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Assessing Concurrent Use of Opioids and Benzodiazepines Using Urine Drug Test Results

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Assessing Concurrent Use of Opioids and Benzodiazepines Using Urine Drug Test Results

by

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Dedication

To my husband, Jaber, who has given me endless love and support over the last 14 years. I began this degree with a 3-month-old baby on my arm and a 2-year old at my feet. Jaber never hesitated to handle extra diapers, doctor's appointments, late-night feedings, and day-time chaos, to help me make it here. A kinder heart does not exist.

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Assessing Concurrent Use of Opioids and Benzodiazepines Using Urine Drug Test Results

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The purpose of this dissertation was to assess concurrent use of benzodiazepines and opioids, using laboratory results from urine toxicology records. The opioid crisis is an ongoing public health issue that has spanned over two decades. Drug overdose death is now the leading cause of accidental deaths among American adults. Patients who take benzodiazepines and opioids concurrently are at even greater risk of overdose than those taking an opioid alone. Prominent agencies including the Centers for Disease Control and Prevention, Food and Drug Administration and the Centers for Medicare and Medicaid Services strongly recommend against co-prescribing opioids and benzodiazepines when possible, and the use of urine drug testing to mitigate patient risks through monitoring and early intervention. Although there have been studies on co-prescribing rates using prescription data, there is little evidence on the rates of patient drug use using UDT data. This dissertation used large, population-based administrative data to address the following research gaps using patient urine drug test (UDT) results: 1) examine trends in concurrent opioid and benzodiazepine use among adult patients and assess whether there was a shift from prescribed to illicit or non-prescribed drug use; 2) determine patient characteristics associated with aberrant UDT results—concurrent use, illicit drug use or non-prescribed use; 3) assess provider response to concurrent use-positive UDT. This research gives an understanding of recent trends and associations with concurrent opioid and benzodiazepine use by patients and may inform more targeted public health practice.

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List of Abbreviations

CBT: cognitive behavioral therapy

CDC: Centers for Disease Control and Prevention

CMS: Centers for Medicare and Medicaid Services

CPT: Current Procedural Terminology

FDA: Food and Drug Administration

GABA: gamma aminobutyric acid

GC/MS: gas chromatography/ mass spectrometry

HPLC: high performance liquid chromatography

IA: immunoassay

ICD: International Classification of Disease

LC/MS: liquid chromatography/mass spectrometry

LOINC: Logical Observation Identifiers, Names, and Codes

MME: morphine milligram equivalents

NSAID: non-steroidal anti-inflammatory drug

NSDUH: National Survey on Drug Use and Health

OUD: opioid use disorder

RFA: radiofrequency ablation

SNRI: serotonin-norepinephrine reuptake inhibitors

SSRI: selective serotonin reuptake inhibitors

SUD: substance use disorder

UDT: urine drug testing

VIF: variance inflation factor

Chapter 1 Concurrent Use and Assessment of Benzodiazepines and Opioids

The Opioid Crisis

The opioid crisis is an ongoing public health issue that has spanned over two decades, and cost an estimated $1.5 trillion from 2001-2020.[1] The surge in opioid-prescribing began during the 1990's when targeted campaigns pushed providers to treat pain relief as a "human right"[2] and pain as the "fifth vital sign",[3] and subsequently contributed to incident opioid misuse, overdose mortality, and heroin use.[3,4] Other events that led to increased opioid-prescribing include the belief that addiction risks were low with chronic opioid use,[5] and aggressive marketing by pharmaceutical companies.[6]

Opioids are a class of drugs used to treat moderate to severe pain, and may be categorized as natural, synthetic, or semi-synthetic. These include prescription drugs such as Vicodin (hydrocodone), pharmaceutical fentanyl, and illicit drugs, heroin and illegally manufactured fentanyl. Opioids function by activating chemical changes in the brain to block pain perception, often giving patients a happy or high feeling due to increased dopamine release.[7] When opioids are used frequently or long-term, this mechanism becomes dysregulated, which desensitizes users and may lead to tolerance, dependence and substance abuse.[8]

Patients on opioids often experience a loss of effectiveness of their baseline dose, after a few weeks, especially when using long-term opioids for chronic pain (greater than 90 days).[9] It is important that opioids are not prescribed unless its benefits greatly outweigh the risks. However, if providers determine an opioid is necessary, the dosage, days supplied should be determined carefully, to reduce negative patient outcomes, including addiction and overdose.[10-12]

Drug-related death has increased six-fold since 1999;[13] In 2019, overdose mortality peaked at 70,630 deaths in the United States—over 70% of which were opioid-related.[14] In addition to mortality, opioid use disorder (OUD) and substance use disorder (SUD) are outcomes of the opioid epidemic that continue to plague public health worldwide. In 2019, an estimated 10.1 million Americans aged 12 and above were afflicted with OUD; 96% of these individuals were misusing prescription pain relievers.[15]

Prescription opioid abuse often leads to illicit drug use. According to the National Survey on Drug Use and Health (NSDUH), 80% of current heroin users report that their substance abuse first began with opioid prescriptions.[16,17] This has also been made evident by the changing waves of opioid overdose deaths observed since the start of the opioid epidemic.[18] In the first wave, between 1999-2010, the majority of opioid deaths were attributed to prescription opioids. The second wave began in 2010 and was marked by an increase in heroin overdose deaths. This led into the third wave, which began in 2013 with a sharp increase in synthetic opioid-related deaths (such as fentanyl), through 2019.

Other trend studies have also shown an increase in mortality due to non-prescribed opioid use and illicit drug use in recent years;[19,20] By 2016, opioid-related deaths were 2.6 times more likely to be due to heroin or synthetic opioid abuse, than in 2012, indicating a significant rise over time. Further, while mortality from non-prescribed use has increased, fewer than 10% received treatment that may help with addiction.[20] As prescription opioid use became more widespread at the start of the opioid crisis, the consequent regulations and limitations to opioid-prescribing[21] may have had the unintended consequence of shifting patients from the prescription to non-prescribed or illicit drug use. It is therefore important to understand trends in patient use of such drugs so that clinical guidelines and public health initiatives may be developed to better target at-risk populations, such as providing access to overdose antagonist drugs, or rehabilitation facilities.

Use of Benzodiazepines

Benzodiazepines are prescription sedatives, categorized as short-, intermediate-, and long-acting, and are commonly used for treating anxiety and panic disorders, insomnia, and depression.[22] These include drugs such as Valium (diazepam), and Xanax (alprazolam), which work by increasing the action of a chemical messenger, gamma-aminobutyric acid (GABA), to slow the central nervous system, and give patients a feeling of calm or tranquility. At higher doses, patients may feel the same sense of euphoria as those on opioids.

Taken alone, long-term benzodiazepine use is associated with cognitive impairment, and increased risk of falls, hip fractures, potentially fatal withdrawal symptoms, poor sleep quality, and mortality.[23-25] Though the use of benzodiazepines alone is not as dangerous as when

combined with opioids, this class of drugs has a high potential for abuse similar to opioids and other addictive drugs, due to the increased release of dopamine.[26] It is especially important to avoid long-term benzodiazepine use when necessary, as patients that become dependent on benzodiazepines have worse withdrawal and rebound symptoms than those withdrawing from opioids.[12]

In recent years, there has also been a growing use of "designer benzodiazepines", which are inexpensive, accessible online, and not approved for medical use anywhere in the world.[27] Because designer drugs are highly potent, any error in measurement of such small quantities, may cause unintended overdoses. Trends in benzodiazepine prescribing were shown to increase in a large sample from outpatient settings between 2003-2015.[28] However, another study saw a significant decreased in benzodiazepine prescribing from 2013-2018, which was limited to older, Medicare enrollees. [28]

Concurrent Use: Opioids and Benzodiazepines

Opioids are associated with the majority of prescription-related mortality; of these deaths, studies have shown that up to 61% of patients who fatally overdosed had a co-prescription for an opioid and benzodiazepine.[29-31] Patients concurrently using opioids and benzodiazepines are also four to ten times more likely to overdose, compared to those prescribed an opioid alone.[12,29,32] Co-prescriptions are also associated with increased adverse events such as falls or injuries, and increased substance abuse.[33]

Neither opioids nor benzodiazepines are considered a first line of treatment, and their combined use is especially advised against.[22,34,35] There are circumstances where concurrent use may be deemed necessary, such as among patients taking a benzodiazepine for depression, who may later experience severe acute pain or develop a chronic illness that requires an opioid.[12] Similarly, in cases where chronic pain opioid users develop severe anxiety or depression that requires a benzodiazepine, concurrent use is considered.

Because both opioids and benzodiazepines act on the central nervous system similarly, when combined, the effect on sedating the respiratory system is exacerbated.[36] Overdose on these drugs causes the breathing rate to significantly slow down, which decreases oxygen supply to

vital organs, that eventually cease to function. Depending on the severity of the overdose, the lack of sufficient oxygen leads to coma and death in as little as a few minutes, to a few hours if emergency care is not provided in time.

Opioid-Prescribing Guidelines and Policies

As early as 2002, three states—Kansas, Michigan and Montana—had developed opioid-prescribing guidelines for treating pain;[21] however, these were not yet backed by quality research and were left to the discretion of physicians. Over the next 18 years, numerous other states and medical societies published similar guidelines,[37-39] however, it was not until March 2016, that the Centers for Disease Control and Prevention (CDC), released its opioid-prescribing guideline for chronic non-cancer pain.[12] This guideline included twelve evidence-based recommendations to assist clinicians with assessment and monitoring strategies related to opioid use, to reduce patient risks for adverse events such as SUD, overdose and death. The Centers for Medicare and Medicaid Services (CMS), has also strongly advised against opioid and benzodiazepine co-prescriptions, citing the Medicare Learning Network's recommendations on reducing co-prescribing.[40] These guidelines and most others advise providers to consider drug alternatives, and use risk stratification tools including urine drug testing (UDT), to screen new patients and monitor those already taking prescribed opioids or benzodiazepines.

In August 2016, the Food and Drug Administration (FDA) also issued a requirement that all opioid and benzodiazepine drug labels must include a black box warning (the strongest warning that may be issued) detailing the risks of concurrent use.[41] In September 2020, they updated the requirement for benzodiazepines to include "the serious risks of abuse, addiction, physical dependence, and withdrawal reactions".[42]

Trends in Concurrent Use

An estimated 59.4 million Americans are using benzodiazepines, opioids or a combination of these—30% of which are older adults, aged 65 and above.[35] From the early 2000's through 2015, the co-prescribing of opioids and benzodiazepines reportedly increased,[43,44] where 50% of co-prescriptions were received on the same day.[45] In a large study of US pharmacy dispensing data, during 2002-2014, there was a 41% increase in co-prescribing, which translated to approximately 2.5 million patients.[46,47] Between 2010-2015, there are different reports on whether the rates of

co-prescriptions increased,[43,44,48] or decreased;[28,35,49] varying study settings, data sources and cohorts may contribute to the conflicting results.

In recent years however, patterns in co-prescribing have repeatedly been shown to decrease. A study of prescription data from 2015-2017 showed a decline in co-prescriptions after the CDC guideline and FDA blackbox requirement in 2016 compared to before these were put in place,[50]. There were greater declines in co-prescription rates among women compared to men.[50] Another study of prescription claims from 2016-2020 showed similar decreases, with greater declines in younger adults (<65 years) compared to those older than 65 years.[35,48,49] Although the number of co-prescriptions has steadily decreased since 2015, or as early as 2010-2013,[28,49] there were still over 1.2 million older adults (≥65 years), and 2.2 million (under 65) who received co-prescriptions in 2020.[35]

Opioid drug alternatives include gabapentin and pregabalin, which are non-narcotic drugs that are effective in treating pain due to fibromyalgia, a musculoskeletal muscle condition, and nerve pain.[51] Over-the-counter drug options include Tylenol (acetaminophen), Advil (ibuprofen), and other non-steroidal anti-inflammatory drugs (NSAIDs). Anti-depressants such as Cymbalta, and Savella may also be used for treating mild or moderate chronic pain, nerve pain and headaches. For shooting pain in localized areas, a variety of topical creams, foams, gels and other drug forms with local anesthetics such as lidocaine, may be used. Other topical applications include muscle relaxers, NSAIDs or capsaicin. Joint or muscle pain may also be treated using steroid injections or temporary nerve block injections.

There are also non-drug alternatives for pain management, which may be used alone or in combination with medication. These include self-care methods such as exercise, yoga, meditation, or hot/cold compresses. More targeted therapy, including occupational therapy for increasing coordination, balance, and range of motion through the practice of daily activities, and physical therapy for enhancing the body's functional movement, also helps decrease pain which increasing physical function. Rehabilitation therapy is also associated with shorter opioid prescription durations,[52] indicating that multimodal treatment to address pain is important. Other non-drug treatments include acupuncture, chiropractic care, and brain stimulation treatments.

Though patients' pain severity varies and may not always be treated effectively without an opioid, the combination with other therapies may help to keep opioid doses low, and short-term.

An alternative drug class to benzodiazepines is selective serotonin reuptake inhibitors (SSRIs) such as Prozac (fluoxetine) and Zoloft (sertraline), which also treat depression, anxiety, and insomnia.[53] SSRIs are safer than benzodiazepines, however these drugs often require weeks before patients notice a difference and must be taken consistently for the medication to work.[54] Serotonin-norepinephrine reuptake inhibitors (SNRIs) work similarly to SSRIs to improve patient mood, but also take time before patients notice changes.[55] Tricyclic antidepressants are another drug alternative, however due to the side effects elicited by drastic chemical changes in the brain, these are seldom used, given SSRIs and SNRIs availability.[56,57]
Buspirone is also an anti-anxiety medication that may be used, but similar to anti-depressants, requires consistent use over time before symptoms improve.[58] Vistrial (hydroxyzine) is a prescription antihistamine that has been approved for anti-anxiety use and may be used "as needed" for less severe cases, though its efficacy compared to benzodiazepines is undetermined.[59]

Non-drug options for improving symptoms of anxiety and depression include lifestyle changes such as prioritizing sleep, meditation, improving nutrition, quitting alcohol use, and starting exercise. Cognitive behavioral therapy (CBT) is an effective non-drug treatment for insomnia, and is preferred by the American College of Physicians as the first line of defense, before considering benzodiazepines or z-drugs.[60] Z-drugs (zolpidem, zaleplon, zopiclone, eszopiclone) are psychoactive drugs that are chemically similar to benzodiazepines, and approved for treating insomnia; though these are an alternative treatment option, z-drugs also increase the risk of falls, fractures, and mortality, especially in older adults.[61]

Urine Drug Testing

Urine drug testing is a helpful tool for monitoring patients on long-term opioids, benzodiazepines, stimulant drugs, and other prescription drugs,[12,62] which offers a more informative clinical picture than relying solely on patient self-reports.[63] Though UDT does not provide measures of the concentration or amount of a drug that was consumed, it helps

objectively present what drugs a patient recently had in their system.[64] This assumes that the urine tested has not been adulterated, belongs to the patient, is interpreted correctly, and that the drug was taken in sufficient quantities detectable by UDT. The detection window, or length of time that a given drug and its metabolite remain in the body is dependent on patient weight, metabolic characteristics, frequency of drug use, drug dosage, and the drug half-life (the time it takes to metabolize and remove half the consumed dose from the system).

Although there are other biological specimens (test matrices) that may be used for drug testing, such as hair, saliva, sweat and blood, urine is the most frequently used matrix, especially in ambulatory and independent laboratory settings, and is the most rigorously researched.[65-68] Drug metabolites are found in higher concentrations in the urine, compared to other specimens.[69,70] UDT is also preferred because of its ease of collection, availability in sufficient amounts, wide accessibility of point-of-care tests, and the time window for drug detection.

Because drug metabolites usually remain in the system longer than the parent drug, urine is the better choice, as it is able to retain both metabolites and parent drugs,[71] compared to blood and oral specimens, which have shorter time windows and are better for detecting parent drugs. Blood testing for drugs is an indicator of what is currently in the system,[64] which is often more helpful in emergency care settings, for example when providers need to immediately determine what drug a patient may have overdosed on. However, in the general outpatient clinics, the use of blood for drug testing is less likely, because it is invasive, costly, requires personnel trained in phlebotomy, and has a shorter detection window. Hair testing is non-invasive and has the longest detection window which may be useful for detecting chronic abuse. However, it cannot detect recent or sporadic drug use. Hair testing is also expensive, may show false-positive results from environmental exposure, and cannot be analyzed if hair is not long enough. Drug use would also have to be quite heavy to be detected in hair, which means earlier signs of SUD development may be missed. Drug testing of other specimens, such as sweat and saliva is also available but less common, has a slower turnaround time, and is not commercially available for as many drugs as there are for UDT.

Presumptive testing

There are two main types of urine drug test methods: urine drug screening (presumptive) and definitive (confirmatory) testing. Presumptive testing is conducted by immunoassays (IA), which

generally employ antibodies to detect the presence of drug metabolites or drug classes in urine, based on a prespecified cutoff level. There are three types: enzyme-linked immunosorbent assay (ELISA), fluorescence polarization immunoassay, and the enzyme-multiplied immunoassay technique. All positive results obtained from a drug screen are considered presumptive-positive, until followed up by definitive testing. Initial screening should always be followed by definitive testing, whether results are positive or negative, as best practices suggest, to provide the most accurate results.[64] However, this is not always possible due to a lack of resources, high costs, insurance limits and difficulty of interpreting complex results.

The advantages of UDT screens are the relative simplicity, low cost, quick results, availability of point-of-care testing and the capacity to test in large batches. The disadvantages are that IAs are not capable of differentiating between specific metabolites or drugs within a class (such as within benzodiazepines). UDT screens also show variable cross-reactivity with some medications, which could lead to false-positive results, and potentially harm patient care if it leads to the decision to discontinue a drug. However, this should not occur solely based on the results of a UDT screen. Patients' complete prescription history, including herbal and over-the-counter drugs or supplements should be considered, and providers must either be trained in UDT interpretation or consult experienced lab personnel to address potential false-positive results.

UDT screens for opioids include IAs for codeine, hydrocodone, methadone, morphine, oxycodone, fentanyl, hydromorphone, meperidine, tapentadol, oxymorphone, buprenorphine, tramadol, and heroin (via morphine detection), among others. Some screens come as panels, such as the "Federal Five", or National Institute on Drug Abuse (NIDA)-5 panel, which is commonly used to test employees for amphetamines, cocaine, marijuana, opiates, and phencyclidine (PCP). There are other, larger panels, such as the 12-drug panel, which expands on the NIDA-5 to include other common opioids/illicit drugs of abuse.

UDT screens for benzodiazepines often detect nordiazepam, oxazepam, and temazepam (metabolites of diazepam).[72] Lorazepam and clonazepam are generally not detectable by IA because of low-cross reactivity with antibodies, therefore it is common that patients taking either of these drugs have a negative screen; in such cases it would be beneficial to follow a negative screen with confirmatory testing. On the other hand, patients with a positive benzodiazepine

UDT screen (with only a lorazepam or clonazepam prescription), may be an indication that they are taking other benzodiazepines than what may be prescribed.

Confirmatory testing

Confirmatory testing is done using specialized test methods, including gas chromatography/mass spectrometry (GC/MS), liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) and high-performance liquid chromatography (HPLC). Traditionally, IA screening is followed by GC/MS, as the gold standard for drug testing. Gas chromatography works by separating the compounds within a urine sample, based on their molecular interactions with the test medium. Once separated, mass spectrometry is used to identify compounds by analyzing their mass-to-charge ratios, which act as a "molecular fingerprint".[72]

New, emerging laboratories that specialize in pain management have begun to run definitive testing alone, specifically LC-MS/MS, and avoid the use of IA screening altogether. LC-MS/MS includes the use of a second mass spectrometry step, which means a second compound-separation step and potentially greater accuracy in detecting a drug's distinctive fingerprint. Though GC/MS is the gold standard, LC-MS/MS has become increasingly popular as it requires less urine volume to run testing and has a lower susceptibility to false results.[73] Pre-analytical preparation of urine when using LC-MS/MS also requires less extensive work than GC/MS prep by avoiding hydrolysis, derivatization and sample cleanup.[74]

The disadvantages to definitive testing, by any method, is the slower turnaround time, much higher costs, and complexity of result interpretation. Unfortunately for these reasons, definitive testing may sometimes be reserved for when UDT screens produce unexpected results, rather than routine use.

UDT Policies and Guidelines

At the state-level, opioid-prescribing guidelines included the use of UDT as a drug monitoring and risk assessment tool, as early as 2002 in a few states, while the majority of other states did not issue any guidance to prescribers pertaining to UDT until 2012-2017, and these ranged from advisory recommendations to law-enforced regulations.[21] Most of these addressed chronic, non-cancer pain, while a few were specific to acute pain, or emergency room care.

The CDC's opioid prescribing guideline also recommends UDT, more specifically baseline testing and annual testing for long-term opioid users, long-term benzodiazepine users, and those taking both drugs. Baseline testing indicates the use of UDT before prescribing any new opioid and is recommended for risk assessment, whereas annual testing is meant as a compliance check, or to re-assess patients that may have been on an opioid, benzodiazepine, or both, for an extended period. Though most of the previously described guidelines' UDT recommendations are specific to noncancer pain, the use of UDT is not limited to chronic, non-cancer pain; the American Society for Clinical Oncology (ASCO), has also advised that UDT should be used for drug monitoring among cancer patients.[75]

In spite of the guidance on UDT among opioid and benzodiazepine users, providers may be cautious about the use of testing due to reimbursement limits, and steep penalties by the government, if overused or misused.[76] For example, when a 5-panel UDT is sufficient, the use of a 12- or 14-drug panel may be considered excessive, if a patient has not shown any signs of abuse or prior history to indicate the need for larger test panels.

Trends in Urine Drug Testing

The rate of UDT varies widely across studies, from 2% to 50%;[77-80] this variation may be explained by different study designs, outcome definitions, sample size limitations, or the use of smaller regional samples. In our large, population-based study among long-term opioid users,[81] we found that despite overall increasing trends from 2012-2018, only 52% of patients that were already on an opioid were tested annually. Those who received a new long-term opioid prescription, were tested at an even lower rate, approximately 11%, by the end of 2018—two years after the release of the CDC guideline. These rates may also have been overestimated due to lower specificity of the CPT codes used to define UDT, than originally expected. Still, UDT rates doubled among prevalent long-term opioid users, and tripled among incident users from 2012–2018. Among cancer patients, a small study found that only 6% received UDT, though this was limited to one year (2011).[82]

Effectiveness of UDT

According to the CDC's opioid-prescribing guideline, there is no consensus among clinicians on whether the use of UDT in pain management is necessary. This disagreement may be due to the potential for result misinterpretation, UDT cost and reimbursement limits, and the "low-quality

evidence" supporting UDT's effectiveness in improving patient outcomes of opioid users (SUD, overdose, death).[12]

Though there are limitations to urine drug testing, UDT has been helpful for monitoring patient compliance to prescribed drug agreements, and assessing new patients for signs of drug abuse.[12,69,72,83-86] UDT does offer a more objective clinical picture on recent patient drug use that may not otherwise be self-reported, including illicit and non-prescribed drug use.[63,87] In addition, UDT assists clinicians in identifying those who are not taking their prescription opioids or benzodiazepines, which may indicate a patient no longer needs the drug, or potentially point to diversion, i.e. the selling or giving away of prescription drugs to others. There is also evidence that more frequent UDT, random testing, or the use of comprehensive UDT has an impact on reducing drug misuse and increasing treatment compliance.[64,86,88-90] One study found that frequent UDT combined with random UDT use was associated with a reduction in overall illicit drug use.[83] This may suggest that UDT is an important tool to help reduce cases of SUD and overdose, if providers are able to identify problematic results and address these with patients in earlier phases of pain management.

Factors associated with receiving UDT

Predictors of urine drug testing include younger age, back pain and general chronic pain indications, residence in the southern US Census region, and common drug abuse diagnoses—alcohol abuse, depression, and mental health disorders.[81] Cancer patients were shown to have a very low likelihood of being tested, which may be due to most opioid-prescribing guidelines targeting non-cancer pain.

A small, regional study of cancer patients found that predictors of UDT also included younger age, as well as earlier cancer stage, higher pain intensity, and lower ratings of fatigue.[82] In a large study of US Veterans, patients who were younger, male, had an urban residence, substance abuse diagnoses, or lower back pain indication had a higher likelihood of receiving UDT.[91] This study also found that Black patients were more likely to be tested, compared to White patients. Other important predictors of UDT included higher pain intensity and opioid dose, post-traumatic stress disorder, schizophrenia, bipolar disorder, and having a primary care physician (vs. nurse practitioner).

Rates and Predictors of Aberrant UDT

Among patients who receive UDT, there have been varying rates of "aberrant results", which is defined differently across studies, but generally indicates unexpected UDT results. A small, retrospective chart review in 2015 (n=474) defined "inconsistent results" as UDT missing prescribed drugs, or finding a list of unexpected drugs (marijuana, heroin/cocaine, non-prescribed opioids and/or benzodiazepines); 45% of the results were inconsistent, where approximately 27% were from missing prescribed drugs, and 21% were positive for marijuana.[92]

Another small study in 2014 (n=150) found that 42.0% of UDT results showed evidence of an "abnormal urine screen", which was defined as missing a prescribed drug, or finding an illicit or non-prescribed drug.[93] A large retrospective study of UDT from 2006-2009 (n=938,586) found unexpected results in 75% of patients; however this included a finding of "lower than expected drug levels" in the system, which is not generally used in the definition of "aberrant UDT".[94] Among those with aberrant results, 38% were missing their prescription drug, 27% had higher than expected drug concentrations (which may indicate patients mixing small amounts of a prescription drug into the urine to make it appear positive), and 11% were positive for illicit drugs. A 2007 study using only the GC/MS method of definitive testing (n=470) found 45% of results had an abnormal urine drug screen. Of these, 20% were positive for illicit drugs, 14% had a non-prescribed drug and 10% were missing a prescription.[95]

Predictors for any aberrant UDT results included male gender, patients with SUD, current smokers, younger age (less than 44 years), lower average prescribed opioid dose, and short-acting opioid use (compared to long-acting opioid use).[78,91]

Aberrant UDT Interpretation and Interventions

The finding of aberrant UDT results, such as missing prescriptions, illicit drug-positive, non-prescribed drug use, adulterated urine or extremely high drug concentrations, may warrant further or repeat testing, clinical re-assessment, or a change in treatment by the provider.

