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- Exercise caution in prescribing benzodiazepines to patients with schizophrenia, given unproven efficacy and safety issues

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Benzodiazepine Use and Risk of Mortality Among Patients With Schizophrenia: A Retrospective Longitudinal Study

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ABSTRACT

Objective: This study examined the association between benzodiazepine use alone or in combination with antipsychotics and risk of mortality in patients with schizophrenia.

Methods: A retrospective longitudinal analysis was performed using Medicaid claims data merged with death certificate data for 18,953 patients (aged 18–58 years) with ICD-9–diagnosed schizophrenia followed from July 1, 2006, to December 31, 2013. Cox proportional hazard analyses were used to estimate the risk of all-cause mortality associated with benzodiazepine use; adjustment was made for a wide array of fixed and time-varying confounders, including demographics, psychiatric and medical comorbidities, and other psychotropic medications.

Results: Of the 18,953 patients diagnosed with schizophrenia, 13,741 (72.5%) were not prescribed a benzodiazepine, 3,476 (18.3%) were prescribed benzodiazepines in the absence of antipsychotic medication, and 1,736 (9.2%) were prescribed benzodiazepines in combination with antipsychotics. Controlling for a wide array of demographic and clinical variables, the hazard of mortality was 208% higher for patients prescribed benzodiazepines without an antipsychotic (HR = 3.08; 95% CI, 2.63–3.61; $P < .001$) and 48% higher for patients prescribed benzodiazepines in combination with antipsychotics (HR = 1.48; 95% CI, 1.15–1.91; $P = .002$). Benzodiazepine-prescribed patients were at greater risk of death by suicide and accidental poisoning as well as from natural causes.

Conclusions: Benzodiazepine use is associated with increased mortality risk in patients with schizophrenia after adjusting for a wide range of potential confounders. Given unproven efficacy, physicians should exercise caution in prescribing benzodiazepines to schizophrenic patients.

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Benzodiazepines are widely used in patients with schizophrenia in conjunction with antipsychotic medications for the treatment of anxiety, sleep disorders, and side effects associated with antipsychotics and for sedation in instances of agitated psychosis.^{1,2} A number of studies estimate rates of benzodiazepine usage ranging from 14% to 79% among patients with schizophrenia.^{3–6} Despite the high prevalence of benzodiazepine use, there is little evidence that these

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drugs are efficacious and safe either alone or in combination with antipsychotics in this population.⁷ There is also concern about the potential for abuse and dependence, adverse effects^{8,9} including increased risk for dementia^{10–12} and psychomotor impairments (eg, fatigue, ataxia, falls, road traffic accidents),^{13–15} cancer,¹⁶ pneumonia, and other infections.¹⁷ Most importantly, there is limited but troubling evidence suggesting that use of benzodiazepines is associated with increased mortality in patients with schizophrenia.^{18,19}

Two recent studies using linked nationwide databases of hospital treatment, medication prescriptions, and mortality registers found that benzodiazepine use was associated with increased mortality in schizophrenia. In a Finnish study¹⁸ of 2,588 patients with schizophrenia hospitalized for the first time between January 1, 2000, and December 31, 2007, benzodiazepine use was associated with a substantial increase in mortality (HR = 1.91); this increase was attributable to both suicidal (HR = 3.83) and nonsuicidal deaths (HR = 1.60). Neither the use of antidepressants nor treatment with 2 or more antipsychotics relative to monotherapy was associated with increased mortality in the same sample. A Danish study¹⁹ of antipsychotic-treated schizophrenic patients found the use of benzodiazepine derivatives with long elimination half-lives (more than 24 hours) to be associated with increased risk of natural death (HR = 1.78), whereas the concomitant use of multiple antipsychotics was not.

