DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30341-3724

November 26, 2001

Lee Lemley
HFD-006
FDA/CDER
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Lemley,

Please add the enclosed documents to Docket No. 01N-0397. If you prefer, I can also send the chart and the text of my presentation electronically.

Sincerely,

Judy Stevens

Judy Stevens, PhD
Epidemiologist
Division of Unintentional Injury Prevention
National Center for Injury Prevention and
Control

Phone: (770) 488-4649
e-mail: jas2@cdc.gov

Population-based epidemiologic studies of medications and motor vehicle crashes

Author	Type of study	Meds	Findings	Strengths & Limitations
Oster 1990 (Mass)	Age up to 65 (65+ excluded) Retrospective cohort Used claims data from lg health insurer 4554 people prescribed BZD during 6/86-9/87 3 controls per case:13,662 Controls prescribed other drugs Matched on age, sex, month of prescription Outcome = mv accident-related medical care based on claims data	BZD vs. non-BZD drugs Looked at claims 3 mo before and 6 mo after BZD scripts Used 3 care vars: medical encounters, ED visits, hospitalizations	Found temporal assoc'n between BZD use and accident-related care. Recently filled prescriptions, any medical encounter: OR=1.28 (1.04-1.56) 3 or more prescriptions ED care OR=2.64 (1.15-6.04) Any medical encounter: OR=1.30 (1.09-1.55)	BZD use inferred from pharmacy claims, nondrug claims from ICD-9-CM codes Found dose-response effect. Control group recv'd drugs other than BZD which may have had CNS effects. Don't know if people who filled prescriptions took meds, how much, or for how long. Adjusted for age, sex, pretreatment medical care use. Some accident-related care may have been for follow-up not new injuries.
Ray 1992 (Tenn)	age 65-84 Medicaid enrollees Retrospective cohort study of 16,262 persons, 38,701 p-y, 495 crashes Linked data from TN Medicaid, drivers lic files, police reports. Outcome = cohort member involved as a driver in a crash in which someone was injured.	BZD Cyclic antidepressants Oral opioids, Antihistamines	Current use of any psychoactive drug RR=1.5 (1.2-1.9) BDZ RR=1.5 (1.1-2.0) CA RR=2.2 (1.3-3.5) Antihist or opiod RR=1.1 (0.7-1.8) RR increased with dose	Extensive data link of meds, ED treatment, hospitalization, nursing home visits, licence restrictions and mv crashes. Could not distinguish between 1st prescription and chronic use.

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Leveille 1994 Seattle, WA	Age 65+ Pop'n based matched case-control of HMO members in Seattle. 234 cases, 447 controls Cases=drivers who sought treatment for mv injury w/in 7 days of crash Rel. affluent pop'n Used tertiles of probability score (liklihood of taking drug on index date) as exposure	BZD, tricyclic antidepressants, opioids, sedating antihistamines Sought medical care up to 7 d. after crash	Risk for injury collision BZD OR=1.5 (ns) CA OR=2.8 Opioids OR=1.5-1.6 (ns) Risk for injurious crash CA OR=2.3 Opiods OR=1.8 No risk seen with antihistamines	Matched analysis adjusted for race, marital status, educ miles driven, use of oral hypoglycemics or insulin for diabetes, chronic disease score. Only included drivers, not passangers, who sought medical care for mv injury. High refusal rate (25% cases, 31% controls) Actual dose was estimated since drugs were prescribed "as needed". May have non-differential misclassification because antihistamines now sold over the counter.
Neutel 1995 (Saskatchewan)	Age 20+ Cohort study of drivers Data collected 1979-1986 from multiple linked databases Filled a BZD prescription (index) vs. had not filled a BZD prescription in the 6 months prior to index prescription. 2 controls, age & sex matched to distrn of BZD users Outcome = hospitalization for mv crash within 2 months of index script	BZD hypnotics BZD anxiolytics Followed for 2 mo.	BZD hypnotics OR=9.1 for 1st wk, decr to 2.4 after 2 mo. BZD anxiolytics OR=13.5 for 1st wk, decr to 1.7 after 2 mo. Incr risk with other types of sedatives	Exposure data indirect Includes passengers hospitalized which would decrease OR Does not include injuries not requiring hospitalization. Cannot determine causality although strongly suggested by large ORs Cannot know if BZDs are being taken as indicated.

