ISSN : 2321-9602

Indo-American Journal of Agricultural and Veterinary Sciences




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Indo-Am. J. Agric. & Vet. Sci., 2020

ISSN 2321–9602 www.iajavs.com
Vol. 13, Issuse 2 May 2020

Indo-American Journal of Agricultural and Veterinary Sciences

Benzodiazepines: A Major Component in Unintentional Prescription Drug OverdosesWith Opioid Analgesics

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Abstract

Despite efforts by medical experts, government regulators, and law enforcement, the misuse and abuse of prescription drugs in the United States is on the rise. Prescription opioid analgesics are the major cause of accidental overdose fatalities. When used alone, benzodiazepines are not very dangerous in terms of overdose. However, benzodiazepine-related fatalities increased from 1999 to 2009 by a factor of 5. Opioid analgesic-related ER visits climbed by 111%, while benzodiazepine-related ER visits increased by 89%. Death rates increased by the greatest amounts from 2003 to 2009 for the prescription medicines oxycodone (264.6%) and alprazolam (233.8%). Therefore, benzodiazepines have an influence on accidental overdose deaths from prescription drugs second only to opioid analgesics. Benzodiazepines and opioid analgesics are often prescribed together. Interactions between benzodiazepines and opioid analgesics are complicated due to their pharmacokinetic nature. These drugs have different pharmacodynamic effects, but when used together they may cause profound respiratory depression. Patients often see many doctors to get the best treatment for their condition, and prescription drug monitoring tools may shed light on patients' benzodiazepine and opioid analgesic prescribing and consumption habits. As the number of people dying from accidental overdoses of prescription drugs rises, health care providers have a responsibility to educate patients and work collaboratively with regulatory bodies and governments to find solutions.

Keywords: unintended, overdose, prescription drug use, benzodiazepines, opioid analgesics

Introduction

Overdose deaths and other complications from abusing prescription drugs have reached epidemic proportions in the United States. In 2009, there were 20,848 prescription drug-related fatalities in the United States, according to the Centers for Disease Control and Prevention.1 Opioid analgesics/narcotics were identified to be the most prevalent kind of prescription drug implicated in fatal overdoses.1,2 While it's well known that opioid analgesics are the most often abused prescription drugs, other drugs in this class are typically disregarded.

Table 1. Benzodiazepine (BZ) deaths, indirect (Ind.) deaths, and major effects as reported from the American Association of Poison Control Centers (AAPCC) from 2006 to 2011.[a,8,13-17]

Item	2006	2007	2008	2009	2010	2011
Deaths	249 (8%)	228 (6%)	272 (7%)	253 (6%)	286 (7%)	253 (6%)
Ind. deaths	10 (0%)	7 (0%)	58 (1%)	14 (0%)	76 (2%)	287 (6%)
Major effect	2962 (92%)	3330 (93%)	3713 (92%)	3758 (93%)	3900 (92%)	3934 (88%)
Total	3221	3565	4043	4025	4262	4474
Total BZ calls	66 177	73 199	78 658	80 548	81 641	82 156
Total calls	2 403 539	2 484 041	2 491 049	2 479 355	2 384 825	2 416 352

[a]Percentages are rounded to the nearest whole number.

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Benzodiazepines and sedative-hypnotic drugs are often detected in the systems of people who have died from overdosing on opioid analgesics. There was an increase of about fivefold from 1999 to 2009 in the number of fatalities attributed to benzodiazepines (5,500).1 However, it is now known that benzodiazepine usage has dramatically grown alongside opiate analgesics.There was either an elevated euphoric impact from the opioids or inadequate pain management, together with possibly concomitant anxiety or mood problems, in three patients with chronic pain who took opiate analgesics and benzodiazepines simultaneously.4

Multiple investigations have indicated that benzodiazepines are the most often present co-intoxicating substances in fatal opioid analgesic overdoses.When used with opioid analgesics, benzodiazepines (classified as psychothera-peutic medicines) were responsible for 48.8% of deaths in West Virginia between 2005 and 2008.5 Most benzodiazepine usage in conjunction with opioids was for diazepam (22.4%) and alprazolam (18.3%). The United States is not alone in experiencing this difficulty. Patients with nonmalignant pain who died from opiate overdoses were more likely to be using benzodiazepines, according to a research conducted in Canada.In a one-year observational analysis of deaths from acute poisonings with opioid analgesics in Norway, benzo- diazepines were recorded as the most common supplementary agent 6 times.7 Opioid users who also drank alcohol had a much lower prevalence rate. Benzodiazepines were given in 69.8% of patients in a study of unintentional fatalities from opioid misusers in the United Kingdom from 1997 to 2007. The frequency of dihydro- codeine and ethanol was lower at 30.3%.8

In this post, we'll take a closer look at how commonly prescribed benzodiazepines are misused, both in tandem with opioid analgesics and on their own, leading to fatal overdoses. It's not uncommon for doctors to prescribe benzos to treat a broad range of symptoms. Patients using opioid analgesics are often given benzodiazepines, and nonmedical benzodiazepine usage has become more common among substance abusers. In 2011, there were 82,156 benzodiazepine exposures reported to the American Association of Poison Control Centers (AAPCC). Intentional abuse, misuse, or a possible suicide accounted for 61 298 of these.9 As a result, the health care system and law enforcement face formidable obstacles in their efforts to ensure proper patient care results and reduce the likelihood of misuse and illicit nonmedical exploitation of these drugs.

