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Drug Abuse Warning Network

The DAWN Report

December 18, 2014

Benzodiazepines in Combination with Opioid Pain Relievers or Alcohol: Greater Risk of More Serious ED Visit Outcomes

Benzodiazepines, such as alprazolam (Xanax®), diazepam (Valium®), clonazepam (Klonopin®), and lorazepam (Ativan®), depress central nervous system (CNS) activity and are used to relieve symptoms of anxiety, panic attacks, and seizures.[1,2] They have been deemed safe and effective when taken as prescribed and directed. However, when combined with other drugs that depress CNS activity, such as alcohol or opioid pain relievers like oxycodone (OxyContin®), hydrocodone (Vicodin®), hydromorphone (Dilaudid®), or morphine, benzodiazepines may present serious or even life-threatening problems. Concerns exist about the increasing number of patients prescribed both benzodiazepines and opioids and about serious complications arising from the use of benzodiazepines with alcohol.[3,4] This report quantifies the increased risk of more serious outcomes such as hospitalization or, rarely, death in the emergency department (ED), when benzodiazepines are combined with alcohol or opioid pain relievers.

The Drug Abuse Warning Network (DAWN) was a public health surveillance system that monitored drug-related ED visits in the United States. To be a DAWN case, an ED visit must have involved a drug, either as the direct cause of the visit or as a contributing factor. This report considers four drug combinations: benzodiazepines alone, benzodiazepines and opioids, benzodiazepines and alcohol, and benzodiazepines, opioids, and alcohol. Visits involving any substance other than these three drugs were excluded. Visits involving suicide attempts or malicious poisonings were also excluded as the intent in these visits is to do harm—an intention that would bias such visits toward more serious outcomes. Visits involving patients seeking drug detoxification were also excluded, as admissions resulting from these visits may not reflect the seriousness of a patient's condition at the time of his or her ED visit.

IN BRIEF

During the 7 years from 2005 to 2011, almost a million (an estimated 943,032) emergency department (ED) visits involved benzodiazepines alone or in combination with opioid pain relievers or alcohol and no other substances.

The predicted risk of a more serious outcome (hospitalization or, rarely, death in the ED rather than treatment and release), was greater than 20 percent for all age categories for benzodiazepines alone. This result shows that ED visits involving benzodiazepines alone pose a significant risk of a more serious outcome, even without combination with other drugs.

Combinations of benzodiazepines with opioid pain relievers or alcohol were associated with a 24 to 55 percent increase in the predicted risk of a more serious outcome compared with benzodiazepines alone.

Increasing age was associated with increasing predicted risk of a more serious outcome for visits involving benzodiazepines alone or in combination with opioid pain relievers or alcohol and no other substances.