To the best of our knowledge, no studies have examined the effects of benzodiazepines on mortality in a US population of individuals with schizophrenia. The primary aim of this study was to examine the association between benzodiazepines either alone or in combination with antipsychotics and excess mortality among a statewide Medicaid population of patients with schizophrenia. Based on the available literature, we hypothesized that current use of benzodiazepines alone or in combination with antipsychotics would be associated with higher mortality risk.

METHODS

Overview of Study Design

A retrospective longitudinal study was used to examine the association between benzodiazepines and mortality in patients with schizophrenia. Adults with schizophrenia were followed from July 1, 2006, to December 31, 2013, unless they died or were no longer enrolled in Medicaid. Study subjects were followed for up to 6.5 years to ascertain risk for mortality. All procedures were approved by the Ohio State University Institutional Review Board.

Sample Selection

Study subjects were included based on the following criteria: (1) age of 18 to 58 years; (2) 2 or more claims for a primary diagnosis of schizophrenia (*International Classification of Diseases*, 9th Revision, Clinical Modification [ICD-CM-9] code 295) from July 1, 2007, to June 30, 2009; (3) continuous enrollment in Medicaid for an 18-month period (6 months prior to the index claim for schizophrenia

- Although benzodiazepines are widely used as adjunctive medications in the treatment of schizophrenia, the long-term effects of benzodiazepine use on mortality are unknown.
- Given unproven efficacy and safety issues, physicians should exercise caution in prescribing benzodiazepines to patients with schizophrenia.

and 12 months after the index claim); and (4) no use of benzodiazepines during the 6-month period prior to the index claim for schizophrenia. Because the focus was on outpatient treatment, we excluded all persons who were placed in a long-term institutional facility (eg, nursing home) for 3 months or more. The final sample consisted of 18,953 patients.

Data Sources

Data for this study were abstracted from 2 data sources: Ohio Medicaid claims and encounter and death certificate files. Medicaid claims data were obtained from the Ohio Department of Jobs and Families, while the death records were obtained from the Ohio Department of Health. Medicaid claims data include information on eligibility status and paid claims for prescription drugs and inpatient and outpatient services. The eligibility files included information on monthly enrollment status, eligibility category (eg, covered family and children, disabled), and demographic characteristics of enrollees (eg, age, sex, race/ethnicity, county of residence). The pharmacy files provided information on prescriptions filled by outpatient pharmacies including prescription and dispense dates, generic name and code, national drug code, dosage, day supply, and quantity. Psychotropic medications were identified from pharmacy files using the dispense date and the generic name codes. The institutional and professional files provided information on service claims for inpatient hospitalizations, physician visits (office- or hospital-based), and other outpatient services and included the dates of service, Current Procedural Terminology/Healthcare Common Procedure Coding System procedure codes, and up to 7 ICD-CM-9 diagnoses.

Information on mortality was abstracted from death certificates. Data on all causes of deaths were based on ICD-10 codes that were reported on death certificates. Medicaid claims data were linked with the death certificate file using a 4-step matching algorithm that has been used in prior research^{20–22}: (1) Social Security number (SSN), last name, first name, sex; (2) SSN, last name, first name, date of birth (month), sex; (3) SSN, first name, date of birth (month), sex; (4) SSN, first name, last name, date of birth (month and year), sex.

Measures

Outcome measures. The primary outcome measure was time to death or the end of the study in cases of censored

Table 1. Demographic and Clinical Characteristics of Adults With Schizophrenia by Mortality Status^a