Statement of the Problem

Benzodiazepine and opiate analgesic abuse-related literature published in English between 1960 and 2012 were located via a search of PubMed and PsycINFO. Clinical investigations comparing these two types of medicines were the focus of the chosen publications. Benzodiazepines, opiate analgesics, prescription medicines, overdose, pharmacokinetics (PK), and pharmacodynamics (PD) were used as search terms to narrow down the massive amount of publications included in this study by using a Boolean operator. Using these 6 criteria, we were able to create over 200 articles. Reports of cases that did not include pharmacokinetic (PK) data were disregarded. The following sources were utilized for this topic, with the exception of retrospective studies that included solely opioid analgesics without benzodiazepines.

In the 1960s, benzodiazepines entered the market. Overdosing on a single medication seldom results in deaths due to the drug's high therapeutic index.10,11 Even more recently, it was found that out of 61 single-drug fatalities, just 1 was attributable to a benzodiazepine while the rest were from opioid analgesics. This study shows that opioid analgesics are more likely than benzodiazepines to be involved in a fatal single-drug overdose.5,12 In addition, only 253 (0.3%) of the 82 156 patients reported to the AAPCC in 2011 died as a direct impact of benzodiazepine exposure (Table 1).9 Health care providers generally agree that benzodiazepines are safe to use in cases of overdose involving a single medication.

Despite a favorable safety profile when taken alone, worrying tendencies have surfaced with benzodiazepines. In the United States, the number of people who went to emergency rooms (EDs) for reasons unrelated to medical treatment with benzo-diazepines rose by 139% between 2004 and 2010, from 174 471 to 408 021.From 2006 to 2011, the number of benzodiazepine exposure reports to the AAPCC rose by 13 percent. These shows account for an ever-increasing share of calls to poison control centers (see Figs. 1 and 2).9,14-18 The Drug addiction Warning Network (DAWN) Report found that between 2004 and 2010, the number of emergency department visits involving opioid analgesics climbed by 156%, from 166 338 to 425 427, although benzodiazepine addiction still has a major effect on the health care system.13 The Centers for Disease Control and Prevention found that between 2004 and 2008, benzodiazepine use increased emergency department visits, with alprazolam having the biggest rise (168.8%), and clonazepam having the lowest.

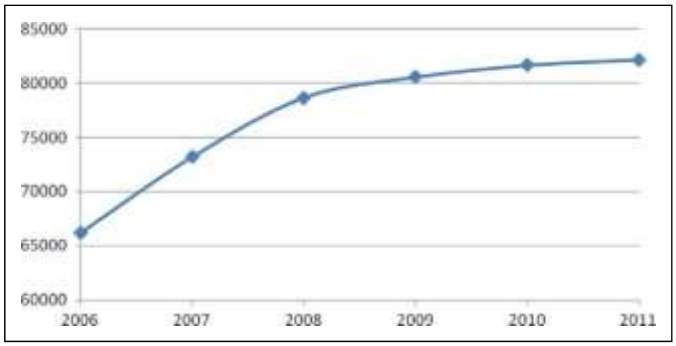

Figure 1. Plot of benzodiazepine exposures/calls reported to theAmerican Association of Poison Control Centers (AAPCC) from2006 to 2011.[8,13-17]

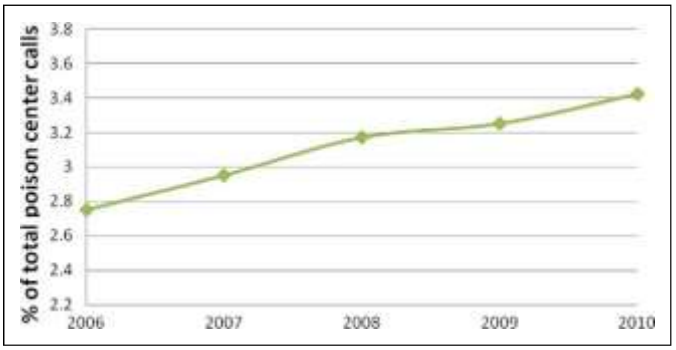

Figure 2. Plot of benzodiazepine exposures/calls as a percentage of total calls reported to the poison centrol centers from 2006 to 2011.[8,13-17]

126.6%, 113% for lorazepam, and 67.4% for diazepam. Alprazolam had an estimated 152,168 visits to the ED in 2010, which was more than twice as many as the 73,452.19 visits seen by the next most common benzodiazepine, clonazepam. About a third of these people required hospitalization.

The majority of the rise in ED visits due to the nonmedical use of prescription or over-the-counter medicines may be attributed to the misuse of opioid analgesics and benzodiazepines. According to AAPCC statistics covering the years 2006-2011, between 20 and 51-year-olds accounted for 72 percent of all benzodiazepine reports. Incidence rates were 8% among adults older than 60 and 10% among children and teenagers 6-19 years old. The 10% observed prevalence among children aged 0-5 years presumably represents accidental ingestions. Females (49 489 vs. 32 268 men) are more likely to have been exposed to toxins.9,14-18 According to statistics from 2010, those above the age of 20 made much more emergency department trips for benzo-diazepines than those under the age of 20 (168.8 trips for every 100,000 people vs. 38.6 trips for every 100,000 people). For narcotic pain medicines, a comparable disparity was noted, with 177.4 visits/100,000 for those over the age of 20 compared to 58.6 for those under.

36.3% of every 100,000 people are treated in hospitals.19 These results imply that adults, as opposed to children, adolescents, and the elderly, are more likely to seek medical attention at an emergency department (ED) or make contact with a poison control center after experiencing a negative reaction to benzodiazepines.

The presence of deadly doses of 1 or more medications in the blood from prescription drug deaths was detected in a research conducted by Mueller and colleagues from 1994 to 2003.20 Twenty-one percent of those who were also abusing prescription medicines also shown signs of alcohol cointoxication. Drug overdose deaths were most usually associated with opioids (77.1%), tranquilizers (34.4%), and antidepressants (25.6%). Benzodiazepines were likely not named as the tran- quilizer category, but this is a reasonable inference given that other medication class groupings were. Sedative-hypnotics are another kind of medication in this category, and they may provide an additional complicating factor.