In the case of aberrant positive or negative IA screening, it is helpful to either repeat the screen, or more importantly use definitive testing to confirm results. Any findings should also be discussed with patients, so that providers may put into context what happened—especially when a prescribed drug is missing, or non-prescribed drug is detected. Providers must also be trained

to correctly interpret UDT results, or otherwise communicate with experienced lab personnel on interpreting UDT findings.

If there is evidence in definitive testing that confirms the presence of illicit substances or non-prescribed drug use, interventions may include the referral to SUD treatment or rehabilitation facilities, as well as drug-tapering or MAT (medically assisted treatment) options to help patients come off the drug of abuse.

Prescribers actively monitoring patients' progress may find that prescribed opioids or benzodiazepines are not taken regularly and may help patients safely taper and discontinue the drug(s). During earlier stages of patients' pain management, prescribers may also change the drug dosage, offer opioid or benzodiazepine substitutes, or offer other non-drug therapy if it is likely that a patient is not benefitting from, or not using the initially prescribed medication.

The CDC recommends beginning opioid tapering plans with a 10% reduction in dosage weekly for opioids, to minimize withdrawal symptoms.[12] However, for patients who have been using opioids or benzodiazepines long-term, more gradual tapering may be required. On the other hand, patients who have experienced overdose on their prescribed opioid dosage (not due to misuse) may need a more rapid taper to avoid overdosing again.

For patients taking benzodiazepines and opioids concurrently, when discontinuation is indicated, it is recommended that the opioid is tapered first, due to the greater anxiety and severity of withdrawal symptoms associated with benzodiazepines, compared to opioids. Benzodiazepine tapering should also be gradual, reducing the dose by 25% every 1-2 weeks, whether combined with an opioid or not, to avoid rebound anxiety, seizures, hallucinations and in rare cases, death; Psychotherapy, such as CBT, is also helpful for patients with anxiety.[12,96] The CDC recommends CBT for patients who have already been tapered from benzodiazepines, or those currently on an opioid, and still experiencing anxiety.

Other special considerations include slower tapering for pregnant women to avoid withdrawal in the fetus, and discontinuation of an opioid (without tapering) when UDT repeatedly show negative results, which may strongly suggest diversion.

Prescriber Response to UDT Results

Clinicians face the dilemma of simultaneously being cautious when prescribing opioids and benzodiazepines, while effectively treating patients. They are also confronted with finding balance between over- and underuse of UDT, and how to address aberrant test results in a safe, effective manner. Before implementing any change in treatment, the interpretation of aberrant UDT results should take into account factors such as the method of testing, potential false positives, drug detection window, missed doses, and interference from other medications a patient may be taking.

In a single-practice study of patient charts (n=474), prescription renewal rates were significantly lower among patients with UDT negative for a prescription, but positive for heroin or cocaine (OR 0.12, 95% CI: 0.03-0.49), compared to those with expected UDT findings.[92] Renewal rates were also decreased in those where the only inconsistency was a missing prescription (OR 0.58 95% CI: 0.39-0.85); Interestingly, those with a missing prescription and positive for marijuana, had a relatively higher renewal rate (OR 0.82 95% CI: 0.55-1.22), though not statistically significant. The leniency towards marijuana-positive results may be due to the growing number of states legalizing or decriminalizing marijuana use in recent years;[97] However, other research shows that marijuana use was the leading cause for opioid discontinuation, where 56% were discontinued for cannabis-positive results, 26% for cocaine, 11.8% for non-prescribed opioids and 5.3% for non-prescribed benzodiazepines.[98]

In another small, single-center study (n=123), any aberrant UDT led to discontinuation in 20% of the total sample, while 55% continued to receive prescription opioids, regardless of whether inconsistent findings included illicit use, or had repeated aberrant UDT,[99] which contradicts Hosain et al's study[92] showing 0% of patients with positive illicit drug use received prescription renewals. However, a limitation of both studies is the small sample, and center-specific results, which may not even be generalizable to each region. There were also conflicting results with middle aged males being the more frequent aberrant-positive subgroup, as opposed to younger females: study design plays an important role in these differences. In 52% of aberrant UDT cases, clinicians planned to alter prescribing by discontinuing or substituting opioids, changing the dosage, or requiring smaller refills, but only implemented these changes in 24%.[100]

Gaps in literature

There have been numerous studies on opioid and benzodiazepine co-prescribing,[28,101-105] in which analyses focused on prescribing patterns of providers; there is less evidence on the rates of concurrent use and illicit drug use by patients in recent years. An important limitation of prescription claims data when studying patient outcomes or characteristics, is not knowing whether patients consumed the medication. With drug diversion a possibility, patients may receive prescription drugs through relatives or other individuals receiving prescriptions, or through others outside of healthcare settings. By studying UDT results, there is greater accuracy in measuring prescription use, but also their non-prescribed and illicit drug use, which is otherwise left to be measured during patient exams by self-report.

Without knowledge of what drugs patients are consuming, there may be missed opportunities of detecting and treating substance abuse cases that otherwise result in fatal and nonfatal overdose. These studies will address the gaps of recent time trends, characteristics and prescriber response related to concurrent use positivity and aberrant UDT. Given the increase in non-prescribed opioid and illicit drug overdose mortality since 2013,[14,19,20] it is important to understand these trends and associated patient characteristics, for better targeting public health efforts that emphasize treating addiction in patients rather than restricting prescribers. A list of opioid, benzodiazepine, and schedule I drugs and their associated LOINCs that will be helpful for future research projects will also be an important product of these studies, as LOINC becomes more standardized and implemented in labs across the country and may serve as a foundation for future studies.

Specific Aims

This research will give insight into patient drug use, including non-prescribed and illicit use by analyzing urine drug test results. This proposal aims to address specific knowledge gaps by analyzing Optum's CDM data to:

Aim 1: Examine trends of UDT-positivity in concurrent opioid and benzodiazepine use from 2013 to 2019 among adult enrollees; Assess whether there was a shift from prescription drug use to non-prescribed or illicit drug use in UDT results.

Aim 2: Determine patient characteristics associated with aberrant UDT results in 2018, including those positive for concurrent use, schedule I drugs, or non-prescribed opioids or benzodiazepines.

Aim 3: Assess changes in opioid or benzodiazepine prescriptions, including discontinuation, dose changes, alternative prescriptions, or referrals to other therapy or rehabilitation, in response to concurrent UDT results in 2018.

General Methods

Insurance claims data from Optum's Clinformatics Datamart (CDM)[106] were used to create datasets from January 1, 2013 to Dec. 31, 2019 for Aim 1, and January 1, 2017 to Dec. 31, 2018 for Aim 2, and January 1, 2017 to Dec. 31, 2019 for Aim 3, to reflect more recent years. CDM offers longitudinal medical insurance data that include member information such as age, gender and insurance eligibility dates; medical claims, including procedures (via CPT codes), diagnoses (ICD codes); pharmacy claims, such as the drugs dispensed, and the quantity, supply, cost and dosage (via NDC codes); lab test result data via LOINC codes, and provider data, such as credentials and affiliations.

In this document, concurrent use refers to the combined use of at least one opioid and at least one benzodiazepine. In the context of urine drug test results, concurrent use refers to the finding of an opioid(s) and benzodiazepine(s) in UDT on the same test date, regardless of whether a patient has the associated prescription for both. The additional indicator of whether these drugs are prescribed or not, will be discussed in terms of aberrant UDT.

"Aberrant UDT" refers to unexpected findings, which include urine drug tests positive for schedule I drugs, or the finding of non-prescribed opioids or benzodiazepines. Schedule I drugs include heroin, cocaine, LSD, bath salts (cathinones), psilocybin, mescaline, MDMA, gamma-hydroxybutyric acid (GHB), marijuana (THC/cannabinoids), ecstasy, methaqualone, and khat.

Opioids include fentanyl, hydrocodone, hydromorphone, levorphanol, codeine, methadone, suboxone, propoxyphene, buprenorphine, morphine, oxycodone, and meperidine. For an opioid to count as non-prescribed, a UDT must be found positive for opioid use outside of the "compliance window". This window begins the first day an opioid was prescribed and lasts for the duration of the days supplied by the prescription. Because most opioids remain in the system for 2-7 days, an additional 7 days were added to the end date for the compliance window to avoid overestimation of opioid misuse.

The benzodiazepines include flurazepam, oxazepam, clorazepate, chlordiazepoxide, alprazolam, lorazepam, clobazam, and diazepam. The compliance window for benzodiazepine use was similarly calculated, however because some are long-acting, an additional 30 days was added to the end date.

Covariates

Other variables included for stratification purposes, or in multivariable analysis models are those on patient demographics, clinical characteristics, and drug characteristics, such as dosage and duration.

Patient Demographics

Though patient demographics are limited in CDM data, there are important variables were available: patient sex (male/female), birth year, from which age was calculated and states, which were grouped into United States Census regions. Geographic region included the four categories, Northeast, South, Midwest and West. Age groups were categorized as as 18-35, 36-45, 46-59, and 60 years and above.

Clinical Characteristics

Variables describing patients' clinical characteristics include the Elixhauser comorbidity score, which calculates the number of comorbidities using ICD codes.[107] Elixhauser scores were

calculated using the 12 months prior to the index UDT date. Similarly, pain indications were measured using ICD codes as a proxy for pain diagnosis, and categorized as back pain, joint, cancer, nerve, musculoskeletal or other chronic pain. Pain indication denotes the reason a prescription opioid was given, not necessarily a patient's diagnosis. Specific diagnoses of alcohol abuse, depression, psychoses and drug abuse were also included, as these conditions are associated with concurrent use or aberrant UDT.[78,108]

Drug Dosage and Duration

Opioid dosage, measured in morphine milligram equivalents (MME), may have an impact on aberrant UDT. Higher average opioid MME has been associated with greater mortality in older adults, whereas lower doses reduce the risk of overdose.[12] Dosage was calculated using conversion factors specific to each opioid, and measured as total MME/day.[109] Long term opioid use was defined as 90 days of consecutive opioid use.

The following chapter was submitted for publication to Preventive Medicine Reports on August 16, 2022 and is currently under review.

Chapter 2: Trends in Co-prescribed Opioids and Benzodiazepines, Non-prescribed Opioids and Benzodiazepines, and Schedule-I Drugs, 2013 to 2019

Introduction

Opioid use is associated with risks of overdose and death; these risks are substantially increased in patients concurrently taking benzodiazepines and opioids, due to the exacerbated effect of respiratory suppression.[1] Concurrent users are at least four times more likely to overdose or experience drug-related emergencies, compared to those taking an opioid alone.[2,3]

To quell these effects, the Centers for Disease Control (CDC) recommends the avoidance of co-prescribing opioids and benzodiazepines, and the use of urine drug testing (UDT) to initially assess and continuously monitor patients taking either or both drugs.[1] The Food and Drug Administration (FDA) also requires a "blackbox" warning to be included on all opioids and benzodiazepines, cautioning the risks of concurrent use.[4]

Trends in co-prescribing of opioids and benzodiazepines increased from early 2000 until 2012, after which two large-scale studies show a decreasing trend through 2018.[5,6] Because most studies on concurrent use have relied on prescription claims or dispensing data, it is less clear whether patient use reflects the same findings. Therefore, time trends in concurrent use positivity were examined using laboratory UDT results from a large insurance claims database, from 2013–2019.

National overdose death involving any opioids increased approximately 72% from 2016–2019,[7] most of which have been attributed to non-prescribed opioids and illicit drugs.[8,9] Because it is common for patients to shift from prescription opioids to non-prescribed and illicit drug use,[10] trends in schedule I drug positivity (illicit drugs) and non-prescribed use of opioids or benzodiazepines were also assessed. We hypothesized that concurrent use shown in UDT results would decrease from 2013-2019. Schedule-I drug use and non-prescribed opioids or benzodiazepines would be expected to increase as a result, to compensate for prescriptions that might have been restricted or discontinued.

Methods

Data

Optum's Clinformatics Datamart (CDM) de-identified insurance claims data were used to pull medical claims and laboratory records by current procedural terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), and logical observation identifiers, names, and codes (LOINC), for UDT associated with opioids, benzodiazepines or schedule I drugs (Appendix Table 1), from January 1, 2013 through December 31, 2019. This study was determined exempt by the Institutional Review Board at the University of Texas Medical Branch at Galveston. To assess yearly match rates between UDT and results, CPT/HCPCS codes were used to represent total UDT (Appendix Table 2), while lab results were counted using drug specific LOINCs (Appendix Table 3). Details on match rates may be found in Appendix Table 4. Because match rates were unexpectedly low, and to avoid discarding 73.8% of UDT results that were unmatched or missing a standard CPT code, data from LOINC-pulled files were used for analysis, rather than matched data. Within each drug category, only LOINC records with interpretable alphabetic or numerical results were included, such as "pos", or "<50", respectively. Overall, the LOINCs with interpretable results in each drug category were 67%, 73%, and 70% for schedule 1, opioid, and benzodiazepine, respectively (Appendix Table 5).

Outcomes

Three non-overlapping outcomes of UDT-positivity were defined: concurrent use, schedule-I use, and non-prescribed opioid and/or benzodiazepine use (misuse). Appendix Table 5 shows how the study cohort for each outcome was generated.

Concurrent use was defined as the percent of individuals with both opioid- and benzodiazepine-positive UDT on the same day, within each quarter. In a sensitivity analysis, concurrent use was also defined as concurrent-positive UDT within 3 days. Similarly, schedule-I use rates were defined as the percent of individuals with positive UDT for any schedule-I use within each quarter. "Any" prescription misuse was defined as any UDT-positive rates for an opioid, benzodiazepine, or both, outside a defined compliance window each quarter, among patient records with ≥180 days continuous enrollment prior to the UDT. The opioid compliance window included the prescription fill date, plus days of supply, plus 7 days to account for the time opioids remain detectable in the system. The compliance period was calculated similarly for

benzodiazepines, with an additional 30 days due to possible long-acting benzodiazepines. In a sensitivity analysis, prescription misuse was counted only if all opioid and/or benzodiazepine use in a quarter was misuse. The misuse rate at each quarter was the percent of individuals with any misuse among those with positive opioid or benzodiazepine UDT in a quarter. The cohort flowchart for each outcome may be found in Appendix Table 5.

Time

Time quarters were grouped as January-March (Q1), April-June (Q2), July-September (Q3), and October-December (Q4) in each year from 2013-2019.

Covariates

Age, sex and United States Census regions were used to stratify time trends. Region was categorized by the US Census Bureau, into the Northeast, South, Midwest and West regions. Age was categorized as <50, 50-59, 60-69, and 70 years and above.

Analysis

Quarterly rates of UDT positivity were plotted for concurrent use, schedule-I use, misuse by age, sex, and region. Joinpoint Regression models, with a maximum of 5 possible joinpoints, were conducted to evaluate any significant changes in time trends. A sequential application of the permutation test using 4500 possible randomly permuted data sets and a Bayesian information criterion were used to determine the optimal number of joinpoints. The slopes were estimated to represent change at a constant percentage every quarter linearly on a log scale. Joinpoint Regression Program 4.9.0.0 (National Cancer Institute), and SAS 9.4 (SAS Institute v. 9.4, Cary, NC) were used for all analyses.

Results

Concurrent use

Figure 2.1 shows trends in concurrent use in the total sample (n=746,672 UDT) and stratified by age, sex and region. Among the total sample, concurrent use rates decreased from 19.3% in Q1 2013, to 9.8% by Q4 2019. Similar patterns were mostly observed by age, sex and region, where all groups' concurrent use decreased with time. Notably, rates were higher in females than in males, lowest in age <50, and highest in the 50-59 and 60-69 age groups. By region, concurrent

use was highest in the South in 2013 (20.3%) and lowest in the Northeast (15.8%). However, by 2019, rates in the Northeast (10.9%) slightly surpassed the South (10.5%).

Table 2.1 presents log-scale slopes and detected joinpoints from joinpoint regression analysis of the studied outcomes. Concurrent-positive UDT showed a 2.3% quarterly decrease from Q1 2013 to Q1 2016, non-significant increase during 2016, 2.8% quarterly decrease from Q4 2016 to Q1 2019, and 9.5% quarterly decrease during 2019. In stratified analyses, joinpoints and slopes were slightly different in females compared to the entire study cohort. However, in males, only one significant joinpoint was found, showing a 1.35% quarterly decrease from Q1 2013 to Q3 2018, followed by a steeper quarterly decrease of 7.47% through Q4 2019.

Concurrent use decreased quarterly by 2.5% from Q1 2013 to Q3 2018, then by 8.2% through 2019 in the <50 age group. Similar trends were observed in the 50-59 group. Among age 60-69, two significant joinpoints indicated a 2.3% quarterly decrease from Q1 2013 to Q1 2016, non-significant increase from Q1 2016 to Q1 2017, and a 3.8% quarterly decrease from Q1 2017 to Q4 2019. The smallest decrease was found in age >70, with a 4.8% quarterly decrease from Q4 2017 through Q4 2019.

By region, concurrent use in the Northeast decreased 1.24% quarterly through the entire period. In the West, there was little change in concurrent use rates, decreasing 0.6% quarterly from Q3 2017 through Q4 2019. In the South, concurrent use decreased quarterly at greater rates with time (slope: -2.62% in Q1 2013-Q1 2016; slope: -2.39% from Q4 2016 to Q1 2019; slope: -9.5%, after Q1 2019); however, in the Midwest, there was a small decrease from Q1 2013 to Q2 2018 (slope: -0.7%), and a larger decrease from Q2 to Q4 2019 (slope: -16.7%).

Schedule I drug use

A total n=756,258 UDT were included in the schedule I cohort. Schedule-I use generally increased from 8.9% in Q1 2013 to 13.8% in Q4 2019, with a noticeable dip between Q3 and Q4 of 2013, from 9.4% to 5.7% (Figure 2.2). Higher schedule-I use was observed in males (12.4%, Q1 2013 to 17.9%, Q4 2019) than females (6.3%, Q1 2013 to 11.1%, Q4 2019). By region, lowest use was observed in the South (7%, Q1 2013 to 11.0%, Q4 2019), followed by the Midwest. The Northeast region had the highest rates, peaking at 19.4%, Q4 2019. By age, the rate of schedule-I use was highest among those <50 (18.3%, Q4 2019). As age group increased,

the magnitude of schedule-I drug use decreased; those ≥70 had the lowest use (5.7%, Q4 2019). Overall, schedule I drug use increased with time in all groups.

Joinpoint analysis of the total cohort detected two significant joinpoints, where there was an 8.3% quarterly decrease from Q1 2013 to Q1 2014, 8.2% increase from Q1 2014-Q2 2015, and a 1.58% increase from Q2 2015 to Q4 2019 (Table 2.1). Females had a higher quarterly decrease (12.7%) in illicit use from Q1 2013 to Q4 2013, which shifted to an increasing quarterly rate of 7.8% from Q 4 2013 to Q2 2015, followed by a slower quarterly increase of 2.1%, Q2 2015 to Q4 2019. Males showed a significant 1.3% quarterly increase from Q2 2015 to Q4 2019.

Age groups <50, 50-59, and 60-69 each had two significant joinpoints; from Q1 2013 to Q1 2014, schedule-I use decreased 8.8% and 8.4% quarterly in age <50 and 50-59, respectively, followed by a greater increase in age 50-59 group (slope:10.7%, Q1 2014 to Q3 2015), than age<50 (slope: 6.7%, in 2014-2015), and the same 1.9% quarterly increase in both through Q4 2019. Age 60-69 showed similar results, although only increased by 3.2% quarterly in 2015-2019. Those ≥70 increased a steady 4.2% ($p<0.001$) quarterly over the entire period.

By region, the Northeast, West and Midwest showed one significant joinpoint and similar trends. In 2014-2019, schedule-I use increased 1.8% and 2.1% quarterly in the Northeast and West, respectively. Similarly, there was a 2.5% quarterly increase in the Midwest, from Q2 2014 to Q4 2019. The South showed a large quarterly decrease of 12.8% from Q1 2013 to Q1 2014, 8.2% quarterly increase in 2014-2015, and slower increase of 2.7% quarterly from Q4 2017 to Q4 2019.

Non-prescribed use

Prescription misuse was assessed from n=452,420 UDT. Overall, misuse decreased from 75.6%, Q1 2013 to 55.1%, Q4 2018, after which the rate increased again to 59.3% in Q4 2019 (Figure 2.3). Similar patterns were observed by sex, although in Q1 2013 misuse was slightly higher in females (76.1%) than males (74.9%) and in Q4 2019, misuse was higher in males (60.9%) than females (58.3%). When stratified by age, misuse rates in 2013 were comparable (73.7-77.5%), decreased over time, and showed similar increases after Q4 2018 as in the total sample. By Q4 2019, ages 50-59, 60-69, and ≥70 had misuse rates of 56.7-58.3%, while age <50 had a higher rate of 68.5%. In the West, Midwest and South, misuse generally decreased over the entire

period, except for an increase from Q4 2018 – Q4 2019. In the Northeast, misuse appeared to fluctuate in early quarters then increase until Q3 2015, before decreasing again through Q4 2019. Differences by region were small in early quarters (74.3-79.9%) and varied more by Q4 2019 (52.2-68.3%).

In the total sample, three significant joinpoints were detected; misuse decreased 0.35% quarterly from Q1 2013 to Q1 2016, decreased 1.5% quarterly in 2016-2017, decreased 3.5% quarterly from Q4 2017 to Q4 2018, and increased 1.9% quarterly from Q4 2018 to Q4 2019 (Table 2.1). The same joinpoints and similar slopes were observed in misuse rates of females. Among males, only two joinpoints were found, with a similar pattern of slopes: small quarterly decrease, followed by a larger rate of decrease, and shift to increasing misuse after Q4 2018.

In age <50, there was a 1.7% quarterly decrease in 2016-2018 and 2.5% increase from Q4 2018 to Q4 2019 in non-prescribed use, the highest slope among the age groups. Age 50-59 misuse decreased 0.7% quarterly Q1 2013 to Q2 2017, decreased 3.3% quarterly Q2 2017 to Q4 2018, and increased 2.3% quarterly Q4 2018 to Q4 2019. Age 60-69 had similar results to the 50-59 group. In age ≥70, significant slopes were found from Q4 2015 to Q4 2017 and from Q4 2017 to Q4 2018, with quarterly decreases of 1.5% and 3.7%, respectively.

In the Northeast region, between Q3 2015 to Q1 2019, misuse decreased 1.76% quarterly. In the West, misuse use decreased 1.1% quarterly from Q1 2013 to Q1 2018, decreased 6.1% quarterly during 2018, and increased 1.7% quarterly from Q4 2018 to Q4 2019. In the Midwest, misuse slightly decreased, by 0.4% quarterly Q1 2013 to Q3 2017, decreased 3.6% quarterly from Q3 2017 to Q3 2018, and increased 2.3% quarterly thereafter. Misuse in the South was similar to that of the Midwest, which decreased 2.3% quarterly from Q2 2016 to Q4 2018, and 2% through Q4 2019.

Sensitivity analyses

When defining concurrent use to include opioid and benzodiazepine UDT dates up to three days apart, similar concurrent use rates were observed. Overall concurrent use trends were similar to those observed in Figure 2.1, decreasing from 19.3% in Q1 2013 to 9.8% in Q4 2019. Joinpoint analysis also showed very similar results.

The overall pattern of non-prescribed use decreased over the entire period, from 76.8% in Q1 2013, to 59.9% in Q4 2019, which was similar whether defining as any misuse or all misused in a quarter. Joinpoint analysis also showed similar results.

Discussion

In this retrospective study of national laboratory data from commercial insurance claims 2013 to 2019, we observed decreasing time trends in concurrent opioid-benzodiazepine use and in non-prescribed prescription drug use accompanied by increasing use of schedule-I drugs, which substantially increased after 2018. Understanding trends in the concurrent drug use has generally been limited to prescription claims studies, associated with providers' behavior rather than patients. This study analyzed national laboratory results to gauge patient use and found that UDT trends are consistent with prior studies on co-prescribing, misuse and illicit drug use.[5,6,11]

The overall decreasing trend in concurrent drug use aligned with expectations from previous literature,[6,12,13] which shows decreasing opioid and benzodiazepine co-prescriptions. Overall, concurrent use already decreased in 2013-2016, but decreased at a somewhat greater rate after the announcement and release of the 2016 CDC opioid-prescribing guideline, and decreased at a greater rate in 2019 after increased prevention measures were put in place by the Centers for Medicare and Medicaid Services (CMS).[1,14] Among some groups, the change in concurrent use rates did not occur immediately after 2016, as seen in males, ages <50, 50-59, ≥70, the West, and in the Midwest, which might indicate a delayed or lessened response to guidelines. Similarly, the linear decrease observed in the Northeast may reflect a lack of any response to the CDC guideline, although this region and the Midwest had smaller sample sizes, and patients of these regions receive UDT at lower rates than the South and West.[15] It is less clear why there was also a larger decline after 2018, however similar patterns were observed in national overdose deaths.[16] Higher concurrent use in females was expected, as females are more likely to be prescribed both concurrently,[2] than males. People under 50 years had the lowest rates, while those 50-69 had the highest, consistent with a previous national study.[17] Benzodiazepine use was also highest among 50-64 year-olds and may explain in part, the increased trends in this group.[18] The South had the highest concurrent use rates, which may be due to the increased prevalence of severe mental illness,[19] UDT rates, and the large market share of CDM data in the South, and potentially indicate a lack of alternative treatments to co-prescribing in this region;[2,15,17]

Schedule-I drug use increased across all ages, regions, and by sex, from Q2 2015 through Q4 2019. A sharp decline in schedule-I use was observed between the last two quarters of 2013, among females, those aged 18-59, and in the Northeast and South. One proposed explanation may be the effect of the Drug Enforcement Agency's rescheduling of hydrocodone in 2014. Although this change occurred late in 2014, the FDA recommended the reschedule months prior, in December 2013. The drop in schedule-I use of the current study coincides with the greater rate of change in opioid-prescribing observed at a similar timepoint in a previous study.[20] Schedule-I use increased at a greater rate from 2014-2015 among females, those aged 18-69, and in the South, then increased at a slower rate. The dramatic increase from 2014-2015 may be due to less accessibility to hydrocodone after 2014.

