HCl	69865021002
Opioid	tapentadol HCl	69865025002
Opioid	tramadol HCl	00093005801
Opioid	tramadol HCl	00093005805
Opioid	tramadol HCl	00378415101
Opioid	tramadol HCl	00378415105
Opioid	tramadol HCl	00378415293
Opioid	tramadol HCl	10370022111
Opioid	tramadol HCl	10370022211
Opioid	tramadol HCl	16714011110
Opioid	tramadol HCl	16714011111
Opioid	tramadol HCl	16714011112
Opioid	tramadol HCl	16714048101
Opioid	tramadol HCl	16714048102
Opioid	tramadol HCl	16714048103
Opioid	tramadol HCl	47335053383
Opioid	tramadol HCl	47335085983
Opioid	tramadol HCl	47335086083
Opioid	tramadol HCl	49884082111
Opioid	tramadol HCl	49884082211
Opioid	tramadol HCl	49884082311
Opioid	tramadol HCl	51079099120
Opioid	tramadol HCl	57664037708
Opioid	tramadol HCl	57664037713
Opioid	tramadol HCl	57664037718
Opioid	tramadol HCl	63739067110
Opioid	tramadol HCl	65162062710
Opioid	tramadol HCl	65162062711
Opioid	tramadol HCl	65162062750
Opioid	tramadol HCl	68084080801
Opioid	tramadol HCl	68180069706
Opioid	tramadol HCl	68382031901

Concurrent Prescription	Generic Name	NDC
Opioid	tramadol HCl	68382031910
Opioid	tramadol HCl	69543013610
Opioid	tramadol HCl	69543013611
Opioid	tramadol HCl	69543013650
Opioid	tramadol HCl	76439013611
Opioid	tramadol HCl	76439013650
Opioid	tramadol HCl/acetaminophen	53746061701
Opioid	tramadol HCl/acetaminophen	53746061705
Opioid	tramadol HCl/acetaminophen	57664053788
Opioid	tramadol HCl/acetaminophen	60505264401
Opioid	tramadol HCl/acetaminophen	68382033401
Opioid	tramadol HCl/acetaminophen	68382033405
Antidepressant	amitriptyline HCl	00378261001
Antidepressant	amitriptyline HCl	00378261010
Antidepressant	amitriptyline HCl	00378262501
Antidepressant	amitriptyline HCl	00378262510
Antidepressant	amitriptyline HCl	00378265001
Antidepressant	amitriptyline HCl	00378265010
Antidepressant	amitriptyline HCl	00378267501
Antidepressant	amitriptyline HCl	00378268501
Antidepressant	amitriptyline HCl	00378269501
Antidepressant	amitriptyline HCl	00603221221
Antidepressant	amitriptyline HCl	00603221232
Antidepressant	amitriptyline HCl	00603221321
Antidepressant	amitriptyline HCl	00603221332
Antidepressant	amitriptyline HCl	00603221421
Antidepressant	amitriptyline HCl	00603221432
Antidepressant	amitriptyline HCl	00603221521
Antidepressant	amitriptyline HCl	00603221525
Antidepressant	amitriptyline HCl	00603221621
Antidepressant	amitriptyline HCl	00603221625
Antidepressant	amitriptyline HCl	00603221721
Antidepressant	amitriptyline HCl	00781148601
Antidepressant	amitriptyline HCl	00781148610
Antidepressant	amitriptyline HCl	00781148701
Antidepressant	amitriptyline HCl	00781148710
Antidepressant	amitriptyline HCl	00781148801
Antidepressant	amitriptyline HCl	00781148810
Antidepressant	amitriptyline HCl	00781148901
Antidepressant	amitriptyline HCl	00781149001
Antidepressant	amitriptyline HCl	00781149101
Antidepressant	amitriptyline HCl	00904020161
Antidepressant	amitriptyline HCl	00904020261
Antidepressant	amitriptyline HCl	16714044601
Antidepressant	amitriptyline HCl	16714044602

Concurrent Prescription	Generic Name	NDC
Antidepressant	amitriptyline HCl	16714044701
Antidepressant	amitriptyline HCl	16714044702
Antidepressant	amitriptyline HCl	16714044801
Antidepressant	amitriptyline HCl	16714044802
Antidepressant	amitriptyline HCl	16714044901
Antidepressant	amitriptyline HCl	16714045001
Antidepressant	amitriptyline HCl	16714045101
Antidepressant	amitriptyline HCl	16729017101
Antidepressant	amitriptyline HCl	16729017117
Antidepressant	amitriptyline HCl	16729017201
Antidepressant	amitriptyline HCl	16729017217
Antidepressant	amitriptyline HCl	16729017301
Antidepressant	amitriptyline HCl	16729017317
Antidepressant	amitriptyline HCl	16729017401
Antidepressant	amitriptyline HCl	16729017501
Antidepressant	amitriptyline HCl	16729017601
Antidepressant	amitriptyline HCl	51079010720
Antidepressant	amitriptyline HCl	51079010763
Antidepressant	amitriptyline HCl	51079013120
Antidepressant	amitriptyline HCl	51079013163
Antidepressant	amitriptyline HCl	51079013320
Antidepressant	amitriptyline HCl	51079013363
Antidepressant	amitriptyline HCl	57664068818
Antidepressant	bupropion HCl	00115544513
Antidepressant	bupropion HCl	00115681108
Antidepressant	bupropion HCl	00115681110
Antidepressant	bupropion HCl	00173013555
Antidepressant	bupropion HCl	00173017755
Antidepressant	bupropion HCl	00173072200
Antidepressant	bupropion HCl	00173094755
Antidepressant	bupropion HCl	00185041001
Antidepressant	bupropion HCl	00185041005
Antidepressant	bupropion HCl	00185041060
Antidepressant	bupropion HCl	00185041501
Antidepressant	bupropion HCl	00185041505
Antidepressant	bupropion HCl	00185041552
Antidepressant	bupropion HCl	00185041560
Antidepressant	bupropion HCl	00185111160
Antidepressant	bupropion HCl	00187073030
Antidepressant	bupropion HCl	00187073090
Antidepressant	bupropion HCl	00187073130
Antidepressant	bupropion HCl	00378043301
Antidepressant	bupropion HCl	00378043501
Antidepressant	bupropion HCl	00378200877
Antidepressant	bupropion HCl	00378200905

Concurrent Prescription	Generic Name	NDC
Antidepressant	bupropion HCl	00378341101
Antidepressant	bupropion HCl	00378341105
Antidepressant	bupropion HCl	00378341201
Antidepressant	bupropion HCl	00378341205
Antidepressant	bupropion HCl	00378341301
Antidepressant	bupropion HCl	00591333105
Antidepressant	bupropion HCl	00591333119
Antidepressant	bupropion HCl	00591333130
Antidepressant	bupropion HCl	00591354005
Antidepressant	bupropion HCl	00591354060
Antidepressant	bupropion HCl	00591354105
Antidepressant	bupropion HCl	00591354125
Antidepressant	bupropion HCl	00591354160
Antidepressant	bupropion HCl	00591354260
Antidepressant	bupropion HCl	00781105301
Antidepressant	bupropion HCl	00781105310
Antidepressant	bupropion HCl	00781106401
Antidepressant	bupropion HCl	00781106410
Antidepressant	bupropion HCl	00781552831
Antidepressant	bupropion HCl	00781552910
Antidepressant	bupropion HCl	00781552931
Antidepressant	bupropion HCl	10370010100
Antidepressant	bupropion HCl	10370010103
Antidepressant	bupropion HCl	10370010150
Antidepressant	bupropion HCl	10370010203
Antidepressant	bupropion HCl	10370010250
Antidepressant	bupropion HCl	13668043060
Antidepressant	bupropion HCl	16729044315
Antidepressant	bupropion HCl	23155019101
Antidepressant	bupropion HCl	23155019201
Antidepressant	bupropion HCl	42806034809
Antidepressant	bupropion HCl	42806034905
Antidepressant	bupropion HCl	42806034909
Antidepressant	bupropion HCl	43547028809
Antidepressant	bupropion HCl	43547028810
Antidepressant	bupropion HCl	43547028850
Antidepressant	bupropion HCl	43547028909
Antidepressant	bupropion HCl	43547028910
Antidepressant	bupropion HCl	43547028950
Antidepressant	bupropion HCl	43547029009
Antidepressant	bupropion HCl	43547029010
Antidepressant	bupropion HCl	43598053601
Antidepressant	bupropion HCl	43598053660
Antidepressant	bupropion HCl	43598053705
Antidepressant	bupropion HCl	43598053760