Prescription drug overdose fatality rates increased between 2003 and 2009, according to data from the Florida Medical Examiners Commission published in the Morbidity and Mortality Weekly report.

jumped from 7.3 per 100,000 in 2003 to 13.4 in 2009, an increase of 84.2 percent.21 Lethal drug concentrations from 1 or more drugs grew by 61% between 1804 and 2905, as measured by the yearly number of deaths recorded by the medical examiner. Oxycodone (264.6%), alprazolam (233.8%), and methadone (79.2%) had the biggest increases. Prescription drug overdose deaths double those of heroin and cocaine combined by 2009. In 2003, oxycodone caused 1.7 deaths for every 100,000 people, whereas alprazolam

caused 1.3 deaths for every 100,000 people, cocaine caused 3.2 deaths for every 100,000 people, and heroin caused 1.4 deaths for every 100,000 people. In 2009, the mortality rates associated with oxycodone and alprazolam were the highest, with 6.4 and 4.4 per 100,000 respectively, while the death rates associated with cocaine and heroin combined were at 3.3 per 100,000. Prescription drug overdose deaths increased in Florida, but those caused by cocaine and heroin decreased. The fatality rate for benzodiazepines (number of deaths/number of exposures) remained stable at 0.3% from 2006 to 2011, according to statistics collected by the national AAPCC.9,14-18

According to the 2010 GBI data, there were at least 560 more fatalities related to prescription medications than to illegal substances (101 vs. 560).22 Alprazolam (231 deaths), oxycodone (171 deaths), methadone (151 deaths), hydrocodone (145 deaths), cocaine (96 deaths), morphine (87 deaths), fentanyl (78 deaths), methamphetamine (65 deaths), and diazepam (55 deaths) were the most commonly detected drugs in toxicology reports of overdose deaths. For every fatal overdose, researchers identified an average of 2.5 substances, some of which were not narcotics like hydrochlorothiazide. Males made up 58.6% of the total fatalities, with Caucasians making up the largest number (90.3%) of any ethnic group. The greatest fatality rate was seen in people aged 35 to 54. Deaths were more likely to occur due to accidents than suicide (93% vs. 8.86%). Although opioid analgesics accounted for the largest share of deaths (58.6%), benzodiazepines came in second (26.5%), and illicit stimulants came in third (14.9%) when broken down by drug class. Similarly, in Kentucky, alprazolam (N 14 286) was listed as the most often used illicit drug.

substance discovered in high frequency among 2011 overdose fatalities. Following morphine (N 154), oxycodone (N 213), and hydrocodone (N 187), the opioid analgesics were next.23

Some intriguing patterns emerged in AAPCC data gathered between 2006 and 2011 (see Table 1).9,14-18 The overall number of benzodiazepine-related fatalities reported to poison control centers remained stable in 2011, but an alarming rise was seen in the number of indirect deaths. Benzodiazepines were detected in the blood or at the site of the fatality in the incidents classified as indirect fatalities by law enforcement, coroner's office, and other sources. Hospitalization, severe life-threatening respiratory depression requiring mechanical ventilation, and shock were all considered to be major impacts. According to the numbers, the number of reported problems with benzodiazepines rose dramatically (by 25%) between 2006 and 2011. Figures 1 and 2 demonstrate that the overall number of calls about benzodiazepines grew by 20% between 2006 and 2011, even if the overall number of calls about drugs and goods did not change during that time. The general population makes up the vast majority (85%) of Poison Control Center callers, with medical professionals making up the remaining 15%.

Prescription drug overdoses are a serious problem, and the GBI findings highlight the difficulties of conducting systematic reviews of benzodiazepines.22 Besides the drug's presence at the time of the autopsy, data from toxicology tests conducted by medical examiners do not give much information. There is a shortage of pertinent data, including patient history, medicine dosages, and more. There is some doubt about the veracity of the information provided by callers who are not trained medical experts.9,14-18 Trying to pin down a single substance as the cause of death is made more difficult by the presence of several medicines. However, trends toward a greater role of benzodiazepines in overdose have emerged. Opioid analgesics are often used with benzodiazepines, either legally bought or illegally obtained. When it comes to pharmaceutical overdose deaths and emergency department visits caused by nonmedical use, benzodiazepines are second only to opioid analgesics.

Benzodiazepine Pharmacology and PKs

An overview of benzodiazepine pharmacology and PK characteristics is necessary since these drugs are often used with opioid analgesics. The g-aminobutyric acid (GABA) neurotransmission is enhanced by benzodiazepines, making them agonists.10,11 There are two known subtypes of GABA receptors: GABAA and GABAB. The GABA receptor mediates neuronal excitability reduction and governs tonic inhibition. Anxiolytic and sedative drugs work by binding to and activating the GABAA receptor. Each GABAA receptor is made up of many subunits (a, b, and g) that wrap around a central pore and allow chloride ions to enter or leave the cell in response to a ligand. Benzodiazepines interact with the GABAA receptor through binding to the a1, a2, a3, and a5 subunits, as well as the b and g subunits. The GABAA a2 subunit site mediates the anxiolytic PD activities of ben- zodiazepines, whereas the GABAA a1 subunit site mediates the sedative effects.11,24