Variable	All Subjects (N = 18,953)	No Benzodiazepine (n = 13,741)	Benzodiazepine Only (n = 3,476)	Benzodiazepine Polypharmacy (n = 1,736)
Mortality	1,877 (9.9)	1,346 (9.8)	368 (10.6)	163 (9.4)
Demographic				
Age, mean (SD), y	42.3 (10.4)	42.4 (10.3)	42.5 (10.3)	41.5 (10.9)
Race				
Non-Hispanic white	10,822 (57.1)	7,471 (54.4)	2,277 (65.5)	1,074 (61.9)
Non-Hispanic black	7,703 (40.6)	5,972 (43.5)	1,116 (32.1)	615 (35.4)
Other ^b	428 (2.3)	298 (2.2)	83 (2.4)	47 (2.7)
Gender				
Male	11,072 (58.4)	8,489 (61.8)	1,772 (51.0)	811 (46.7)
Female	7,881 (41.6)	5,252 (38.2)	1,704 (49.0)	925 (53.3)
Marital status				
Single	12,675 (67.2)	9,316 (67.8)	2,291 (65.9)	1,068 (61.5)
Married	838 (4.4)	571 (4.2)	173 (5.0)	94 (5.4)
Divorced/separated	3,448 (18.3)	2,234 (16.3)	774 (22.3)	440 (25.3)
Widowed	261 (1.4)	164 (1.2)	52 (1.5)	45 (2.6)
Unknown	1,731 (9.2)	1,456 (10.6)	186 (5.3)	89 (5.1)
Residence				
Non-metro	2,774 (14.6)	1,858 (13.5)	609 (17.5)	307 (17.7)
Metro	16,179 (85.4)	11,883 (86.5)	2,867 (82.5)	1,429 (82.3)
Months of enrollment, median (IQR)	72 (57–73)	72 (53–73)	72 (62–74)	72 (68–74)
Clinical				
Psychiatric comorbidities				
Substance abuse	4,921 (26.0)	3,323 (24.2)	1,040 (29.9)	558 (32.1)
Anxiety disorder	1,266 (6.7)	755 (5.5)	317 (9.1)	194 (11.2)
Depressive disorder	1,657 (8.7)	997 (7.3)	416 (12.0)	244 (14.1)
Bipolar disorder	3,128 (16.5)	1,909 (13.9)	797 (22.9)	422 (24.3)
Other mental health disorders ^c	5,191 (27.4)	3,361 (24.5)	1,199 (34.5)	631 (36.4)
Charlson Comorbidity Index score				
0	14,725 (77.7)	11,027 (80.2)	2,516 (72.4)	1,182 (68.1)
1	2,921 (15.4)	1,928 (14.0)	636 (18.3)	357 (20.6)
2	776 (4.1)	459 (3.3)	196 (5.6)	121 (7.0)
≥3	531 (2.8)	327 (2.4)	128 (3.7)	76 (4.4)
Any prior hospitalizations	4,236 (22.4)	2,766 (20.1)	975 (28.1)	495 (28.5)
Comedication				
Any antidepressant	4,175 (22.0)	2,413 (17.6)	748 (21.5)	1,014 (58.4)
Any mood stabilizer	4,634 (24.4)	2,616 (19.0)	844 (24.3)	1,174 (67.6)
Any antiparkinson drug	4,768 (25.2)	2,894 (21.1)	908 (26.1)	966 (55.6)
Any hypnotic	1,628 (8.6)	718 (5.2)	366 (10.5)	544 (31.3)

^aValues shown as n (%) unless otherwise noted.^bOther race includes Hispanic, Asian, Native American, multiple races, and other non-Hispanic.^cOther mental health diagnosis includes all diagnoses between ICD-CM-9 codes 290 and 319 not included in other categories.

Abbreviation: IQR = interquartile range.

data. The secondary outcome measures were deaths due to suicide and accidental poisoning and deaths due to natural causes. Data on all causes of death were based on ICD-10 codes that were recorded in death certificates.

Key explanatory variable. The key explanatory variable was a 3-level variable coded as 0 = no benzodiazepines, 1 = benzodiazepine alone, and 2 = benzodiazepine and antipsychotic polypharmacy. For the purpose of this study, polypharmacy was defined as any overlapping prescription fills for an antipsychotic medication and benzodiazepine for 60 days or more.