Concurrent Prescription	Generic Name	NDC
Antidepressant	bupropion HCl	43598053860
Antidepressant	bupropion HCl	43598065505
Antidepressant	bupropion HCl	43598065530
Antidepressant	bupropion HCl	43598065605
Antidepressant	bupropion HCl	43598075160
Antidepressant	bupropion HCl	43598075205
Antidepressant	bupropion HCl	43598075260
Antidepressant	bupropion HCl	43598075360
Antidepressant	bupropion HCl	45963014130
Antidepressant	bupropion HCl	45963014190
Antidepressant	bupropion HCl	45963014205
Antidepressant	bupropion HCl	45963014230
Antidepressant	bupropion HCl	45963014290
Antidepressant	bupropion HCl	47335073613
Antidepressant	bupropion HCl	47335073686
Antidepressant	bupropion HCl	47335073688
Antidepressant	bupropion HCl	47335073713
Antidepressant	bupropion HCl	47335073786
Antidepressant	bupropion HCl	47335073788
Antidepressant	bupropion HCl	47335073886
Antidepressant	bupropion HCl	47781063730
Antidepressant	bupropion HCl	49909001030
Antidepressant	bupropion HCl	51079004720
Antidepressant	bupropion HCl	51079010903
Antidepressant	bupropion HCl	51079039220
Antidepressant	bupropion HCl	52427057530
Antidepressant	bupropion HCl	59746031560
Antidepressant	bupropion HCl	59746031660
Antidepressant	bupropion HCl	59746031760
Antidepressant	bupropion HCl	60505015701
Antidepressant	bupropion HCl	60505015801
Antidepressant	bupropion HCl	64679083001
Antidepressant	bupropion HCl	67767014205
Antidepressant	bupropion HCl	67767014230
Antidepressant	bupropion HCl	67767014290
Antidepressant	bupropion HCl	68001019800
Antidepressant	bupropion HCl	68001019900
Antidepressant	bupropion HCl	68001026403
Antidepressant	bupropion HCl	68001026404
Antidepressant	bupropion HCl	68001026405
Antidepressant	bupropion HCl	68001028703
Antidepressant	bupropion HCl	68001028704
Antidepressant	bupropion HCl	68001030800
Antidepressant	bupropion HCl	68001030900
Antidepressant	bupropion HCl	68001032103

Concurrent Prescription	Generic Name	NDC
Antidepressant	bupropion HCl	68001032105
Antidepressant	bupropion HCl	68001032203
Antidepressant	bupropion HCl	68001032205
Antidepressant	bupropion HCl	68180031902
Antidepressant	bupropion HCl	68180031906
Antidepressant	bupropion HCl	68180031909
Antidepressant	bupropion HCl	68180032002
Antidepressant	bupropion HCl	68180032006
Antidepressant	bupropion HCl	68180032009
Antidepressant	bupropion HCl	68382035405
Antidepressant	bupropion HCl	68382035406
Antidepressant	bupropion HCl	69097087502
Antidepressant	bupropion HCl	69097087505
Antidepressant	bupropion HCl	69097087512
Antidepressant	bupropion HCl	69097087602
Antidepressant	bupropion HCl	69097087612
Antidepressant	bupropion HCl	69097087703
Antidepressant	bupropion HCl	69097087712
Antidepressant	bupropion HCl	69097087803
Antidepressant	bupropion HCl	69097087807
Antidepressant	bupropion HCl	69097087812
Antidepressant	bupropion HCl	69097087903
Antidepressant	bupropion HCl	69097091707
Antidepressant	bupropion HCl	69097091807
Antidepressant	citalopram hydrobromide	00054006258
Antidepressant	citalopram hydrobromide	00093474205
Antidepressant	citalopram hydrobromide	00185037201
Antidepressant	citalopram hydrobromide	00185037301
Antidepressant	citalopram hydrobromide	00378623101
Antidepressant	citalopram hydrobromide	00378623105
Antidepressant	citalopram hydrobromide	00378623201
Antidepressant	citalopram hydrobromide	00378623205
Antidepressant	citalopram hydrobromide	00378623301
Antidepressant	citalopram hydrobromide	00378623305
Antidepressant	citalopram hydrobromide	00456402001
Antidepressant	citalopram hydrobromide	00456404001
Antidepressant	citalopram hydrobromide	00713474101
Antidepressant	citalopram hydrobromide	00904608461
Antidepressant	citalopram hydrobromide	13107000505
Antidepressant	citalopram hydrobromide	13107000601
Antidepressant	citalopram hydrobromide	13107000605
Antidepressant	citalopram hydrobromide	13668000901
Antidepressant	citalopram hydrobromide	13668000905
Antidepressant	citalopram hydrobromide	13668001001
Antidepressant	citalopram hydrobromide	13668001005

Concurrent Prescription	Generic Name	NDC
Antidepressant	citalopram hydrobromide	13668001101
Antidepressant	citalopram hydrobromide	13668001105
Antidepressant	citalopram hydrobromide	24658014001
Antidepressant	citalopram hydrobromide	24658014110
Antidepressant	citalopram hydrobromide	24658014201
Antidepressant	citalopram hydrobromide	24658014210
Antidepressant	citalopram hydrobromide	31722020601
Antidepressant	citalopram hydrobromide	31722020605
Antidepressant	citalopram hydrobromide	31722020701
Antidepressant	citalopram hydrobromide	31722020705
Antidepressant	citalopram hydrobromide	31722020801
Antidepressant	citalopram hydrobromide	31722020805
Antidepressant	citalopram hydrobromide	42806002110
Antidepressant	citalopram hydrobromide	54458088910
Antidepressant	citalopram hydrobromide	54458088916
Antidepressant	citalopram hydrobromide	54458098010
Antidepressant	citalopram hydrobromide	54458098016
Antidepressant	citalopram hydrobromide	54458098110
Antidepressant	citalopram hydrobromide	54458098112
Antidepressant	citalopram hydrobromide	54458098116
Antidepressant	citalopram hydrobromide	54838054070
Antidepressant	citalopram hydrobromide	57664050713
Antidepressant	citalopram hydrobromide	57664050813
Antidepressant	citalopram hydrobromide	57664050818
Antidepressant	citalopram hydrobromide	57664050888
Antidepressant	citalopram hydrobromide	57664050988
Antidepressant	citalopram hydrobromide	59746054301
Antidepressant	citalopram hydrobromide	59746054405
Antidepressant	citalopram hydrobromide	59746054601
Antidepressant	citalopram hydrobromide	59746054605
Antidepressant	citalopram hydrobromide	65162005203
Antidepressant	citalopram hydrobromide	65162005210
Antidepressant	citalopram hydrobromide	65162005250
Antidepressant	citalopram hydrobromide	65162005303
Antidepressant	citalopram hydrobromide	65162005310
Antidepressant	citalopram hydrobromide	65162005350
Antidepressant	citalopram hydrobromide	65162005403
Antidepressant	citalopram hydrobromide	65162005410
Antidepressant	citalopram hydrobromide	65162005450
Antidepressant	citalopram hydrobromide	65862000501
Antidepressant	citalopram hydrobromide	65862000505
Antidepressant	citalopram hydrobromide	65862000601
Antidepressant	citalopram hydrobromide	65862000605
Antidepressant	citalopram hydrobromide	65862000701
Antidepressant	citalopram hydrobromide	65862000705