In this study, schedule-I use rates of 8.8-13.9% were generally consistent with recent CDC reports, which showed illicit drug use rates ranged from 8.1%-23.9%, in adults aged 18 and above, by 2018.[21] Males had higher rates of schedule-I drug use than females, which was expected.[22] The Northeast had the highest schedule-I use of all regions, while the South had the lowest;[23] these regional differences have been observed previously, suggesting primarily illicit drugs use in the Northeast, and prescription opiate abuse in the South, shown by corresponding overdose deaths in these regions. Schedule-I use was lower in age ≥70 and increased as age decreased, which aligned with literature showing greater illicit use in younger individuals than older.[24] Given that older individuals are up to 80% less likely to receive UDT than those under 50, it may explain why no change in illicit use was observed, and trends increased linearly in ages ≥70.[15]

We found 75.6% any misuse in Q1 2013 and 59.3% in Q4 2019. Previous studies have shown benzodiazepine misuse rates of 6.1-82.5%, and opioid misuse rates of 9.9-58%, though sample sizes and definitions of prescription misuse varied.[25-28] The somewhat higher rates of misuse found in this study may be due to the broader definition of non-prescribed use, which included those without a prescription, and those with prescriptions that may have been used in a manner not recommended by the provider. Additionally, misuse rates may be inflated due to selection bias of the misuse cohort; if providers sense a patient is at risk for misuse, there may be a differential in UDT requests, capturing more positive results among those more likely to

misuse.[29,30] UDT is also more common among patients that have indications for opioids or benzodiazepine use, such as those with various chronic pain indications and psychoses.[15]

The gradual decrease in misuse from 2013-2017 and the steeper decrease from 2017-2018 generally parallels the decreasing trend in co-prescribing opioids and benzodiazepines, and may indicate the shift to opioid and benzodiazepine alternatives, gabapentinoid and SSRI/SNRIs respectively, that provide a safer drug option, especially among the older population.[6] However, the decrease was somewhat unexpected, given the recent increased mortality associated with prescription misuse.[8] Beginning Q4 2018, non-prescribed use began to increase, which is consistent with the recent uptick in overdose deaths involving benzodiazepines and opioids between 2019-2020.[31]

Considering the observed trends in the context of 1) findings on increased mortality from illicit use and prescription misuse, 2) few of such patients receiving drug abuse treatment, and 3) the ineffectiveness of solely restricting opioid-prescribing, highlights the need for increased access to rehabilitation facilities for treatment. These findings also support the need for targeted public health initiatives, especially in males, younger individuals, and in Northeastern regions. The focus of public health efforts may require reorientation towards patient recovery rather than provider restriction.

Limitations

There are several limitations. First, insurance claims data limit generalizability to insured individuals, and therefore misses an important population affected by the opioid crisis—uninsured individuals living in poverty, which may underestimate drug use trends. Second, reliable race/ethnicity information is not available in CDM data and therefore could not be studied, though racial disparities in opioid compliance monitoring have been observed.[30] Third, only independent laboratories were used, missing any tests that were done in a hospital setting. However, 116 labs were included; approximately 49% of results came from one large lab, 25% from another large lab, and 12% from a third lab. Fourth, some results were excluded for having uninterpretable values, which may have biased the sample, though it is uncertain how this could impact trends. However, the percent of annual UDT with interpretable results increased over time, indicating improvement of UDT results. Finally, match rates between procedure codes and results were unexpectedly low (Appendix Table 4). However, few UDT results included in the

study were missing a CPT (<1%); instead, a nonstandard CPT code was often used, specific to benzodiazepines, opioids, and specific schedule-I drugs, though it's unknown whether these codes link to standard CPT codes in a system outside of CDM data.

Conclusion

Concurrent opioid and benzodiazepine use decreased 2013-2019, and at a greater rate after the 2016 CDC guideline and FDA warnings against concurrent use, and in 2019 after CMS implemented increased safety measures against concurrent use. There was an increase in schedule-I use from 2013-2019 and a decline in prescription misuse, which began to increase after 2018. The continued increase in schedule-I drug use, while concurrent opioid and benzodiazepine use decreased, indicates a potential shift from prescribed to illicit use and emphasizes the need to support addiction recovery programs, and focus public health interventions on patient recovery and prevention.

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Table 2.1. Joinpoints in Trends and Slopes of Quarterly Concurrent Use, Schedule I Drug Use, and Any Non-prescribed Use, 2013-2019

Concurrent Use[a]			**Schedule I Drug Use**			**Non-Prescribed Use**[b]		
Study period	Slope[c]	*P* value	Study period	Slope[c]	*P* value	Study period	Slope[c]	*P* value
Total			**Total**			**Total**		
Q1 2013 -Q1 2016	-2.3	<.001	Q1 2013-Q1 2014	-8.29	0.061	Q1 2013-Q1 2016	-0.35	0.006
Q1 2016-Q4 2016	5.0	0.216	Q1 2014-Q2 2015	8.17	0.064	Q1 2016-Q4 2017	-1.57	< 0.001
Q4 2016-Q1 2019	-2.8	<.001	Q2 2015-Q4 2019	1.58	< 0.001	Q4 2017-Q4 2018	-3.54	< 0.001
Q1 2019-Q4 2019	-9.5	<.001				Q4 2018-Q4 2019	1.95	0.002
Female			**Female**			**Female**		
Q1 2013-Q1 2016	-2.18	< 0.001	Q1 2013-Q4 2013	-12.72	0.01	Q1 2013-Q1 2016	-0.33	0.014
Q1 2016-Q4 2016	6.06	0.128	Q4 2013-Q2 2015	7.86	0.003	Q1 2016-Q4 2017	-1.48	< 0.001
Q4 2016-Q2 2019	-3.05	< 0.001	Q2 2015-Q4 2019	2.11	< 0.001	Q4 2017-Q4 2018	-4.04	< 0.001
Q2 2019-Q4 2019	-12.36	0.004				Q4 2018-Q4 2019	1.78	0.005
Male			**Male**			**Male**		
Q1 2013-Q3 2018	-1.35	<.001	Q1 2013-Q1 2014	-8.32	0.064	Q1 2013-Q2 2016	-0.39	0.001
Q3 2018-Q4 2019	-7.47	<.001	Q1 2014-Q2 2015	7.83	0.084	Q2 2016-Q4 2018	-2.16	< 0.001
			Q2 2015-Q4 2019	1.32	< 0.001	Q4 2018-Q4 2019	1.74	0.007
Age <50			**Age <50**			**Age <50**		
Q1 2013-Q3 2018	-2.54	<.001	Q1 2013-Q1 2014	-8.88	0.044	Q1 2013-Q1 2016	0.11	0.48
Q3 2018-Q4 2019	-8.17	<.001	Q1 2014-Q4 2015	6.72	0.006	Q1 2016-Q4 2018	-1.73	< 0.001
			Q4 2015-Q4 2019	1.99	< 0.001	Q4 2018-Q4 2019	2.58	0.002
Age 50-59			**Age 50-59**			**Age 50-59**		
Q1 2013-Q3 2018	-1.42	<.001	Q1 2013-Q1 2014	-8.49	0.058	Q1 2013-Q2 2017	-0.70	< 0.001
Q3 2018-Q4 2019	-7.85	<.001	Q1 2014-Q3 2015	10.73	0.002	Q2 2017-Q4 2018	-3.37	< 0.001
			Q3 2015-Q4 2019	1.92	< 0.001	Q4 2018-Q4 2019	2.32	0.014
Age 60-69			**Age 60-69**			**Age 60-69**		

Q1 2013-Q1 2016	-2.35	<0.001	Q1 2013-Q4 2013	-9.36	0.325	Q1 2013-Q3 2017	-0.71	< 0.001
Q1 2016-Q1 2017	3.75	0.278	Q4 2013-Q1 2015	14.2	0.036	Q3 2017-Q4 2018	-3.96	< 0.001
Q1 2017-Q4 2019	-3.83	<.001	Q1 2015-Q4 2019	3.19	< 0.001	Q4 2018-Q4 2019	2.03	0.001
Age 70 and above			**Age 70 and above**			**Age 70 and above**		
Q1 2013-Q4 2017	-0.40	0.268	Q1 2013-Q4 2019	4.15	< 0.001	Q1 2013-Q4 2015	-0.02	0.931
Q4 2017-Q4 2019	-4.80	<0.001				Q4 2015-Q4 2017	-1.51	<0.001
						Q4 2017-Q4 2018	-3.72	0.002
						Q4 2018-Q4 2019	0.84	0.252
Northeast region			**Northeast region**			**Northeast region**		
Q1 2013-Q4 2019	-1.24	<0.001	Q1 2013-Q1 2014	-8.98	0.075	Q1 2013-Q4 2014	-0.43	0.389
			Q1 2014-Q4 2019	1.82	<0.001	Q4 2014-Q3 2015	2.88	0.369
						Q3 2015-Q1 2019	-1.76	<0.001
						Q1 2019-Q4 2019	0.95	0.567
West region			**West region**			**West region**		
Q1 2013-Q3 2017	-0.32	0.237	Q1 2013-Q1 2014	-7.01	0.169	Q1 2013-Q1 2018	-1.06	<0.001
Q3 2017-Q4 2019	-0.614	<0.001	Q1 2014-Q4 2019	2.16	<0.001	Q1 2018-Q4 2018	-6.09	0.011
						Q4 2018-Q4 2019	1.68	0.035
Midwest region			**Midwest region**			**Midwest region**		
Q1 2013-Q3 2018	-0.72	<0.001	Q1 2013-Apr2014	-7.82	0.161	Q1 2013-Q3 2017	-0.4	<0.001
Q3 2018-Q2 2019	-6.06	0.301	Q2 2014-Q4 2019	2.59	<0.001	Q3 2017-Q3 2018	-3.55	0.006
Q2 2019-Q4 2019	-16.79	0.020				Q3 2018-Q4 2019	2.34	<0.001
South region			**South region**			**South region**		
Q1 2013-Q1 2016	-2.62	<0.001	Q1 2013-Q1 2014	-12.82	0.008	Q1 2013-Q2 2016	-0.25	0.070
Q1 2016-Q4 2016	5.71	0.242	Q1 2014-Q4 2015	8.18	<0.001	Q2 2016-Q4 2018	-2.31	<0.001
Q4 2016-Q1 2019	-2.39	<0.001	Q4 2015-Q4 2017	-0.94	0.268	Q4 2018-Q4 2019	1.92	0.014
Q1 2019-Q4 2019	-9.5	<0.001	Q4 2017-Q4 2019	2.68	<0.001			

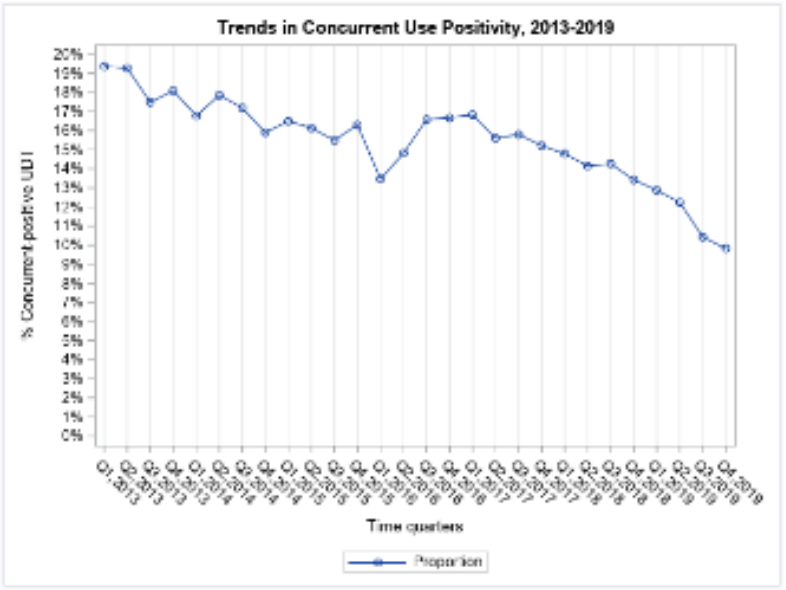
Abbreviations: Q1: first quarter; Q2: second quarter; Q3: third quarter; Q4: fourth quarter

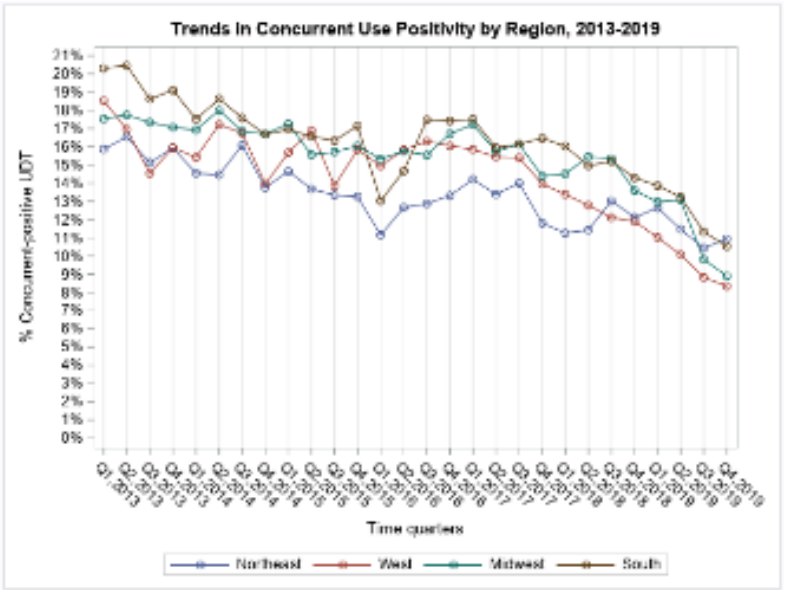
[a] Sensitivity analysis where concurrent use was counted in opioid and benzodiazepine UDT up to three days apart showed three joinpoints at the same quarters found when defining concurrent use as UDT on the same day. The slopes were also very similar, with a 2.3% decrease quarterly from Q1 2013 to Q1 2016 ($p<0.001$), 5.1% increase quarterly from Q1 2016 to Q4 2016 ($p=0.209$), 2.8% quarterly decrease from Q4 2016 to Q1 2019 ($p< 0.001$) and 9.1% quarterly decrease from Q1 2019 to Q4 2019 ($p<0.001$).

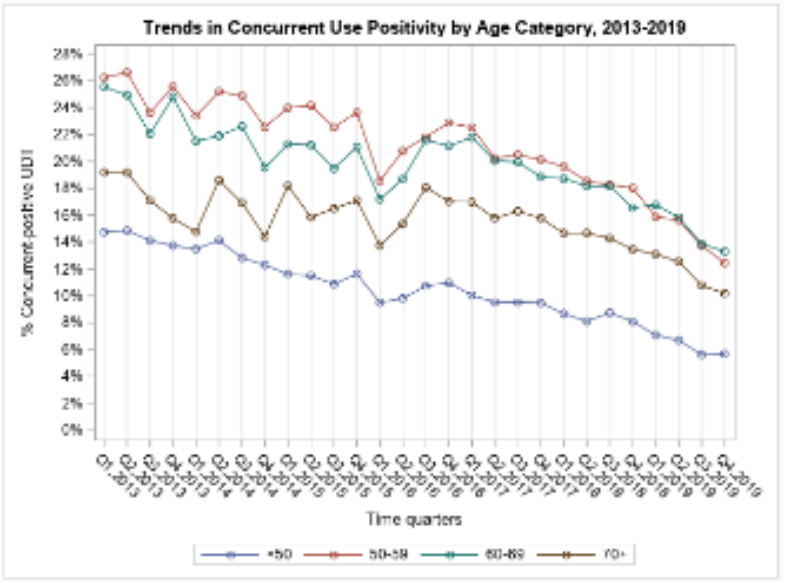
[b] Sensitivity analysis of non-prescribed use showed 3 joinpoints, with slopes that decreased quarterly by 0.4% from Q1 2013 to Q1 2016 ($p=0.001$), decreased 1.5% from Q1 2016 to Q4 2017 ($p< 0.001$), decreased 3.5% quarterly from Q4 2017 to Q4 2018 ($p< 0.001$), and increased 1.8% quarterly from Q4 2018 to Q4 2019 ($p=0.001$).

[c] Slope represents percent change of the quarterly rate of in UDT-positivity for each category of drug use linearly on a log scale.

Figure 2.1. Panel of Graphs: Concurrent Opioid and Benzodiazepine Use, 2013-2019







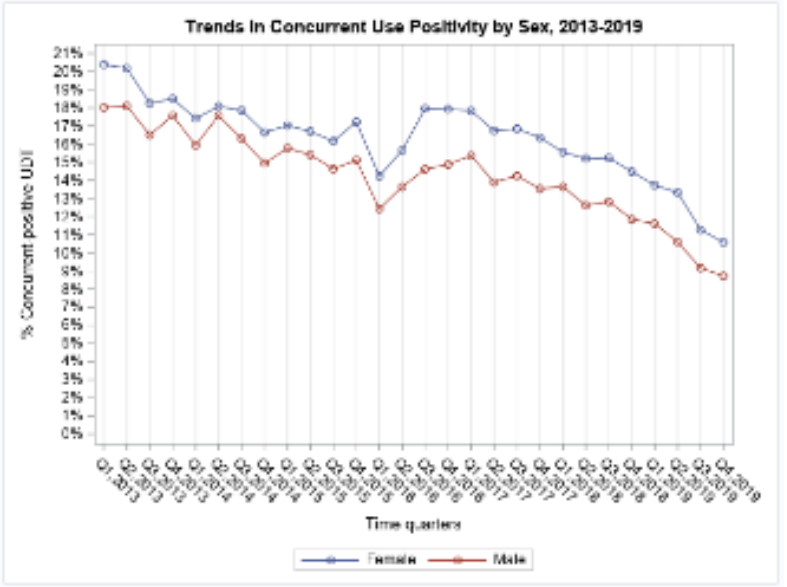


Figure 2.2 Panel of Graphs: Schedule I Drug Use, 2013-2019

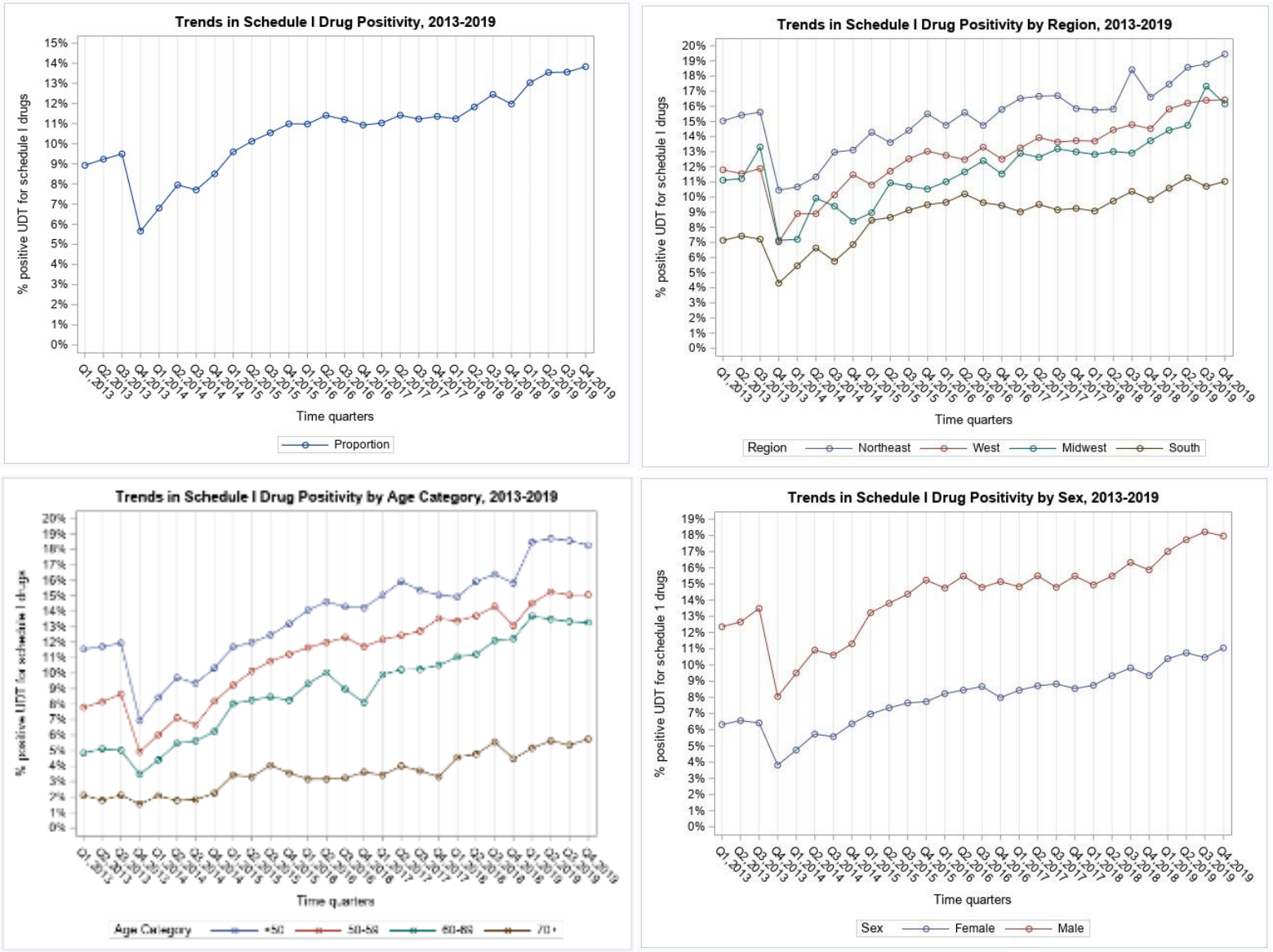
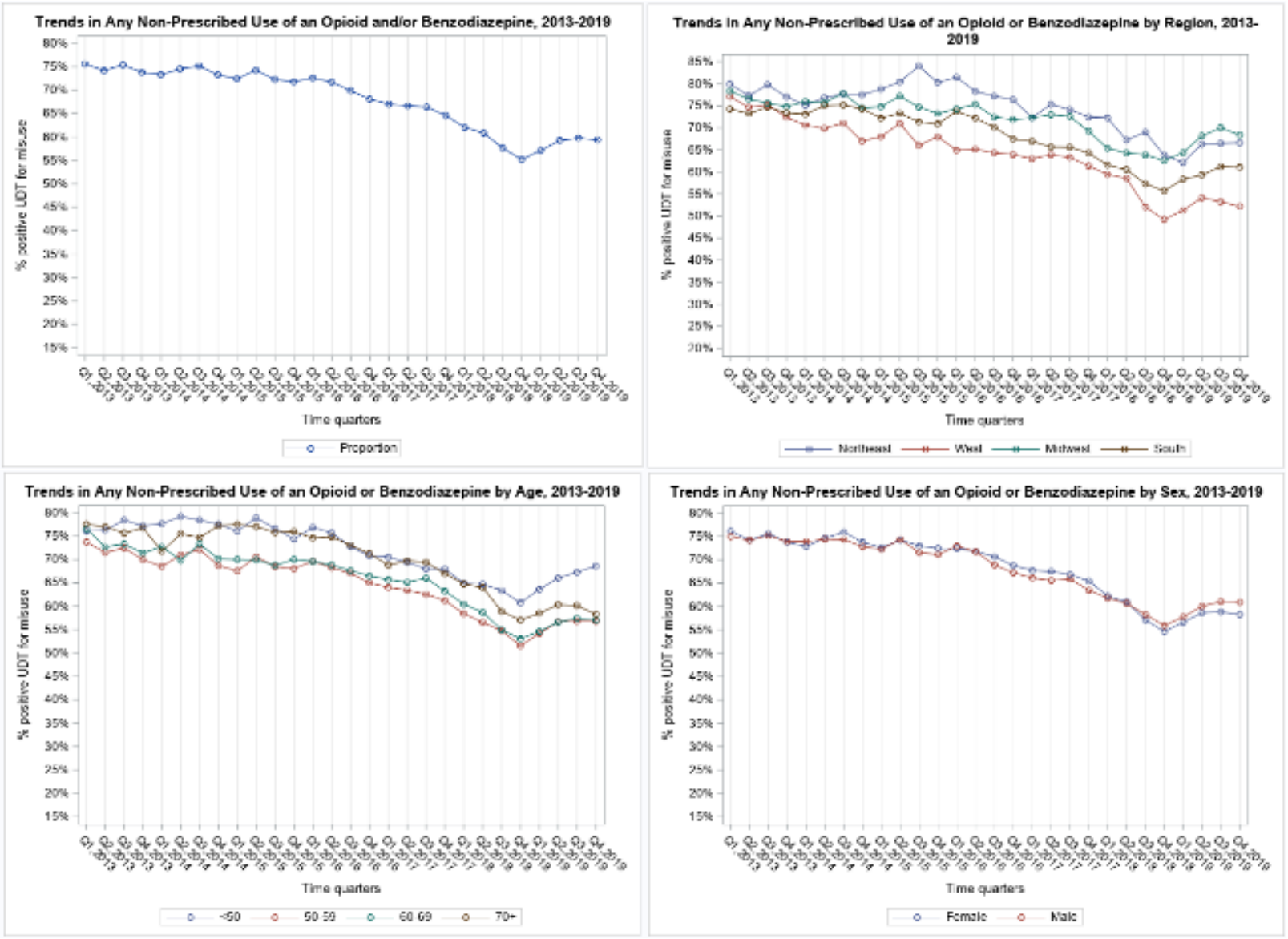


Figure 2.3. Panel of Graphs: Non-prescribed Use of Opioid and/or Benzodiazepines, 2013-2019



The following chapter was submitted for publication to the American Journal of Preventive Medicine October 15, 2022, passed initial review and is currently under external peer-review.