Covariates. Fixed and time-varying covariates were used to measure relevant demographic, clinical, and treatment characteristics. Demographic variables included the patient's age (18–30, 31–40, or 41–58 years), sex, race/ethnicity (white, black, or other), marital status (single, married, separated/divorced, or widowed), area of residence (metro or non-metro), and months of enrollment. Based on claims in the

6 months prior to the index diagnosis date, subjects were classified as having treatment for substance abuse disorder (ICD-9-CM 291, 292, and 303–305), anxiety disorder (ICD-9-CM 300.00, 300.2, 300.3, and 308.3), depressive disorder (ICD-9-CM 296.2, 296.3, 300.4, and 311), bipolar disorder (ICD-9-CM 296.0, 296.1, 296.4–296.9, and 301.13), and other mental health disorders (ICD-9-CM 290–319 except as noted previously). The Charlson Comorbidity Index²³ was used to capture medical comorbidities. Comedications were treated as time-varying covariates and included the use of antidepressants, mood stabilizers (includes both anticonvulsants and lithium), antiparkinson drugs, and hypnotics.

Statistical Analysis

Cox proportional hazard regression with time-varying drug use was used to establish the association between benzodiazepines alone or in combination with antipsychotics

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Table 2. Hazard Ratios (HRs) of the Association Between Benzodiazepine Use and Mortality

Drug	n	Unadjusted			Adjusted ^a		
		HR	95% CI	P Value	HR	95% CI	P Value
No benzodiazepine	13,741	1.00	...	...	1.00	...	...
Benzodiazepine only	3,476	2.56	2.19–2.98	<.001	3.08	2.63–3.61	<.001
Benzodiazepine polypharmacy	1,736	1.44	1.14–1.83	.002	1.48	1.15–1.91	.002

^aThe hazard ratios for the model are adjusted for antidepressant use, anticonvulsant use, lithium use, antiparkinson drug use, hypnotic use, age, race, gender, residence, months enrolled in the study, substance abuse, anxiety disorder, depressive disorder, bipolar disorder, other mental health disorders, Charlson Comorbidity Index score, and any prior hospitalization.

Symbol: ... = not applicable.

and all-cause mortality. By using the start and stop dates of the benzodiazepines alone or benzodiazepines in combination with antipsychotics and no benzodiazepines by default, we were able to set up a database in which we knew the status (either on or off) of these drugs at all possible time points. In addition, this database was generated simultaneously with all of the start and stop dates of antidepressants, anticonvulsants, mood stabilizers, antiparkinson drugs, and hypnotic drugs. Thus, we had the status (either on or off) of these additional drugs. The stop date was based on the length of the prescription relative to the fill date (coded the start date for these analyses), plus an additional 30 days were added to the stop date to allow for drug washout. Using the Cox model, we ran an unadjusted analysis using only the 3 benzodiazepine states (none, alone, or in combination with antipsychotics) as the risk factor. An adjusted analysis was run using benzodiazepine states, antidepressants, anticonvulsants, lithium, antiparkinson drugs, and hypnotic time-varying drugs and the fixed variables mentioned previously in the Covariates section.

Several subpopulations of the database were created for specific combinations of antipsychotic and benzodiazepines. In each of these subpopulations, the subjects all had the same combination of antipsychotic use, antidepressant use, and mood stabilizers. We generated mortality incidence rates per 1,000 person-years of follow-up for these subpopulations along with the 95% confidence intervals for those with and without benzodiazepine use. All analyses were run using Stata 13.1 (StataCorp LP, College Station, TX).²⁴