Concurrent Prescription	Generic Name	NDC
Antidepressant	citalopram hydrobromide	68645046754
Antidepressant	citalopram hydrobromide	68645051454
Antidepressant	citalopram hydrobromide	68645055954
Antidepressant	citalopram hydrobromide	68645056954
Antidepressant	citalopram hydrobromide	68645057054
Antidepressant	citalopram hydrobromide	68645057154
Antidepressant	citalopram hydrobromide	69097082207
Antidepressant	citalopram hydrobromide	69097082307
Antidepressant	citalopram hydrobromide	69097082312
Antidepressant	citalopram hydrobromide	69097082407
Antidepressant	citalopram hydrobromide	69097082412
Antidepressant	citalopram hydrobromide	76282020710
Antidepressant	clomipramine HCl	00378302501
Antidepressant	clomipramine HCl	00378305001
Antidepressant	clomipramine HCl	00378307501
Antidepressant	clomipramine HCl	00406880601
Antidepressant	clomipramine HCl	00406880701
Antidepressant	clomipramine HCl	00406880801
Antidepressant	clomipramine HCl	00781202701
Antidepressant	clomipramine HCl	00781203701
Antidepressant	clomipramine HCl	00781204701
Antidepressant	clomipramine HCl	00832063011
Antidepressant	clomipramine HCl	00832063111
Antidepressant	clomipramine HCl	00832063211
Antidepressant	clomipramine HCl	51672401105
Antidepressant	clomipramine HCl	51672401106
Antidepressant	clomipramine HCl	51672401205
Antidepressant	clomipramine HCl	51672401206
Antidepressant	clomipramine HCl	51672401305
Antidepressant	clomipramine HCl	51672401306
Antidepressant	desipramine HCl	00781197201
Antidepressant	desipramine HCl	00781197301
Antidepressant	desipramine HCl	00781197401
Antidepressant	desipramine HCl	00781197501
Antidepressant	desipramine HCl	00781197650
Antidepressant	desipramine HCl	00781521801
Antidepressant	desipramine HCl	00955103110
Antidepressant	desipramine HCl	23155058001
Antidepressant	desipramine HCl	23155058101
Antidepressant	desipramine HCl	23155058325
Antidepressant	desipramine HCl	45963034102
Antidepressant	desipramine HCl	45963034202
Antidepressant	desipramine HCl	45963034302
Antidepressant	desipramine HCl	45963034502
Antidepressant	desipramine HCl	45963034650

Concurrent Prescription	Generic Name	NDC
Antidepressant	desipramine HCl	69238105301
Antidepressant	desipramine HCl	69238105501
Antidepressant	desipramine HCl	69238105701
Antidepressant	desipramine HCl	69238106101
Antidepressant	desvenlafaxine	44183088031
Antidepressant	desvenlafaxine	44183089031
Antidepressant	desvenlafaxine	63304019130
Antidepressant	desvenlafaxine	63304019230
Antidepressant	desvenlafaxine succinate	00008121030
Antidepressant	desvenlafaxine succinate	00008121101
Antidepressant	desvenlafaxine succinate	00008121114
Antidepressant	desvenlafaxine succinate	00008121130
Antidepressant	desvenlafaxine succinate	00008122201
Antidepressant	desvenlafaxine succinate	00008122214
Antidepressant	desvenlafaxine succinate	00008122230
Antidepressant	desvenlafaxine succinate	00008122250
Antidepressant	desvenlafaxine succinate	00054040013
Antidepressant	desvenlafaxine succinate	00054040022
Antidepressant	desvenlafaxine succinate	00054040113
Antidepressant	desvenlafaxine succinate	00054040122
Antidepressant	desvenlafaxine succinate	00054060313
Antidepressant	desvenlafaxine succinate	00378423077
Antidepressant	desvenlafaxine succinate	00378423093
Antidepressant	desvenlafaxine succinate	00378423177
Antidepressant	desvenlafaxine succinate	00378423193
Antidepressant	desvenlafaxine succinate	00591365930
Antidepressant	desvenlafaxine succinate	00591366030
Antidepressant	desvenlafaxine succinate	00591406030
Antidepressant	desvenlafaxine succinate	51991031133
Antidepressant	desvenlafaxine succinate	51991031190
Antidepressant	desvenlafaxine succinate	51991031233
Antidepressant	desvenlafaxine succinate	51991031290
Antidepressant	desvenlafaxine succinate	59762121003
Antidepressant	desvenlafaxine succinate	59762121103
Antidepressant	desvenlafaxine succinate	59762122203
Antidepressant	desvenlafaxine succinate	68180059206
Antidepressant	desvenlafaxine succinate	68180059209
Antidepressant	desvenlafaxine succinate	68180059306
Antidepressant	desvenlafaxine succinate	68180059309
Antidepressant	doxepin HCl	00093961212
Antidepressant	doxepin HCl	00378104901
Antidepressant	doxepin HCl	00378104910
Antidepressant	doxepin HCl	00378312501
Antidepressant	doxepin HCl	00378312510
Antidepressant	doxepin HCl	00378425001

Concurrent Prescription	Generic Name	NDC
Antidepressant	doxepin HCl	00378425010
Antidepressant	doxepin HCl	00378537501
Antidepressant	doxepin HCl	00378641001
Antidepressant	doxepin HCl	49884021701
Antidepressant	doxepin HCl	49884021801
Antidepressant	doxepin HCl	49884021901
Antidepressant	doxepin HCl	49884022001
Antidepressant	doxepin HCl	49884022201
Antidepressant	doxepin HCl	49884022203
Antidepressant	doxepin HCl	49884022205
Antidepressant	doxepin HCl	51079043620
Antidepressant	doxepin HCl	51079043720
Antidepressant	doxepin HCl	51079065120
Antidepressant	doxepin HCl	54838051240
Antidepressant	doxepin HCl	60432065104
Antidepressant	doxepin HCl	69238116609
Antidepressant	doxepin HCl	69238117009
Antidepressant	doxepin HCl	69238117109
Antidepressant	doxepin HCl	69238117309
Antidepressant	duloxetine HCl	00002323560
Antidepressant	duloxetine HCl	00002324030
Antidepressant	duloxetine HCl	00002324090
Antidepressant	duloxetine HCl	00002327004
Antidepressant	duloxetine HCl	00002327030
Antidepressant	duloxetine HCl	00093754206
Antidepressant	duloxetine HCl	00093754356
Antidepressant	duloxetine HCl	00093754456
Antidepressant	duloxetine HCl	00228289006
Antidepressant	duloxetine HCl	00228289103
Antidepressant	duloxetine HCl	00228289150
Antidepressant	duloxetine HCl	00228289203
Antidepressant	duloxetine HCl	00228289296
Antidepressant	duloxetine HCl	13668010960
Antidepressant	duloxetine HCl	13668011005
Antidepressant	duloxetine HCl	13668011030
Antidepressant	duloxetine HCl	13668011105
Antidepressant	duloxetine HCl	13668011130
Antidepressant	duloxetine HCl	13811066260
Antidepressant	duloxetine HCl	13811066330
Antidepressant	duloxetine HCl	13811066430
Antidepressant	duloxetine HCl	27241009706
Antidepressant	duloxetine HCl	27241009803
Antidepressant	duloxetine HCl	27241009809
Antidepressant	duloxetine HCl	27241009903
Antidepressant	duloxetine HCl	27241009990