The pharmacokinetics and metabolism of benzos have been extensively studied. Phase I hepatic metabolism is responsible for the benzodiazepine

phase II glucuronidation and cytochrome P450 (CYP450) oxidation.10 It is CYP3A4 that metabolizes the benzos alprazolam, triazolam, and midazolam.Diazepam, once taken, is metabolized into oxazepam and desmethyldizazepam (DMDZ) via the cytochrome P450 2C19 enzyme system.26 One percent to six percent of Caucasians, one percent to seven and a half percent of African Americans, and twelve percent to twenty-three percent of Asians are poor metabolizers (PMs) due to the CYP2C19 polymorphism.27 Direct conjugation via phase II glucuronidation occurs for lorazepam, temazepam, and oxazepam. Based on how long it takes for them to be eliminated from the body, benzodiazepines are categorized as either short-acting, intermediate-acting, or long-acting. The elimination half-life of midazolam and triazolam is less than 2 hours, making them short-acting drugs.24 The elimination half-life of intermediate drugs like alprazolam, lorazepam, and oxazepam ranges from 10 to 20 hours.23 Due to the DMDZ present, both diazepam and chlordiazepoxide have a lengthy elimination half-life (50-

100 hours).10,24 Age, possible drug-drug interactions, and the buildup of active metabolites in renal failure and other circumstances after overdose may all significantly alter the pharmacokinetics (PK) of benzodiazepines.

Only 12 of the 99 patients treated between 1962 and 1975 for benzodiazepine overdose were admitted solely because of benzodiazepines.28 Twenty-one out of thirty-one patients with a central nervous system (CNS) depression score of 3 (minimal response to maximum painful stimuli) or 4 (no response to maximum painful stimuli) using a system developed by Matthew and Lawson had the most severe intoxication.29 Among these individuals, 14 needed help breathing. Patients who used benzodiazepines in combination with other psychotropic medicines (11/18) or with nonbarbiturate sedative-hypnotics (7/12) had the same thing. With chlordiazepoxide 4000 mg and diazepam 400 mg, only 1 of 12 patients treated with benzodiazepines alone had CNS depression of grade 3 or 4. This preliminary research showed that overdose circumstances using benzodiazepines were more dangerous when additional CNS depressants were present. Two hospitalized patients who had attempted suicide swallowed quantities of diazepam (500 and 2000 mg), resulting in plasma diazepam concentrations 100 times greater than those associated with regular therapeutic doses (typically 300-700 ng/mL).30-33 After receiving naloxone, both patients showed rapid improvement and were released from the hospital the following day. Naloxone wouldn't slow down the benzo-diazepines' effects, but it may rule out an opiate overdose if the patient felt better after taking it. The patient's quick improvement was not attributable to the rapid clearance of the medicine from the body, since plasma dia- zepam concentrations and its metabolites progressively fell over the following 1–2 weeks.

Three patients who overdosed on lorazepam had plasma drug concentrations 5 to 15 times greater than those associated with conventional therapeutic dosages (usual range 17-50 ng/mL).34,35 Within 24 to 30 hours, all three patients had made full recoveries, and the elimination half-life of lorazepam was 9.3 to 22.3 hours, which is comparable to that seen in healthy volunteers at therapeutic dosages.

Concentrations of Drugs in Plasma

and clinical outcome were evaluated in 21 patients with an acute overdose with benzodiazepine derivatives.[36] Diazepam was reported in 18 patients with plasma diazepam levels from 585 to 8635 ng/mL. Four patients had taken only diazepam with the highest diazepam plasma concentration of 4792 ng/ mL and desmethyldiazepam 2266 ng/mL (usual normal range 300-700 ng/mL for both compounds).[31-33] None of these patients displayed any clinically excessive sedative symptoms and were discharged within 24 hours. Five patients ingested both diaze- pam and ethanol, and only patient was in coma with a plasma diazepam concentration >8000 ng/mL on admission and required ventilation. The patients recovered within 24 hours and were discharged without sequelae. In all, 9 patients had benzo- diazepines with other CNS depressants and 4 patients had a coma grade of 3 or greater (Matthew and Lawson scale)[29] that required intubation. Plasma diazepam concentrations were moderately elevated and ranged from 993 to 1727 ng/mL in 4 patients. One patient had ingested oxazepam with a plasma drug concentration of 9540 ng/mL (usual normal range 200-500 ng/mL)[37] with only drowsiness and was discharged within 24 hours. These results indicate that benzodiazepine plasma concentrations are not pre- dictive of clinical outcome, and that the overdose severity is dependent on whether other CNS depressants are taken. Other important factors must be taken into consideration regarding benzodiazepine disposition in overdose situations. Volume of distribution, impaired hepatic function, and drug–drug interac-tions (via CYP inhibition) can contribute to prolong or enhancebenzodiazepine adverse events.

Opiate Analgesic Pharmacology and PKs

An overview of benzodiazepine pharmacology and PK characteristics is necessary since these drugs are often used with opioid analgesics. The g-aminobutyric acid (GABA) neurotransmission is enhanced by benzodiazepines, making them agonists.10,11 There are two known subtypes of GABA receptors: GABAA and GABAB. The GABA receptor mediates neuronal excitability reduction and governs tonic inhibition. Anxiolytic and sedative drugs work by binding to and activating the GABAA receptor. Each GABAA receptor is made up of many subunits (a, b, and g) that wrap around a central pore and allow chloride ions to enter or leave the cell in response to a ligand. Benzodiazepines interact with the GABAA receptor through binding to the a1, a2, a3, and a5 subunits, as well as the b and g subunits. The GABAA a2 subunit site mediates the anxiolytic PD activities of ben- zodiazepines, whereas the GABAA a1 subunit site mediates the sedative effects.11,24

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Drug Interactions With Benzodiazepines, Opioid Analgesics, and Alcohol

The pharmacokinetic (PK) and pharmacodynamic (PD) effects of benzodiazepines and opioid analgesics are intricately intertwined. Commonly prescribed medicines that are substrates, inhibitors, or inducers of the cytochrome P450 3A4 system have a high potential for interaction with opioids that are processed by this system.40,41 The order of administration of CYP3A4 substrates and inhibitors like alprazolam may affect the extent to which opioid blood concentrations are increased or the extent to which the opioid is converted to its active metabolite. Phase II glucuronidation medication interactions include less .likely to happen than oxidative metabolism during phase I of CYP. However, large quantities of oxazepam inhibited dihy- drocodeine in hepatic microsomes by 35% in in vitro tests.44 Drug interactions may arise via a variety of pathways, so clinicians need to be on the lookout for them. Drug-drug interactions are already complicated, but the CYP2C19 and CYP2D6 polymorphisms may be a factor in how diazepam and opioid analgesics are metabolized. If a person has polymorphisms (PMs) in both CYP2D6 and CYP2C19, even little doses of hydrocodone and diazepam might have a profound effect on their central nervous system (CNS).