RESULTS

Table 1 shows the demographic and clinical characteristics for the overall study sample and by benzodiazepine use. The mean age of the patients was 42.3 (SD = 10.4) years; 57.1% were non-Hispanic white, 40.6% were non-Hispanic black, and 2.3% were of other racial and ethnic backgrounds; 58.4% were male; and 67.2% were single. The median number of months of enrollment was 72 (IQR = 57–73). Of the 18,953 patients diagnosed with schizophrenia, 13,741 (72.5%) were not prescribed a benzodiazepine, 3,476 (18.3%) were prescribed benzodiazepines alone, and 1,736 (9.2%) were prescribed benzodiazepines in combination with antipsychotics. Nearly 1 in 10 of the patient sample died during the study period. Patients who

were prescribed benzodiazepines alone or in combination with antipsychotics were more likely to be non-Hispanic white, female, separated, and divorced. The groups prescribed benzodiazepines, particularly in combination with antipsychotics, also had higher rates of psychiatric and medical comorbidities than nonusers of benzodiazepines and received more prescriptions for other psychotropic drugs (Table 1). During the 6-year follow-up period, 5,212 patients (27.5%) were prescribed benzodiazepines, the most common being lorazepam (55.7%, n = 2,904), clonazepam (42.1%, n = 2,196), and alprazolam (15.5%, n = 810).

Table 2 presents the unadjusted and adjusted hazard ratios (HRs) from the Cox proportional hazard analysis of the association between benzodiazepines and all-cause mortality. Controlling for a broad array of demographic and clinical variables, the hazard of mortality was 208% higher for patients who were prescribed benzodiazepines without an antipsychotic (HR = 3.08; 95% CI, 2.63–3.61; $P < .001$) and 48% higher for patients prescribed benzodiazepines in combination with antipsychotics (HR = 1.48; 95% CI, 1.15–1.91; $P = .002$). The HR for suicide and accidental poisoning was 180% higher for patients prescribed benzodiazepines only (HR = 2.80; 95% CI, 1.45–5.42; $P = .002$) and 296% higher for patients prescribed benzodiazepines in combination with antipsychotics (HR = 3.96, 95% CI, 2.06–7.63, $P < .001$). For deaths by natural causes, the HR was 215% higher for patients prescribed benzodiazepines only (HR = 3.15; 95% CI, 2.68–3.71; $P < .001$) and 33% higher for patients prescribed benzodiazepines in combination with antipsychotics (HR = 1.33; 95% CI, 1.01–1.75; $P = .04$).

Given previous literature regarding associations between benzodiazepines and specific causes of death,^{11,16,17} we conducted an exploratory analysis and found that, among the benzodiazepine-treated groups, the crude proportion of patients dying from infectious diseases, nervous disorders, and diseases of the respiratory and digestive systems was higher compared to the non-benzodiazepine group. Accidental poisoning was also notably higher in the benzodiazepine groups compared to the non-benzodiazepine group.

Table 3 shows polypharmacy treatment patterns by benzodiazepine use and total mortality rates. In all examined combinations of antipsychotics, antidepressants, and mood stabilizers, mortality rates were twice as high for benzodiazepine-treated subjects compared to those who did not receive a benzodiazepine.