Concurrent Prescription	Generic Name	NDC
Antidepressant	duloxetine HCl	31722058160
Antidepressant	duloxetine HCl	31722058230
Antidepressant	duloxetine HCl	31722058330
Antidepressant	duloxetine HCl	43547037906
Antidepressant	duloxetine HCl	43547038003
Antidepressant	duloxetine HCl	43547038009
Antidepressant	duloxetine HCl	43547038103
Antidepressant	duloxetine HCl	43547038111
Antidepressant	duloxetine HCl	47335038186
Antidepressant	duloxetine HCl	47335038188
Antidepressant	duloxetine HCl	47335038281
Antidepressant	duloxetine HCl	47335038283
Antidepressant	duloxetine HCl	47335038318
Antidepressant	duloxetine HCl	47335038383
Antidepressant	duloxetine HCl	51991074605
Antidepressant	duloxetine HCl	51991074690
Antidepressant	duloxetine HCl	51991074710
Antidepressant	duloxetine HCl	51991074790
Antidepressant	duloxetine HCl	51991074810
Antidepressant	duloxetine HCl	51991074890
Antidepressant	duloxetine HCl	51991075033
Antidepressant	duloxetine HCl	55111060860
Antidepressant	duloxetine HCl	55111060930
Antidepressant	duloxetine HCl	55111061030
Antidepressant	duloxetine HCl	57237001760
Antidepressant	duloxetine HCl	57237001830
Antidepressant	duloxetine HCl	57237001890
Antidepressant	duloxetine HCl	57237001899
Antidepressant	duloxetine HCl	57237001930
Antidepressant	duloxetine HCl	57237001990
Antidepressant	duloxetine HCl	57237001999
Antidepressant	duloxetine HCl	60505299506
Antidepressant	duloxetine HCl	60505299603
Antidepressant	duloxetine HCl	60505299703
Antidepressant	duloxetine HCl	66993066260
Antidepressant	duloxetine HCl	66993066305
Antidepressant	duloxetine HCl	66993066330
Antidepressant	duloxetine HCl	66993066405
Antidepressant	duloxetine HCl	66993066430
Antidepressant	duloxetine HCl	68001025506
Antidepressant	duloxetine HCl	68001025604
Antidepressant	duloxetine HCl	68001025605
Antidepressant	duloxetine HCl	68001025608
Antidepressant	duloxetine HCl	68001025704
Antidepressant	duloxetine HCl	68001025708

Concurrent Prescription	Generic Name	NDC
Antidepressant	duloxetine HCl	68084068301
Antidepressant	duloxetine HCl	68180029407
Antidepressant	duloxetine HCl	68180029503
Antidepressant	duloxetine HCl	68180029506
Antidepressant	duloxetine HCl	68180029509
Antidepressant	duloxetine HCl	68180029603
Antidepressant	duloxetine HCl	68180029606
Antidepressant	duloxetine HCl	68180029609
Antidepressant	duloxetine HCl	68180029706
Antidepressant	duloxetine HCl	68382038514
Antidepressant	duloxetine HCl	68382038606
Antidepressant	duloxetine HCl	68382038706
Antidepressant	duloxetine HCl	69097029703
Antidepressant	duloxetine HCl	69097029802
Antidepressant	duloxetine HCl	69097029902
Antidepressant	escitalopram oxalate	00093585001
Antidepressant	escitalopram oxalate	00093585005
Antidepressant	escitalopram oxalate	00093585101
Antidepressant	escitalopram oxalate	00093585105
Antidepressant	escitalopram oxalate	00093585201
Antidepressant	escitalopram oxalate	00093585205
Antidepressant	escitalopram oxalate	00378385577
Antidepressant	escitalopram oxalate	00378385610
Antidepressant	escitalopram oxalate	00378385677
Antidepressant	escitalopram oxalate	00378385710
Antidepressant	escitalopram oxalate	00378385777
Antidepressant	escitalopram oxalate	00456200501
Antidepressant	escitalopram oxalate	00456201001
Antidepressant	escitalopram oxalate	00456202001
Antidepressant	escitalopram oxalate	13668013501
Antidepressant	escitalopram oxalate	13668013505
Antidepressant	escitalopram oxalate	13668013601
Antidepressant	escitalopram oxalate	13668013605
Antidepressant	escitalopram oxalate	13668013610
Antidepressant	escitalopram oxalate	13668013701
Antidepressant	escitalopram oxalate	13668013705
Antidepressant	escitalopram oxalate	13668013710
Antidepressant	escitalopram oxalate	16729016801
Antidepressant	escitalopram oxalate	16729016817
Antidepressant	escitalopram oxalate	16729016901
Antidepressant	escitalopram oxalate	16729016917
Antidepressant	escitalopram oxalate	16729017001
Antidepressant	escitalopram oxalate	16729017017
Antidepressant	escitalopram oxalate	31722024990
Antidepressant	escitalopram oxalate	31722025090

Concurrent Prescription	Generic Name	NDC
Antidepressant	escitalopram oxalate	31722025190
Antidepressant	escitalopram oxalate	31722056924
Antidepressant	escitalopram oxalate	33342003711
Antidepressant	escitalopram oxalate	43547028010
Antidepressant	escitalopram oxalate	43547028011
Antidepressant	escitalopram oxalate	43547028110
Antidepressant	escitalopram oxalate	43547028111
Antidepressant	escitalopram oxalate	43547028210
Antidepressant	escitalopram oxalate	54838055170
Antidepressant	escitalopram oxalate	54879001001
Antidepressant	escitalopram oxalate	59746027901
Antidepressant	escitalopram oxalate	59746028001
Antidepressant	escitalopram oxalate	59746028101
Antidepressant	escitalopram oxalate	65162070588
Antidepressant	escitalopram oxalate	65862037301
Antidepressant	escitalopram oxalate	65862037401
Antidepressant	escitalopram oxalate	65862037405
Antidepressant	escitalopram oxalate	65862037501
Antidepressant	escitalopram oxalate	65862037505
Antidepressant	escitalopram oxalate	68001019500
Antidepressant	escitalopram oxalate	68001019600
Antidepressant	escitalopram oxalate	68001019603
Antidepressant	escitalopram oxalate	68001019700
Antidepressant	escitalopram oxalate	68001019703
Antidepressant	escitalopram oxalate	68084061701
Antidepressant	escitalopram oxalate	68180013501
Antidepressant	escitalopram oxalate	68180013601
Antidepressant	escitalopram oxalate	68180013701
Antidepressant	escitalopram oxalate	68645044770
Antidepressant	escitalopram oxalate	68645044870
Antidepressant	escitalopram oxalate	68645051954
Antidepressant	escitalopram oxalate	68645052054
Antidepressant	escitalopram oxalate	69097084705
Antidepressant	escitalopram oxalate	69097084805
Antidepressant	escitalopram oxalate	69097084905
Antidepressant	escitalopram oxalate	76282024990
Antidepressant	escitalopram oxalate	76282025010
Antidepressant	escitalopram oxalate	76282025090
Antidepressant	escitalopram oxalate	76282025110
Antidepressant	escitalopram oxalate	76282025190
Antidepressant	fluoxetine HCl	00093718810
Antidepressant	fluoxetine HCl	00093718856
Antidepressant	fluoxetine HCl	00093719801
Antidepressant	fluoxetine HCl	00093719805
Antidepressant	fluoxetine HCl	00093719856

Concurrent Prescription	Generic Name	NDC
Antidepressant	fluoxetine HCl	00121072104
Antidepressant	fluoxetine HCl	00378073401
Antidepressant	fluoxetine HCl	00378073493
Antidepressant	fluoxetine HCl	00378073501
Antidepressant	fluoxetine HCl	00378073593
Antidepressant	fluoxetine HCl	00378541028
Antidepressant	fluoxetine HCl	00378542028
Antidepressant	fluoxetine HCl	00777310402
Antidepressant	fluoxetine HCl	00777310502
Antidepressant	fluoxetine HCl	00777310530
Antidepressant	fluoxetine HCl	00777310730
Antidepressant	fluoxetine HCl	00781282201
Antidepressant	fluoxetine HCl	00781282210
Antidepressant	fluoxetine HCl	00781282301
Antidepressant	fluoxetine HCl	00781282310
Antidepressant	fluoxetine HCl	00781282401
Antidepressant	fluoxetine HCl	00781282410
Antidepressant	fluoxetine HCl	00781282431
Antidepressant	fluoxetine HCl	00904578561
Antidepressant	fluoxetine HCl	13668044330
Antidepressant	fluoxetine HCl	13668047330
Antidepressant	fluoxetine HCl	13668047391
Antidepressant	fluoxetine HCl	16714035201
Antidepressant	fluoxetine HCl	16714035301
Antidepressant	fluoxetine HCl	31722090301
Antidepressant	fluoxetine HCl	31722090401
Antidepressant	fluoxetine HCl	31722090405
Antidepressant	fluoxetine HCl	31722090410
Antidepressant	fluoxetine HCl	42543072501
Antidepressant	fluoxetine HCl	42543072510
Antidepressant	fluoxetine HCl	42543072601
Antidepressant	fluoxetine HCl	42543072610
Antidepressant	fluoxetine HCl	42543072701
Antidepressant	fluoxetine HCl	42543072705
Antidepressant	fluoxetine HCl	42543072730
Antidepressant	fluoxetine HCl	43598056601
Antidepressant	fluoxetine HCl	47781060030
Antidepressant	fluoxetine HCl	49884033501
Antidepressant	fluoxetine HCl	49884033511
Antidepressant	fluoxetine HCl	49884033601
Antidepressant	fluoxetine HCl	49884033611
Antidepressant	fluoxetine HCl	49884046811
Antidepressant	fluoxetine HCl	49884073501
Antidepressant	fluoxetine HCl	49884087201
Antidepressant	fluoxetine HCl	49884087205