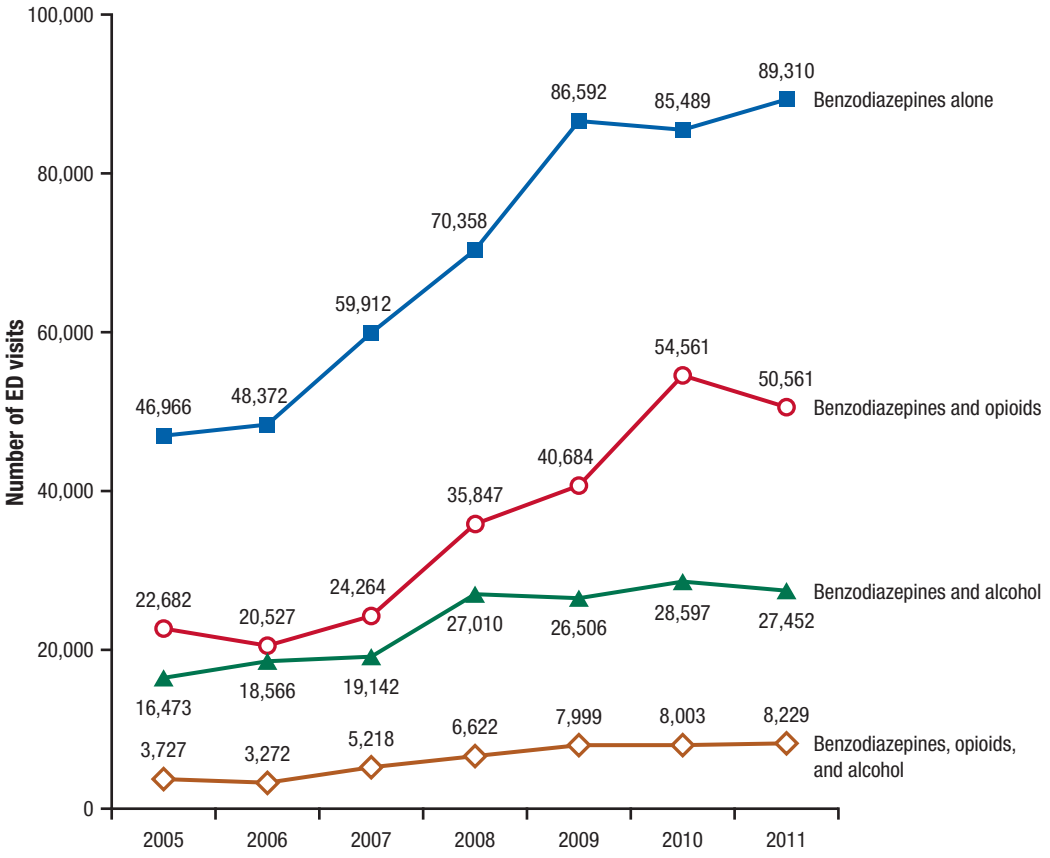
Methodology

Logistic regression is a statistical method used to determine if there is a relationship (that is, an association) between an outcome with two possibilities and a known characteristic, such as gender. All ED visit outcomes were grouped into two categories for this report: (1) "less serious outcomes" indicated that the patient was treated and released to home, to police custody, or with a referral to another provider, and (2) "more serious outcomes" indicated admission to the same hospital where the ED was located (any department), transfer to another medical facility, or death.[5,6,7]

This report uses logistic regression to examine the association between ED visit outcome and the four drug combinations discussed above, patient age, gender, and the year in which the visit occurred. Data from 2005 to 2011 were combined to ensure adequate sample size; however, there were two concerns. First, there has been an increasing preference for prescribing alprazolam over time, which may carry a higher risk of complications than other benzodiazepines and which may have changed the association of benzodiazepines with ED visit outcome.[8] Second, the introduction in 2010 of a tamper-resistant formulation for the extended-release formulations of the widely prescribed opioid pain reliever oxycodone may have reduced the incidence of this drug's abuse.[9]

Figure 1 shows trends from 2005 to 2011 for each drug combination. Year of collection was included in the

Figure 1. Estimated number of emergency department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol,* by year and drug combination (patients aged 12 and older): 2005 to 2011



* No other drugs were involved.

Source: 2005 to 2011 SAMHSA Drug Abuse Warning Network (DAWN).

initial logistic regression models in order to explore the possibility that combining data from different years might have obscured the effects of changes over time. Year of collection did not have a statistically significant association with predicted ED visit outcome; therefore, it seemed unlikely that combining data from 2005 to 2011 caused associations of the drug combinations with visit outcome to go undetected over that time period.

Gender was not found to have a significant association with ED visit outcome once age and drug combination were controlled for, but ED visit outcome was significantly associated with age. Based on examination of associations with outcome, age groups were collapsed into four categories: aged 12 to 34, aged 35 to 44, aged 45 to 64, and aged 65 or older. (Visits by patients aged 11 or younger were excluded from this report.) The final models used in this report estimated the association between ED visit outcome and the four drug combinations, the four age categories, and the interaction of the drug combinations and age categories for visits involving benzodiazepines combined with opioids or alcohol.

