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RELATIONSHIPS INVOLVING THE CONCERN OF DRUG OVERDOSE AND BENZODIAZEPINE DOSAGE FOR SLEEP PROBLEMS: A CLINICAL DIAGNOSTIC BASED CROSS-SECTIONAL STUDY

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Abstract
Adolescent sleep disturbances are treated with benzodiazepines; nonetheless, overdoses on these drugs do happen frequently in conjunction with opioids. Our research sought to determine the associations between the risk of medication overdose and the dosage of benzodiazepines used to treat sleep disorders. The study analyzed patient-level information from April 2021 to May 2023 in various settings in Pakistan, focusing on young individuals diagnosed with sleep disturbances and starting therapy with benzodiazepines or alternative medications. The study used the Kaplan-Meier estimator to estimate the cumulative incidence of overdoses, Cox proportional hazards regression models to estimate hazard ratios and 95% confidence intervals, and logistic regression to estimate propensity scores. The study aimed to identify young individuals with sleep disturbances and their adherence to benzodiazepines or alternative medications. The study found that benzodiazepines, particularly those prescribed for sleep disorders, can increase the risk of drug overdose in young individuals. The adjusted 6-month risk of drug overdose was 1.6% for benzodiazepine initiators, compared to 0.6% for comparator therapy. Young adults were more likely to experience drug overdose, with a higher risk of benzodiazepine treatment.
Keywords: concern, drug overdose, benzodiazepine, dosage, sleep problems

INTRODUCTION

Sleep is essential for maintaining vital functions, such as immune and inflammation regulation, memory consolidation, energy conservation, and removing metabolic waste. The American Heart Association lists sleep as one of the eight crucial elements of cardiovascular health (1-4). The two main components of sleep are the amount and quality of sleep. A typical global healthcare issue, inadequate sleep is linked to a host of detrimental health consequences, with the complete clinical condition of chronic insomnia affecting less than 10% of the general population (5). More than 5% of adults receive a prescription for benzodiazepines, and usage is rising, mostly among middle-aged adults, whose use has climbed by almost 50% (6). However, research indicates that the highest prevalence of benzodiazepine use, 8.6%, is found among persons 65 years of age and older (7). Given the risks involved, prescribing to adults has been viewed as possibly improper for decades.

Nevertheless, as the use of benzodiazepines has increased, so too have the adverse events that are linked with them for adults of all ages. Given the higher risk of overdose and overdose death among opioid users who also receive co-prescription benzodiazepines, one area of concern has been their combination of use with opioids. However, benzodiazepines have their own set of dangers. Beyond older persons and co-prescription with opioids, concerns about the prescribing of benzodiazepines have expanded (8).

There are detrimental effects on one's health linked to insomnia. There are both pharmaceutical and nonpharmacologic treatments for insomnia; as a first line of treatment, cognitive behavioral therapy is usually advised. There are also several pharmaceutical treatments available by prescription. However, many of these, especially for longer-term care, have scant or poor quality evidence of efficacy or safety. There is even less data on the safety and tolerability of prescription insomnia medications for youngsters (under the age of 18). One class of drugs called benzodiazepines is given to treat sleep disturbances; the U.S. Food and Drug Administration has approved specific benzodiazepines for treating insomnia in adults (≥18 years of age). While benzodiazepines are often prescribed, even to children, their recommendation for insomnia in children is less prevalent than that of adults due to the lack of safety and efficacy information for lower age groups. It is advised to use benzodiazepines for no more than four weeks of treatment when prescribed for any age group (9). Benzodiazepine use disorders, overdose, and non-medical use are among the serious dangers associated with benzodiazepines (10–12).

Since the start of the prescription opioid epidemic, benzodiazepine-attributed morbidity and death have grown (16). This is because using benzodiazepines in combination with opioids and other central nervous system depressants increases the risk of overdose (13–15). Compared to 6872 overdose deaths in 2011, benzodiazepines were linked to 12290 overdose deaths in 2020 (17). People who overdose on benzodiazepines, both fatally and nonfatally, often had previous prescriptions for the drugs (18–20). Treatment with benzodiazepines was linked to a higher risk of all-cause mortality than treatment with selective serotonin reuptake inhibitors in an adult comparative safety investigation (21). Following benzodiazepine treatment for sleeplessness, there was no comparison evidence regarding the risks of drug overdose among young persons. The years of adolescence and early adulthood are crucial for assessing the risk of drug overdose following prescription benzodiazepine medication. Adolescence is often the time when people are first exposed to alcohol and other drugs. During this developmental stage, non-medical prescription drug use rises, and prescription benzodiazepine misuse increases as well; 3.8% of young adults (18–25 years old) and 1.5% of youths (12–17 years old) report having misused prescription benzodiazepines in the previous year (22). Considering that there are alternative pharmacologic therapies for sleep disorders available (23), it is crucial to investigate if treating with benzodiazepines has a higher risk of overdose when compared to alternative drugs that are frequently recommended. The majority of contemporary research on benzodiazepines has not mainly addressed benzodiazepine abuse but rather has concentrated on the misuse of tranquilizers and sedative medications in conjunction with opiate usage.