Concurrent Prescription	Generic Name	NDC
Antidepressant	fluoxetine HCl	49884087211
Antidepressant	fluoxetine HCl	49909000530
Antidepressant	fluoxetine HCl	50111064701
Antidepressant	fluoxetine HCl	50111064702
Antidepressant	fluoxetine HCl	50111064703
Antidepressant	fluoxetine HCl	50111064801
Antidepressant	fluoxetine HCl	50111064802
Antidepressant	fluoxetine HCl	50111064803
Antidepressant	fluoxetine HCl	50111064844
Antidepressant	fluoxetine HCl	52427057630
Antidepressant	fluoxetine HCl	54838052340
Antidepressant	fluoxetine HCl	55111014810
Antidepressant	fluoxetine HCl	55111015001
Antidepressant	fluoxetine HCl	55111015010
Antidepressant	fluoxetine HCl	55111015030
Antidepressant	fluoxetine HCl	55111028448
Antidepressant	fluoxetine HCl	62332002231
Antidepressant	fluoxetine HCl	62332002291
Antidepressant	fluoxetine HCl	62332002331
Antidepressant	fluoxetine HCl	62332002430
Antidepressant	fluoxetine HCl	62332002431
Antidepressant	fluoxetine HCl	62332002491
Antidepressant	fluoxetine HCl	62332024230
Antidepressant	fluoxetine HCl	62332024330
Antidepressant	fluoxetine HCl	62332024331
Antidepressant	fluoxetine HCl	63304063201
Antidepressant	fluoxetine HCl	63304063230
Antidepressant	fluoxetine HCl	65862019201
Antidepressant	fluoxetine HCl	65862019299
Antidepressant	fluoxetine HCl	65862019301
Antidepressant	fluoxetine HCl	65862019399
Antidepressant	fluoxetine HCl	65862019401
Antidepressant	fluoxetine HCl	65862019405
Antidepressant	fluoxetine HCl	65862019430
Antidepressant	fluoxetine HCl	65862019499
Antidepressant	fluoxetine HCl	68001012900
Antidepressant	fluoxetine HCl	68001012903
Antidepressant	fluoxetine HCl	68645013054
Antidepressant	fluoxetine HCl	68645013154
Antidepressant	fluoxetine HCl	75834014830
Antidepressant	fluvoxamine maleate	00228284803
Antidepressant	fluvoxamine maleate	00228284903
Antidepressant	fluvoxamine maleate	00378040701
Antidepressant	fluvoxamine maleate	00378041201
Antidepressant	fluvoxamine maleate	00378041401

Concurrent Prescription	Generic Name	NDC
Antidepressant	fluvoxamine maleate	10370017511
Antidepressant	fluvoxamine maleate	10370017611
Antidepressant	fluvoxamine maleate	60505016401
Antidepressant	fluvoxamine maleate	60505016501
Antidepressant	fluvoxamine maleate	60505016601
Antidepressant	fluvoxamine maleate	62559015801
Antidepressant	fluvoxamine maleate	62559015901
Antidepressant	fluvoxamine maleate	62559016001
Antidepressant	imipramine HCl	00781176201
Antidepressant	imipramine HCl	00781176401
Antidepressant	imipramine HCl	00781176601
Antidepressant	imipramine HCl	00781176613
Antidepressant	imipramine HCl	49884005401
Antidepressant	imipramine HCl	49884005501
Antidepressant	imipramine HCl	49884005510
Antidepressant	imipramine HCl	49884005601
Antidepressant	imipramine HCl	49884005610
Antidepressant	imipramine HCl	53489033001
Antidepressant	imipramine HCl	53489033101
Antidepressant	imipramine HCl	53489033201
Antidepressant	imipramine HCl	64125013301
Antidepressant	imipramine HCl	64125013501
Antidepressant	imipramine HCl	68180031201
Antidepressant	imipramine HCl	68180031301
Antidepressant	imipramine HCl	69315013301
Antidepressant	imipramine HCl	69315013401
Antidepressant	imipramine HCl	69315013501
Antidepressant	imipramine pamoate	00054027313
Antidepressant	imipramine pamoate	00054027413
Antidepressant	imipramine pamoate	00054027613
Antidepressant	imipramine pamoate	68180031406
Antidepressant	imipramine pamoate	68180031506
Antidepressant	levomilnacipran HCl	00456220228
Antidepressant	levomilnacipran HCl	00456221230
Antidepressant	levomilnacipran HCl	00456222030
Antidepressant	levomilnacipran HCl	00456224030
Antidepressant	levomilnacipran HCl	00456228030
Antidepressant	mirtazapine	00093720656
Antidepressant	mirtazapine	00093720756
Antidepressant	mirtazapine	00093720856
Antidepressant	mirtazapine	00093730465
Antidepressant	mirtazapine	00115165308
Antidepressant	mirtazapine	00115165408
Antidepressant	mirtazapine	00378351501
Antidepressant	mirtazapine	00378351510

Concurrent Prescription	Generic Name	NDC
Antidepressant	mirtazapine	00378351593
Antidepressant	mirtazapine	00378353001
Antidepressant	mirtazapine	00378353005
Antidepressant	mirtazapine	00378353070
Antidepressant	mirtazapine	00378353093
Antidepressant	mirtazapine	00378354501
Antidepressant	mirtazapine	00378354505
Antidepressant	mirtazapine	00378354570
Antidepressant	mirtazapine	00378354593
Antidepressant	mirtazapine	00591111710
Antidepressant	mirtazapine	00591111730
Antidepressant	mirtazapine	00591111810
Antidepressant	mirtazapine	00591111830
Antidepressant	mirtazapine	00591111930
Antidepressant	mirtazapine	00591246915
Antidepressant	mirtazapine	00591247015
Antidepressant	mirtazapine	13107000105
Antidepressant	mirtazapine	13107000130
Antidepressant	mirtazapine	13107000305
Antidepressant	mirtazapine	13107000334
Antidepressant	mirtazapine	13107003105
Antidepressant	mirtazapine	13107003134
Antidepressant	mirtazapine	13107003205
Antidepressant	mirtazapine	13107003234
Antidepressant	mirtazapine	16714070601
Antidepressant	mirtazapine	16714070701
Antidepressant	mirtazapine	16714070801
Antidepressant	mirtazapine	16714070901
Antidepressant	mirtazapine	51079008620
Antidepressant	mirtazapine	51079008656
Antidepressant	mirtazapine	51079008820
Antidepressant	mirtazapine	57237000705
Antidepressant	mirtazapine	57237000730
Antidepressant	mirtazapine	57237000805
Antidepressant	mirtazapine	57237000830
Antidepressant	mirtazapine	57237000905
Antidepressant	mirtazapine	57237000930
Antidepressant	mirtazapine	57237001005
Antidepressant	mirtazapine	57237001030
Antidepressant	mirtazapine	57237001106
Antidepressant	mirtazapine	57237001206
Antidepressant	mirtazapine	57237001306
Antidepressant	mirtazapine	57664049983
Antidepressant	mirtazapine	57664050018
Antidepressant	mirtazapine	57664050083