Overview

A sample of over 58,000 patient visits collected by DAWN between 2005 and 2011 represented an estimated 943,032 visits that were analyzed for this report. The estimated total number of ED visits from 2005 to 2011 is shown in Table 1 by age group and drug involvement.[10]

Table 1. Estimated number of emergency department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol,* 2005 through 2011, by drug combination and age (patients aged 12 and older)

Drug combination	Aged 12 to 34	Aged 35 to 44	Aged 45 to 64	Aged 65 or older
Benzodiazepines alone	174,998	88,644	150,780	72,575
Benzodiazepines and opioids	90,225	48,471	90,256	20,175
Benzodiazepines and alcohol	63,155	42,783	53,454	4,447
Benzodiazepines, opioids, and alcohol	16,662	11,098	13,532	1,777

* No other drugs were involved.

Source: 2005 to 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Risk of More Serious Outcomes

Overall, 62 percent of visits involving benzodiazepines combined with opioids or alcohol resulted in a less serious outcome, and 38 percent resulted in a more serious outcome. The logistic regression model discussed above was used to predict risk of a visit resulting in a more serious outcome. In this case, risk is simply the proportion of individuals who experience a more serious outcome. Table 2 shows this risk by age and drug combination. For example, Tables 1 and 2 show that in the estimated 174,998 ED visits among patients aged 12 to 34 involving a benzodiazepine alone, patients faced a predicted 28 percent risk of a more serious outcome. In other words, the model predicts that 28 percent of such visits will result in a more serious outcome, and 72 percent will result in a less serious outcome. The estimated 90,225 patients aged 12 to 34 who combined a benzodiazepine with an opioid faced a 37 percent risk of a more serious outcome.

Table 2. Predicted risk (in percent) of a more serious outcome* from emergency department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol, 2005 through 2011, by drug combination and age (patients aged 12 and older)**

Drug combination	Aged 12 to 34	Aged 35 to 44	Aged 45 to 64	Aged 65 or older
Benzodiazepines alone	28%	30%	37%	39%
Benzodiazepines and opioids	37%	43%	47%	59%
Benzodiazepines and alcohol	35%	43%	51%	55%
Benzodiazepines, opioids, and alcohol	39%	47%	57%	70%

* All estimated risks are statistically significantly greater than 20% at the .05 level.

** No other drugs were involved.

Source: 2005 to 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Comparing the Association of Drug Combinations and Patient Age with ED Visit Outcome

To compare the associations between the ED visit outcome and two different drug combinations or two different age groups, one may calculate a ratio of the appropriate risks. Tables 3 and 4 show these risk ratios for different age groups within each drug combination and different drug combinations within each age group.

For example, Table 3 shows that for visits involving only benzodiazepines, the predicted risk ratio of a more serious outcome between patients aged 65 or older and those aged 12 to 34 is 1.36. This means that patients aged 65 or older faced a 36 percent greater risk of a more serious outcome than patients aged 12 to 34 even though both groups had taken benzodiazepines alone. In another example, Table 4 shows that for patients aged 12 to 34, the predicted risk ratio of a more serious outcome for a visit involving a benzodiazepine with alcohol versus a visit involving a benzodiazepine alone was 1.24. This means that the predicted risk of a more serious outcome increased by 24 percent, from the 28 percent shown in Table 2 when a visit made by a patient aged 12 to 34 involved a benzodiazepine alone to the 35 percent shown in Table 2, when a visit made by a patient aged 12 to 34 involved benzodiazepines combined with alcohol.

In general, a risk ratio of 1 indicates that the risk of a more serious outcome is the same for the two groups being compared. For example, if the predicted risk of a more serious outcome is the same for males and females, then the risk ratio for males versus females would be 1. Only predicted risk ratios that are statistically significantly greater than 1 at the .05 level are shown in Tables 3 and 4.[11] However, the lack of statistical significance does not necessarily mean that there is no difference in risk between two age groups or drug combinations and an ED visit outcome. It may simply be the case that there were insufficient visits with the drug combinations and age groups to give the level of confidence needed to publish a result. For this reason, the reader is cautioned

Table 3. Predicted marginal risk ratios of a more serious outcome for emergency-department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol,* 2005 through 2011, age categories within drug combinations (patients aged 12 and older)

Age group	Benzodiazepines only	Benzodiazepines and opioids	Benzodiazepines and alcohol	Benzodiazepines, opioids, and alcohol
65 or older vs. 12 to 34	1.36	1.59	1.57	**
65 or older vs. 35 to 44	1.28	1.37	**	**
65 or older vs. 45 to 64	**	1.27	**	**
35 to 44 vs. 12 to 34	**	**	**	**
45 to 64 vs. 12 to 34	1.29	1.25	1.47	**
45 to 64 vs. 35 to 44	1.21	**	1.20	**

* No other drugs were involved.