Given that older persons who have been prescribed benzodiazepines at the most excellent rates are more likely to experience adverse side effects from them and use alcohol and other substances at higher rates than previous aging cohorts, the absence of knowledge regarding abuse among this population is especially startling (24). Only one study examined the potential for benzodiazepine abuse among older

persons in the United States, according to a recent systematic review (25) of opioid and benzodiazepine usage among adults over the age of 65. Surprisingly, little is known about benzodiazepine usage despite its ubiquitous use, abuse potential (27), and associated dangers. Therefore, we set out to determine whether and to what extent recent prescription opioid use influences the association between treatment for sleep disorders in young people and benzodiazepines and the risk of drug overdose in the six months following the initiation of therapy. Our research sought to determine the associations between the risk of medication overdose and the dosage of benzodiazepines used to treat sleep disorders.

METHODS

The April 2021–May 2023 patient-level information on enrollment details, prescription drugs dispensed, and inpatient, outpatient, and emergency department (ED) medical contacts was used to identify the study cohort. The study was conducted in several settings, including the Punjab AIDS Control Programme and DHQ Hospital Pakpatan, Pakistan; the Women Medical and Dental College in Abbottabad, Pakistan; the Rehman Medical Institute in Peshawar, Pakistan; the Pakistan Atomic Energy Commission Hospital in Islamabad, Pakistan; the King Edward Medical University/Mayo Hospital in Lahore, Pakistan; and the Govt. Kot Khawaja Saeed Hospital in Lahore, Pakistan. The young participants in the study ranged in age from 14 to 35. We identified young individuals who had recently been diagnosed with a sleep disturbance and were starting therapy with benzodiazepines or another alternative medication. A one-year washout period without a previous prescription for benzodiazepines, clonidine, or an alternate pharmacologic treatment (hydroxyzine, trazodone, sedative-hypnotic Z-drugs) was used to characterize new use. Although clonidine was included in the washout phase, it was not included as an alternate pharmacologic treatment for insomnia among young adults, even though it is frequently used for sleep disturbances in younger teens. In the previous year, it was mandatory to maintain continuous enrollment with prescription drug coverage. This study was approved under expedited review by the institutional review board at Rutgers University. The reporting guidelines for observational studies, developed by strengthening the Reporting of Observational Studies in Epidemiology (STROBE), were adhered to in our report. Before starting treatment, we needed an insomnia diagnosis (International Statistical Classification of Diseases and Related Health Problems) made 25 days or less in advance. Clinical contraindications (such as sleep apnea), epilepsy diagnoses, combination therapies, starting trazodone at higher dosages, and starting treatment with one or more drug classes were among the other cohort exclusions. An active comparator design was employed. The start of alternative prescription sleep problem therapies, involving several drug classes, served as our comparator. The comparison group selection was based on treatment standards and prescribing practices, as there was no perfect comparison. In the comparator group were Z-drugs, hydroxyzine, and trazodone. Given the likelihood that they were starting trazodone (>150 mg/d) for depression, we eliminated young people. More clonidine users were added to the comparator group for sensitivity analysis. We identified drug overdose incidents from inpatient or emergency department records throughout the first six months of treatment. Both outcomes include fatal overdoses if patients are sent to an emergency department or hospital; otherwise, they mainly capture nonfatal overdose episodes. Patient-level characteristics were included to characterize the study population and act as confounders. Demographic features like age and gender were also included. In addition, we considered claims related to psychotherapy, contact with a mental health professional, and the type of physician linked to the diagnosis of sleep problems. One or more opioid prescriptions written 90 days or fewer before the commencement of benzodiazepine or comparator treatment were considered a recent opioid prescription, which was used as a stratification variable. A statistical analysis was conducted between June 1 and July 1st of 2023. We compared comparable initiators and benzodiazepines while also characterizing the research population. We calculated the duration of the treatment; discontinuation was defined as not filling a prescription for 30 days following the end of the previous prescription supply. The comparative group's definition of discontinuation was the absence of further drug prescriptions. Next, we used the Kaplan-Meier estimator to estimate the cumulative incidence of 3- and 6-month overdoses, and we used Cox proportional hazards regression models to estimate the hazard ratios (H.R.s)

and 95% confidence intervals (C.I.s). The Cox proportional hazards regression model was fitted with the inverse probability of treatment weights; no further factors were used. For adjusted H.R.s, twice as robust 95% C.I.s were computed.