Concurrent Prescription	Generic Name	NDC
Antidepressant	mirtazapine	57664050183
Antidepressant	mirtazapine	57664051083
Antidepressant	mirtazapine	60505024701
Antidepressant	mirtazapine	60505024708
Antidepressant	mirtazapine	60505024801
Antidepressant	mirtazapine	60505024808
Antidepressant	mirtazapine	60505024901
Antidepressant	mirtazapine	60505024908
Antidepressant	mirtazapine	63739035510
Antidepressant	mirtazapine	63739035610
Antidepressant	mirtazapine	65862002106
Antidepressant	mirtazapine	65862002206
Antidepressant	mirtazapine	65862002306
Antidepressant	mirtazapine	66993070930
Antidepressant	mirtazapine	66993071130
Antidepressant	mirtazapine	66993071230
Antidepressant	nortriptyline HCl	00093081001
Antidepressant	nortriptyline HCl	00093081005
Antidepressant	nortriptyline HCl	00093081101
Antidepressant	nortriptyline HCl	00093081105
Antidepressant	nortriptyline HCl	00093081201
Antidepressant	nortriptyline HCl	00093081205
Antidepressant	nortriptyline HCl	00093081301
Antidepressant	nortriptyline HCl	00093081305
Antidepressant	nortriptyline HCl	00121067816
Antidepressant	nortriptyline HCl	00591578601
Antidepressant	nortriptyline HCl	00591578605
Antidepressant	nortriptyline HCl	00591578701
Antidepressant	nortriptyline HCl	00591578705
Antidepressant	nortriptyline HCl	00591578710
Antidepressant	nortriptyline HCl	00591578801
Antidepressant	nortriptyline HCl	00591578901
Antidepressant	nortriptyline HCl	51672400101
Antidepressant	nortriptyline HCl	51672400102
Antidepressant	nortriptyline HCl	51672400105
Antidepressant	nortriptyline HCl	51672400201
Antidepressant	nortriptyline HCl	51672400202
Antidepressant	nortriptyline HCl	51672400205
Antidepressant	nortriptyline HCl	51672400301
Antidepressant	nortriptyline HCl	51672400302
Antidepressant	nortriptyline HCl	51672400305
Antidepressant	nortriptyline HCl	51672400401
Antidepressant	nortriptyline HCl	51672400405
Antidepressant	nortriptyline HCl	51862001501
Antidepressant	nortriptyline HCl	51862001505

Concurrent Prescription	Generic Name	NDC
Antidepressant	nortriptyline HCl	51862001601
Antidepressant	nortriptyline HCl	51862001605
Antidepressant	nortriptyline HCl	51862001701
Antidepressant	nortriptyline HCl	51862001801
Antidepressant	paroxetine HCl	00093711598
Antidepressant	paroxetine HCl	00093711698
Antidepressant	paroxetine HCl	00093712198
Antidepressant	paroxetine HCl	00378200393
Antidepressant	paroxetine HCl	00378200493
Antidepressant	paroxetine HCl	00378200593
Antidepressant	paroxetine HCl	00378700110
Antidepressant	paroxetine HCl	00378700193
Antidepressant	paroxetine HCl	00378700210
Antidepressant	paroxetine HCl	00378700293
Antidepressant	paroxetine HCl	00378700310
Antidepressant	paroxetine HCl	00378700393
Antidepressant	paroxetine HCl	00378700410
Antidepressant	paroxetine HCl	00378700493
Antidepressant	paroxetine HCl	00904567861
Antidepressant	paroxetine HCl	13107015405
Antidepressant	paroxetine HCl	13107015430
Antidepressant	paroxetine HCl	13107015490
Antidepressant	paroxetine HCl	13107015530
Antidepressant	paroxetine HCl	13107015599
Antidepressant	paroxetine HCl	13107015630
Antidepressant	paroxetine HCl	13107015699
Antidepressant	paroxetine HCl	13107015705
Antidepressant	paroxetine HCl	13107015730
Antidepressant	paroxetine HCl	13107015790
Antidepressant	paroxetine HCl	13107015799
Antidepressant	paroxetine HCl	43547034703
Antidepressant	paroxetine HCl	43547034709
Antidepressant	paroxetine HCl	43547034711
Antidepressant	paroxetine HCl	43547034803
Antidepressant	paroxetine HCl	43547034809
Antidepressant	paroxetine HCl	43547034811
Antidepressant	paroxetine HCl	43547034903
Antidepressant	paroxetine HCl	43547034909
Antidepressant	paroxetine HCl	43547034950
Antidepressant	paroxetine HCl	43547035003
Antidepressant	paroxetine HCl	43547035009
Antidepressant	paroxetine HCl	43547035011
Antidepressant	paroxetine HCl	52817014050
Antidepressant	paroxetine HCl	52817014090
Antidepressant	paroxetine HCl	52817014190

Concurrent Prescription	Generic Name	NDC
Antidepressant	paroxetine HCl	52817014390
Antidepressant	paroxetine HCl	54458098810
Antidepressant	paroxetine HCl	54458098816
Antidepressant	paroxetine HCl	54458098910
Antidepressant	paroxetine HCl	54458098916
Antidepressant	paroxetine HCl	54458099010
Antidepressant	paroxetine HCl	54458099016
Antidepressant	paroxetine HCl	57664042513
Antidepressant	paroxetine HCl	59746045710
Antidepressant	paroxetine HCl	59746045890
Antidepressant	paroxetine HCl	59746046010
Antidepressant	paroxetine HCl	60505008301
Antidepressant	paroxetine HCl	60505008302
Antidepressant	paroxetine HCl	60505008304
Antidepressant	paroxetine HCl	60505008401
Antidepressant	paroxetine HCl	60505008402
Antidepressant	paroxetine HCl	60505008404
Antidepressant	paroxetine HCl	60505009701
Antidepressant	paroxetine HCl	60505009702
Antidepressant	paroxetine HCl	60505010101
Antidepressant	paroxetine HCl	60505010102
Antidepressant	paroxetine HCl	60505010104
Antidepressant	paroxetine HCl	60505040205
Antidepressant	paroxetine HCl	60505366403
Antidepressant	paroxetine HCl	60505366603
Antidepressant	paroxetine HCl	60505367303
Antidepressant	paroxetine HCl	60505367403
Antidepressant	paroxetine HCl	60505367503
Antidepressant	paroxetine HCl	62175047032
Antidepressant	paroxetine HCl	62175047132
Antidepressant	paroxetine HCl	62175047232
Antidepressant	paroxetine HCl	63739096310
Antidepressant	paroxetine HCl	68180064506
Antidepressant	paroxetine HCl	68180064606
Antidepressant	paroxetine HCl	68180064706
Antidepressant	paroxetine HCl	68382000105
Antidepressant	paroxetine HCl	68382000106
Antidepressant	paroxetine HCl	68382000116
Antidepressant	paroxetine HCl	68382009705
Antidepressant	paroxetine HCl	68382009706
Antidepressant	paroxetine HCl	68382009710
Antidepressant	paroxetine HCl	68382009716
Antidepressant	paroxetine HCl	68382009801
Antidepressant	paroxetine HCl	68382009805
Antidepressant	paroxetine HCl	68382009806

Concurrent Prescription	Generic Name	NDC
Antidepressant	paroxetine HCl	68382009810
Antidepressant	paroxetine HCl	68382009816
Antidepressant	paroxetine HCl	68382009905
Antidepressant	paroxetine HCl	68382009906
Antidepressant	paroxetine HCl	68382009910
Antidepressant	paroxetine HCl	68382009916
Antidepressant	phenelzine sulfate	00071035060
Antidepressant	phenelzine sulfate	43386036021
Antidepressant	phenelzine sulfate	59762011901
Antidepressant	protriptyline HCl	00054021025
Antidepressant	protriptyline HCl	00054021125
Antidepressant	protriptyline HCl	50383095910
Antidepressant	protriptyline HCl	64980015801
Antidepressant	protriptyline HCl	64980015901
Antidepressant	sertraline HCl	00049490030
Antidepressant	sertraline HCl	00049491030
Antidepressant	sertraline HCl	00378812101
Antidepressant	sertraline HCl	00378812105
Antidepressant	sertraline HCl	00378812701
Antidepressant	sertraline HCl	00378812705
Antidepressant	sertraline HCl	16714060102
Antidepressant	sertraline HCl	16714061101
Antidepressant	sertraline HCl	16714061104
Antidepressant	sertraline HCl	16714061105
Antidepressant	sertraline HCl	16714061201
Antidepressant	sertraline HCl	16714061204
Antidepressant	sertraline HCl	16714061205
Antidepressant	sertraline HCl	16714061206
Antidepressant	sertraline HCl	16714061301
Antidepressant	sertraline HCl	16714061304
Antidepressant	sertraline HCl	16714061305
Antidepressant	sertraline HCl	16714061306
Antidepressant	sertraline HCl	16729021510
Antidepressant	sertraline HCl	16729021615
Antidepressant	sertraline HCl	16729021616
Antidepressant	sertraline HCl	16729021715
Antidepressant	sertraline HCl	16729021716
Antidepressant	sertraline HCl	31722021205
Antidepressant	sertraline HCl	31722021230
Antidepressant	sertraline HCl	31722021290
Antidepressant	sertraline HCl	31722021305
Antidepressant	sertraline HCl	31722021330
Antidepressant	sertraline HCl	31722021405
Antidepressant	sertraline HCl	31722021430
Antidepressant	sertraline HCl	54458094710