** The predicted risk ratio was not significantly greater than 1 at the .05 level.

Source: 2005 to 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Table 4. Predicted marginal risk ratios of a more serious outcome for emergency-department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol,* 2005 through 2011, drug combinations within age category (patients aged 12 and older)

Drug combination	Aged 12 to 34	Aged 35 to 44	Aged 45 to 64	Aged 65 or older
Benzodiazepines, opioids, and alcohol vs. benzodiazepines only	1.38	1.55	1.55	**
Benzodiazepines, opioids, and alcohol vs. benzodiazepines and opioids	**	**	**	**
Benzodiazepines, opioids, and alcohol vs. benzodiazepines and alcohol	**	**	**	**
Benzodiazepines and opioids vs. benzodiazepines only	**	1.43	1.27	1.54
Benzodiazepines and alcohol vs. benzodiazepines only	1.24	1.43	1.41	1.42
Benzodiazepines and alcohol vs. benzodiazepines and opioids	**	**	1.10	**

* No other drugs were involved.

** The predicted risk ratio was not significantly greater than 1 at the .05 level.

Source: 2005 to 2011 SAMHSA Drug Abuse Warning Network (DAWN).

against using Table 2 to calculate risk ratios. If sufficient evidence exists to assert that the risk ratio is different from 1, then the predicted risk ratio is shown in Tables 3 and 4.

Discussion

Combining benzodiazepines with opioid pain relievers or alcohol significantly increases the risk of a more serious ED visit outcome. This is true when no other drugs are present and across age groups. Further, older patients experience increased risk of a more serious outcome, even for visits involving benzodiazepines alone. There was insufficient statistical power to state confidently that the presence of all three drugs increased the risk of a more serious outcome.

Most of the age/drug combination categories contain relatively large numbers of ED visits. The risks of more serious outcomes associated with visits involving only benzodiazepines are statistically significantly greater than 20 percent for all four age groups. Together, these facts suggest that individuals are at risk and that the baseline risks are high enough to suggest a public health concern. Further, the predicted risk ratios suggest that combining benzodiazepines with opioid pain relievers or alcohol increases the risk of a more serious outcome sufficiently to warrant concern.

The increased risks reported here complement recent findings showing that the annual number of patients prescribed benzodiazepines, as well as the number prescribed both benzodiazepines and opioids, have increased over the past decade.[3] Increased awareness among prescribers and patients of the risks of combining these medications may help to reduce ED visits and hospitalizations and prevent deaths.

Not all visits involving benzodiazepines combined with opioids are a result of prescribing practices. Sometimes patients take more than the prescribed dose of a medication, either because they perceive that the prescribed dose is not effective in controlling their symptoms or because they enjoy the effects of larger doses. Researchers have described the practice of combining benzodiazepines and opioids as both ubiquitous and substantial.[12] They report that drug users take benzodiazepines to enhance the high associated with abuse of opioids.

The increase in the number of individuals taking benzodiazepines and combining them with other drugs, along with the risks associated with such combinations, suggests that prescribers need more information about reducing such risks. Patients may require additional reminders to read the warning labels on benzodiazepines and opioids that advise against combining them with alcohol. Further, the findings add urgency to efforts to stem the abuse of prescription opioids.