RESULTS AND DISCUSSION

In Table 1, drug overdose incidents involving young individuals starting benzodiazepine or comparator medication for sleep disorders were covered. When compared to the comparison group, benzodiazepine initiators had a somewhat lower likelihood of having previous diagnoses for drug use disorders, cannabis use disorders, opioid use disorders, or suicide ideation and a higher likelihood of having recent nonspecific anxiety diagnoses. These disparities vanished once the propensity score was applied for the adjusted analysis. Before stopping their medication, the majority of participants completed one prescription (benzodiazepine group, with one fill; comparator group). For users of benzodiazepines, the median days' supply for the initial prescription was 20 (IQR, 10–30 days), whereas for the comparator group, it was 30 days (IQR, 30–30 days). Users of benzodiazepines and the comparison group continued receiving treatment three months after the commencement of the treatment, and at six months, they were still receiving treatment. Table 1 has further information below. Benzodiazepine and comparator initiators were balanced on measured variables (standardized differences, ≤0.00) in the propensity score–weighted cohort. The crude cumulative incidence of drug overdose during the 6-month follow-up was 0.8% for the comparison group and 0.4% for benzodiazepine initiators (Table 2). For young person's beginning benzodiazepine treatment for a sleep disturbance, the adjusted cumulative incidence of drug overdose at six months was 1.0% (Table 2).

Table 1: *Incident drug overdoses: Young People Initiating Benzodiazepine or Comparator Treatment for Sleep Disorder*

Characteristic	Study cohort, un-weighted			Inverse probability of treatment weighting		
	No. (%)		*p*-Value	Weighted, No (%)		*p*-Value
	Benzodiazepine initiators (n = 850)	Comparator group (n = 1240)		Benzodiazepine initiators (n = 895)	Comparator group (n = 898)	
Male	49%	48.4%	0.20	42%	40.1%	0.01
Age at treatment initiation (Years)	11.4%	16.2%	0.32	18.5%	20.2%	0.62
14-24	28.1%	12.6%	0.01	12%	14.2%	0.00
25-35	29.0%	13.4%	0.00	48.6%	50.2%	0.01
Comorbid psychiatric diagnoses, one y						
Anxiety disorder, unspecified						
Recent diagnosis (≤30 d)	39.1%	16.8%	0.42	18.1%	18.3%	0.02
Past diagnosis only (31-365 d)	4.4%	5.9%	0.02	6.5%	6.2%	0.00
Major depressive disorder						
Recent diagnosis (≤30 d)	18.9%	19.1%	0.03	19.0%	18.5%	0.01
Past diagnosis only (31-365 d)	6.2%	7.1%	0.02	6.4%	6.2%	0.01
Generalized anxiety disorder						
Recent diagnosis (≤30 d)	11.5%	7.4%	0.04	8.6%	8.6%	0.01
Past diagnosis only (31-365 d)	2.4%	2.8%	0.03	2.9%	2.7%	0.01
Other depressive disorder	5.7%	4.8%	0.04	5.3%	5.1%	0.01
Acute stress	2.8%	1.4%	0.10	1.8%	1.8%	0.00
Suicidal ideation diagnosis	1.7%	2.8%	0.04	2.6%	2.5%	0.01
Self-harm diagnosis	0.3%	0.7%	0.04	0.5%	0.6%	0.02
Cannabis use disorder	1.8%	2.4%	0.03	2.4%	2.3%	0.03
Opioid use disorder	1.1%	1.4%	0.04	1.4%	1.3%	0.01
Medications, one y						
SSRI						
Recent prescription (≤90 d)	37.4%	27.8%	0.01	30.6%	30.6%	0.00
Prior prescription only (91-365 d)	4.0%	4.3%	0.01	4.4%	4.2%	0.01
Opioid (prescription)						
Recent prescription (≤90 d)	15.2%	13.3%	0.05	14.3%	13.9%	0.01
Prior prescription only (91-365 d)	20.2%	19.5%	0.02	19.7%	19.7%	0.00
Skeletal muscle relaxant						
Recent prescription (≤90 d)	4.6%	4.4%	0.01	4.4%	4.4%	0.00