As was previously reported, the receptor networks targeted by benzodiazepines and opioid analgesic PD are distinct. Both types of drugs are central nervous system depressants, and they have the same effect on breathing through two distinct pharmacologic routes.46 Therefore, there may be catastrophic effects for individuals who use benzodiazepines in addition to opioid analgesics. Moreover, drug tolerance, dependency, and withdrawal are all serious problems with both groups of medications.

Additional pharmacokinetic (PK) and pharmacodynamic (PD) interactions between alcohol and benzo-diazepines result in enhanced central nervous system depression. Alcohol's role in prescription medication overdoses was greater than that of opioid analgesics combined with benzodiazepines, although it was still substantial. According to a study by Hakkinen and coworkers, of 182 people who died from buprenorphine toxicity, 82% also used benzodiazepines and 52% used alcohol.47 The greatest incidence (N 107), followed by alprazolam (N 53) and temazepam (N 48), was seen in the long-acting benzodiazepine group, which includes chlordiazepoxide, demoxepam, and diazepam. There has been a lot of research on the pharmacokinetic and pharmacodynamic interactions between benzodiazepines and alcohol.10,12 Alcohol dehydrogenase, aldehyde dehydrogenase, and cytochrome P450 2E1 are all involved in the hepatic metabolism of ethanol.12 It does not seem that benzodiazepines or opioid analgesics have a direct interaction with the phase I oxidative CYP metabolism or the phase II glucuronidation systems. Alcohol inhibits the elimination of benzodiazepines that are demethylated or hydro-xylated (such as diazepam), according to previous investigations. Clearance of lorazepam was shown to be decreased by alcohol but clearance of oxazepam was unaffected. The effects of alcohol on benzodiazepine disposition vary with the quantity ingested and the duration of usage. Most controlled investigations of alcohol and benzodiazepine interaction employ a single-alcohol dose administration, making it hard to extrapolate results to "real world" conditions. It is well established that the CNS depressive properties of both alcohol and benzo- diazepine, including respiratory depression, are amplified when used together. The increased PD effects when benzodiazepines are co-administered may be explained by the fact that alcohol exerts the majority of its pharmaco-logic action at the ion-gated channels of GABAA receptors.48

When opiates and alcohol are combined, similar to the ben-zodiazepines, an enhanced PD CNS depressant effect occurs albeit by different pharmacologic mechanisms.

Controlled clinical PK and PD studies with alcohol and opiates can be very difficult to conduct as research conditions may not represent the ‘‘real world’’ of their use in patients. However, it was reported that in healthy volunteers that combined ethanol and oxycodone enhanced drug-liking actions, increased drug- taking behavior, and euphoria were found.[49] A significant PK drug–drug interaction between alcohol and morphine was not found in healthy volunteers.[50] Since alcohol and opioid analge- sics are metabolized by different hepatic enzymes, the likeli- hood of a PK drug–drug interaction is unlikely and enhanced CNS depression occurs via PD effects. Further increased PK and PD actions occur when all 3 agents are involved. Unlike many drug overdoses, direct pharmacologic antagonists for benzodiazepines (flumazenil) and opioid analgesics (naloxone)are available for acute treatment to reverse their toxic effects when the patient can be promptly treated while balancing the risk of using agents.[51-53]

Review of the Clinical Studies and Challenges Associated With Benzodiazepines

The clinical uses of benzodiazepines are many. These substances have antispastic, anticonvulsant, and hypnotic actions in addition to their anxiolytic ones.12 One of the most common mental health issues in the world today is anxiety.For the treatment of anxiety disorders, the Food and Drug Administration also approves alprazolam and clonazepam.24 Benzodiazepines will remain popular since they are effective treatments for a wide range of medical problems.

In a study conducted between June 2004 and December 2005, Havens and coworkers reported assessing benzodiazepine usage among opioid users in a rural community context.54 The participants in the study (N = 221) all filled out questionnaires and were interviewed by the researchers. Opioid and benzodiazepine usage in the last 30 days for medicinal purposes was considered medical use. The use of drugs was considered nonmedical if they were obtained without a valid prescription. Ninety-two percent of the 221 patients reported using benzodiazepines at some point in their lives to help with the symptoms of sadness and anxiety. Only about a third of patients received a prescription, yet almost all of them took alprazolam (88.3% of patients) or diazepam (63.8% of patients). More over half (58.4%) of individuals who obtained benzodiazepines without a prescription obtained them via friends or family members rather than illegal traffickers. About a quarter of patients reported using the drug for more than 13 years, and the median term of use was 8 years. Some of the study's flaws were its inability to distinguish between those who used benzodiazepines for non-medical reasons and those who used them for medical purposes, as well as its failure to evaluate benzodiazepine misuse and dependency.