Table 3. Polypharmacy Treatment Patterns and Total Mortality Rates

Polypharmacy Combination Pair	No. of Deaths	Person-Years	Mortality Rate per 1,000 Person-Years	95% CI
No antipsychotic, antidepressant, or mood stabilizer				
With no benzodiazepine use	846	45,314	18.7	17.5–20.0
With benzodiazepine use	110	2,775	39.6	32.9–47.8
Antidepressant and mood stabilizer (no antipsychotic)				
With no benzodiazepine use	881	47,360	18.6	17.4–19.9
With benzodiazepine use	115	2,920	39.4	32.8–47.3
Antidepressant (no antipsychotic or mood stabilizer)				
With no benzodiazepine use	863	46,075	18.7	17.5–20.0
With benzodiazepine use	111	2,810	39.5	32.8–47.6
Mood stabilizer (no antipsychotic or antidepressant)				
With no benzodiazepine use	859	46,052	18.7	17.4–19.9
With benzodiazepine use	112	2,847	39.3	32.7–47.3
1 antipsychotic (no antidepressant or mood stabilizer)				
With no benzodiazepine use	953	50,584	18.8	17.7–20.1
With benzodiazepine use	116	2,956	39.2	32.7–47.1
1 antipsychotic and antidepressant (no mood stabilizer)				
With no benzodiazepine use	1,011	54,123	18.7	17.6–19.9
With benzodiazepine use	129	3,150	41.0	34.5–48.7
1 antipsychotic and mood stabilizer (no antidepressant)				
With no benzodiazepine use	881	47,360	18.6	17.4–19.9
With benzodiazepine use	115	2,920	39.4	32.8–47.3
1 antipsychotic, antidepressant, and mood stabilizer				
With no benzodiazepine use	1,101	61,169	18.0	17.0–19.1
With benzodiazepine use	147	3,673	40.0	34.1–47.0
≥ 2 antipsychotics (no antidepressant or mood stabilizer)				
With no benzodiazepine use	969	54,261	17.9	16.8–19.0
With benzodiazepine use	120	3,119	38.5	32.2–46.0
≥ 2 antipsychotics and antidepressant (no mood stabilizer)				
With no benzodiazepine use	1,090	62,122	17.5	16.5–18.6
With benzodiazepine use	140	3,720	37.6	31.9–44.4
≥ 2 antipsychotics and mood stabilizer (no antidepressant)				
With no benzodiazepine use	1,101	63,314	17.4	16.4–18.4
With benzodiazepine use	148	4,094	36.2	30.8–42.5
≥ 2 antipsychotics, antidepressant, and mood stabilizer				
With no benzodiazepine use	1,402	83,918	16.7	15.9–17.6
With benzodiazepine use	223	6,954	32.1	28.1–36.6

DISCUSSION

Benzodiazepines are commonly prescribed to patients diagnosed with schizophrenia, with just over one-fourth of the 18,953 patients in this population-based study receiving treatment that included a benzodiazepine. Given how commonly benzodiazepines are prescribed to schizophrenic patients, our finding that benzodiazepine use, both alone and in combination with antipsychotics, is associated with an increased risk of all-cause mortality is particularly troubling. These findings confirm the results of 2 European studies^{18,19} that have investigated the use of benzodiazepines and mortality in schizophrenia. Although the research designs differ, our results are strikingly similar in terms of the direction and magnitude of effects. In the case of schizophrenic patients prescribed benzodiazepines without an antipsychotic, the hazard of death in the current study was over 3 times higher compared to those not treated with benzodiazepines, even after adjusting for a wide range of potential confounding variables, including physical and psychiatric comorbidities and other psychotropic

medications. The risk conferred by benzodiazepine use was significant regardless of whether death was accidental, self-inflicted, or due to “natural causes.” For example, the risks of death classified as due to suicide and accidental poisoning were higher for benzodiazepine users than for nonusers. Similarly, a higher proportion of patients taking benzodiazepines died of infectious diseases, nervous disorders, and diseases of the respiratory and digestive systems in the current study in comparison to those who were benzodiazepine free.

A simple explanation for the observed association between benzodiazepine use and all-cause mortality is not forthcoming, as benzodiazepine-treated patients appear at greater risk to die by suicide and self-poisoning as well as “natural causes.” Prior research suggests that benzodiazepines are associated with increased risk for infectious diseases,^{17,25} and our results provide some support for these findings. Some have hypothesized that benzodiazepines attenuate the immune response, potentially increasing the risk for infectious diseases and cancer.^{26,27} Although the exact mechanisms are unknown, animal

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studies suggest that benzodiazepines increase susceptibility to infection, including pneumonia, perhaps via activation of GABA_A receptors on immune cells.^{28–32} In the case of suicide and accidental poisoning, benzodiazepines may increase the likelihood of impulsive responding and dysphoric mood, potentially increasing the risk for self-injury. For example, in a study of antidepressant-treated adolescents with resistant depression, the use of adjunctive benzodiazepines was found to be associated with a heightened risk for self-harm and suicidal adverse events.³³ Use of benzodiazepines may cause disinhibition and increase vulnerability to violent and high-risk behaviors such as suicide.²⁷ Suicide has been reported as a common outcome in chronic benzodiazepine dependence,^{34,35} and discontinuation of long-term benzodiazepine use may exacerbate anxiety and distress, potentially contributing to suicidal behavior.