Concurrent Prescription	Generic Name	NDC
Antidepressant	sertraline HCl	59762006701
Antidepressant	sertraline HCl	59762490001
Antidepressant	sertraline HCl	59762490002
Antidepressant	sertraline HCl	59762490004
Antidepressant	sertraline HCl	59762490005
Antidepressant	sertraline HCl	59762491001
Antidepressant	sertraline HCl	59762491002
Antidepressant	sertraline HCl	59762491004
Antidepressant	sertraline HCl	59762491005
Antidepressant	sertraline HCl	59762494001
Antidepressant	sertraline HCl	59762496001
Antidepressant	sertraline HCl	65862001101
Antidepressant	sertraline HCl	65862001105
Antidepressant	sertraline HCl	65862001130
Antidepressant	sertraline HCl	65862001201
Antidepressant	sertraline HCl	65862001205
Antidepressant	sertraline HCl	65862001230
Antidepressant	sertraline HCl	65862001301
Antidepressant	sertraline HCl	65862001305
Antidepressant	sertraline HCl	65862001330
Antidepressant	sertraline HCl	68180035106
Antidepressant	sertraline HCl	68180035109
Antidepressant	sertraline HCl	68180035202
Antidepressant	sertraline HCl	68180035205
Antidepressant	sertraline HCl	68180035206
Antidepressant	sertraline HCl	68180035209
Antidepressant	sertraline HCl	68180035302
Antidepressant	sertraline HCl	68180035305
Antidepressant	sertraline HCl	68180035306
Antidepressant	sertraline HCl	68180035309
Antidepressant	sertraline HCl	68645048770
Antidepressant	sertraline HCl	68645048870
Antidepressant	sertraline HCl	68645048970
Antidepressant	sertraline HCl	68645049801
Antidepressant	sertraline HCl	68645049901
Antidepressant	sertraline HCl	68645050001
Antidepressant	sertraline HCl	68645052154
Antidepressant	sertraline HCl	68645052254
Antidepressant	sertraline HCl	68645052354
Antidepressant	sertraline HCl	69097083302
Antidepressant	sertraline HCl	69097083305
Antidepressant	sertraline HCl	69097083312
Antidepressant	sertraline HCl	69097083402
Antidepressant	sertraline HCl	69097083412
Antidepressant	sertraline HCl	69097083502

Concurrent Prescription	Generic Name	NDC
Antidepressant	sertraline HCl	69097083512
Antidepressant	sertraline HCl	76282021218
Antidepressant	sertraline HCl	76282021290
Antidepressant	sertraline HCl	76282021305
Antidepressant	sertraline HCl	76282021318
Antidepressant	sertraline HCl	76282021330
Antidepressant	sertraline HCl	76282021405
Antidepressant	sertraline HCl	76282021418
Antidepressant	tranylcypromine sulfate	00591559001
Antidepressant	tranylcypromine sulfate	49884003201
Antidepressant	tranylcypromine sulfate	64980018301
Antidepressant	venlafaxine HCl	00008083321
Antidepressant	venlafaxine HCl	00008083322
Antidepressant	venlafaxine HCl	00008083603
Antidepressant	venlafaxine HCl	00008083621
Antidepressant	venlafaxine HCl	00008083622
Antidepressant	venlafaxine HCl	00008083721
Antidepressant	venlafaxine HCl	00008083722
Antidepressant	venlafaxine HCl	00093019901
Antidepressant	venlafaxine HCl	00093738001
Antidepressant	venlafaxine HCl	00093738101
Antidepressant	venlafaxine HCl	00093738201
Antidepressant	venlafaxine HCl	00093738301
Antidepressant	venlafaxine HCl	00093738456
Antidepressant	venlafaxine HCl	00093738498
Antidepressant	venlafaxine HCl	00093738505
Antidepressant	venlafaxine HCl	00093738556
Antidepressant	venlafaxine HCl	00093738598
Antidepressant	venlafaxine HCl	00093738605
Antidepressant	venlafaxine HCl	00093738656
Antidepressant	venlafaxine HCl	00093738698
Antidepressant	venlafaxine HCl	00131326532
Antidepressant	venlafaxine HCl	00131326546
Antidepressant	venlafaxine HCl	00131326632
Antidepressant	venlafaxine HCl	00131326646
Antidepressant	venlafaxine HCl	00131326732
Antidepressant	venlafaxine HCl	00131326746
Antidepressant	venlafaxine HCl	00131326832
Antidepressant	venlafaxine HCl	00131326846
Antidepressant	venlafaxine HCl	00378488101
Antidepressant	venlafaxine HCl	00378488201
Antidepressant	venlafaxine HCl	00378488301
Antidepressant	venlafaxine HCl	00378488401
Antidepressant	venlafaxine HCl	00378488501
Antidepressant	venlafaxine HCl	00603614921

Concurrent Prescription	Generic Name	NDC
Antidepressant	venlafaxine HCl	00603615021
Antidepressant	venlafaxine HCl	00603615025
Antidepressant	venlafaxine HCl	00603615721
Antidepressant	venlafaxine HCl	13668001830
Antidepressant	venlafaxine HCl	13668001890
Antidepressant	venlafaxine HCl	13668001930
Antidepressant	venlafaxine HCl	13668001990
Antidepressant	venlafaxine HCl	13668002030
Antidepressant	venlafaxine HCl	13668002090
Antidepressant	venlafaxine HCl	13811067510
Antidepressant	venlafaxine HCl	13811071230
Antidepressant	venlafaxine HCl	13811071290
Antidepressant	venlafaxine HCl	13811071330
Antidepressant	venlafaxine HCl	13811071390
Antidepressant	venlafaxine HCl	13811071430
Antidepressant	venlafaxine HCl	13811071490
Antidepressant	venlafaxine HCl	13811071530
Antidepressant	venlafaxine HCl	13811071590
Antidepressant	venlafaxine HCl	16714031101
Antidepressant	venlafaxine HCl	16714031201
Antidepressant	venlafaxine HCl	16714031301
Antidepressant	venlafaxine HCl	16714031401
Antidepressant	venlafaxine HCl	16714031501
Antidepressant	venlafaxine HCl	16714065501
Antidepressant	venlafaxine HCl	16714065601
Antidepressant	venlafaxine HCl	16714065701
Antidepressant	venlafaxine HCl	16714065801
Antidepressant	venlafaxine HCl	16714065901
Antidepressant	venlafaxine HCl	23155024601
Antidepressant	venlafaxine HCl	23155024609
Antidepressant	venlafaxine HCl	23155024701
Antidepressant	venlafaxine HCl	23155024709
Antidepressant	venlafaxine HCl	23155024801
Antidepressant	venlafaxine HCl	23155024809
Antidepressant	venlafaxine HCl	23155024901
Antidepressant	venlafaxine HCl	23155024909
Antidepressant	venlafaxine HCl	23155025001
Antidepressant	venlafaxine HCl	23155025009
Antidepressant	venlafaxine HCl	29033004530
Antidepressant	venlafaxine HCl	29033004630
Antidepressant	venlafaxine HCl	29033004690
Antidepressant	venlafaxine HCl	47335075883
Antidepressant	venlafaxine HCl	47335075983
Antidepressant	venlafaxine HCl	47335076083
Antidepressant	venlafaxine HCl	51079048220