Patients who suffer from schizophrenia, bipolar disorder, and major depressive disorder often get benzo prescriptions. There may be a lot of anxiety symptoms.55,56 Between 60% and 74% of patients in a retrospective study of New Hampshire Medicaid recipients from January 1995 to December 1999 had been using benzodiazepines for more than 4 months. Opiate analgesics are appropriate for patients with various mental health disorders. Bernandy and coworkers evaluated benzodiazepine usage among veterans with PTSD from 1999 to 2009.57 The number of veterans diagnosed with PTSD almost tripled between 1999 and 2009, from 170 685 to 498 081. While the percentage of people using benzodiazepines over this time period decreased from 36.7% to 30.6%, 64.1% of the veterans in this research used the drugs for more than 90 days. Unfortunately, the usage of opioid analgesics was not evaluated. From 2003 to 2010, Hawkins and coworkers examined benzodiazepine and opioid analgesic use among veterans with post-traumatic stress disorder (N = 64 872).58 Medication usage for more than 90 days was considered long-term. Nearly half of the benzodiazepine users in the research reported taking the drug for an extended length of time, and 28% of those users were given lorazepam or clonazepam. Between 2003 and 2010, the percentage of long-term benzodiazepine users who also used opioid analgesics climbed from 52.0% to 63.1%, while the percentage of long-term opiate users who also used benzodiazepines rose from 33.3% to 46.6%. The complicated therapy regimens required for patients with mental illnesses and veterans with PTSD make it difficult for health care providers to prescribe benzodiazepines appropriately. The growing population of veterans, especially those returning from Iraq and Afghanistan, may be offsetting a downward trend in benzodiazepine use among patients with PTSD.59 Further thorough research and attention are needed to address the rising prevalence of opioid analgesic use among veterans with PTSD.

The effects of benzodiazepines on mortality in a broad middle-aged population were studied by Hausken and colleagues.60 Participants self-administered questionnaires and underwent medical exams, with the population including men (N 15 606) and women (N 14 748) aged 40 to 42 years from 2 Norwegian counties. The research was conducted in two counties over the course of six years, first from 1985 to 1988 and then from 1986 to 1989. Anxiolytic and hypnotic usage was roughly 2.5 times as common among women. Daily benzodiazepine users, both men and women, had greater hazard ratios for death compared to those who did not take the drug. The hazard ratios were 3.1 and 2.7, respectively. The hazard ratios dropped from 2.7 to 2.4 for males and 2.1 to 1.6 for women once smoking and opioid use were taken into account. The hazard ratios dropped to 1.5 in men and 1.7 in women when additional possible confounding factors were included in the study (such as alcohol usage, medical problems, etc).

Three population-based registry studies and six prospective cohort studies- 61 were described in Charlson and colleagues' systematic review of benzodiazepine-related mortality. Estimates and methods of data analysis varied throughout the three studies based on registries of the general population. The original research relied on

on data from US poison control centers, and showed that the odds ratio (OR) for death from ben- zodiazepine poisoning in those aged >60 years was an alarming 7.1 (95% CI 3.2-15.5). When other medications, such as alcohol, were taken into account, the small positive association between benzodiazepines and driving deaths in the second research disappeared. Finally, the third research found that benzodiazepines were only partially responsible for mortality (3.8% vs. 71%) since they were often taken in conjunction with opioids.

All six of the prospective cohort studies were conducted in developed nations of Europe and North America. These investigations yielded contradictory and inconsistent findings. Opioid analgesics and benzo-diazepines were implicated in almost 50% of the fatal overdoses. The information accuracy and death certificates may not be standardised in these large population and cohort studies due to serious constraints in design and data gathering. There will inevitably be data issues and misclassifications due to this circumstance. It may be difficult to draw firm conclusions from questionnaires and databases due to the possibility of omissions, underreporting, and the presence of several confounding variables. Because of variations in duration, consistency, and dose, it might be difficult to reliably categorize people as benzodiazepine users, benzodiazepine abusers, or benzodiazepine nonusers. Calls to poison control centers from the general public are not always reliable sources of information due to a lack of medical training or expertise. It is difficult to attribute deaths solely to toxic benzodiazepine blood concentrations, particularly when other medications, such as opiates, are also present. Finally, pinpointing benzodiazepine use as the only cause of mortality in a research is made more difficult by the interplay of social and economic elements involved. Overestimating the risk of fatality from prescription medication overdose remains difficult due to the many factors and variables involved.

There hasn't been a lot of research on how various benzodiazepines compare to one another in terms of overdose toxicity. Overdoses of oxazepam were observed to be less sedating than those of other benzodiazepines, whereas overdoses of temazepam were reported to be more sedating.62 However, temazepam in the United Kingdom is formulated differently than in the United States, and this difference may affect drug absorption and play a significant role in overdose situations. There were reports of sharp increases in both ER visits and fatalities associated with alprazolam.12,19 Intentional overdoses were used to evaluate the relative toxicity of alprazolam (N 131) vs diazepam (N 823) and other benzodiazepines (N 1109).63 Compared to diazepam and other benzodiazepines, alprazolam overdoses were more likely to result in hospitalization, coma, and the need for mechanical breathing and treatment with flumazepam. Each benzodiazepine's influence in relation to the total number of prescriptions should be carefully evaluated. The difficulties related to alprazolam and other benzodiazepine overdoses have worsened as their usage has spread beyond the medical community and into the illegal market. Determination.