With regard to clinical implications, this study in combination with previous work suggests that the routine, ongoing prescription of benzodiazepines in schizophrenia should be discouraged in the absence of additional, prospective study, or at the very least approached with caution. Whether brief, targeted use of benzodiazepines in high-acuity clinical situations should be reevaluated is unclear given this study's reliance on claims data. Our findings nevertheless suggest that the ongoing prescription of benzodiazepines to patients with schizophrenia should be undertaken only after serious reflection on the balance between potential risks and benefits and appropriate informed consent. Patients, family members, and caregivers should be educated with regard to potential mortality risks associated with benzodiazepine use.

Strengths and Limitations

The strengths of this study include: (1) a large population-based sample of patients with schizophrenia; (2) longitudinal analysis of benzodiazepine use at all time points during the course of the study; (3) control of multiple confounders including demographics, psychiatric and medical comorbidities, and use of other psychotropic medications;

and (4) drug data based on prescription data rather than self-report, which is subject to recall bias. However, several limitations need to be considered. First, because the data are from a single state Medicaid population, study findings may not be generalizable to other state programs or non-Medicaid populations, although there is no reason to believe that these results would not be typical. Second, because of the observational nature of the data, it is not possible to infer causality. Third, although we controlled for a wide range of potential confounders, it is impossible to exclude confounding arising from unmeasured factors or measurement error. For example, we were unable to control for lifestyle factors such as smoking and obesity, which may be associated with mortality. Fourth, we must acknowledge that the rationale for benzodiazepine treatment in this observational sample is unclear. One potential concern is that a benzodiazepine may have been initiated in the course of a serious medical illness as a confounder, though our impression on review of the data is that the preponderance of use appeared to be for purely psychiatric reasons. Fifth, diagnoses of schizophrenia were based on claims-based data and were not subject to expert validation through standardized diagnostic procedures. Finally, although pharmacy claims are considered reliable and avoid problems of recall bias associated with self-reports, they do not measure actual consumption of medication.

CONCLUSIONS

Benzodiazepines are commonly prescribed as adjunctive medications in the treatment of schizophrenia. In this population-based study, we found that benzodiazepine use alone or in combination with antipsychotic medications was strongly associated with increased risk for mortality in patients with schizophrenia after adjusting for a wide range of potential confounders. Given the lack of efficacy and apparent safety issues with benzodiazepine use, physicians should exercise caution when considering the routine prescription of benzodiazepines in this vulnerable patient population.

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POSTTEST

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1. Results of this study showed that the use of benzodiazepines in patients with schizophrenia was associated with an increased risk of dying from all the following **except**:
 - a. Infectious disease
 - b. Cancer
 - c. Suicide
 - d. Diseases of the respiratory system
2. A 29-year-old man with schizophrenia is brought to the emergency department with purposeless agitation, signs of autonomic instability, and a low grade fever suggesting catatonia. Initial medical evaluation is unremarkable, and there is no history suggesting substance abuse or withdrawal. You obtain informed consent from the guardian and order a single dose of lorazepam, but a resident asks about the association of benzodiazepines with increased mortality in schizophrenia. Which of the following responses is most appropriate?
 - a. Cancel the lorazepam order and administer intramuscular haloperidol
 - b. Cancel the lorazepam order and repeat the urine drug screen
 - c. Explain that the observed association does not imply causality and discuss how your risk-benefit assessment supports the use of lorazepam in this situation
 - d. Cancel the lorazepam order and administer a test dose of diphenhydramine