Chapter 3: Patient Characteristics Associated with Aberrant Urine Drug Tests: Co-prescribed Opioids and Benzodiazepines, Non-prescribed Opioids and Benzodiazepines, and Schedule-I Drugs

Introduction

Urine drug testing (UDT)—a mandated recommendation for risk assessments and compliance monitoring of patients on long-term opioids, benzodiazepines and other controlled drugs, is grossly underutilized.[1-3] The CDC, FDA and others warn providers to avoid opioid and benzodiazepine co-prescribing, a practice that increases the risk of substance abuse disorder, overdose and death.[1,4] To prevent these negative outcomes, UDT is important for early recognition of high-risk users of opioids, benzodiazepines or their combination. Thus, it is important to study facilitators and barriers to guideline-recommended UDT in patients receiving scheduled/controlled prescription drugs, to inform clinical guideline development and government policy, on slowing the drug overdose epidemic in the US.

Predictors of receiving UDT include younger age, back pain or general chronic pain indications, urban and Southern residence, and common drug abuse diagnoses—alcohol abuse, depression, and mental health disorders.[3,5] In a small study of cancer patients, predictors of UDT also included younger age, earlier cancer stage, higher pain intensity, lower ratings of fatigue, and Black race.[6] Studies more specifically assessing predictors of aberrant UDT results have focused on outcomes of non-prescribed drug use and illicit drug use, finding associations between illicit or non-prescribed use and male sex, substance abuse disorder diagnosis, current smoking status, younger age, lower average prescribed opioid dose, and short-acting opioid use.[5,7-10] These studies were limited in generalizability, had small sample sizes, or did not include concurrent use in urine drug test results.

Characteristics of individuals receiving co-prescriptions were studied and found that significant predictors included female sex, older age, depression diagnosis, lower income, smoking, and disability; [11-13] however, less is known about predictors of concurrent use in the context of aberrant UDT results, which may portray patient use more accurately than prescriptions, as

patients may receive non-prescribed drugs from other sources. The main objective of this study was therefore to determine predictors of concurrent use, schedule-I drug use and non-prescribed use of opioids or benzodiazepines, to identify and provide clinicians with patient characteristics associated with aberrant UDT, using laboratory results from one of the nation's largest commercial insurance databases.

Methods

Data and Cohort

Optum's CDM data from October 2, 2016 through December 31, 2018 were used to identify study cohorts, patient characteristics, and outcomes. Data included enrollment records, National Drug Codes (NDC) from pharmacy claims, International Classification of Disease codes (ICD-10) from medical claims, and laboratory records with logical observation identifiers, names, and codes (LOINC). Detailed cohort selection is included in Table 3.1. Patients were selected if they had LOINC records for UDTs with interpretable results for an opioid, benzodiazepine or schedule-I UDT, as determined by the Food and Drug Administration (FDA), from January 1, 2018 through December 31, 2018 (Appendix Table 1).

Schedule-I drug use was determined by UDT-specific LOINCs for heroin, cocaine, LSD, bath salts (cathinone/cathine), mescaline, MDMA, gamma-hydroxybutyric acid (GHB), marijuana (THC/cannabinoids), ecstasy, methaqualone, or khat. Opioid drug use included UDT-specific LOINCs for fentanyl, hydrocodone, hydromorphone, codeine, methadone, suboxone, propoxyphene, buprenorphine, morphine, oxycodone, and meperidine. Benzodiazepine LOINCs included flurazepam, oxazepam, clorazepate, chlordiazepoxide, alprazolam, lorazepam, clobazam, midazolam, temazepam, triazolam, diazepam, and estazolam. LOINCs representing a "benzodiazepine panel" and an "opioid panel" were also included.

Within each drug use category of consolidated UDT, patients with continuous enrollment from January 1, 2017 through December 31, 2017 were selected, to establish patients' clinical and drug characteristics before their index UDT. Among eligible patients, those with missing demographic information were excluded.

Outcomes

Three outcomes of aberrant UDT results found in 2018 were studied. The primary outcome was concurrent use, defined as those with a positive opioid UDT and positive benzodiazepine UDT on the same day. The second outcome was schedule-I drug use, defined as any positive UDT for schedule-I drugs. The third outcome was any non-prescribed opioid and/or benzodiazepine use. Non-prescribed use indicates that UDT for either or both drugs was found positive on a date outside of the compliance window for either or both drugs. The compliance window for opioids was the fill date plus the days supplied, plus an additional seven days for which an opioid may remain in the system and be detected by UDT. Similarly, the compliance window for benzodiazepines was the fill date plus the days supplied, plus 30 days to account for longer-acting benzodiazepines.

Patient Characteristics

The main independent predictors of interest included 1) patient demographics: sex, age (<50, 50-59, 60-69, ≥70), and US Census region (Northeast, West, Midwest, South); 2) clinical characteristics: Elixhauser comorbidity score (0,1-2, 3-4, ≥5), diagnoses of depression, substance abuse, psychoses, and alcohol abuse, prior UDT found positive for schedule-I drug use (yes, no, not tested), concurrent use (yes, no, not tested), or misuse of opioids and/or benzodiazepines (yes, no, not tested), number of UDT in the prior year (0,1, 2-3, ≥4); and 3), and combined opioid dosage and duration, where low dose refers to <50 MME/day and high dose was ≥50 MME/day, and short-term was <90 days use, while long-term indicated ≥90 days for a total of five groups (no opioid, low dose/short-term, low dose/long-term, high dose/short-term, high dose/long-term).

UDT frequency, prior drug use variables, Elixhauser score, and drug characteristics were determined using 2017 data. UDT frequency included the total count of any UDT CPT/HCPCS codes shown in Appendix Table 4, consolidated by date. Prior schedule-I drug use, concurrent use, or misuse of opioids and/or benzodiazepines was measured as any positive UDT for each category. Elixhauser score was calculated using previously described methods, after removing individual diagnoses of depression, psychoses, alcohol abuse and drug abuse.[14] MME per day was calculated by multiplying opioid quantity, dosage strength and conversion factors as described by the CDC,[15,16] then divided by total days supplied; overlapping opioid prescriptions

were accounted for by summing daily MME from multiple prescriptions, where applicable. Long term opioid use was determined by counting consecutive days of opioid use within 2017. Some prescriptions may have been filled late 2016 and carried over into 2017, while some may have been filled in late 2017 and ended in 2018. To count the days of opioid use in 2017 only, prescription data from the last quarter of 2016 was included, and the prescription duration was truncated to exclude days in 2016 and 2018, to calculate opioid duration use and daily MME.

Statistical analysis

Descriptive statistics were generated, and associations among patients that had UDT results for all three drug use categories were assessed using the chi-squared test. Multivariable logistic regression models were used to estimate the odds ratios and 95% confidence intervals for the effect of demographic, clinical and drug characteristics on the likelihood of each drug use outcome, while controlling for all other covariates. Multicollinearity was assessed to ensure stable model estimates and was defined as variables having tolerance<0.1 or a variance inflation factor (VIF)>10. Statistical significance was determined as $p<0.05$, and all tests were two sided. Data management and statistical analyses were performed using SAS 9.4 (SAS Institute v. 9.4, Cary, NC).

Results

Patient characteristics

Table 3.2 shows patient characteristics, by drug-positivity within each category of drug use. Among the concurrent use cohort (n=78,661), those with UDT positive for concurrent use (15.6%) were older, predominantly female (63.83%), and residing in the South (57.73%). Their clinical characteristics included a majority without UDT in the previous year (52.40%), diagnosed with depression (34.70%), or substance abuse disorder (22.46%), while only 3.45% and 2.16% had alcohol abuse or psychosis diagnoses, respectively. Drug characteristics of concurrent-positive individuals included a majority with low dose/short term opioid use (35.42%), followed by high dose/long term use (21.84%). Prior concurrent use was observed in 24.52% of patients, while 2.89% had prior schedule-I use and 28.21% had prescription misuse in the previous year.

In the schedule-I use cohort (n=78,950), among patients positive for schedule-I drugs (12.1%), most patients were under 50 years old (36.32%), male (53.25%), and residing in the South

(44.76%). Clinical characteristics included 21.31% with depression diagnoses, 20.65% with substance abuse, and few with diagnoses of alcohol abuse (5.50%) or psychosis (2.78%). The majority had no other Elixhauser comorbidities (59.51%). Drug characteristics of schedule-I use patients showed 35.87% had low dose/short-term opioid use, 33.14% did not have any opioid, and most did not receive UDT in the prior year (72.23%). Previous schedule-I use was observed in 13.6% of patients, while only 4.07% had prior concurrent use and 13.36% had prior misuse.

In the non-prescribed use cohort (n=57,989), among individuals with misuse (57.0 %) the majority were patients ≥70 years (34.69%), female (58.41%), and residing in the South (53.37%). Patients' clinical characteristics consisted of 23.67% with depression, 18.42% with substance abuse, 3.2% with alcohol abuse, 1.46% with psychosis diagnoses, and 46.79% without other Elixhauser comorbidities. Most patients did not have any UDT in the previous year (60.92%), had low dose/short term opioid use (42.38%) or no opioid use (24.73%) in the prior year. Few patients had previous schedule-I use (2.16%), some had concurrent use (7.70%) and a greater amount showed prescription misuse (27.81%)

There were 47,714 patients with UDT results for all three outcomes, including patients with positive UDT for multiple drug categories (Figure 3.1). Chi square results for associations between drug use categories among this cohort may be found in Appendix Table 6. Patients with concurrent use were more likely to have non-prescribed use (70.40% vs 53.08%, $p<0.0001$) and slightly more likely to have schedule-I drug-use than those without concurrent use (14.98% vs 10.72%, $p<0.0001$). However, the association between non-prescribed use and schedule-I use was weaker (12.11% vs 11.11%, $p=0.0008$). Multivariable associations between all independent predictors and drug use outcomes may be found in Table 3.3.

Concurrent Use

Patients of all age groups above 50 were 1.48-1.70 times more likely to have positive UDTs for concurrent use than those <50 years, while males were less likely than females (OR: 0.83 95% CI: 0.79-0.87). Other predictors of concurrent use included patient residence, where those in the West were 21.7% less likely to be concurrent users than those in the Northeast (OR 0.78 95% CI: 0.71-0.86). Compared to no opioid use, all opioid dose and duration categories were associated with concurrent use, with the strongest association found among high dose/long-term users (OR 4.82 95% CI 4.44-5.23).

Clinical predictors of concurrent use included any Elixhauser scores which increased the likelihood 11-17%, and diagnoses of depression (OR: 1.57 95% CI: 1.48-1.67) and to a lesser extent, substance abuse disorders (OR: 1.20 95% CI: 1.12-1.27). However, patients diagnosed with alcohol abuse were 14% less likely to have concurrent use (OR: 0.86 95% CI: 0.76-0.98). The number of UDT received in the prior year was also associated with concurrent use, and this association strengthened as the frequency of UDT increased (≥4 UDT, OR: 1.78 95% CI: 1.63-1.96). Patients with UDT positive for concurrent use in the previous year were 10.7 times more likely to continue to have concurrent use in 2018, compared to those not tested.

Schedule-I Use

Patient demographics associated with schedule-I drug use included age, where patients were increasingly less likely to use schedule-I drugs as age groups increased (age 50-59 OR: 0.87 95% CI: 0.82-0.93, age>70, OR: 0.29 95% CI: 0.27-0.31) compared to age (<50). Other predictors included male sex (OR 1.77 95% CI: 1.69-1.86), residence in the South (OR 0.62 95% CI: 0.57-0.67) and Midwest region (OR 0.70 95% CI: 0.64-0.78), compared to the Northeast. Patients with Elixhauser scores of 1-2 or 3-4 were 10% and 13% less likely to have schedule-I use, while those with ≥5 had the lowest odds of illicit use (OR 0.76 95% CI 0.69-0.84). Those with a diagnosis of alcohol abuse, psychoses or depression were 19.2-29.1% more likely to use schedule-I drugs, and those with substance use disorder were 47.0% more likely, compared to those not diagnosed. Patients with high dose/long-term opioids were 36.7% more likely to have schedule-I use drugs compared to those who did not have any opioid use. The number of UDTs received in the prior year was also a significant predictor, in which those who received 1-3 UDT were approximately 25% less likely to use schedule-I drugs, while those testing ≥4 times did not significantly reduce the odds of use. Prior schedule-I drug use was the strongest predictor of current illicit use (OR 18.46 95% CI: 16.32-20.88).

Non-prescribed Use

Age and sex were not significant predictors of prescription opioid or benzodiazepine misuse. Patients residing in the West were least likely to misuse compared to the Northeast (OR 0.77 95% CI: 0.71-0.84). Patients with a higher number of comorbidities had slightly lower odds of non-prescribed use (Elixhauser score 3-4, OR 0.87 95% CI: 0.82-0.93). Substance abuse diagnosis (OR 1.17 95% CI 1.11-1.23) was associated with misuse, as well as depression and

alcohol abuse diagnoses, though to a lesser extent (ex. Depression OR:1.07 95% CI: 1.02-1.12). All opioid use decreased the likelihood of misuse, compared to no opioid use, where the strongest association was found in those with high dose/long-term opioid use (OR 0.14 95% CI: 0.13-0.15). Individuals who were tested and found positive for any misuse in the prior year, were 88% more likely to show misuse.

Discussion

In this retrospective study of laboratory results from CDM insurance data, independent predictors of concurrent use, schedule-I drug use, and non-prescribed opioid or benzodiazepine use were assessed. In a subset of patients who received tests for all three drug categories, those who concurrently used opioids and benzodiazepines were more likely to have misused either or both of these drugs. Concurrent users were also more likely to use schedule-I drugs compared to those negative for concurrent use, reinforcing the abuse potential of combined opioid and benzodiazepine use,[1] and potentially representing the large portion of misusers receiving diverted drugs from relatives or other sources, or noncompliance with prescriptions.[17]

Age ≥50 was associated with a higher likelihood of concurrent use and lower likelihood of schedule-I drug use, but was not associated with prescription misuse, compared to those <50 years old. This aligns with previous literature showing older individuals are more likely to need opioids and/or benzodiazepines, often related to higher prevalence of comorbidities,[18] and less likely to abuse illicit substances, than younger individuals.[19] The finding that age is not associated with misuse is less clear, but may be because younger individuals are more likely to abuse opioids, while older individuals are more likely to abuse benzodiazepines, therefore nullifying the association with any misuse.

Sex was significantly associated with concurrent use and schedule-I use, where males were less likely to use opioids and benzodiazepines concurrently, but more likely to use schedule-I drugs than females; this was also consistent with previous literature showing females more frequently prescribed opioids or benzodiazepines, likely related to their greater likelihood of seeking medical care than males.[12,20,21] Males have higher a risk for substance use disorder, therefore the finding on increased schedule-I drug use in males was expected.[7,22] As with age, the lack of association between sex and misuse was somewhat unexpected, however, previous studies have shown females are more likely to misuse prescriptions if the intention is to self-medicate with

opioids or benzodiazepines, while males are more likely to misuse prescriptions if the intention is to "get high".[23,24] In this study, patient intent could not be determined, as self-reported measures are not available and may explain in part, the nonsignificant association.

Residence in the West region was associated with a decreased likelihood of concurrent use and prescription misuse, as previously reported,[25] showing lowest benzodiazepine use and misuse in the West. Residence in the South was associated with decreased schedule-I drug use and prescription misuse, compared to the Northeast region, which may be due to the highest rates of schedule-I drug use being observed in the Northeast.[26] The Midwest was also associated with lower schedule-I drug use; however, this region had smaller sample sizes in some categories, which may have misrepresented true rates due to insufficient data.[25]

Increased Elixhauser comorbidity score (≥1, compared to 0) was associated with an 11-17% increased likelihood of concurrent use but decreased the likelihood of schedule-I drug use. The association of having any comorbidity with concurrent use is expected, as patients should not receive opioids or benzodiazepines unless medically necessary; likewise, concurrent use is greater among those with poorer health.[13] However, it is unclear why a higher comorbidity score is associated with lower risk of schedule-I use. It may that such patients have establish care with a provider and are less likely to seek other drug sources.

Specific diagnoses of depression and substance abuse were associated with increased likelihood of concurrent use and schedule-I use, and to a lesser extent with non-prescribed use; these findings were expected given that patients with depression are more likely to receive opioids,[27] have co-prescriptions of opioids and benzodiazepines,[18] and to abuse schedule-I drugs.[28] Alcohol abuse was also associated with an increased likelihood of schedule-I drug use and prescription misuse, as it is known that alcohol and non-prescribed or schedule-I drugs are often mixed.[29] On the other hand, having an alcohol abuse diagnosis decreased the likelihood of concurrent use, which may be due to the known detrimental effects of mixing alcohol with opioids or sedative/hypnotics, such as benzodiazepines; providers should be aware of pharmacological interactions of drugs with other substances and may therefore avoid writing co-prescriptions for patients diagnosed with an alcohol abuse disorder.[30,31] Psychosis diagnosis was only associated with schedule-I drug use, which increased the likelihood of substance use in other previous reports.[32,33]

Opioid dosage and duration are important predictors which greatly increased the likelihood of concurrent use. Previous studies have shown that patients using opioids long-term are more likely to be diagnosed with depression, substance abuse, and psychoses;[34,35] the worsening of these conditions may eventually lead a patient to require combined therapy with a benzodiazepine. Conversely, patients with any opioid dose or duration, especially high dose/long-term, have decreased likelihood of prescription misuse. Though it may appear that higher dosage or long-term use may help manage pain, long-term and high-dose opioid use is not meant to be used indefinitely, loses effectiveness over time, and increases the likelihood of illicit use.[1]

Because concurrent use is advised against by multiple governing and healthcare agencies, close monitoring, and more frequent testing of patients that do co-use these drugs is emphasized as much as biweekly.[1,2] The finding that greater frequency of UDT is associated with concurrent use may therefore represent that higher-risk individuals, with poorer health that warrant more frequent UDT, and thus a greater likelihood of capturing any concurrent use. Patients with 2-3, or ≥4 UDT in the previous year were more likely to have concurrent use, while those with 1 or 2-3 UDT were less likely to have schedule-I use, and only those with 2-3 UDT were less likely to show prescription misuse. In schedule-I drug use and prescription misuse models, the reverse association observed may be that UDT deters patients from any drug abuse. However, UDT ≥4 showed no association; it may be that too frequent of UDT allows patients to prepare for and "pass" UDT, especially if non-random and unmonitored,[2] though it is unknown whether these UDT were random, monitored, or scheduled well in advance.

Finally, in all drug use models, prior drug use-positivity was a strong predictor, especially among concurrent users, who were 10.7 times more likely to continue concurrent use, and schedule-I drug users, who were 18.4 times more likely to continue use, compared to those not tested for corresponding drug use. Likewise, in all models, those tested and found negative for previous drug use were less likely to continue use, especially among concurrent users (40% less likely) and misusers (74% less likely), compared to those not tested. These findings highlight the importance of UDT monitoring of concurrent users, as well as tapering or discontinuing opioids and benzodiazepines as recommended by the CDC, and offering substance use disorder treatment as needed.

Limitations

An important limitation was the exclusion of demographics that are known to affect drug use outcomes, such as race/ethnicity, and smoking.[18] The use of insurance claims also limits generalizability to insured adults, excluding uninsured individuals, who may be disproportionately affected by the opioid crisis and have significantly decreased access mental health care and to substance use disorder treatments UDT results may be biased due to missing or uninterpretable results as a limitation of using insurance claims data, though it is uncertain the impact this would have on results. Selection bias is also likely, given that physicians may test individuals at differential rates where focus is placed on patients who are more likely to abuse drugs, or have greater comorbidities associated with concurrent opioid and benzodiazepine use such as depression and psychoses.[3] However, the strengths of the study include the large sample size from all regions of the US, inclusion of important diagnoses, and the use of laboratory results to measure direct patient drug use that is often missed in self-report measures.

Conclusion

This study found important predictors of concurrent opioid/benzodiazepine use, prescription misuse and schedule-I drug use. Concurrent use predictors included female sex, older age, drug-abuse related diagnoses, and a greater number of UDT. Overall findings support the need for increasing CDC-recommended strategies of prescribing drug alternatives, avoiding co-prescriptions when possible, and increasing UDT monitoring of vulnerable patients. Targeted health initiatives—such as patient education on disposal of unused prescriptions to avoid diversion and misuse, or increased access to substance use disorder treatment facilities—may help reduce polysubstance use and potentially mitigate the growing public health crisis of drug overdose deaths in the US.

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Table 3.1. Selection of Adults within Each Drug Use Cohort in 2018.

Selection Criteria	n
Schedule-I Drug Use	
Schedule 1 UDT Records	1,259,896
UDT records with results	926,996
UDT consolidated[a]	194,529
Selected annual UDT	123,892
1-year continuous enrollment in 2017	80,404
Complete covariate information	78,950
Positive UDT	6,296
Concurrent Use	
Opioid UDT total LOINC	3,581,014
UDT records with results	2,865,811
UDT consolidated[a]	223,489
Benzo UDT total LOINC	1,485,706
UDT records with results	1,156,376
UDT consolidated[a]	199,097
Concurrent UDT consolidated[a]	195,959
Select annual UDT	122,819
1-year continuous enrollment in 2017	80,033
Complete covariate information	78,661
Positive UDT	12,333
Non-prescribed Use	
Positive opioid UDT	133,090
180-day eligibility prior to opioid UDT	113,219
Positive benzo UDT	38,563
180-day eligibility prior to benzo UDT	32,760
Select annual UDT	73,884
1-year continuous enrollment in 2017	58,153

Complete covariate information	57,989
Any misuse	32,929

[a] Because a single LOINC code may represent one drug test or multiple drugs in a panel, LOINC records were consolidated by person, and date; whether a patient received a panel for multiple drugs within a category (schedule-I, benzo, opioid), or a single test for any of these, it was counted once.