Prior prescription only (91-365 d)	5.5%	5.8%	0.01	5.8%	5.6%	0.01
SNRI	5.1%	4.6%	0.02	5.1%	4.8%	0.01
Non-SSRI or SNRI antidepressant	10.6%	9.7%	0.03	10.3%	10.1%	0.01
Stimulant	2.4%	2.8%	0.04	10.5%	10.4%	0.00
Antipsychotic	5.7%	4.8%	0.07	4.4%	4.2%	0.01
NSAID	2.8%	1.4%	0.01	21.5%	21.4%	0.00
Antihistamine	1.7%	2.8%	0.01	8.7%	8.4%	0.01
Health care use						
Inpatient psychiatric admission, one y	2.9%	4.4%	0.03	4.2%	4.0%	0.01
ED visit, recent (≤3 mo)	14.7%	12.7%	0.01	13.7%	13.3%	0.01
Psychotherapy claim, recent (≤30 d)	8.4%	8.7%	0.00	9.3%	8.7%	0.02
Psychiatry contact (≤90 d)	6.6%	7.3%	0.01	7.5%	7.1%	0.02
Other diagnoses, 1 y						
Fatigue, malaise	39.1%	36.8%	0.10	20.0%	19.9%	0.00
Migraine, headache	4.4%	5.9%	0.01	17.9%	17.6%	0.01
Low-back pain	29.1%	26.8%	0.00	9.9%	9.7%	0.01
Nonspecific chest pain	6.4%	6.9%	0.06	7.2%	7.1%	0.01
Syncope, dizziness	6.7%	5.6%	0.04	6.0%	6.0%	0.00
Pregnancy	4.7%	3.5%	0.06	3.8%	3.8%	0.00
Poisoning, adverse effect						
Recent poisoning (≤30 d)	0.9%	1.1%	0.02	1.0%	1.0%	0.00
Prior poisoning only (31-365 d)	0.8%	0.8%	0.01	0.9%	0.8%	0.00

Table 2: *The rate of drug overdose cumulatively and the risk ratio within six months of starting benzodiazepine or comparator treatment for sleep disorders*

Analytical Variables	**Cumulative Incidence %**			**H.R. (95% Cl)**
	3 Months	6 Months	Difference at six months	
Goal to Address Analysis				
Crude				
Benzodiazepine Treatment	0.4	0.8	0.2	1.11 (0.94-1.31)
Comparator Treatment	0.5	0.9	1 Ref.	1 Ref.
Adjusted				
Benzodiazepine Treatment	0.4	0.6	0.3	1.25 (1.03-1.51)
Comparator Treatment	0.5	0.5	1 Ref.	1 Ref.
Goal to address Analysis [b]				
Crude				
Benzodiazepine Treatment	0.6	1.8	0.4	1.31 (1.07-1.61)
Comparator Treatment	0.8	1.1	1 Ref.	1 Ref.
Adjusted				
Benzodiazepine Treatment	0.6	1.6	0.6	1.44 (1.14-1.80)
Comparator Treatment	0.8	1.2	1 Ref.	1 Ref.

The benzodiazepine group had an adjusted 6-month risk of drug overdose of 1.6%, while the comparator group had an adjusted 6-month risk of 0.6% in the as-treated study. The adjusted 6-month cumulative incidence of drug overdose for young individuals (14–35 years old) was 0.9% for benzodiazepine initiators and 0.6% for initiators of comparator therapy. As opposed to comparator treatment, benzodiazepine treatment was linked in the adjusted analysis for young adults to a higher risk of drug overdose (Table 3). When SIPTW was used, the results were consistent. When IPTW was used, the propensity score distribution tails were more heavily trimmed, people between the ages of 10 and 11 were omitted, and clonidine initiators were added to the comparator group (n = 4252), as shown in Table 3. More details are given below in Table 3.

Table 3: *Adjusted Results of Secondary and Sensitivity Analyses Assessing the Comparative Risk of Drug Overdose for Comparator Treatment Initiators vs. Benzodiazepine Initiators*