Impact of Physician and Pharmacy Shopping and Prescription Drug-Monitoring Programs

Patients who purchase opioid analgesics and benzodiazepines from many pharmacies and have been prescribed these substances by different doctors may raise suspicions about their legality of use. Wilsey and coworkers analyzed the PMP data in California to determine the prevalence of multiple provider events, which were defined as a patient receiving the identical prescription from two or more practitioners filled by two or more pharmacies over a 30-day period.64 The highest percentage of prescriptions written by more than one doctor was for opioids (12.8%), followed by benzodiazepines (4.2%) and stimulants (1.4%). Patients who were prescribed more than one kind of restricted drug were more likely to see several doctors to get their medicine. There is no universally accepted definition of patient "shopping" between healthcare providers or pharmacies. According to previous research, "doctor shopping" is defined as filling prescriptions from more than six different doctors in the year leading up to a death.A patient was considered to be pharmacy-shopping if they filled at least two prescriptions for the same drug class during a 12-month period (64, 65).66 This research was carried out in the Netherlands, and it distinguished between infrequent (visiting one or two pharmacies) and frequent (visiting three to four pharmacies) pharmacy shopping. Unexpectedly, 99.2% of the patients were classified as seldom consumers, 1.0% as occasional shoppers, and 0.2% as frequent heavy shoppers. In 26.9% of the non-heavy shoppers, benzodiazepines were prescribed. A higher percentage of benzodiazepines were prescribed (> 72%) even though moderate and heavy shoppers were far less common than light shoppers.

Using a case controlled research design, Pierce and colleagues compared deaths with physician and drugstore shopping and defined pharmacy shopping as patients filling prescriptions from 4 or more pharmacies during a 6-month time period.67 Patients who visited many doctors or pharmacies before to death were overrepresented among those who did not survive (36% versus 1.3%). About 20.2% of the doctors surveyed also shopped at pharmacies, while 55.6% of the pharmacies surveyed also had doctors as customers. Physician shoppers (OR, 1.598-2.573) and pharmacy shoppers (OR, 2.253-4.732) were shown to have a significantly higher risk of drug-related death than other types of drug purchasers (P .05). There was a statistically significant increase in the risk of death from any cause among those who had recently filled prescriptions for both benzodiazepines (7.213, 3.334-15.605) and opioid analgesics (3.398, 1.601-7.211). Most drug overdose deaths were expected to occur when opiates were combined with

benzos (14.917, 7.004-31.767).

The PMPs were developed to lessen the likelihood of illegal drug use while having little influence on lawful prescriptions.68 Opioid analgesic and restricted drug treatment programs have been established in some but not all states. According to the CDC, these PMPs combined with insurance restrictions may curb unnecessary opioid usage and stop patients from shopping around for doctors.3 Other efforts included bettering medical practice in prescribing opioids and enhancing and enforcing current legislation. Nonetheless, sales of banned narcotics, such as opiate analgesics, have skyrocketed despite the PMPs' installation.69 Variables that constituted physician shopping were found in the PMPs studies, however pharmacy shopping was less well-defined. The PMPs have shown that many doctors often prescribe a mixture of opiate analgesics and benzodiazepines for patients.55,58 Georgia's PMP for 2013 was just authorized by the state legislature; the Peach State was one of the latest to adopt such a measure.70

Only in New York may you participate in a PMP program designed specifically for benzodiazepines. A duplicate prescription program (TPP) was used in its first rollout in 1989.71 Over the last five years, New York's program has grown from monitoring just schedule II opioids to include monitoring schedule III opioids. Numerous research using the NY database found that benzodiazepine usage declined, but that this trend was not without unexpected repercussions for some populations. New York saw a significant rise in the use of meprobamate, hydroxyzine, and nonbenzodiazepine hypnotics after its introduction in 1989, whereas the rest of the country saw a decline in the use of anxiolytics and hypnotics overall, with the exception of benzodiazepine anticonvulsants.72 After the program was introduced, many doctors had negative opinions about it. Benzodiazepine consumption decreased more dramatically among patients with persistent mental illness, seizure disorders, cancer, and cardiac diseases than among any other category. Benzodiazepine use decreased more dramatically among the poor, the urban, and people of color than among the Caucasian population as a whole.71 There was no evidence that the TPP decreased the misuse of benzodiazepines. The rate of hip fractures and falls among the elderly who used benzodiazepines did not vary noticeably either before or after the TPP was put into place. The New York course does include information on PMPs' real-world uses.71 Unintentional overdoses may be reduced by reducing benzodiazepine availability (e.g., by restricting refills) for properly prescribed patients. Compared to Pennsylvania's PMP, New York's is better supported by the state government and uses tamper-proof, serialized prescription forms for opioid analgesics.72 New York's opiate analgesic per capita consumption in 2006 was found to be double that of Pennsylvania's. Pennsylvania had a mortality rate from opioid overdoses that was 1.6% greater than New York's. According to DAWN 2007 statistics, the mortality rate associated with opioid analgesics was greater in Philadelphia (10.2/100,000 people) than in New York City (3.5/100,000 people).73 Perhaps the regulatory climate in New York is different, accounting for these variations.

Pharmacoeconomic Impact

The United States is experiencing an epidemic of prescription drug abuse and accidental overdose, notably with opioid analgesics when combined with benzo-diazepines. This has implications for prescribing agreements with healthcare entities, treatment programs, and patient risk assessments.74 The pharmacoeconomic burden of these medicines on the health care system is substantial, not to mention the morbidity and death associated with their overuse and unintentional overdose. Estimated yearly direct expenses for opiate abusers in 2003 USD were $15,884, whereas those for non-abusers were just $1,830.75,76 Opiate addicts spent just 13% of their direct spending on medicine, whereas 82% was spent on hospitalization and doctor visits. Public funding for benzodiazepines mostly comes from Medicaid.77 The number of benzodiazepine prescriptions written in the United States more than quadrupled between 1991 and 2009, from 8.0 million to 17.1 million, while the number of Americans enrolled in Medicaid rose from 22.9 million to 53.6 million. Medicaid spending for benzodiazepines increased by 30%, from $131 million to $171 million, between 2012 and 2016. The total direct expenses for benzodiazepines have been reduced since their generic equivalents became available. Over the last two decades, there has been a steady growth in the number of prescriptions written for generic versions of alprazolam and lorazepam. Using a retrospective examination of paid claims in a commercially insured population, Pergolizzi was able to quantify the impact of opioid drug-drug interactions from a pharma-coeconomic standpoint.When compared to matching patients without a suspected PK opioid drug-drug interaction, those 78 patients who got opioids metabolized via the CYP system had higher overall total expenses (mean US$8165 vs US$7498, P .01). The retroactive aspect of using claims data significantly hampered efforts to demonstrate a causal association between drug-drug interactions and higher costs. PD interactions were not evaluated, although they cannot be ignored, particularly in the presence of benzodiazepines.79 The Centers for Disease Control and Prevention (CDC) predicted a US$72.5 billion dollar loss to insurance companies due to the misuse of opioid analgesics between 1999 and 2008.80 The cost to the healthcare system is enormous when opioid analgesic and benzodiazepine overdoses occur accidentally.