Table 3.2. Patient Characteristics by Drug Concurrent Use, Schedule-I use, and Prescription Misuse

Characteristics	Concurrent Use				Schedule-I Use				Non-prescribed Use			
	No (n=66,328)		Yes (n=12,333)		No (n=69,340)		Yes (n=9,610)		No (n=24,920)		Yes (n=33,069)	
	n, %		n, %		n, %		n, %		n, %		n, %	
Age	p<.0001				p<.0001				p<.0001			
<50	18,808	28.36%	1,814	14.71%	17,666	25.48%	3,490	36.32%	3,527	14.15%	5,412	16.37%
50-59	11,454	17.27%	3,022	24.50%	12,259	17.68%	2,210	23.00%	5,744	23.05%	6,610	19.99%
60-69	16,175	24.39%	4,028	32.66%	17,469	25.19%	2,680	27.89%	7,903	31.71%	9,577	28.96%
≥70	19,891	29.99%	3,469	28.13%	21,946	31.65%	1,230	12.80%	7,746	31.08%	11,470	34.69%
Sex	p<.0001				p<.0001				0.7938			
Female	39,708	59.87%	7,872	63.83%	43,053	62.09%	4,493	46.75%	14,583	58.52%	19,316	58.41%
Male	26,620	40.13%	4,461	36.17%	26,287	37.91%	5,117	53.25%	10,337	41.48%	13,753	41.59%
Region	p<.0001				p<.0001				p<.0001			
Northeast	5,525	8.33%	827	6.71%	5,501	7.93%	1,126	11.72%	1,310	5.26%	2,602	7.87%
Midwest	17,963	27.08%	3,001	24.33%	17,874	25.78%	3,090	32.15%	7,681	30.82%	8,510	25.73%
West	7,016	10.58%	1,385	11.23%	7,360	10.61%	1,093	11.37%	2,678	10.75%	4,308	13.03%

South	35,824	54.01%	7,120	57.73%	38,605	55.67%	4,301	44.76%	13,251	53.17%	17,649	53.37%
Elixhauser Score	p<.0001				p<.0001				p<.0001			
0	38,949	58.72%	4,502	36.50%	38,316	55.26%	5,719	59.51%	9,227	37.03%	15,472	46.79%
1-2	9,962	15.02%	2,686	21.78%	10,968	15.82%	1,618	16.84%	5,536	22.22%	6,284	19.00%
3-4	8,757	13.20%	2,524	20.47%	9,899	14.28%	1,241	12.91%	5,155	20.69%	5,609	16.96%
5+	8,660	13.06%	2,621	21.25%	10,157	14.65%	1,032	10.74%	5,002	20.07%	5,704	17.25%
Depression	p<.0001				p<.0001				p<.0001			
No	54,954	82.85%	8,053	65.30%	55,889	80.60%	7,562	78.69%	18,311	73.48%	25,240	76.33%
Yes	11,374	17.15%	4,280	34.70%	13,451	19.40%	2,048	21.31%	6,609	26.52%	7,829	23.67%
Substance Abuse	p<.0001				p<.0001				p=0.1050			
No	57,635	86.89%	9,563	77.54%	59,884	86.36%	7,626	79.35%	20,198	81.05%	26,978	81.58%
Yes	8,693	13.11%	2,770	22.46%	9,456	13.64%	1,984	20.65%	4,722	18.95%	6,091	18.42%
Alcohol abuse	p=0.0053				p<.0001				p=0021			
No	64,349	97.02%	11,907	96.55%	67,400	97.20%	9,081	94.50%	24,231	97.24%	32,009	96.79%
Yes	1,979	2.98%	426	3.45%	1,940	2.80%	529	5.50%	689	2.76%	1,060	3.21%

Psychoses	p<.0001				p<.0001				p=0.6967			
No	65,328	98.49%	12,066	97.84%	68,310	98.51%	9,343	97.22%	24,565	98.58%	32,585	98.54%
Yes	1,000	1.51%	267	2.16%	1,030	1.49%	267	2.78%	355	1.42%	484	1.46%
Opioid Dosage and Duration[a]	p<0.0001				p<0.0001				p<0.0001			
No opioid	22,415	33.79%	1,431	11.60%	21,221	30.60%	3,185	33.14%	1,445	5.80%	8,179	24.73%
Low dose, short-term	26,746	40.32%	4,368	35.42%	27,742	40.01%	3,447	35.87%	9,517	38.19%	14,015	42.38%
Low dose, long-term	8,386	12.64%	2,451	19.87%	9,638	13.90%	1,146	11.93%	5,065	20.33%	5,801	17.54%
High dose, short-term	3,136	4.73%	1,389	11.26%	3,804	5.49%	627	6.52%	2,910	11.68%	1,813	5.48%
High dose, long-term	5,645	8.51%	2,694	21.84%	6,935	10.00%	1,205	12.54%	5,983	24.01%	3,261	9.86%
Number of UDT	p<.0001				p<.0001				p<.0001			
0	46,639	70.32%	6,463	52.40%	46,729	67.39%	6,941	72.23%	13,410	53.81%	20,147	60.92%
1	9,398	14.17%	2,210	17.92%	10,355	14.93%	1,146	11.93%	4,390	17.62%	5,734	17.34%

2-3	7,145	10.77%	2,431	19.71%	8,543	12.32%	876	9.12%	5,026	20.17%	4,891	14.79%
≥4	3,146	4.74%	1,229	9.97%	3,713	5.35%	647	6.73%	2,094	8.40%	2,297	6.95%
Prior illicit use	p<.0001				p<.0001				p<.0001			
No	18,823	28.38%	4,499	36.48%	21,998	31.72%	1,401	14.58%	9,329	37.44%	10,002	30.25%
Yes	1,308	1.97%	356	2.89%	411	0.59%	1,312	13.65%	575	2.31%	715	2.16%
Not tested	46,197	69.65%	7,478	60.63%	46,931	67.68%	6,897	71.77%	15,016	60.26%	22,352	67.59%
Prior concurrent use	p<.0001				p<.0001				p<.0001			
No	19,183	28.92%	2,191	17.77%	19,096	27.54%	2,233	23.24%	8,607	34.54%	8,431	25.50%
Yes	902	1.36%	3,023	24.51%	3,164	4.56%	391	4.07%	1,474	5.91%	2,545	7.70%
Not tested	46,243	69.72%	7,119	57.72%	47,080	67.90%	6,986	72.70%	14,839	59.55%	22,093	66.81%
Prior non-prescribed use	p<.0001				p<.0001				p<.0001			
No	6,366	9.60%	1,591	12.90%	6,995	10.09%	834	8.68%	6,731	27.01%	1,758	5.32%
Yes	8,880	13.39%	3,479	28.21%	10,757	15.51%	1,284	13.36%	3,587	14.39%	9,198	27.81%
Not tested	51,082	77.01%	7,263	58.89%	51,588	74.40%	7,492	77.96%	14,602	58.60%	22,113	66.87%

Table 3.3. Multivariable Associations of Patient and Drug Characteristics and UDT-Positivity in Concurrent Use, Schedule-I Drug Use and Prescription Opioid or Benzodiazepine Misuse

Characteristics	Concurrent Use			Schedule-I Drug Use			Non-prescribed Use		
	OR	95% CI		OR	95% CI		OR	95% CI	
Age									
<50		REF			REF			REF	
50-59	1.698	1.580	1.824	0.876	0.82	0.935	0.994	0.934	1.057
60-69	1.707	1.594	1.828	0.754	0.708	0.804	0.999	0.942	1.059
≥70	1.473	1.374	1.579	0.295	0.274	0.318	1.03	0.971	1.093
Sex									
Female		REF			REF			REF	
Male	0.836	0.799	0.875	1.778	1.697	1.863	1.014	0.977	1.053
Region									
Northeast		REF			REF			REF	
Midwest	1.057	0.953	1.174	0.708	0.643	0.78	1.036	0.946	1.135
West	0.779	0.709	0.856	0.947	0.871	1.029	0.779	0.717	0.847

South	0.951	0.872	1.038	0.620	0.574	0.670	0.905	0.836	0.979
Elixhauser Score									
0		REF			REF			REF	
1-2	1.170	1.085	1.261	0.905	0.832	0.983	0.947	0.892	1.006
3-4	1.122	1.038	1.212	0.878	0.801	0.961	0.879	0.827	0.935
≥5	1.119	1.034	1.211	0.764	0.693	0.843	0.932	0.875	0.993
Depression									
No		REF			REF			REF	
Yes	1.576	1.488	1.670	1.192	1.108	1.281	1.073	1.023	1.126
Substance Abuse									
No		REF			REF			REF	
Yes	1.202	1.130	1.279	1.47	1.366	1.582	1.176	1.117	1.239
Alcohol abuse									
No		REF			REF			REF	
Yes	0.871	0.767	0.989	1.291	1.144	1.457	1.147	1.024	1.283
Psychoses									

No		REF			REF			REF	
Yes	1.015	0.864	1.22	1.278	1.086	1.504	1.015	0.87	1.183
Opioid Dosage and Duration[a]									
No opioid		REF			REF			REF	
Low dose, short-term	2.100	1.962	2.248	1.087	1.025	1.153	0.307	0.288	0.327
Low dose, long-term	3.297	3.046	3.570	1.131	1.040	1.230	0.246	0.229	0.264
High dose, short-term	4.652	4.231	5.115	1.321	1.187	1.470	0.156	0.143	0.170
High dose, long-term	4.826	4.445	5.239	1.367	1.254	1.490	0.142	0.132	0.153
Number of UDT									
0		REF			REF			REF	
1	1.028	0.958	1.105	0.735	0.676	0.799	0.948	0.896	1.003
2-3	1.417	1.319	1.523	0.759	0.692	0.834	0.851	0.802	0.903
≥4	1.788	1.631	1.961	1.036	0.93	1.155	0.947	0.874	1.027
Prior drug use[a]									
No	0.402	0.379	0.428	0.438	0.408	0.471	0.261	0.245	0.278

Yes	10.749	9.859	11.720	18.463	16.325	20.882	1.884	1.791	1.981
Not tested	REF			REF			REF		

Abbreviations: OR: odds ratio; CI: confidence interval; REF: reference group; MME: morphine milligram equivalents; UDT: urine drug test

[a] Prior drug use refers to prior concurrent use in 2017 in the concurrent use model, prior schedule-I drug use in the illicit use model, and prior misuse of benzodiazepines and/or opioids in the non-prescribed use model.

Figure 3.1. Three-way Venn diagram showing Overlap of Drug Use Outcomes

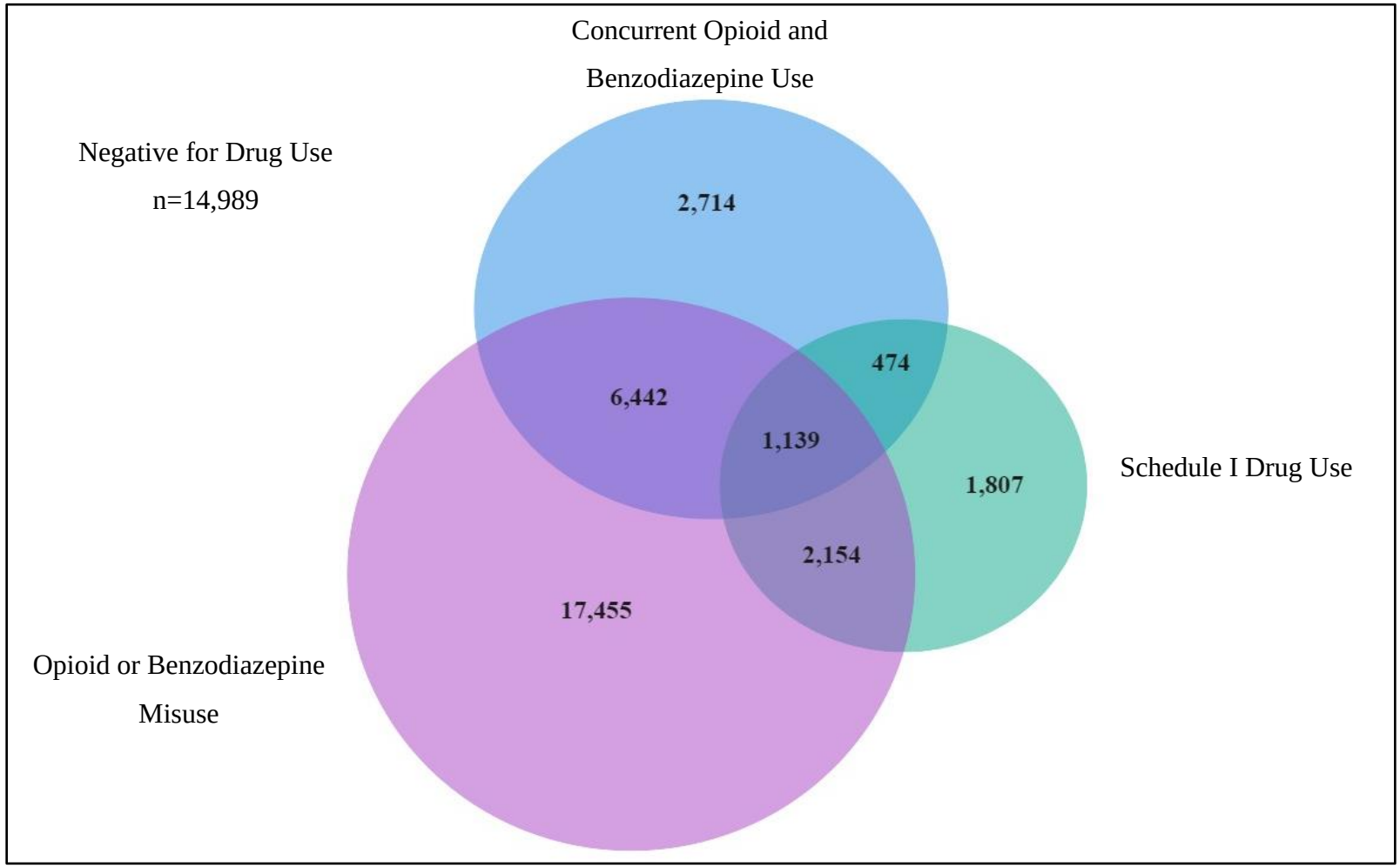

Fig. 3.1. Of the total (n=47,714), there were 14,989 (31.41%) patients with UDT negative for any drug use, while the remaining 68.59% were positive for one or more drug use categories. Of the 32,725 patients with positive UDT, the majority were positive for prescription opioid or benzodiazepine misuse only (53.38%), 31.20% were positive for at least two drug use categories (n= 10,209), and 5.52% schedule-I drug use and 8.29% concurrent use, respectively.

Chapter 4: Prescriber Response to Concurrent Opioid and Benzodiazepine Urine Drug Test Results

Introduction

Urine drug testing (UDT) is a valuable tool for patient risk assessments and drug monitoring, and has been recommended by the Centers for Disease Control (CDC), as well as professional organizations such as the Federation of State Medical Boards (FSMB) and American Society of Interventional Pain Physicians (ASIPP), as a part of comprehensive chronic pain management.[1-3] Patients on long-term opioids, benzodiazepines or both, are at greater risk of developing substance use disorder, and experiencing drug-related emergencies such as overdose or death;[4-6] UDT at least once annually is recommended to monitor patients, especially those with co-prescriptions for both opioids and benzodiazepines.[2] A number of limitations to UDT, including the potential for false-positive results, lack of provider training on result interpretation, and the increased likelihood of adulteration when collection is unmonitored, may explain in part why rates of UDT use by providers have been highly variable (2-52%).[7-11]

Although rates of opioid and benzodiazepine co-prescription rates have steadily decreased in recent years,[12,13] there were still over 3.4 million adults who received co-prescriptions in 2020,[14] emphasizing the need for UDT monitoring in co-use patients. Rates of aberrant UDT, in which unexpected results are observed, have varied from 42-75%, with most studies focusing on illicit drug use, non-prescribed use, or urine adulteration.[11,15-17] A previous study among patients with inconsistent UDTs showed prescription renewal rates were significantly higher when nonprescribed opioids or benzodiazepines were present (63.6%), than when illicit drugs, heroin or cocaine, were present (0.0%).[15] Another study showed prescribers planned to discontinue, change dosage, refer to an addiction treatment facility or make other modifications to opioid prescriptions in 30% of patients after observing aberrant UDT, including unexpected benzodiazepines or opioids.[18] However, both studies were single-centered or regional, and limited in sample size.

Because of increased risks of injuries, overdose and death associated with concurrent opioid and benzodiazepine use, the CDC and FDA recommend alternative drugs for benzodiazepines (SSRI/SNRIs) or opioids (gabapentinoids), as well as non-drug treatment (physical or occupational therapy, acupuncture, cognitive brain therapy, radiofrequency ablation), dosage

reduction, or over-the-counter medicine.[2,3,19] The objective of this study was to determine whether prescribers adjust patient treatment in response to observing concurrent use-positive UDTs, among a cohort of adult patients in 2018, using UDT results from a national commercial insurance database.

Methods

Data and Cohort

Optum's CDM data were used to identify the study cohort, predictors, outcomes and follow-up periods, between October 2, 2016 through December 31, 2019. Data included pharmacy claims via National Drug Codes (NDC), medical claims via diagnoses with International Classification of Disease codes (ICD-10), CPT codes for procedures and treatments, laboratory records using logical observation identifiers, names, and codes (LOINC), demographics, and insurance eligibility information. Opioid and benzodiazepine UDT included drugs found in Appendix Table 1. LOINC records for any opioid or benzodiazepine UDT in 2018 were first selected (Appendix Table 3).

The cohort selection flowchart may be found in Table 4.1. UDT with interpretable alphabetic or numerical results were then selected and consolidated by date. Among these, records showing an opioid and benzodiazepine UDT on the same day were selected and defined as "concurrent UDT". An index UDT date was chosen per person, as the first occurrence of any positive concurrent UDT in 2018. Patients that did not have continuous insurance enrollment in the year prior to the index UDT date were excluded. Among eligible patients, those with missing information on demographics, age, sex and region were also excluded in the final sample.

Outcomes

Prescriber response to concurrent use was measured as an initiation or change in treatment, after observation of the concurrent use-positive UDT. The following outcomes were included 1) first provider office visit, 2) non-drug treatment initiation, 3) opioid discontinuation 4) benzodiazepine discontinuation, 5) initiation of opioid alternative, gabapentin or pregabalin (referred to in this study as GABA), and 6) initiation of a benzodiazepine alternative (SSRI or SNRI). The follow-up period for the first provider visit and non-drug treatment initiation was one year after the index UDT, while all other outcome measures were limited to 90 days post-UDT. Follow-up times of 365 days were also assessed as sensitivity analyses. We selected 90

days because approximately 99% of patients had their provider visit within 90 days (Figure 4.1 panel A). Additionally, changes in opioid and benzodiazepine dosage were described. For all outcomes, patients were right-censored if they did not have a treatment change or lost insurance coverage within the applicable follow-up period.

A composite outcome showing overlap between non-drug treatment, any opioid change and any benzodiazepine change was described using a Venn diagram (Figure 4.2). Patients who did not have 90 days of continuous eligibility after their index UDT were excluded. Opioid changes were considered as those discontinued from an opioid, had decreased MME, or initiated a GABA drug within 90 days after the index UDT. Similarly, benzodiazepine changes were defined as discontinuation, decreased DME, or initiation of an SSRI/SNRI within 90 days after UDT.

Provider office visits and non-drug treatments were defined using CPT codes (Appendix Table 7) and followed up for the first office visit or treatment date post-UDT. Non-drug treatment included physical or occupational therapy, cognitive behavioral therapy (CBT), radiofrequency ablation (RFA), acupuncture, referral to a substance abuse rehabilitation program, and other less common treatments. A new GABA initiation was defined among patients that did not have a GABA prescription in the 90 days before the index UDT but initiated one within the 90 days in the follow-up period. SSRI/SNRI initiation was similarly defined.

Among a cohort of patients that had an opioid any time in the 90 days prior to their index UDT, opioid discontinuation was measure as no longer with an opioid prescription in the 90 days post-UDT. The discontinuation date was defined as the last date an opioid prescription was active, by adding the days of supply to the prescription fill date. Among those who still had opioid prescription in the 90-day follow-up period, opioid prescription change was measured as the daily MME decreased, increased or remained the same between the last prescription before the index UDT and the first prescription opioid after UDT within 90 days. MME was calculated using previously described methods.[2] Benzodiazepine changes were defined similarly for discontinuation and dosage change. Though there is disagreement on the use of benzodiazepine equivalence calculations, for research purposes, daily diazepam milligram equivalents (DME) were used to calculate dosage changes.[20,21]

Independent Variables

Demographic variables included age (<50, 50-59, 60-69, ≥70), sex, and US Census region

(Northeast, West, Midwest, South). Clinical characteristics included depression, substance abuse, psychoses, and alcohol abuse diagnoses, Elixhauser comorbidities[22] (0,1-2, 3-4, ≥5) excluding the ones described above, prior concurrent use UDT (positive, negative, not tested) in the year before index UDT, the frequency of UDT in the 365 days prior to UDT (0,1, 2-3, ≥4), and prior non-drug treatment (yes/no). Drug characteristics included a variable on duration and dosage of the opioid (no opioid, short-term and low-dose, short-term and high-dose, long-term and low-dose, or long-term and high-dose) in the year before, where long term indicates ≥90 days of use and high dose indicates ≥50 daily MME. We also identified GABA use (yes/no), SSRI/SNRI use (yes/no), opioid use (yes/no), benzodiazepine use (yes/no) in the 90 days before UDT, and daily DME (no benzodiazepine, <10, 10-20, or ≥20 DME/day) of the last prescription within 90 days before UDT.

Statistical Analysis

All analyses were performed using SAS 9.4 (SAS Institute v. 9.4, Cary, NC), using default settings unless otherwise stated, for generating descriptive statistics. Event-free survival curves were generated using the Kaplan Meier method. Multivariable Cox proportional hazard models were used to determine the time to an office visit, new treatment or drug initiation, or discontinuation among adults that tested positive for concurrent use, while controlling for independent variables previously described. The discrete method was used for handling ties, due to a large number of ties in time for each outcome. Two-tailed statistical tests were considered significant if the p-value was <0.05.

Results

A total of 12,493 patients who had concurrent UDT-positive results and all covariate information, were selected into the study (Table 4.1). Table 4.2 shows baseline patient characteristics of the total cohort. Most patients were over 50 years old (84.84%), female (63.96%), and residing in the South (58.19%). A large portion of patients had depression (43.41%) or SUD diagnoses (29.66%), while few had an alcohol abuse diagnosis (4.27%) or psychosis diagnosis (2.48%), and 1-2 other Elixhauser comorbidities (30.08%) in the year prior to their index UDT. Approximately 33.07% of patients had low dose/short-term opioid use in the year prior to UDT, while 25.09% had high dose and long-term opioid use. The number of UDT received in the year prior were approximately equally distributed (20.57–29.72%). Prior

concurrent use-positivity was only observed in 20.10%, while the majority was not tested for concurrent use (55.74%). Nearly all patients did not receive prior non-drug therapy (99.19%) in the year before index UDT. In the 90 days before UDT, most patients also did not have a GABA drug (68.72%), or SSRI/SNRI (58.22%), while the majority did have a benzodiazepine (77.96%) or opioid (87.10%) in this period (Table 4.2). Among patients taking a benzodiazepine in the 90 days prior, most had a daily dosage of ≥10 DME.

Figure 4.1 displays Kaplan Meier estimated survival times for the outcomes measuring time to a provider office visit (panel A), non-drug treatment (panel B), opioid discontinuation (panel C), benzodiazepine discontinuation (panel D), initiation of a GABA drug (panel E), and initiation of a SSRI or SNRI (panel F). In the office visit cohort, nearly all patients received an office visit within 365 days of their concurrent use-positive UDT (Figure 4.1, Panel A). The mean time to a provider office visit post-UDT was 35.5 (standard error [SE], 0.4) days and median was 26 days (95% CI 25-26). Most patients saw primary care providers (56%); other specialties included pain medicine (11%), neurology (5.2%), and physical medicine and rehabilitation (4.2%) (Appendix Table 8). The rate of non-drug treatment was 13.29% within 90 days, 20.49% by 180 days, and 31.54% by 365 days post-UDT (Figure 4.1, Panel B). Among those that received non-drug treatments, the majority received physical or occupational therapy (46%), followed by referral to an addiction rehabilitation center (26%), while others received RFA (15%), massage therapy (5%), acupuncture (<1%), CBT (2%) or other methods (6%).

Few patients (4.01%) that had an opioid prescription prior to their index UDT (pre-UDT), were discontinued from it within the 90 days following UDT observation (post-UDT). MME was compared in the pre- and post-UDT period (Appendix Table 9). Most patients with continued opioid use had the same daily opioid dosage (53.54%) before and after UDT, 13.29% had increased daily MME, and 16.78% had decreased MME, of which only 2.8% decreased MME by 20% or less. More patients were discontinued from benzodiazepines (7.63%) than opioids (Figure 4.1, Panel D). Most patients did not have a change in daily dosage (57.78%), only 6.50% received an increase in daily DME, while 7.73% had reduced daily DME, after concurrent use-positive UDT was observed (Appendix Table 9).

Initiation of opioid drug alternatives also showed relatively few patients received an alternative drug; 8.11% of patients initiated a GABA within 90 days after UDT (Figure 4.1, Panel E).

Comparatively, 10.0% of patients initiated a SSRI/SNRI within 90 days after UDT (Figure 4.1, Panel F). Among the 1,611 patients that did not receive an opioid prescription in the 90 days before their index UDT, 21.10% received a prescription post-UDT. Similarly, of the 2,754 patients without a benzodiazepine pre-UDT, 24.40% received one after UDT results were observed.

Among 11,987 patients with 90-day continuous enrollment post-UDT, 71.06% did not receive any treatment change, while only 28.94% did (Figure 4.2). Most of these were non-drug therapy initiation only (34.12%), followed by opioid changes (28.34%) or benzodiazepine changes (22.72%) only. The remaining 14.82% received treatment changes from multiple categories, of which only 1% (n=37) received all three.

Our sensitivity analyses showed the rate of opioid discontinuation, benzo discontinuation, GABA initiation, and SSRI/SNRI initiation were 4.42%, 8.62%, 9.32%, and 11.40%, respectively, at 1 year of follow-up. These results did not differ a lot from the rates at 90 days.

Multivariable Cox models

Table 4.3 shows multivariable hazard ratios (HR) for associations between each independent variable and all outcomes, while controlling for all other covariates. In the provider visit cohort, the rate of office visits was slightly lower in males than females (HR 0.95 95% CI: 0.91-0.99), and in those that tested positive or negative for concurrent use, compared to those not tested. However, office visits were especially higher among patients with ≥5 Elixhauser comorbidities (HR 1.73 95% CI 1.62-1.84), a depression diagnosis (HR 1.11 95% CI: 1.07-1.16), having any opioid use (HR 1.21 95% CI: 1.13-1.30, high-dose/long term), and having at least 1 UDT in the previous year (HR 1.52 95% CI: 1.43-1.62, ≥4 UDT).

In the non-drug treatment cohort, as age group increased, the rate of non-drug therapy decreased (HR 0.72, 95% CI 0.65-0.81, age ≥70), and was 20% lower in males compared to females. Non-drug treatment rates were also lower in the South (HR 0.80, 95% CI 0.70-0.92), in patients with high dose/long-term opioid use (HR 0.87, 95% CI 0.76-0.99), and in those previously testing positive for concurrent use (HR 0.87, 95% CI 0.80-0.95). Increased rates of non-drug therapies were observed in those with Elixhauser comorbidities ≥5, depression, alcohol abuse, psychoses, and those with a frequency of prior year UDT ≥2.

Rates of opioid discontinuation decreased with age (HR 0.69, 95% CI 0.51-0.93, ≥70 years old) and was lower in patients residing in the South, West, having 2-3 UDT, and among those with any opioid use, especially those with high dose/long-term use (HR 0.17, 95% CI 0.12-0.23). On the other hand, patients were more likely to be discontinued from opioids if they were male (HR 1.26, 95% CI 1.03-1.54), or had a substance abuse, or alcohol abuse diagnosis (ex. HR 1.61, 95% CI 1.08-2.39). Similarly, patients were more likely to be discontinued from benzodiazepines if they were male, and less likely if they had any opioid dosage or duration. In the benzodiazepine discontinuation cohort however, age was not an important predictor, and those in the South were twice as likely to be discontinued (HR 2.02, 95% CI 1.21-3.36). Other important predictors included depression and substance abuse diagnoses, and prior positive UDT for concurrent use, which were all associated with lower rates of benzodiazepine discontinuation (HR 0.53, 95% CI 0.39-0.72, prior concurrent-positive).