Secondary or sensitivity analysis	As-treated analysis	Intention-to-treat analysis
	H.R. (95% CI)	H.R. (95% CI)
Opioid prescription		
Recent opioid prescription		
Benzodiazepine treatment	2.01 (1.24-3.25)	2.07 (1.37-3.12)
Comparator treatment	1 Ref.	1 Ref.
No recent opioid prescription		
Benzodiazepine treatment	1.31 (1.00-1.70)	1.10 (0.88-1.36)
Comparator treatment	1 Ref.	1 Ref.
Age at treatment initiation		
14-35 y		
Benzodiazepine treatment	1.63 (1.25-2.12)	1.48 (1.19-1.85)
Comparator treatment	1 Ref.	1 Ref.
IPTW, extended trimming (1st percentile, 99th percentile)		
Benzodiazepine treatment	1.59 (1.26-2.01)	1.32 (1.09-1.59)
Comparator treatment	1 Ref.	1 Ref.
Age 14-35y		
Benzodiazepine treatment	1.45 (1.15-1.82)	1.26 (1.04-1.53)
Comparator treatment	1 Ref.	1 Ref.
Expanded comparison group		
Benzodiazepine treatment	1.50 (1.19-1.88)	1.29 (1.06-1.58)
Comparator treatment (with clonidine)	1 Ref.	1 Ref.
Antidepressant prescription		
Recent antidepressant prescription		
Benzodiazepine treatment	1.42 (1.05-1.92)	1.23 (0.97-1.57)
Comparator treatment	1 Ref.	1 Ref.
No recent antidepressant prescription		
Benzodiazepine treatment	1.64 (1.14-2.36)	1.32 (0.97-1.81)
Comparator treatment	1 Ref.	1 Ref.

Our findings imply that employing nonbenzodiazepine therapy may lower drug overdoses in this population. Using benzodiazepines and opioids at the same time increases the risk of overdose and death (28–30), especially in young adults and adolescents. Nonbenzodiazepine sleep medicine should be seriously explored for young individuals with insomnia who have not responded to nonpharmacologic therapies. This is especially true for those who have recently been prescribed opioids. For existing prescription opioid users seeking treatment for insomnia, cautious prescribing is required due to the increased overdose risks associated with opioid users concurrently utilizing Z-drugs (31). The more excellent correlation observed in young individuals might stem from their utilization and availability of drugs that elevate the risk of a drug overdose when combined with benzodiazepines. Given the lack of research supporting adolescent sleep aids, doctors may exercise greater caution when recommending those (32). Adolescents with more severe sleep disorders or comorbidities may benefit from this approach and be offered pharmacologic treatment for insomnia, which may be linked to their greater rate of drug overdoses. More research is necessary to examine benzodiazepine treatment and drug overdose risk within specific age groups, given the variation in treatment methods and drug overdose risk among individuals. Drug overdose incidents were noted among young individuals taking comparator medications, even though the risk of drug overdose was higher for those starting benzodiazepines. Insomnia and psychiatric disorders frequently coexist (33), which raises the possibility of an overdose. Prescription decisions should be guided by other safety concerns, even though our analysis concentrated on the danger of overdose. For instance, there is evidence linking sleep aids to suicidal thoughts and attempts (34), and Z-drugs have a boxed warning about significant harm from

complicated sleep behaviors (35). We combined young people starting Z-drugs, hydroxyzine, and trazodone to avoid estimating treatment comparisons one-to-one. When choosing a prescription drug for youth insomnia, there is clinical ambiguity. Based on assessed variables, the comparability of each medication's initiator—benzodiazepine vs. other—in our comparator group showed clinical equipoise and supported the composite comparator group. The active comparator architecture decreases potential confounding by indication. Future studies should look specifically at the hazards associated with treating sleep disorders because, as far as we know, there is little information on the possibility of overdosing on these medications in young individuals. The study on benzodiazepine overdoses has some limitations, such as a focus on overdoses addressed in hospital or emergency department settings, limiting the analysis to those with private insurance, and possible residual confounding by alcohol and drug usage. The study did not take into account specifics about benzodiazepines or changes in the overdose pandemic. Additionally, there was no clinical information available, and the study did not include youths with undefined sleep disorder diagnosis codes or insomnia. Treatment may be guided by future research.

CONCLUSION

The risk of drug overdose and the quantity of benzodiazepines given for sleep disorders are correlated, the study concludes. When managing patients' sleep disorders, it's critical to take into account the increased risk of drug overdose associated with benzodiazepine medication when weighed against alternative pharmacological regimes. Extensive knowledge of the hazards of benzodiazepines and other treatments for sleep problems is necessary during the young and the early stages of adulthood. This is due to the importance of sleep issues and the possibility that treating insomnia could prevent unfavorable consequences. Because there aren't enough large-scale head-to-head trials comparing the safety of benzodiazepines and alternative sleep aids in teenagers, choices regarding treatment for insomnia must be guided by ongoing qualitative research evaluating the relative efficacy of pharmaceutical medicines. We seek to determine the 6-month risk of drug overdose following benzodiazepine initiation of therapy for sleep problems as well as offer comparable probabilities of drug overdose between triggers of additional pharmaceutical therapies to aid in the decision to prescribe and to promote constant surveillance for this young patient group.

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