Addressing the Need

The National Drug Control Strategy (NDCS) proposed the following measures to curb the problem and epidemic of prescription drug abuse: education, drug monitoring, correct disposal, and enforcement.81 The Centers for Disease Control and Prevention (CDC) advocated for many of the same measures advocated for by the NDCS, including prescription drug monitoring systems, patient review and restriction programs, health care provider accountability, regulations to prevent prescription drug misuse and prevention, and improved access to substance addiction

treatment.82 Evidence-based recommendations and preventative measures for using prescription databases may cut down on "doctor shopping" and unneeded opioid usage.

analgesics.2 Opioid and schedule II–IV drug PMPs have been adopted in the majority of states. More people are dying from overdoses because they are using benzodiazepines and opiate analgesics together. The PMPs should include measures to limit pharmacy shopping as well as those to limit visits to multiple doctors. For populations at increased risk of prescription drug overdose, such as Medicaid patients and low-income groups, this may be of critical importance.2 Regrettably, there is no ironclad assurance that PMPs will reduce improper pharmaceutical usage. When benzodiazepines are part of the PMPs, there is no longer a need for the TPP. The ability of PMPs to notify prescribers and pharmacists of suspicious patient shopping behavior, on the other hand, may prompt the necessary actions for health care providers to closely assess patient treatment, screen patients for drug misuse, and assist them in gaining access to treatment. Monitoring of all banned drugs in classes II–V and "best" practice models were cited as examples of what makes for a "ideal" PMP.83

To keep up with the ever-changing nature of substance misuse issues, new laws and stricter enforcement of current ones are required.81,82 While the frequency of drug overdose deaths vary from state to state,73 it is essential that regulatory agencies have the resources necessary to adopt and maintain PMPs. The prescriptions written by illicit pain clinics (e.g., "pill mills") and other nonmedical institutions may be reduced by the joint enforcement efforts of state and federal agencies.

All medical professionals and patients need better education and practice in accordance with evidence-based recommendations for the safe and effective prescription of opioid analgesics and benzodiazepines.81,82 Health care providers, especially prescribers and pharmacists, need to be aware of the intricate pharmacokinetic (PK) and pharmacodynamic (PD) drug-drug interactions between these two medications. Medical personnel may ignore the risk to patients when benzodiazepines are coupled with opioid analgesics, despite the fact that benzodiazepines alone are generally safe medicines. To reduce the number of accidental overdose deaths, health care systems should include accredited continuing education programs for prescribers and health care professionals on the use of opioid analgesics and benzodiazepines. To cut down on illegitimate prescriptions, pharmacists may use PMPs to thoroughly check benzodiazepine and opiate prescriptions and verify suspicious prescriptions. If a pharmacist has reason to believe a prescription is being used illegally, he or she may refuse to complete the order and instead contact the appropriate authorities. Opioid analgesics, benzodiazepines, and the combination of the two all need patient counseling. Patients should be warned about getting these drugs from loved ones and on how to safely dispose of them. It may be challenging for the healthcare system to strike a balance between preventing the misuse and abuse of prescription drugs and ensuring that patients have uninterrupted access to therapy. Maximum therapeutic advantages and minimal harmful effects may be achieved by the establishment of precise patient treatment objectives and results in conjunction with ongoing contact with health experts. All medical staff must keep a close eye on their patients at all times. In cases when a shift in the patient's symptoms coincides with a change in the drug's pharmacokinetic or pharmacodynamic properties, careful

There has to be a patient evaluation. Benzodiazepines, opioid analgesics, and other drugs may have been acquired illegally or through friends and family, thus it is important to test patients for the presence of these substances in their systems.

Conclusions

Prescription drug overdose deaths have become an epidemic in the United States, posing a major challenge to the health care system. Opioid analgesics are the most often implicated class of prescription drugs in accidental overdose. When used alone, benzodiazepines are quite safe. However, benzodiazepines may be dangerous when used with opioid analgesics or other CNS depressants like alcohol. Overdoses using two classes of medications have caused a dramatic increase in both emergency department visits and mortality over the last few years. It is important to take into account the complicated pharmacokinetic (PK) and pharmacodynamic (PD) interactions between benzodiazepines and opioid analgesics when prescribing for and monitoring patients. When utilizing these drugs, it is important to identify the desired treatment goals. Patients need to be carefully informed of realistic therapeutic goals and potential undesirable side effects of drugs. Multiple factors and complicating situations make it difficult to substantiate a relationship between benzodiazepine usage and death in studies and medical examiner reports. PMPs and similar systematic monitoring systems are used by healthcare companies to reduce the frequency with which patients "shop" for doctors and drugs. Unintentional overdose from prescription drugs has a large pharmacoeconomic effect on the healthcare system. Overall aims to maximize patient care with adequate safety measures may be provided by health care professionals working collaboratively with regulatory bodies and legislatures.

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