In the GABA initiation cohort, rates of new gabapentin or pregabalin prescriptions were higher among patients with Elixhauser comorbidities ≥5 (HR 1.44, 95% CI 1.11-1.87), psychoses (HR 1.50, 95% CI 1.01-2.21) and those with any opioid use (HR 2.27, 95% CI 1.56-3.31, high dose/long-term). Important predictors associated with decreased rates of SSRI/SNRI initiation included age 60-69 and ≥70, male sex, and prior concurrent use-positivity (ex. HR 0.76, 95% CI 0.61-0.93, prior concurrent-positive UDT). In contrast, SSRI/SNRI initiation was greater among patients with depression (HR 2.02, 95% CI 1.73-2.37) and any opioid use regardless of dose and duration (HR 2.08, 95% CI 1.50-2.88).

Discussion

In this study of concurrent opioid and benzodiazepine users in 2018, most patients received a provider office visit within one year after providers observed concurrent use-positive UDT results. However less patients received non-drug treatment alternatives, and few initiated a GABA, or SSRI/SNRI within 90 days of UDT result observations. Opioids or benzodiazepines were also found to be discontinued at low rates. The overall rate of any provider response within 90 days was also low, just under 30%. The high rate of patients seeing their provider after their concurrent use-positive results indicates that providers have an opportunity to discuss options with their patients, while the low rates of treatment changes or initiation show that these are not implemented as frequently, or soon enough after UDT.

Alternative treatment initiation

Approximately 31% of patients initiated alternative therapy within one year post-UDT, which may be aimed at addressing chronic pain or mental disorders, to replace the need for opioids and/or benzodiazepines, respectively. This is a low response rate considering the risks associated with concurrent use, and benefits of using non-opioid or non-drug treatment. A recent, large study of Veterans showed that patients receiving care from facilities with higher non-drug therapy use or non-opioid drug use, were less likely to initiate a long-term opioid in the following year, thus lessening their risk of overdose or death.[23] Because opioids have not been shown to be more effective than non-opioid drugs or therapy options, the CDC recommends that clinicians provide other treatment options first, before initiating an opioid.[2,24] It is possible that patients tried non-drug treatments that were not covered by their insurance and not captured in CDM data, such as self-care methods of exercise or meditation. A study of 936 veterans found that approximately 20% used relaxation techniques, yoga or tai chi as their non-pharmacological therapy for chronic pain,[25] while another study found that up to 50.9% used exercise as their mode of chronic pain treatment.[26]

In multivariable analysis (Table 4.3), males, older patients, high dose/long term opioid users, and those with prior concurrent use were less likely to initiate non-drug treatment. Patients on long-term/high dose opioids and those with prior concurrent use had lower rates of new non-drug treatment likely because prolonged use of opioids and continued concurrent use status delay or prevent initiation of other therapies. Patients may have already become accustomed to opioid use, making it difficult to switch to other treatment options. However, given the known risks of concurrent use, in such cases it may be more beneficial to offer non-drug therapy sooner, and begin decreasing opioid dosage to taper patients off the drug completely, followed by the benzodiazepine if necessary. Rates of non-drug treatment were increased in patients with greater comorbidities, depression, alcohol abuse, psychoses and UDT frequency, which could be due to the greater likelihood these patients see providers and therefore have more opportunity to receive other treatments. Patients in the South also received non-drug treatment at lower rates, potentially highlighting the fact that mental illness rates are highest in the Southern regions and may require continued concurrent use;[27] A recent study also showed patients residing in the South were less likely to receive non-pharmacological treatment, however the association was not significant.[25] Other recent reports show the West, and more so the South, have the lowest

concentration of physical/occupational therapists per 100,000 people, which may partly explain the association 88etweenn non-pharmacological therapy with these regions.[28,29]

Opioid and benzodiazepine prescription changes

The relatively low rate of opioid discontinuation is expected, as is the majority of patients remaining on opioids;[30] the rate of patients receiving opioid dosage reductions was comparable to a previous study.[31] Males and patients with substance or alcohol abuse disorders were discontinued at greater rates, which has also been previously shown.[32] Older patients and those with higher dosage and duration of opioids were discontinued at lower rates than younger, as expected,[26] however the association the South and West region was less understood; it may be partly due to the higher likelihood of continuing opioid use or having concurrent use, in these regions.[27,32,33] Patients on high-dose or long-term opioids should not be immediately discontinued, rather they should slowly be tapered off an opioid at around 10-25% daily MME per week,[2] therefore the decreased rate of opioid discontinuation in high dose/long-term individuals, compared to short-term/low-dose individuals was expected. In approximately 13% of patients, opioid MME was increased after concurrent use UDT was observed; it may be that patients did not feel adequately treated due to disease progression, or developed tolerance for their previous dosage, two common reasons for opioid dose escalation.[34] One study also found that 25% of opioid dose increases had no documented prescribing rationale.[35] On the other hand, approximately 14% of patients had reduced opioid dosage post-UDT (>20% MME reduction), similar to a recent study showing 23.1% had reduced opioid dosage;[31] the lower rate in this study is likely due to the higher MME reduction cutoff and shorter follow up period. The observation that opioid discontinuation rates were lower than MME reduction rates suggests that provider response generally adheres to recommendations for the high-risk group included in this cohort.

The rate of benzodiazepine discontinuation was slightly higher than opioid discontinuation (7.63%). In multivariable analysis, the benzodiazepine discontinuation model showed some similar and conflicting predictors as in the opioid discontinuation model. Because benzodiazepine withdrawal symptoms are worse than those experiencing opioid withdrawal, the CDC recommends first tapering an opioid until it is discontinued, and then slowly tapering the benzodiazepine; abruptly discontinuing a benzodiazepine, puts patients at risk of rebounding anxiety, hallucinations, and sometimes death.[2] Important predictors that increased the rate of

benzodiazepine discontinuation included male sex, and residence in the West. Unlike the opioid discontinuation cohort, patients with depression or substance abuse disorder were less likely to be discontinued from a benzodiazepine. This may be because it is safer for patients to be tapered from an opioid first, then slowly discontinuing their benzodiazepine as needed. Some patients (6.50%) had an increase in benzodiazepine DME, which is somewhat unexpected given that it is uncommon for daily-use benzodiazepine dosage to be increased, as these usually have an intermediate or slow-release onset.[36] These patients may be increasing dosage due to tolerance after long-term use or disease progression, for example if depression symptoms worsen. The 7.32% of patients showing a >20% DME decrease represents those who switched from higher dose benzodiazepines to lower, or perhaps switching between benzodiazepines with different DME, as commonly done before tapering.[37]

Alternative drug initiation

Gabapentin and pregabalin, and SSRIs/SNRIs have generally been considered safer alternatives for opioids and benzodiazepines, respectively, and are recommended in place of either or both drugs, to avoid concurrent opioid and benzodiazepine use. However, there is growing concern whether GABA drugs are truly safer than opioids to use.[38,39] The 8.11% initiation rate was similar to a recent report's rate of the same year (10.9%),[110] and somewhat lower than rates of another study (15%);[13] the slightly lower rate of this study may be due to its measure of new initiations, rather than counting any current gabapentinoid prescriptions. Significant factors that were associated with increased rates of GABA initiation included having ≥5 Elixhauser comorbidities, consistent with previous literature.[40] Other important factors included psychosis diagnosis and any opioid use; the association of GABA drug initiation with psychosis may be due to the sedating effect of GABA on the nervous system, that mimics anti-psychotic treatment, as demonstrated in a small pilot study,[41] however, greater evidence is needed to prove its effectiveness for psychoses. Because GABA drugs are an alternative often used in place of opioids, it is expected that patients on opioids would be more likely to initiate a new GABA drug as observed,[13] however it is not understood why rates did not differ by opioid dose and duration.

The 10% initiation rate of SSRI/SNRIs of this study was similar to another study's findings in the same year 2018.[42] Independent variables that increased rates of SSRI/SNRI initiation included depression diagnosis and any opioid use, though there was little variation by opioid

dosage and duration. These results are expected and indicate that providers offer patients benzodiazepine alternatives when they are on opioids, however the overall rate of patients receiving such alternatives was only 16%. On the other hand, prior concurrent use positivity, male sex, and age ≥60 was associated with lower rates of SSRI/SNRI initiation. It may be that patients with continued concurrent use were captured in this cohort, who may find it challenging to switch to a benzodiazepine alternative due to their dependence on it and difficulty of weaning off a benzodiazepine.[2] Although the time to initiating an opioid or benzodiazepine alternative in both cohorts was relatively quick among those recipients, rates were low.

Overall rates of non-drug treatment, alternative drug initiation or opioid/benzodiazepine discontinuation within each cohort and as a whole were low, and may have several reasons. One possibility is that providers may take care to avoid severe withdrawal symptoms by avoiding sudden discontinuation of either an opioid or benzodiazepine. Another reason is that providers are being cautious with how they interpret UDT; they could benefit from assistance with result interpretation[43] to avoid restricting a prescription, and unnecessarily affecting patients based on erroneous readings. The use of diagnostic management teams (DMTs) may be a helpful resource in correct UDT interpretation, in which a group of medical experts consider the full clinical picture of a patient when selecting and interpreting laboratory tests. Because of potential false-positives and interference from other medications or supplements, unexpected opioid or benzodiazepine positivity in UDT upon first observation should therefore not immediately warrant discontinuation or prescriptions changes, but should at least be discussed with patients, to adapt treatment plans if needed. However, because prior concurrent use significantly reduced rates of non-drug treatment initiation, benzodiazepine discontinuation and SSRI/SNRI initiation, there is concern that providers are delayed in taking steps towards decreasing or preventing concurrent opioid and benzodiazepine use, despite the strong evidence that reinforces its unsustainability and harmful effects.

This study may be improved if reproduced using multiple aberrant UDT observations. Previous studies have also used single[15,18,44], or “at least one” aberrant UDT[45] to assess similar outcomes, though it may be more appropriate to include multiple UDT showing consistent results, to better gauge patient use and associated provider response. Additionally, the use of electronic health record (EHR) data may fill some of the gaps of insurance claims data, including more detailed

information on patient demographics, provider notes after consulting with patients, and more complete information on lab testing, such as repeat screening, or confirmatory testing, in response to potentially-aberrant screening results.

Future research could examine the initiation of medication-assisted treatment (MAT) as an outcome, which was not included in this study and may have underestimated prescriber response. MAT drugs, methadone, buprenorphine, or naltrexone may be prescribed to help patients with opioid use disorder recover and may have been an indication of provider response.

Other important studies that would further our understanding of patient outcomes associated with UDT could focus on determining characteristics and specialties of providers that have made changes in response to UDT results. Because providers included in this study may vary greatly in their educational background, training and specialty, their attitude towards the use of UDT and how to respond to aberrant results will also vary. Understanding this variation could allow for the development of training programs and potential guidelines specific to increasing the use of UDT (or using more efficiently) that could help standardize the implementation of UDT related to pain management.

Limitations

Alternative treatments or drugs that are not covered by insurance were not captured, such as over-the-counter medication that providers may have suggested for patients to take in place of opioids and/or benzodiazepines. Similarly, for patients that may have had few or no comorbidities, provider suggestions to begin a “self-care” routine such as self-guided meditation, or exercise regimens would also not be captured, although there is a lack of definitive evidence on the effectiveness of such methods.[46] Provider response in this study was based on a single observation of concurrent-positive UDT, rather than multiple lab results consistently showing aberrant behavior. Numerous guidelines suggest the use of UDT to assess patients for drug use, however the guidance on how providers approach aberrant UDT is limited to recommendations of using individualized judgement to determine treatment changes, if any. One UDT may not have been enough in this case for some providers to take action, while others may have used the index UDT with prior history to change treatment.

It is also important to note that individuals included in this study may be differentially selected, as patients diagnosed with depression or drug abuse are more likely to receive UDT.[10] It is also possible that discontinuation results were overestimated; if patients did not get a new prescription after their index UDT or for example, if an opioid or benzodiazepine prescription were intended to be taken "as needed" and captured in the pre-UDT period, it would also appear as a discontinuation. Important variables such as race/ethnicity and other socioeconomic status variables could not be studied using CDM data. Finally, provider characteristics' impact on outcomes could not be studied, such as provider intent, as previously done through patient chart studies.[18,47] It is assumed that each outcome is a result of providers observing concurrent use positivity, however it is possible that other motives for observed drug initiation or changes exist.

Conclusion

Among patients with UDT positive for concurrent opioid and benzodiazepine use in 2018, almost all patients followed up with a doctor's office visit, however only 28.94% received any treatment changes within 90 days of UDT observation. Because long-term opioid use and prior concurrent use generally decreased occurrences of treatment changes, this may highlight a need to focus future care on preventive measures at earlier stages, before opioid use and/or concurrent use is established.

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Table 4.1. Selection of Adults with UDT Positive for Concurrent Use, 2018

Selection Criteria	n
Opioid UDT total LOINC	3,581,014
UDT records with results	2,865,811
UDT consolidated[a]	223,489
Benzo UDT total LOINC	1,485,706
UDT records with results	1,156,376
UDT consolidated[a]	199,097
Concurrent UDT consolidated[a]	195,959
Total Positive Concurrent UDT	26,068
Select UDT[b]	17,711
One-year continuous enrollment prior to index UDT date	12,936
Total cohort with all covariate information	12,493

[a] Concurrent tests were consolidated by UDT date; whether a patient received a panel for multiple drugs or a single test, it was counted once per day.

[b] If there were multiple, positive concurrent opioid and benzodiazepine UDT, the first UDT date was chosen.

Table 4.2. Baseline Pre-UDT Patient Characteristics Among the Total Cohort

Characteristics	Total cohort (n=12,493)	
	n	%
Age		
<50	1,894	15.16
50-59	3,102	24.83
60-69	4,103	32.84
≥70	3,394	27.17
Sex		
Female	7,990	63.96
Male	4,503	36.04
Region		
Northeast	766	6.13
Midwest	3,035	24.29
West	1,422	11.38
South	7,270	58.19
Elixhauser Score		
0	2,107	16.87
1-2	3,758	30.08
3-4	3,299	26.41
5+	3,329	26.65
Depression		
No	7,070	56.59
Yes	5,423	43.41
Substance Abuse		
No	8,788	70.34
Yes	3,705	29.66
Alcohol abuse		
No	11,960	95.73
Yes	533	4.27
Psychoses		
No	12,183	97.52
Yes	310	2.48
Opioid Dosage and Duration[a]		
No opioid	1,267	10.14
Low dose, short-term	4,132	33.07
Low dose, long-term	2,082	16.67

High dose, short-term	1,877	15.02
High dose, long-term	3,135	25.09
Benzodiazepine DME[c]		
No benzodiazepine	2,754	22.04
<10 DME/day	2,879	23.04
10-20 DME/day	3,763	30.12
≥20 DME/day	3,097	24.79
Number of UDT		
0	3,060	24.49
1	3,150	25.21
2-3	3,713	29.72
≥4	2,570	20.57
Prior concurrent use		
No	3,019	24.17
Yes	2,511	20.10
Not tested	6,963	55.74
Prior non-drug therapy		
No	12,392	99.19
Yes	101	0.81
Prior GABA use[b]		
No	8,585	68.72
Yes	3,908	31.28
Prior SSRI/SNRI use[b]		
No	7,273	58.22
Yes	5,220	41.78
Prior Benzodiazepine use[b]		
No	2,754	22.04
Yes	9,739	77.96
Prior Opioid use[b]		
No	1,611	12.90
Yes	10,882	87.10

[a] Low dose: <50 daily MME, high dose: ≥50 daily MME, short-term: <90 days opioid use, long-term: ≥90 days of opioid use, in the year prior to index UDT

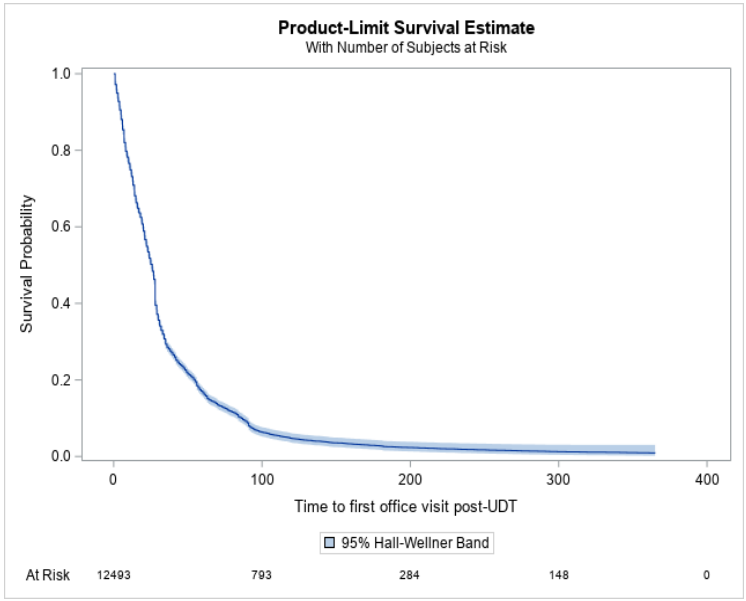
[b] prescriptions within the 90 days prior to the index UDT

[c] DME: diazepam milligram equivalents, measured in the last benzodiazepine prescription before the index UDT. Prescriptions ending earlier than 90 days before the index UDT were not counted.

Figure 4.1. Panel of graphs estimating the time to A) the first office visit, B) new non-drug treatment, C) Opioid Discontinuation, D) Benzodiazepine Discontinuation, E) new Gabapentin/Pregabalin, or F) new SSRI/SNRI.

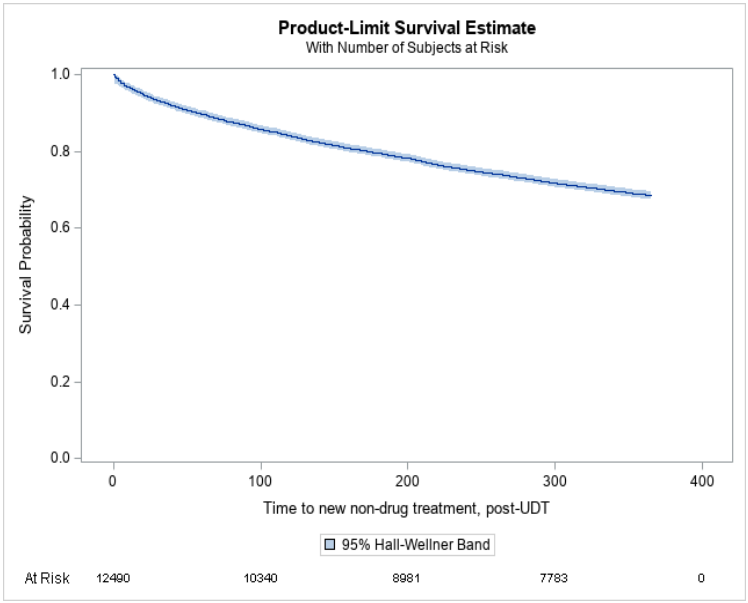
A)

n=12,493

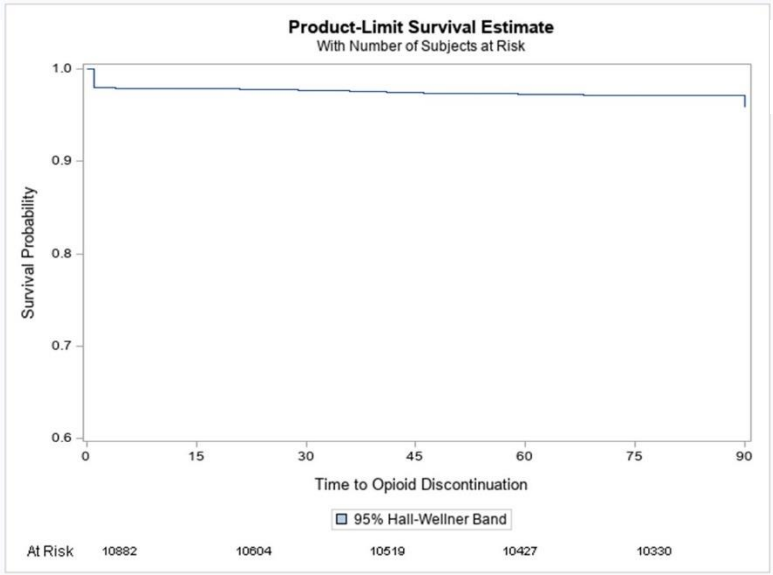


B)

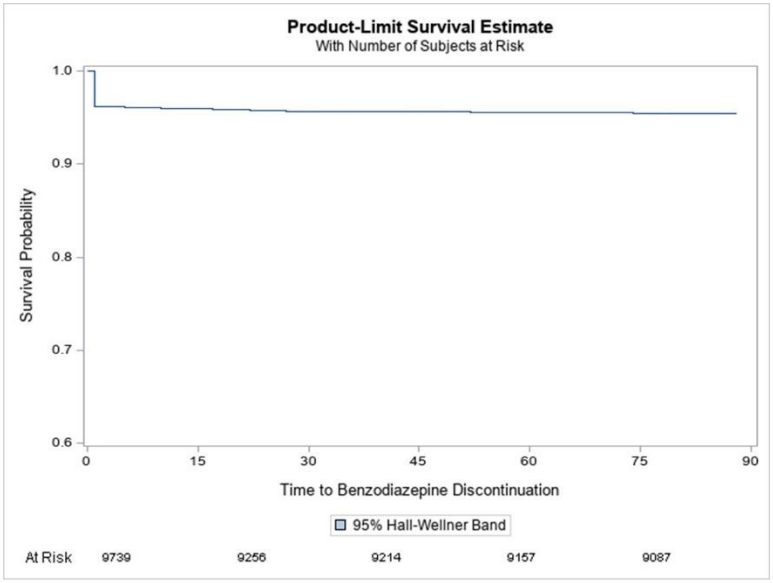
n=12,490



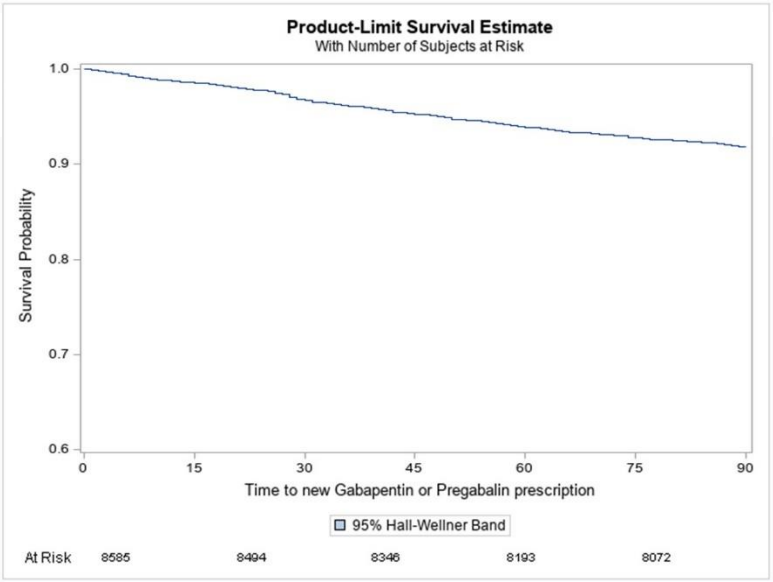
C)
n=10,882



D)
n=9,739



E)
n=8,585



F)
n=7,273

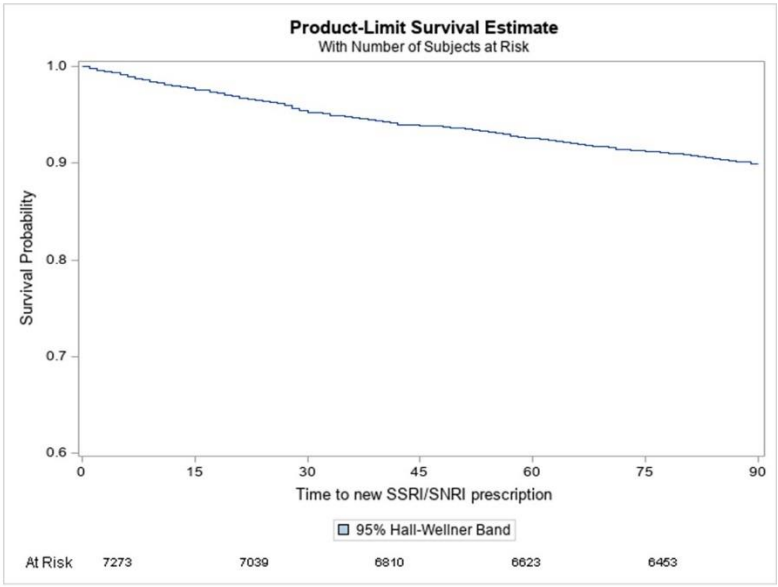


Fig. 4.1 shows Kaplan Meier curves for treatment change outcomes. The Y-axes of panels C-F were adjusted for clarity.