Concurrent Prescription	Generic Name	NDC
Antidepressant	venlafaxine HCl	52817013110
Antidepressant	venlafaxine HCl	52817013210
Antidepressant	venlafaxine HCl	52817013310
Antidepressant	venlafaxine HCl	57237017290
Antidepressant	venlafaxine HCl	57237017301
Antidepressant	venlafaxine HCl	57237017401
Antidepressant	venlafaxine HCl	57237017501
Antidepressant	venlafaxine HCl	57237017590
Antidepressant	venlafaxine HCl	57237017601
Antidepressant	venlafaxine HCl	57664039288
Antidepressant	venlafaxine HCl	57664039388
Antidepressant	venlafaxine HCl	57664039488
Antidepressant	venlafaxine HCl	57664039588
Antidepressant	venlafaxine HCl	57664039688
Antidepressant	venlafaxine HCl	59762018001
Antidepressant	venlafaxine HCl	59762018002
Antidepressant	venlafaxine HCl	59762018003
Antidepressant	venlafaxine HCl	59762018101
Antidepressant	venlafaxine HCl	59762018102
Antidepressant	venlafaxine HCl	59762018201
Antidepressant	venlafaxine HCl	59762018202
Antidepressant	venlafaxine HCl	60505377803
Antidepressant	venlafaxine HCl	60505378009
Antidepressant	venlafaxine HCl	62332000831
Antidepressant	venlafaxine HCl	62332000931
Antidepressant	venlafaxine HCl	62332001031
Antidepressant	venlafaxine HCl	62332001131
Antidepressant	venlafaxine HCl	62332001231
Antidepressant	venlafaxine HCl	64679071601
Antidepressant	venlafaxine HCl	64679071604
Antidepressant	venlafaxine HCl	64679071701
Antidepressant	venlafaxine HCl	64679071801
Antidepressant	venlafaxine HCl	65162030009
Antidepressant	venlafaxine HCl	65162030209
Antidepressant	venlafaxine HCl	65162030509
Antidepressant	venlafaxine HCl	65162030609
Antidepressant	venlafaxine HCl	65162030709
Antidepressant	venlafaxine HCl	65580030103
Antidepressant	venlafaxine HCl	65580030109
Antidepressant	venlafaxine HCl	65580030203
Antidepressant	venlafaxine HCl	65580030209
Antidepressant	venlafaxine HCl	65580030303
Antidepressant	venlafaxine HCl	65580030309
Antidepressant	venlafaxine HCl	65580030403
Antidepressant	venlafaxine HCl	65580030409

Concurrent Prescription	Generic Name	NDC
Antidepressant	venlafaxine HCl	65862052730
Antidepressant	venlafaxine HCl	65862052790
Antidepressant	venlafaxine HCl	65862052799
Antidepressant	venlafaxine HCl	65862052830
Antidepressant	venlafaxine HCl	65862052890
Antidepressant	venlafaxine HCl	65862052899
Antidepressant	venlafaxine HCl	65862069701
Antidepressant	venlafaxine HCl	65862069705
Antidepressant	venlafaxine HCl	65862069730
Antidepressant	venlafaxine HCl	65862069790
Antidepressant	venlafaxine HCl	68001015600
Antidepressant	venlafaxine HCl	68001015800
Antidepressant	venlafaxine HCl	68001015900
Antidepressant	venlafaxine HCl	68001016000
Antidepressant	venlafaxine HCl	68025007930
Antidepressant	venlafaxine HCl	68025007990
Antidepressant	venlafaxine HCl	68025008130
Antidepressant	venlafaxine HCl	68025008230
Antidepressant	venlafaxine HCl	68025008290
Antidepressant	venlafaxine HCl	68382001801
Antidepressant	venlafaxine HCl	68382001901
Antidepressant	venlafaxine HCl	68382002001
Antidepressant	venlafaxine HCl	68382002101
Antidepressant	venlafaxine HCl	68382003406
Antidepressant	venlafaxine HCl	68382003410
Antidepressant	venlafaxine HCl	68382003416
Antidepressant	venlafaxine HCl	68382003506
Antidepressant	venlafaxine HCl	68382003510
Antidepressant	venlafaxine HCl	68382003516
Antidepressant	venlafaxine HCl	68382003606
Antidepressant	venlafaxine HCl	68382003610
Antidepressant	venlafaxine HCl	68382003616
Antidepressant	venlafaxine HCl	68382010101
Antidepressant	vortioxetine hydrobromide	64764055030
Antidepressant	vortioxetine hydrobromide	64764056030
Antidepressant	vortioxetine hydrobromide	64764058030
Antidepressant	vortioxetine hydrobromide	64764072030
Antidepressant	vortioxetine hydrobromide	64764073030
Antidepressant	vortioxetine hydrobromide	64764075030
Trazodone	trazodone HCl	00555073302
Trazodone	trazodone HCl	00603616002
Trazodone	trazodone HCl	00603616021
Trazodone	trazodone HCl	00603616028
Trazodone	trazodone HCl	00603616032
Trazodone	trazodone HCl	00603616102

Concurrent Prescription	Generic Name	NDC
Trazodone	trazodone HCl	00603616120
Trazodone	trazodone HCl	00603616121
Trazodone	trazodone HCl	00603616128
Trazodone	trazodone HCl	00603616132
Trazodone	trazodone HCl	00904655461
Trazodone	trazodone HCl	13668033001
Trazodone	trazodone HCl	43595008003
Trazodone	trazodone HCl	50111043301
Trazodone	trazodone HCl	50111043302
Trazodone	trazodone HCl	50111043303
Trazodone	trazodone HCl	50111043401
Trazodone	trazodone HCl	50111043402
Trazodone	trazodone HCl	50111043403
Trazodone	trazodone HCl	50111044101
Trazodone	trazodone HCl	50111044102
Trazodone	trazodone HCl	53489051001
Trazodone	trazodone HCl	53489051101
Trazodone	trazodone HCl	53489051701
Trazodone	trazodone HCl	60505265300
Trazodone	trazodone HCl	60505265301
Trazodone	trazodone HCl	60505265305
Trazodone	trazodone HCl	60505265401
Trazodone	trazodone HCl	60505265405
Trazodone	trazodone HCl	60505265501
Trazodone	trazodone HCl	60505265505
Trazodone	trazodone HCl	60505265901
Trazodone	trazodone HCl	60505408903
Trazodone	trazodone HCl	68084012501
Trazodone	trazodone HCl	68382080501
Trazodone	trazodone HCl	68382080505
Trazodone	trazodone HCl	68382080510
Trazodone	trazodone HCl	68382080601
Trazodone	trazodone HCl	68382080605
Trazodone	trazodone HCl	68382080610
Trazodone	trazodone HCl	68382080701
Trazodone	trazodone HCl	68382080705

Table A.5. BZRA Medication Primary Indications, Classifications for Onset of Effect, and Prescription Strength Conversion Factors

Type	Primary Indication	Onset of Effect	Brand	Generic	Conversion Factor (DME*)
Benzodiazepines	Anxiolytic	Short to Intermediate	Xanax	Alprazolam	10.00
			Klonopin	Clonazepam	10.00
			Ativan	Lorazepam	5.00
		Long	Librium	Chlordiazepoxide	0.40
			Onfi	Clobazam	0.50
			Tranxene	Clorazepate	0.67
			Valium	Diazepam	1.00
	Sedative/ Hypnotic	Short to Intermediate	Prosom	Estazolam	7.50
			Restoril	Temazepam	0.50
			Halcion	Triazolam	20.00
		Long	Dalmane	Flurazepam	0.33
Z-drugs	Sedative/ Hypnotic	Short to Intermediate	Lunesta	Eszopiclone	0.67
			Sonata	Zaleplon	0.50
			Ambien	Zolpidem	0.50

*Diazepam Milligram Equivalents (DME)