End Notes

1. Pfizer, Inc. (2011). *Xanax® alprazolam tablets, USP*. (2011). http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018276s044,021434s006lbl.pdf
2. Roche. (2009). *Klonopin® tablets (clonazepam) Klonopin® wafers (clonazepam orally disintegrating tablets)*. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017533s045,020813s005lbl.pdf
3. Kao, M.-C., Zheng, P., & Mackey, S. (2014, March). *Trends in benzodiazepine prescription and co-prescription with opioids in the United States, 2002–2009*. Poster presented at the annual meeting of the American Academy of Pain Medicine, Phoenix, Arizona. Retrieved from http://www.painmed.org/2014posters/abstract-109/
4. Gudin, J. A., Mogali, S., Jones, J. D., & Comer S. D. (2013). Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgraduate Medicine, 125*(4), 115–130.
5. Outcome in DAWN was an imperfect measure of the association of a substance or substances or age with the seriousness of an ED visit. In DAWN, information on co-morbidities that may have affected admission or mortality was limited to diagnoses in the ED record. DAWN also did not collect information on the insurance status of patients, which may also have affected the decision to admit.
6. DAWN captured only those deaths occurring in the ED. Deaths before arrival in the ED or after the patient leaves the ED were not recorded in the DAWN ED sample. For a number of reasons, deaths occurring in the ED itself are rare (an estimated 0.28 percent of visits included in this analysis ended with the patient dying in the ED); thus, insufficient visits were available to support a separate analysis of this outcome. The relatively small categories “not documented,” “other,” and “left against medical advice” were excluded as it was not possible to determine the seriousness of the outcome in those visits.
7. Jones, C. M., Paulozzi, L. J., & Mack, K. A. (2014). Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths—United States, 2010. *MMWR Weekly, 63*(40), 881–885.

8. IMS Health. (2013). Top 25 medicines by dispensed prescriptions (U.S.). Retrieved from http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/2012_U.S/Top_25_Medicines_Dispensed_Prescriptions_U.S..pdf

9. Food and Drug Administration. (2010, April). Oxycontin–Questions and answers. Retrieved from http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm207196.htm

10. Separation of the visits in which patients took their own medication as prescribed and without alcohol from other visits was explored, but there were too few visits to support separate estimates and predictions with the desired level of precision.

11. Risk comparisons were shown in such a way that increased risks from combining substances or increasing age would result in risk ratios greater than 1. If the risks were inverted they would be less than 1 and would show the decrease in risk from not combining other drugs with a benzodiazepine or from being younger.

12. Jones, J. D., Mogali, S., & Comer, S. D. (2012). Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug and Alcohol Dependence, 125*(1–2), 8–18.

Suggested Citation

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (December 18, 2014). *The DAWN Report: Benzodiazepines in Combination with Opioid Pain Relievers or Alcohol: Greater Risk of More Serious ED Visit Outcomes.* Rockville, MD.

The Substance Abuse and Mental Health Services Administration (SAMHSA) is the agency within the U.S. Department of Health and Human Services that leads public health efforts to advance the behavioral health of the nation. SAMHSA's mission is to reduce the impact of substance abuse and mental illness on America's communities.

The Drug Abuse Warning Network (DAWN) was a public health surveillance system that monitored drug-related morbidity and mortality. DAWN used a probability sample of hospitals to produce estimates of drug-related emergency department (ED) visits for the United States and selected metropolitan areas annually from 2004 to 2011. DAWN also produced annual profiles of drug-related deaths reviewed by medical examiners or coroners in selected metropolitan areas and states through 2010.

Any ED visit related to recent drug use was included in DAWN. All types of drugs—licit and illicit—were covered. Alcohol involvement was documented for patients of all ages if it occurred with another drug. Alcohol was considered an illicit drug for patients under age 21 and was documented even if no other drug was involved. The classification of drugs used in DAWN was derived from the Multum *Lexicon*, copyright 2012 Lexi-Comp, Inc., and/or Cerner Multum, Inc. The Multum Licensing Agreement governing use of the *Lexicon* can be found at http://www.samhsa.gov/data/sites/default/files/MultumLicenseAgreement/MultumLicenseAgreement.pdf.

DAWN was one of three major surveys conducted by the SAMHSA's Center for Behavioral Health Statistics and Quality (CBHSQ). For more information on other CBHSQ surveys, go to http://www.samhsa.gov/data/. SAMHSA had a contract with Westat (Rockville, MD) to operate the DAWN system, and with RTI International (Research Triangle Park, NC) to produce publications.

For publications and additional information about DAWN, go to http://www.samhsa.gov/data/emergency-department-data-dawn.

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