Figure 4.2. Venn Diagram showing Overlap of Non-Drug Treatment, Opioid Changes and Benzodiazepine Changes

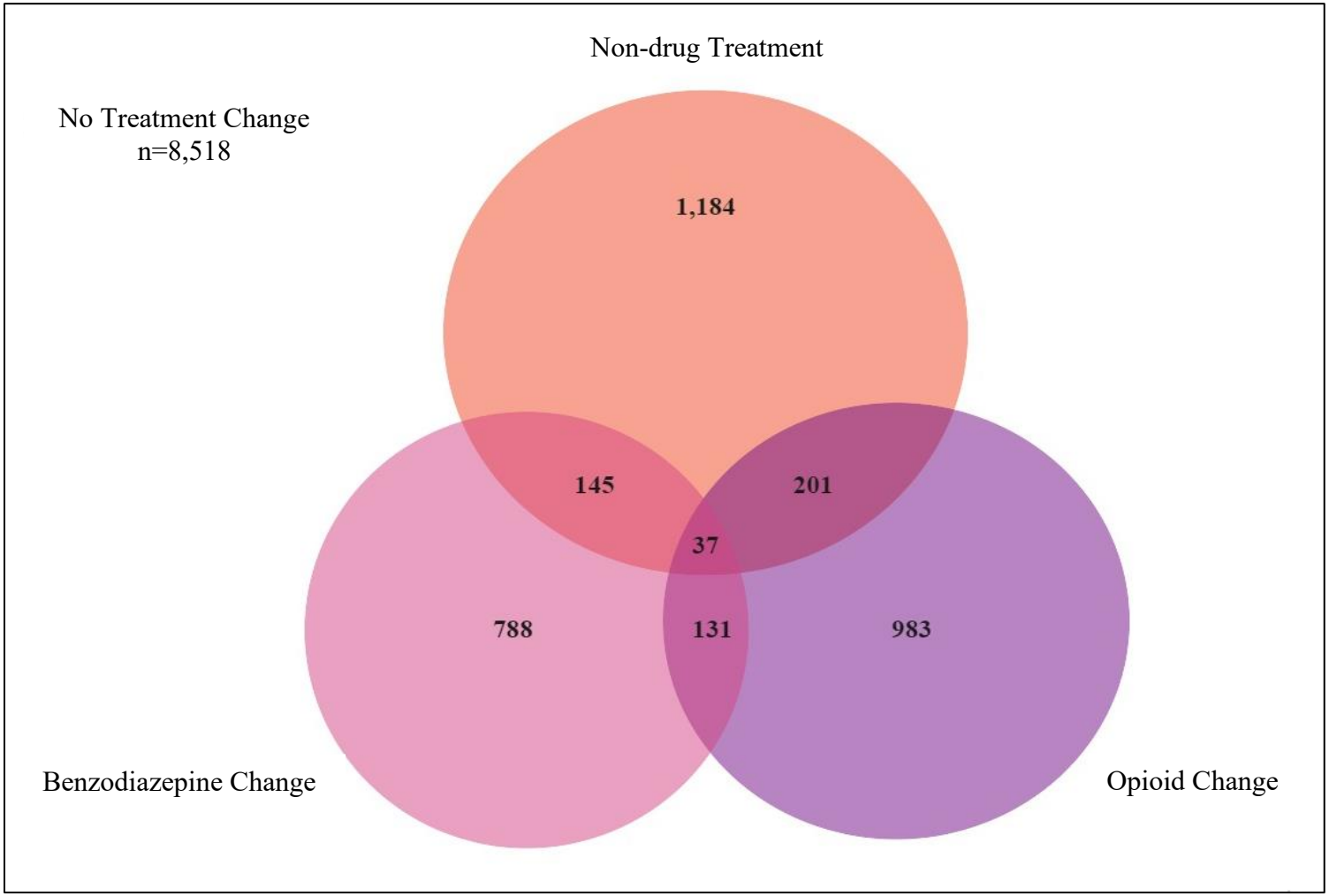


Fig. 4.2: Among the 11,987 patients with 90-day continuous enrollment after index UDT, 71.06% did not receive a treatment change (n=8,518). Of the 28.94% (n=3,469) that did have a treatment change, most were non-drug therapies only (34.12%), followed by prescription opioid changes (28.34%) or benzodiazepine changes (22.72%) only. 14.82% received multiple treatment changes.

Table 4.3. Multivariable Associations of Patient, Drug or Clinical Characteristics and Provider Response Outcomes

Variables	Non-drug Treatment			Opioid Discontinuation			Benzodiazepine Discontinuation			GABA initiation			SSRI/SNRI initiation		
	HR	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**	
Age															
<50		REF			REF			REF			REF			REF	
50-59	0.89	0.80	0.98	0.71	0.52	0.95	0.80	0.59	1.09	1.25	0.97	1.61	0.91	0.73	1.14
60-69	0.80	0.73	0.89	0.75	0.57	0.99	0.87	0.64	1.16	0.93	0.72	1.20	0.79	0.63	0.98
≥70	0.72	0.65	0.81	0.69	0.51	0.93	0.86	0.63	1.19	0.94	0.72	1.23	0.69	0.54	0.88
Sex															
Female		REF			REF			REF			REF			REF	
Male	0.80	0.75	0.86	1.26	1.03	1.54	1.27	1.04	1.56	0.90	0.77	1.06	0.63	0.53	0.74
Region															
Northeast		REF			REF			REF			REF			REF	
Midwest	0.95	0.81	1.11	0.68	0.43	1.07	1.28	0.73	2.25	1.21	0.77	1.88	1.07	0.72	1.60
South	0.80	0.70	0.92	0.61	0.41	0.90	1.22	0.74	2.01	1.42	0.97	2.10	1.15	0.81	1.63
West	0.91	0.79	1.05	0.62	0.41	0.93	2.02	1.21	3.36	1.46	0.98	2.19	1.11	0.77	1.61
Elixhauser Score															
0		REF			REF			REF			REF			REF	
1-2	0.86	0.78	0.96	1.01	0.75	1.34	0.92	0.68	1.24	0.96	0.75	1.23	0.80	0.63	1.01
3-4	1.05	0.94	1.17	0.80	0.58	1.09	0.96	0.70	1.32	1.09	0.84	1.41	0.95	0.75	1.21
5+	1.16	1.03	1.29	0.72	0.51	1.00	1.22	0.89	1.69	1.44	1.11	1.87	1.02	0.79	1.31
Depression															
No		REF			REF			REF			REF			REF	

Yes	1.26	1.18	1.35	1.22	0.99	1.50	0.76	0.61	0.94	1.11	0.95	1.31	2.02	1.73	2.37
Substance Abuse															
No		REF			REF			REF			REF			REF	
Yes	0.98	0.91	1.06	1.28	1.03	1.60	0.74	0.58	0.93	1.14	0.96	1.35	1.15	0.97	1.35
Alcohol abuse															
No		REF			REF			REF			REF			REF	
Yes	1.22	1.06	1.42	1.61	1.08	2.39	0.89	0.54	1.45	1.36	0.98	1.88	0.81	0.55	1.19
Psychoses															
No		REF			REF			REF			REF			REF	
Yes	1.32	1.10	1.57	1.57	0.97	2.56	0.91	0.48	1.69	1.50	1.01	2.21	1.07	0.68	1.68
Opioid Dosage and Duration[a]															
No opioid		REF			N/A			REF			REF			REF	
Low dose, short-term	1.13	1.00	1.27		REF		0.43	0.29	0.64	2.82	1.97	4.04	2.63	1.93	3.58
Low dose, long-term	0.93	0.81	1.06	0.43	0.32	0.56	0.29	0.18	0.44	2.62	1.79	3.85	2.16	1.54	3.02
High dose, short-term	0.99	0.86	1.13	0.28	0.20	0.39	0.42	0.27	0.64	2.92	1.99	4.29	2.34	1.65	3.30
High dose, long-term	0.87	0.76	0.99	0.17	0.12	0.23	0.36	0.24	0.54	2.27	1.56	3.31	2.08	1.50	2.88
Number of UDT															
0		REF			REF			REF			REF			REF	
1	0.96	0.87	1.06	0.86	0.67	1.11	1.38	1.03	1.84	0.89	0.72	1.11	0.88	0.71	1.08
2-3	1.12	1.02	1.24	0.55	0.41	0.74	1.42	1.06	1.91	1.03	0.83	1.29	0.88	0.71	1.08
≥4	1.29	1.16	1.43	0.98	0.72	1.33	1.38	0.99	1.92	1.06	0.83	1.36	0.88	0.69	1.11
Prior concurrent use															
Not tested		REF			REF			REF			REF			REF	

Yes	0.87	0.80	0.95	0.81	0.61	1.08	0.53	0.39	0.72	0.85	0.69	1.05	0.76	0.61	0.93
No	0.95	0.87	1.03	1.03	0.80	1.32	1.25	0.99	1.58	1.07	0.88	1.29	0.85	0.71	1.03

Abbreviations: REF: reference group; N/A: not applicable

[a] Low dose: <50 daily MME, high dose: ≥50 daily MME, short-term: <90 days opioid use, long-term: ≥90 days of opioid use

Chapter 5 Conclusions

By the end of 2019, nearly 16% of opioid-related overdose deaths in the US also involved the use of benzodiazepines.[112] Concurrent use of opioids and benzodiazepines is associated with an increased risk of overdose death, respiratory suppression, development of substance abuse disorder, falls, and other adverse events.[12,29,32,33] Because neither drug is considered a first line of treatment, and alternative medication or therapy is available, combined use is especially advised against when possible.[22,34,35]

The increased risk of substance use disorder that comes with concurrent use, often also leads to suicide ideation and development of mental illnesses.[113] In 2018, approximately 19 million adolescents and adults needed substance abuse treatment, but only 1.4% received it. As rates of addiction, prescription misuse, and illicit drug abuse cases remain high in the US, while substance abuse treatment resources remain underused, prevention of new substance abuse cases becomes even more important, to limit the worsening direct and unintended effects of the opioid crisis.

The purpose of this dissertation was to 1) examine recent time trends in concurrent use and determine whether there was a shift to illicit drug use or non-prescribed use, 2) determine important patient characteristics of concurrent users, illicit drug users, and prescription opioid or benzodiazepine misusers, and 3) gauge provider response to concurrent use positivity in UDT, using large, national insurance claims data with laboratory records of recent years.

Aim 1: Trends in Concurrent Use, Illicit use and Prescription Misuse

The main findings of Aim 1 were that schedule I drug use continued to increase from 2013-2019, while concurrent opioid and benzodiazepine use and prescription misuse generally decreased during this time period. A sudden decrease in schedule I drug use was observed at the end of 2013, coinciding with a previous study which found opioid-prescribing practices change at a similar timepoint.[114] During last quarter of 2013, the FDA made recommendations in preparation for the upcoming reschedule of hydrocodone from a schedule III drug to schedule II (more restrictive) by the DEA;[115] the sudden drop in illicit use in 2013, followed by the surge after 2014 may have been a result of patients finding alternate sources to hydrocodone, which became much less accessible.

Concurrent use decreased at a greater rate after 2016, during which the CDC's opioid prescribing guideline for chronic pain was officially published and the FDA announced a black box warning requirement on prescription opioids and benzodiazepines—both of which cautioned providers against co-prescribing of these drugs.[41] A greater decline in concurrent use rates was also observed in 2019, the year in which CMS implemented greater safety measures against concurrent use, such as alerting pharmacists of co-prescribed opioids and benzodiazepines, prompting additional review before dispensing prescriptions.[116] The decreasing trends in concurrent use coupled with increasing rates of illicit use seem to indicate a shift in drug use, which could be compensation for prescriptions that increasingly became difficult to obtain, as opioid-prescribing guidelines became widespread and more policies and regulations were put in place.

The observed decrease of misuse of prescription opioids and/or benzodiazepines generally aligned with recent literature on co-prescription trends, which have declined,[28,35,47] likely due in part to the increased use of gabapentinoid drugs and SSRI/SNRIs, which are considered as alternatives for opioids and benzodiazepines, respectively.[8] However, one unexpected finding was the turning point in the last quarter of 2018, where prescription misuse began to increase again. Though less understood, this increase in misuse parallelled the uptick in overdose deaths related to concurrent use.[117]

Illicit drug use, and prescription misuse and overdose continue to rise, despite efforts by the CDC, FDA, DEA, CMS and others, to focus on prevention at the provider level. Implications of this study include a need for public health reassessment that may require a shift of focus from provider restriction, to improving patients' access to and the availability of substance abuse recovery programs. Focused health interventions that benefit patient recovery, rather than placing blame or preventing necessary care may be more beneficial in preventing negative outcomes, though this would require further research.

Aim 2: Predictors of Concurrent Use, Illicit use and Prescription Misuse

Key findings of Aim 2 included the strong association of prior concurrent opioid and benzodiazepine use with continued concurrent use, schedule I drug use and misuse of either or both an opioid and benzodiazepine, in the following year. Prior concurrent use patients were nearly 11 times more likely to continue concurrent drug use than those not tested, while prior

schedule I drug users were approximately 18 times more likely, strongly emphasizing the repeated warnings and guidance against co-prescriptions. Study findings also highlighted the importance of UDT monitoring, and the need for utilizing alternative treatments or drugs to avoid co-prescriptions when possible, two strategies recommended by the CDC, especially among vulnerable individuals such as long-term opioid users or concurrent users.[12]

An important predictor of concurrent use identified was opioid dose and duration, where a 2 to 4-fold increased likelihood was observed in patients with various opioid dosage and durations, compared to those not using opioids, reinforcing the danger of extended use or high dose opioids. On the other hand, long term opioid use with any dosage decreased prescription misuse, possibly because patients may have felt adequately treated and did not need to resort to illegal sources to self-medicate. However, although this association appeared favorable among prescription misusers, long-term or high-dose opioid use is known to lose effectiveness with time, sometimes very quickly, and is not meant as an indefinite or sustainable solution for chronic pain.[9]

Overall this study identified characteristics that may be helpful for risk assessments to identify patients needing more frequent UDT, and who may need to be given alternative treatment, be tapered from an opioid, benzodiazepine or both, or seek rehabilitation services, to lessen their likelihood of future concurrent use or illicit drug use. Targeted health initiatives, such as patient education on disposal of unused prescriptions may also help reduce occurrences of substance abuse or polysubstance use, by decreasing drug diversion and subsequent misuse of unused prescriptions. To help reduce the rate of continued concurrent use or illicit drug use, increased access to substance abuse treatment facilities could alleviate some of the public health burden associated with drug overdose deaths in the US. However, even though earlier treatment of patients with substance abuse can be effective and has led to lower relapse rates and longer drug abstinence, few patients receive substance abuse treatment in both younger populations (11%) and older (<10%).[20,118-120]

Aim 3: Provider Response to Concurrent Use Positivity in UDT

The findings of Aim 3 revealed that nearly all patients with UDT in 2018 showing concurrent opioid and benzodiazepine use received an office visit within one year of their UDT result observation. However, relatively few patients (28.9%) received opioid or benzodiazepine

changes (including dosage reduction, drug alternative, or discontinuation) or non-drug treatment, such as physical therapy or cognitive behavioral therapy. The 71% majority of patients did not receive any treatment change from providers within 90 days of their concurrent use-positive UDT, indicating low response rates from providers to a harmful combination of prescription drugs.

About 13% of patients initiated non-drug treatment within 90 days, which only increased to 31% by one year and was predominantly representing physical and occupational therapy. Studies have shown that non-pharmacological treatment is effective in significantly reducing chronic pain, including cancer pain.[121-123] Because prescribing guidelines advise that opioids are not to be used as first-line treatment of pain, and with the availability of other evidence-based treatment modalities, it is important providers consider using non-drug therapies at greater rates.

Though both opioid and benzodiazepine discontinuation rates were low (<10%), this indicates providers may be cautious of cutting patients off from highly addictive drugs that can have severe, sometimes fatal, withdrawal symptoms especially among concurrent users.[12,124,125] Rather, when providers decide on discontinuing an opioid or benzodiazepine, patients must be tapered slowly each week, at a rate that is dependent on duration, dosage and clinical characteristics, but generally not more than 10-25%. MME and DME reductions over 20% were observed, which could have been among patients that were able to tolerate it, based on their clinical background. Some patients received an increase in dosage, which may indicate development of tolerance to current dosage due to misuse or long-term use, or a need for greater pain management in cases of disease progression, which are both common reasons for opioid dose escalation.[126]

Finally, because rates of alternative drugs gabapentinoids and SSRI/SNRIs, have increased over time, it was expected greater use of alternatives would be observed.[28] However, although the time to initiation was relatively quick in this study, the rate of initiating these drugs was low. GABA drugs and SSRI/SNRIs are recommended to be used in place of opioids and benzodiazepines respectively, though there is increasing concern about the safety of gabapentinoids due to its potential for abuse.[127] However, GABA drugs generally are safe if used as recommended by providers, and with strict care and monitoring of patients with substance abuse disorder.[128] Similarly, some providers may be wary of using SSRI/SNRIs due to their

slow-acting mechanism, and adverse effects, even though these drugs have been shown to be as effective as benzodiazepines in treating disorders such as depression and anxiety.[129] Though patients may want to see immediate changes to debilitating conditions that benzodiazepines or opioids may offer, providers are still advised to try other treatment options first, and consider patients' risk of adverse events in the context of their entire clinical picture; in other words, though a patient may feel immediate relief day-to-day with concurrent use, over time their health may deteriorate as a result of its negative effects.

A significant predictor found in most of the multivariable models of this study was long term opioid use, which decreased the likelihood or rate of treatment changes by prescribers. This likely implies that long term users may not be amenable to change once they have become established in their opioid treatment. It is therefore important in such patients to put more effort towards preventive care at earlier stages of developing treatment plans, i.e. before long-term opioid use, or tolerance to dosage can be established, and after which could be difficult to change. Overall, this study shows that while there is some response by providers (in approximately 28% of patients), the rate is lower than is beneficial to high-risk patients, and is delayed, considering the effect of long term opioid use on receiving treatment and alternative non-drug therapies.

Clinical and policy implications

Indications for ordering UDT include pre-employment drug testing, initial risk assessments before prescribing a controlled substance such as an opioid, compliance monitoring with continued care, and abstinence monitoring in patients treated for substance abuse. Historically, providers have not only had difficulty with deciding who to order UDT for and how to interpret results, but also in deciding the next steps to take once a UDT result is determined.[100,130,131] The complexity associated with UDT interpretation is due to potential false-positives from cross-reactivity, varying methods for drug or drug class identification, differing cutoff values for UDT positivity across laboratories, reimbursement limits, and lack of training provided to prescribers. Once a UDT result is determined however, an additional dilemma arises, of deciding next steps on how to move forward with each unique patient's care. Providers are tasked with striking a balance between over- and under-prescribing opioids or benzodiazepines, while also trying to avoid negative outcomes such as dependance, or development of substance abuse disorder.

Implications of these studies showed a general shift from prescribed use to illicit use, an overall high rate of prescription misuse (prescription use not as intended according to days of supply, quantity, and UDT detection windows), and relatively low prescriber response to ill-advised concurrent use. Although there has clearly been an increase in the awareness and response to CDC recommendations on opioid and benzodiazepine prescribing, the results of these studies indicate that effective strategies to reduce the need for long-term opioid use, or concurrent use are still lacking. As previously cited studies report, access to drug addiction recovery programs or rehabilitation centers is also alarmingly low. Even with the decreasing rates of concurrent use and opioid prescribing, failure to address and implement risk-reduction strategies for those who have already developed tolerance, dependence or substance abuse disorders, continues to contribute to the effects of the opioid crisis, as has been observed in recent overdose trends.[117,132] Further, this may have been exacerbated in the last two years, after the devastating spread of Covid-19. Because Covid-19 infections can lead to severe respiratory distress, the demand for effective solutions is necessary, especially in avoiding concurrent use and its potential respiratory suppression dangers.

Regional differences observed in the trends study highlight some regions that are especially in need of attention by policy makers, to assist in increasing the availability of rehabilitation services, and at the provider level, to apply risk reduction strategies as early in the pain management process as possible, avoiding long-term opioid use, high daily MME dosage, and increasing the frequency of UDT (within reason), to better capture their patient's clinical picture and adapt treatment as needed. Recognizing regional variation in patient drug use and time trends is especially important in developing effective, preventive health initiatives, though more research with other data sources would be valuable to better understand the variation.

Significance

Previous studies on trends in concurrent use have relied on insurance claims or dispensing data, which assumes drug use based on prescriptions.[28,35,48] Others rely on self-report from patients, which is likely to be biased towards compliant use as compared to lab test results; patients are less likely to disclose information that is not favorable or that may lead to prescription discontinuation.[133] Patients may self-medicate with one or multiple prescription or illicit drugs;[30] usually, this substance abuse cannot be captured using prescription data. An important literature

gap addressed by the studies of this dissertation is the direct patient use measured by laboratory results from UDT, the most commonly used test matrix for drug testing.[66] Also, though earlier studies of UDT aberrance rates and predictors do exist, most were single-centered or local, small-scale, or in earlier dates preceding CDC guidelines, and may not be as relevant to recent times;[82,92,99,134] this dissertation used recent, pre-covid data on a national scale to be more representative of a large portion of the insured US population of adults.

There also has not been any study to date, that defined and analyzed LOINCs for illicit (schedule I) drugs, opioids, or benzodiazepines; Over 840 UDT LOINCs were collected and grouped into important drug use categories (available in Appendix Table 3), adding to the literature a resource for future drug use studies using UDT LOINCs.

This dissertation addressed several research gaps. Aim 1 identified time trends in patient drug use, to address whether changes in prescription misuse, illicit use or concurrent use existed after important federal agencies gave clear warnings and guidance on safer prescribing practices; this was the first study to use UDT results to examine how policy impacts drug use rates. This Aim pinpointed rates of drug use changes by annual quarters, and allowed for the observation of shifting drug use, while also studying how these rates varied by patient demographics. Aim 2 was completed at the patient level, to specifically address individual characteristics associated with the various types of aberrant drug use. This aim determined the association between aberrant drug use types, including concurrent opioid/benzodiazepine use, in a post-CDC guideline time period. Aim 3 addressed important literature gaps on how providers have responded to concurrent use-positivity in UDT, which has not previously been studied with UDT results or on the national scale used in this study. This aim investigated multiple recommended strategies for safer prescribing, including both dosage reduction or discontinuation of opioids and benzodiazepines, initiation of alternative drugs, and use of non-drug treatment, as well as forming a composite outcome of all strategies, to gauge overall provider response to concurrent use UDT results.

Limitations

There are limitations that must be taken into consideration when interpreting results of all three studies, including limitations to the data source, inclusion of potential UDT false-positives from

urine drug screening (which is commonly used for its low-cost, availability and rapid turnaround time) and exclusion of others.

Some UDT LOINC results were excluded from analysis due to uninterpretable values, which may have biased the study samples; however, as in Aim 1, the percent of annual UDT with interpretable results increased over time, indicating improvement of UDT results. Later years seemingly had better UDT results, which were used for Aim 2 and 3.

Next, although UDT may be a more reliable source of patient use, it is possible that some results that appeared compliant were due to methods patients use to "pass" a UDT when unmonitored during collection, such as the use of adulterated urine or urine not their own, use of urine-clearing chemicals, or even adapting their drug use around scheduled UDT/provider visits. Due to limitations of UDT, drug-positivity rates and trends may have been underestimated; this is also supported by a study in 2018 suggesting a high frequency of monthly UDT is required to capture aberrant use, however this was assuming a low rate of aberrant UDT.[90]

The use of CDM data provides detailed information on prescription claims, laboratory results, and has data points in all US states, however, a major limitation of using insurance claims data, is limited external validity of the studies. An important population affected by the opioid crisis, uninsured individuals living in poverty, are not represented may have higher rates of prescription or illicit misuse, further leading to underestimates in trends and associations observed in these studies. Because there was also a lack of uniformity across US labs in coding CPT and LOINCs, some codes were missing or had non-standard values, presenting a potential source of error if important results could not be represented.

To understand generalizability of these results, from our previously published study using the same data source for UDT trends and factors associated with receiving UDT,[81] the distributions of patient characteristics were examined and compared to results from Aim 2 of this dissertation, which also focused on characteristics. Comparing the results of each study in 2018, patient demographic distributions of those receiving UDT (previous study) compared with those that had UDT results (Aim 2) by sex, were very similar. Comparing by age group, more younger patients (<50 years) had results and less patients aged 50-69 had results, than those that had received UDT, while those 70 and above had the similar distribution. By region, less UDT results were available in the South and West, slightly more in the Northeast, and nearly double the number of

UDT results were available in the Midwest, compared to those that received any UDT in the previous study. The similarities in the distributions of characteristics between studies indicates at least by gender, in older patients and in the Northeast, the results are generalizable. However, the more substantial differences in demographic distributions between patients that received UDT and those with results may be due to a number of reasons, though further research is warranted with other data sources. First, the previous study relied solely on CPT codes to count "any UDT", while the present studies included all applicable drug use LOINCs, whether or not they had the same associated CPTs previously published, which may explain some of the variation. Second, previously published CPT codes did not include non-standard CPT codes that may be more widely used in the independent labs included in Aim 2. Third, the cohorts were different, in which the present studies generally used those with any associated UDT results, not limited to long-term opioid users as in the previous study. Fourth, differences by region may represent a differing distribution of drug testing completed in independent labs vs hospital labs, the latter which was not studied in Aim 2, and may also explain some of the variation. For example, the lower proportion of patients in the South having results compared to the higher number that have UDT may reflect that Southern regions complete more UDT in hospital settings. Finally, the uncertainty caused by missing results from blank or missing LOINCs may also be a factor.

Race/ethnicity and smoking status is a patient characteristic that is important for drug monitoring UDT; [108] previous studies have shown that drug use, especially illicit drug use, varies by race and predominantly affects White people, though greater risk reduction strategies are used for Black people.[135,136] Racial disparities in opioid compliance monitoring have also been observed.[30] UDT variation by racial differences could not be determined in this study, as race is only available in CDM data via proxy, by zipcode, which is likely unreliable.

Selection bias is another important limitation that likely affected results; physicians may offer patients UDT at different rates, focusing on those who are more likely to abuse drugs, or those with greater comorbidities that are associated with concurrent use, such as depression and psychoses.[81] Therefore, some of the observed results may simply be due to patients more likely to be selected into the sample, rather than an accurate estimate of associations.

The high rate of false-negatives in UDT for benzodiazepines is also a limitation that could have underestimated concurrent use positivity in all three studies.[140] A recent, small study showed that

there are methods that may be used to increase the sensitivity of benzodiazepine UDT,[141] however it is unknown whether these methods were used for the benzodiazepine tests included in the studies.

Other limitations to the studies include unknown effects of provider characteristics on patient outcomes, such as provider intent, which was previously included in patient chart studies.[100,130] Because insurance claims data were used, many assumptions must be made, including that provider response was based on their observation of concurrent use UDT; it is possible they had other motives for initiating or discontinuing drugs, or non-drug treatment, but this is uncertain without specific chart notes. Pre-employment drug testing is also very common and may have an impact on some studies of aberrant UDT results, depending on the data source. However, in these studies, it is not expected that positive UDT from workplace testing were included because 1) insurance does not cover pre-employment UDT and 2) the clinical LOINC used to define drug use did not include workplace UDT, therefore removing some of the ambiguity of whether included UDT were specific to patients receiving primary care.

Future research

Because the pandemic has introduced a new dimension to the opioid crisis, effects of Covid-19 on concurrent use, illicit use and prescription misuse will be important for continuing to develop risk reduction strategies, in post-covid times. Future research that may help increase the historically low use of UDT, include studies of provider attitudes and indications for UDT use. A small, recent study found that nearly one third of providers misinterpreted UDT results, when comparing their interpretation to that of the laboratory.[134] By understanding the greatest limiting factors to its use, identified issues can be addressed using focused courses, training programs or other methods.

Another recently published study showed that the use of UDT lab results is highly useful in informing mortality rates associated with drug use, at the county, state and national level.[137] This presents a data source to identify real-time patterns in drug use, abuse and prescription misuse, without having to wait for overdose or mortality to occur, and study retrospectively. Future studies can therefore use this type of data, which came from a substance abuse facility setting, for faster, and reliable public health surveillance, which would address some of the uncertainty that came with using LOINC data of this study. The setting in which UDT results are obtained

could also be broadened, to make studies more generalizable, such as those in primary care. An extension of these aims could also include the examination of other illicit drugs, such as schedule II stimulants, barbiturates, and others, known to contribute to substance abuse disorders and overdose mortality.

Patient outcome research may also be done using UDT, to study incident, adverse events such as fatal or non-fatal overdose, hospitalizations, development of substance use or opioid use disorders, and mortality. This may be done using more recent CDM data that may be linked with mortality data, while other outcomes could be studied using ICD or CPT codes for associated diagnoses, emergency room visits, or hospitalization respectively. The implications of such patient-outcome studies could be helpful for informing clinicians' healthcare decisions, including how frequently patients should be urine drug tested, and who is more likely to benefit from UDT.

Future studies may also examine the use of laboratory vs hospital drug testing and how these differ by patient demographics, using other data sources to compare with these CDM data studies, and better understand what may be affecting the variation in demographics among patients that receive UDT vs those that have UDT results.

In November 2022, the CDC published an updated version of their Opioid-Prescribing Guideline,[142] which is not expected to make an impact on how the results of this dissertation may be interpreted, rather may stress the importance of results. In the updated guideline, it is reiterated that there is no available evidence that supports the use of UDT in preventing negative outcomes, however testing still provides useful information on drug use that is often not self-reported by patients. The guideline also reinforces the need for "frequent reassessments" of high-risk patients, including those on concurrent opioids and benzodiazepines to mitigate risks. It is explicitly stated for clinicians to use toxicology screening "as appropriate to assess for concurrent substance use that might place patients at higher risk", meaning not necessarily in a universal manner, but individualize UDT ordering based on patient risk. Though this does not explicitly state the use of urine testing specifically, it is implied because of earlier mention that UDT is most frequently used and indicated. Because the results of this dissertation found concurrent users are especially at risk of continued use and eventual illicit and non-prescribed use, the new CDC guideline supports the use of UDT as a risk reduction tool in this population and in opioid or benzodiazepine users in general.

Conclusion

Overall, the use of urine drug test results offers an inside, objective look at patient drug use, that when interpreted cautiously, provides clinicians with a more detailed clinical picture and information on drug use that is important for risk assessments, and more reliable than subjective, patient self-reports. There is a need not only for greater use of UDT in opioid pain management and treatment of depression and mental disorders, but for a reorientation of public health focus to early prevention of opioid or benzodiazepine use, patient recovery programs, and development of strategies to help patients receive adequate care safely, avoiding self-medication and drug abuse.

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Appendix

Appendix Table 1. List of drugs included in opioid, benzodiazepine or schedule I drug UDT

Opioids	fentanyl[a], hydrocodone, hydromorphone, codeine, methadone, suboxone, propoxyphene, levorphanol, buprenorphine, morphine, oxycodone, meperidine, opioid panel
Benzodiazepines	flurazepam, oxazepam, clorazepate, chlordiazepoxide, alprazolam, lorazepam, clobazam, midazolam, temazepam, triazolam, diazepam, estazolam, benzodiazepine panel
Schedule I drugs[b]	heroin, cocaine, LSD, bath salts (cathinone/cathine), mescaline, psilocybin, MDMA, gamma-hydroxybutyric acid (GHB), marijuana (THC/cannabinoids), ecstasy, methaqualone, khat

[a] Because illicit fentanyl is indistinguishable from prescribed fentanyl by UDT, fentanyl was counted for the opioid drug category, and not in the schedule I category.

[b] As defined by the Food and Drug Administration.

Appendix Table 2. CPT and HCPCS codes used for all drug tests related to Schedule I drugs, opioids and benzodiazepines.

CPT/ HCPCS[a,b]	Description	2013	2014	2015	2016	2017	2018	2019	Schedule I	Benzo	Opioid
G0659	definitive drug test	0	0	0	0	1	1	1	1	1	1
G0483	definitive drug test	0	0	0	1	1	1	1	1	1	1
G0482	definitive drug test	0	0	0	1	1	1	1	1	1	1
G0481	definitive drug test	0	0	0	1	1	1	1	1	1	1
G0480	definitive drug test	0	0	0	1	1	1	1	1	1	1
G0479	presumptive drug test	0	0	0	1	0	0	0	1	1	1
G0478	presumptive drug test	0	0	0	1	0	0	0	1	1	1
G0477	presumptive drug test	0	0	0	1	0	0	0	1	1	1
G6058	drug confirmation	0	0	1	0	0	0	0	1	1	1
G6056	opiates/metabolites	0	0	1	0	0	0	0	1	0	1
G6046	dihydromorphinone	0	0	1	0	0	0	0	1	0	1
G6045	dihydrocodeinone	0	0	1	0	0	0	0	1	0	1
G6044	cocaine	0	0	1	0	0	0	0	1	0	0
G6031	benzodiazepines	0	0	1	0	0	0	0	0	1	0
80373	tramadol	0	0	1	1	1	1	1	0	0	1
83925	opiates	1	1	0	0	0	0	0	1	1	1
82649	dihydromorphinone	1	1	0	0	0	0	0	1	0	1
82646	dihydrocodeinone	1	1	0	0	0	0	0	1	0	1
82520	cocaine	1	1	0	0	0	0	0	1	0	0
G0434	presumptive drug test	1	1	1	0	0	0	0	1	1	1
G0431	presumptive drug test	1	1	1	0	0	0	0	1	1	1
83992	phencyclidine	1	1	1	1	1	1	1	1	0	0
83789	mass spectrometry drug test	1	1	1	1	1	1	1	1	1	1
80365	oxycodone	0	0	1	1	1	1	1	0	0	1
80364	opiates 5+	0	0	1	1	1	1	1	1	1	1
80363	opiates 3-4	0	0	1	1	1	1	1	1	0	1

80362	opiates 1-2	0	0	1	1	1	1	1	1	0	1
80361	opiates 1+	0	0	1	1	1	1	1	1	0	1
80360	methylphenidate	0	0	1	1	1	1	1	1	0	0
80359	MDA/MDMA	0	0	1	1	1	1	1	1	0	0
80358	methadone	0	0	1	1	1	1	1	1	0	1
80356	heroin metabolite	0	0	1	1	1	1	1	1	0	1
80354	fentanyl	0	0	1	1	1	1	1	1	0	1
80353	cocaine	0	0	1	1	1	1	1	1	0	0
80349	cannabinoids	0	0	1	1	1	1	1	1	0	0
80348	buprenorphine	0	0	1	1	1	1	1	0	0	1
80347	benzos 13+	0	0	1	1	1	1	1	0	1	0
80346	benzos 1-12	0	0	1	1	1	1	1	0	1	0
80307	presumptive drug test	0	0	0	0	1	1	1	1	1	1
80306	presumptive drug test	0	0	0	0	1	1	1	1	1	1
80305	presumptive drug test	0	0	0	0	1	1	1	1	1	1
80304	presumptive drug test	0	0	1	1	0	0	0	1	1	1
80303	presumptive drug test	0	0	1	1	0	0	0	1	1	1
80302	presumptive drug test	0	0	1	1	0	0	0	1	1	1
80301	presumptive drug test	0	0	1	1	0	0	0	1	1	1
80300	presumptive drug test	0	0	1	1	0	0	0	1	1	1
80154	benzodiazepines	1	1	0	0	0	0	0	0	1	0
80102	presumptive drug test	1	1	0	0	0	0	0	1	1	1
80101	presumptive drug test	1	1	0	0	0	0	0	1	1	1
80100	presumptive drug test	1	1	0	0	0	0	0	1	1	1

[a] Some CPT/HCPCS codes were not specific to a drug class or metabolite, such as CPT code 80307 for “presumptive drug testing”, which may include other drugs for testing.

[b] Due to the regular deletion or addition of billing codes annually, CPT and HCPCS codes differed by year, particularly for 2015.

[c] Indicators for schedule I drug, opioid or benzodiazepine were assigned to CPT/HCPCS codes and LOINCs. Distinct patient records that had both a valid CPT/HCPCS code and LOINC on the same drug test date in each respective category were considered a match.

Appendix Table 3. Excel Table of LOINC codes for Opioid, Benzodiazepine and Schedule I UDT (double-click)

Schedule I drugs	Benzodiazepines	Opioids
72795-8	59589-2	16334-5
67838-3	59590-0	18383-0
79237-4	94108-8	86604-6
72796-6	97159-8	49753-7
78858-8	94110-4	49751-1
79144-2	78758-0	58362-5
79236-6	28073-5	82371-6
87762-1	51776-3	77774-8
72797-4	61030-3	58361-7
73687-6	58365-8	89305-7
79238-2	94112-0	3508-9
72798-2	58364-1	16250-3
72793-3	19328-4	70206-8
73686-8	16348-5	3507-1
79242-4	61036-0	16197-6
72794-1	19326-8	13641-6
79232-5	19325-0	19411-8
79233-3	19330-0	19414-2
50594-1	19329-2	19413-4
3394-4	94115-3	51739-1
16226-3	58363-3	58391-4
70146-6	60677-2	89310-7
3393-6	49876-6	19449-8
14315-6	94105-4	19448-0
8192-7	86605-3	14066-5
8193-5	3313-4	16211-5
14314-9	59615-5	19446-4
43984-4	9351-8	19451-4
43985-1	16203-2	19450-6
19065-2	94116-1	51955-3
19358-1	78781-2	64131-6
19357-3	86224-3	51448-9
13479-1	42235-2	93465-3

Appendix Table 4. CPT/HCPCS and LOINC Urine Drug Test Match rates

		2013	2014	2015	2016	2017	2018	2019	Total
(1) Denominator (UDT CPTs from medical claims)	(a) Total[a]	2,498,414	3,040,025	4,016,981	2,407,000	2,487,679	2,525,005	2,567,906	19,543,010
	(b) Independent Labs[b]	1,754,510	2,055,384	2,644,958	1,043,290	1,061,640	1,088,403	933,146	10,581,331
	(c) Total consolidated[c]	1,336,615	1,487,391	2,163,096	978,327	1,004,843	1,033,852	904,735	8,908,859
(2) Numerator (UDT LOINCs from lab claims)	(a) Total LOINC records	3,063,782	2,768,202	2,553,245	3,417,170	4,637,687	6,326,616	5,590,132	28,356,834
	(b) Total consolidated[d]	406,419	417,475	512,677	721,650	909,715	1,099,469	1,107,920	5,175,325
	(c) Matched[e]	261,043	223,509	216,599	135,087	172,396	198,332	148,502	1,355,468
	(d) Unmatched[f]	145,376	193,966	296,078	586,563	737,319	901,137	959,418	3,819,857
Match Rate	2c/1c	19.53%	15.03%	10.01%	13.81%	17.16%	19.18%	16.41%	15.21%

[a] All records that included CPT/HCPC codes related to UDT for schedule I drugs, opioids or benzodiazepines.

[b] CDM only includes lab results from independent laboratories, therefore tests (CPT/ HCPCS) codes were limited to those from independent labs.

[c] Independent lab records were consolidated by person, date and CPT/HCPCS code.

[d] Because a single CPT could be associated with many LOINCs (due to drug panels) the lab records were consolidated based on person, date, and test type (opioid, benzo, schedule 1) prior to matching.

[e] Indicators for schedule I drug, opioid or benzodiazepine were assigned to CPT/HCPCS codes and LOINCs. Distinct patient records that had both a valid CPT/HCPCS code and LOINC on the same drug test date in each respective category were considered a match.

[f] Although few LOINCs had a missing CPT (<1%) in each drug category, a large portion of LOINCs included in the cohorts (54.6% of schedule I UDT, 64.9% of benzodiazepine UDT, 67.5% of opioid UDT) were associated with unexpected CPT codes. These included invalid CPT codes such as '99999' or '1111', valid CPT codes that were broad (82540 "chemistry procedure"), or non-standard CPT values that may be laboratory-specific, such as "OPI_2" for opioids, or "BZD_2" for benzodiazepines, which led to a non-match.

Appendix Table 5. Cohort Flowchart for Selection of UDTs for Joinpoint Regression Analysis

	2013	2014	2015	2016	2017	2018	2019	Total
Total UDT LOINC records	3,063,782	2,768,202	2,553,245	3,417,170	4,637,687	6,326,616	5,590,132	28,356,834
Schedule 1 UDT Records	619,922	534,612	485,253	719,004	943,440	1,259,896	1,202,946	5,765,073
UDT records with results[a]	283,165	264,101	290,914	515,136	737,175	926,996	866,352	3,883,839
UDT consolidated[b]	83,622	83,631	90,488	137,661	160,656	194,529	195,262	945,849
Selected UDT[c]	62,754	60,459	66,431	106,340	135,171	162,596	162,507	756,258
Opioid UDT total LOINC	1,680,332	1,533,339	1,447,865	1,937,942	2,698,663	3,581,014	3,082,370	15,961,525
UDT records with results[a]	932,923	857,050	762,666	1,414,382	2,215,909	2,865,811	2,655,119	11,703,860
UDT consolidated[b]	87,286	88,414	104,940	150,897	183,403	223,489	220,270	1,058,699
Benzo UDT total LOINC	763,528	700,251	620,127	760,224	995,584	1,485,706	1,304,816	6,630,236
UDT records with results[a]	403,919	379,144	307,581	515,683	773,972	1,156,376	1,096,984	4,633,659
UDT consolidated[b]	81,560	81,242	89,981	134,919	162,305	199,097	202,266	951,370
Concurrent UDT (same day)								
UDT consolidated[b]	81,101	80,705	88,973	133,197	160,257	195,959	198,935	939,127
Select UDT[c]	60,992	58,778	65,712	103,056	133,984	161,866	162,284	746,672
Concurrent Use Positive	11,320	9,919	10,569	16,004	21,244	22,942	18,537	110,535
Concurrent UDT (3 days)								
UDT consolidated[b]	93,027	94,943	102,256	147,029	173,709	214,257	219,614	1,044,835
Select UDT[c]	60,992	58,781	65,717	103,068	134,079	161,997	162,441	747,075

Concurrent Use Positive	11,325	9,924	10,575	16,019	21,307	23,020	18,596	110,766
Non-prescribed Use								
Positive opioid UDT	45,468	42,619	52,656	80,616	109,377	133,090	123,376	587,202
180-day eligibility prior to opioid UDT	38,811	36,170	43,194	65,186	91,065	113,219	105,118	492,763
Positive benzo UDT	18,025	16,653	17,914	26,267	33,543	38,563	33,809	184,774
180-day eligibility prior to benzo UDT	15,353	14,034	14,422	21,015	27,704	32,760	28,676	153,964
Select UDT[d]	35,027	32,395	38,923	59,280	84,373	104,924	97,601	452,523
Any misuses	26,573	24,330	28,580	42,000	56,377	62,688	58,068	298,616
Benzodiazepine misuse only	5,425	5,358	5,813	8,818	10,681	11,979	9,262	57,336
Opioid misuse only	16,184	14,619	18,310	26,942	37,992	43,794	43,349	201,190
Both misused	4,964	4,353	4,457	6,240	7,704	6,915	5,457	40,090
No misuse	8,454	8,065	10,343	17,280	27,996	42,236	39,533	153,907
Select UDT[e]	35,015	32,380	38,910	59,273	84,351	104,902	97,589	452,420
All misuse	26,169	23,980	28,265	41,576	55,787	61,771	57,388	294,936
Benzodiazepine misuse only	5,484	5,394	5,877	8,863	10,751	11,949	9,248	57,566
Opioid misuse only	15,880	14,341	18,045	26,585	37,505	43,063	42,765	198,184
Both misused	4,805	4,245	4,343	6,128	7,531	6,759	5,375	33,811
No misuse	8,846	8,400	10,645	17,697	28,564	43,131	40,201	157,484

[a] Of the 20,221,358 UDT records with interpretable results, 3,883,839 (19.2%) were schedule I UDT, 4,633,659 (22.9%) were benzodiazepine UDT, and 11,703,860 (57.9%) were opioid UDT.

[b] Tests were consolidated by UDT date; whether a patient received a panel for multiple drugs within a drug use category (schedule I , benzo, opioid), or a single test for any of these, it was counted once. The median (interquartile range) for number of UDT per person, per date increased from 3(2,4) in 2013 to 4(2,6) in 2019 in the schedule I category, decreased from 11 (4,16) in 2013 to 8(3,24) in 2019 among opioid UDT, and decreased from 6(1,8) to 1(1,12) in benzodiazepine UDT. Decreases in median tests among opioids and benzodiazepines occurred in 2015-2019, where LOINCs for panels such as “benzodiazepine panel” (LOINC 3390-2), or “opiates panel” (LOINC 3879-4) were more frequently use, than individual LOINCs for multiple drugs.

[c] Any positive UDT test in a quarter was selected. For those without positive results, the first UDT per person, per quarter was selected.

[d] Any misuse for an opioid or benzodiazepine in a quarter was selected, which may overestimate misuse. For those without any misuse, the first positive UDT per person, per quarter was selected. In the case of multiple tests where some indicated misuse and others indicated compliance, any misuse in a quarter was chosen which overestimated the rate of misuse.

[e] Misuse was counted if all opioid and/or benzodiazepine use in a quarter was misuse, which underestimated the rate of misuse.

Appendix Table 6. Associations between concurrent use, illicit use, and on-prescribed use

Non-prescribed Drug Use, n %					
Concurrent Use, n %		**No**	**Yes**	Total	P
	No	17,336 **46.92%**	19,609 **53.08%**	36,945	<.0001
	Yes	3,188 **29.60%**	7,581 **70.40%**	10,769	
	Total	20,524	27,190	47,714	
Schedule-I Drug Use, n %					
Concurrent Use, n %		**No**	**Yes**	Total	P
	No	32,984 **89.28%**	3,961 **10.72%**	36,945	<.0001
	Yes	9,156 **85.02%**	1,613 **14.98%**	10,769	
	Total	42,140	5,574	47,714	
Schedule-I Drug Use, n %					
Non-prescribed Use, n %		**No**	**Yes**	Total	P
	No	18,243 **88.89%**	2,281 **11.11%**	20,524	0.0008
	Yes	2,3897 **87.89%**	3,293 **12.11%**	27,190	
	Total	42,140	5,574	47,714	

Abbreviations: P: p-value for chi square test

Appendix Table 7. CPT or ICD-10 codes used to define outcomes

Outcome	**CPT/ICD Codes**	
Office visit	For established patients	99211, 99212, 99213, 99214, 99215
Non-drug treatment[52,138]	Acupuncture	97810, 97811, 97780, 97813, 97814, 20560, 20561
	Radiofrequency ablation	64633, 64634, 64635, 64636
	Physical/occupational therapy	97161, 97162, 97163, 97001, 97750, 97535, 97530, 97112, 97110, 97760, 97116, 97014, G0283, G0283, 97018, 97113, 97165, 97166, 97167, 97546, 97545, 97542, 97537, 97535, 97633, 97150, 97139, 97129, 97113, 97112, 97110, 97150, 97039, 97012, 97016, 97022, 97028, G0281, G0329
	Massage Therapy	97124, 97140, 97012, 97036
	Cognitive behavioral therapy	96152, 96150, 97532
	Other non-drug therapy[a]	97026,97024, 97032, 97035, E0762, 97010, 97033, 97034, E0935, E0936
	Referral to rehab program	90792, 90791, 99408, 99409, G0397, H0050, G0396

[a]Other therapies include low-level laser therapy, microwave diathermy, transcutaneous electrical nerve stimulation, phonopheroesis/ ultrasound, cryotherapy/superficial heat, iontophoresis, contrast bath, continuous passive motion exercise.

Appendix Table 8. Provider Specialties Associated with Office visits, post-UDT

Type of Provider/Specialty[a]	n	%
Advanced Practice Registered Nurses	710	5.68%
Dentist	6	0.05%
Emergency Medicine	83	0.66%
Family Medicine	3,091	24.74%
General Surgery	104	0.83%
Internal Medicine	2,956	23.66%
Neurology	646	5.17%
Orthopedic Surgery	376	3.01%
Pain Management	1,374	11.00%
Physical Medicine & Rehab	529	4.23%
Physician Assistant	249	1.99%
Surgical Subspecialties	88	0.70%
Other	1,810	14.49%
Unknown	471	3.77%
Total	12,493	100%

[a] Provider specialties were grouped as in Romman et al.[139]

Appendix Table 9. MME and DME changes between pre- and post-UDT period

Opioid MME change	N	%		Benzodiazepine DME change	n	%
No Opioid[a]	1,611	12.90		No Benzodiazepine[a]	2,754	22.04
No change in MME	6,689	53.54		No change in DME	7,218	57.78
Increase MME	1,661	13.29		Increase DME	812	6.50
Decreased ≤20% MME	350	2.80		Decreased ≤20% DME	52	0.41
Decreased >20% MME	1,746	13.98		Decreased >20% DME	914	7.32
Discontinued Opioid	436	3.49		Discontinued Benzo	743	5.95

[a] Refers to the 90-day period before the index UDT.

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Taha, S., Lopez, D., Gutierrez, S.
Society for Epidemiologic Research, San Diego, CA
Accepted April 15, 2021

Assessment of Diversity and Inclusion at the University of Texas Medical Branch's Graduate School of Biomedical Sciences
Nunez, L., **Taha, S.,** Stalnaker, L., Peek, K.
Public Health Symposium, University of Texas Medical Branch, Galveston, TX (virtual)
April 7, 2021

Trends in Urine Drug Testing Among Long-Term Opioid Users, 2011-2018
Taha, S., Westra, J., Raji, M., Kuo, YF.
Public Health Symposium, University of Texas Medical Branch, Galveston, TX (virtual)
April 7, 2021

Predicting Outcome of the Specialist of Blood Banking Certification Examination By Academic Performance
Riddle, D., **Taha, S.,** Walker, L.
Transfusion: Annual AABB Meeting
September, 2020

OTHER:

Master Thesis
Screening for Y-Chromosome Microdeletions in Azoospermic Palestinian Males
Birzeit University, Birzeit, West Bank 2016

INVITED PRESENTATIONS—OFF CAMPUS:

03/2021	**Is it Worth it? Dangers of Drunk and Drugged Driving** College of the Mainland Texas City, TX 1 hour presentation to undergraduate students
10/2019	**A Career in Medical Laboratory Science** University of Houston, Houston, TX 1 hour presentation to undergraduate biotechnology students

INVITED LECTURES—ON CAMPUS:

10/2020	**Introduction to Literature Searches and Reference Managers** University of Texas Medical Branch, 1 hour presentation to undergraduate and graduate students

COMMITTEE RESPONSIBILITIES:

09/2021-present	**Graduate Student Organization GSBS Curriculum Committee** Act as a representative for students from the PMPH department, to develop and implement a curriculum most effective for students.
10/2020-2/2020	**UTMB Diversity & Inclusion Symposium Planning Committee** Recruit guest speakers, analyze survey results, organize symposium, create flyers and collect relevant student abstracts.
07/2019-09/2020	**UTMB Chemical Safety Committee** Committee Member, ensure CLS lab meets chemical safety standards set by UTMB.

TEACHING ASSISTANT RESPONSIBILITIES AT UTMB:

FALL 2019	CLLS 3405/5405 Intermediate Pathogenic Microbiology Lab Contact Hours: 10
SPRING 2019	CLLS3307 Molecular Biology and 6307 4090 Molecular Diagnostics Lab Contact Hours: 34
FALL 2018	CLLS 3405/5405 Intermediate Pathogenic Microbiology Lab Contact Hours: 48

	CLLS 3200_5200 Introduction to Laboratory Operations Lab Contact Hours: 20
SPRING 2018	CLLS3307 Molecular Biology and 6307 4090 Molecular Diagnostics Lab Contact Hours: 34
FALL 2017	CLLS 3405/5405 Intermediate Pathogenic Microbiology Lab Contact Hours: 15
	CLLS 3200_5200 Introduction to Laboratory Operations Lab Contact Hours: 15

MEMBERSHIP IN SCIENTIFIC SOCIETIES/PROFESSIONAL ORGANIZATIONS:

2017-2019	American Society for Clinical Laboratory Sciences (ASCLS)

ACADEMIC SERVICES—PEER REVIEW OF MANUSCRIPTS

2022	Pain Medicine
2021	Texas Public Health Journal

HONORS AND AWARDS:

2021-2022	Charles F. Otis Clinical Research Award
2021-2022	Herzog Scholar Award, Herzog Foundation Fund UTMB
2020/2021	Eleanor Dupree Otis Biostatistics Award
2020-2021	Herzog Scholar Award, Herzog Foundation Fund UTMB
2019-2020	Herzog Scholar Award, Herzog Foundation Fund UTMB