Population-based epidemiologic studies of medications and motor vehicle crashes

Hemmelgarn 1997 (Quebec)	Aged 67-84 w. licenses, followed from 1990-1993. Nested case-control study within cohort of 224,73 drivers in Quebec provence. 5,579 drivers involved in injurious crash, 10 controls per case selected from randomly selected subcohort of 13,256 Outcome=at least 1mv injury, not nec driver. Linked to computerized files with prescription data. Prescriptions filled at pharmacy	All BZD listed in Quebec formulary Followed for 1 year. Current exposure=use on index day Ref group=no BZD use in 365 days before index date	Time periods of new, continuous use (days): 7, 8-30, 31-60, 61-365 Long half-life BZD Current use OR=1.28 OR=1.45 in 1st wk OR=1.26 for up to 1 yr Short half-life Current use OR=0.96 OR=1.04 initial wk, OR=0.91 continued use. No dose effects for current use or for first 7 days of use.	Controlled for sex, age, urban region, history of mv crash in prev 2 yrs, use of other CNS drugs, chronic disease score. Used computerized records rather than self report Could not ascertain noncompliance or irregular use. Lacked information about dementia, driving frequency, alcohol use although these unlikely to have confounded results.
Barbone 1998 (UK)	Drivers ≥18 yrs Case-crossover design study pop'n =410,306 in Tayside Region, UK cases = 1st mv crash attended by police between 8/1/92-6/30/95 Used a psychoactive drug between 8/1/92 and date of crash. Prescription info included drug, dose and duration; calc'd periods of use. Compared use of drug on day of crash vs use on same day of wk of each of up to 18 preceeding wks	BZD, Tricyclic antidepressants Selective serotonin-reuptake inhibitors Other psychoactive drugs.	Most risk for anxiolytics. Highest risks for drivers < 45. No incr risk for 65+ BZD half life: short OR=4.0 (1.31-12.2) [all took zopiclone] med OR=1.19 (0.82-1.73) long OR=2.03 (1.41-2.93) Dose-response seen for BZD, not other drugs.	Appropriate only for transient use. Extended use would not show a diff between control and exposure periods. Hypnotics taken at night, anxiolytics prescribed for daytime. May not have recorded less severe crashes.

FDA/NTSB Joint Public Meeting, Washington DC, November 14, 2001
Transportation Safety and Potentially Sedating or Impairing Medications
Witness Panel II - Epidemiology
Judy Stevens, Ph.D.

Today I would like to address what epidemiology can tell us about medications and driving impairment. There is a longstanding concern that commonly used psychoactive medications such as sedatives and tranquillizers may impair driving ability. Today I am going to be focusing on the evidence provided by a number of population-based epidemiologic studies that examine the association between medications and traffic crashes. Unlike small scale clinical studies, these epidemiologic studies used data from large populations to assess the public health effect of medication use on driving safety. These studies estimate the relative risk of motor vehicle crashes associated with certain types of medications, while adjusting for factors that might affect the relationship between driving and medication use, such as age, previous medical care, and health status.

Based on epidemiology, what do we currently know about this problem? Between 1990 and 1998, there were six large population-based epidemiologic studies published that examined the association between medications and traffic crashes. The majority, four of the six, only included drivers aged 65 years and older, while only two included drivers of all ages. These studies used databases that linked Medicare or other large health care databases with emergency or hospital records, pharmacy and prescription data, drivers' license records, and motor vehicle crash reports.

The studies looked at a limited number of psychoactive drugs. All six studies included benzodiazepines (BZDs); three studies also included cyclic antidepressants; two included oral opioids and antihistamines; and one included selective serotonin reuptake inhibitor antidepressants.

Over time, studies defined medications more precisely. For example, while five studies looked at BZDs as a group, two more recent studies also assessed long and short-acting BZDs separately. Two studies divided BZDs into sedative hypnotics (that are prescribed for insomnia) and anxiolytics (that are prescribed to relieve anxiety). Three studies included dose-response effects; two compared risks for short- vs. long-term use, and two compared crash risk for long- and short-acting BZDs.

To summarize the results of these studies, despite study limitations, evidence from this research suggests that BZDs increase crash risk as much as 50% and this risk increases with increasing dose or with taking more than one BZD. Two studies suggest that this risk drops with continued use. The majority of the risk may be with the long acting drugs. With the short-acting medications, crash risk seems to be highest during the first week or two of therapy. Among the BZDs, hypnotics that are taken at night appear to pose less risk than anxiolytics that are usually taken during the day.

A limited number of studies provide less convincing evidence about other drugs. Results from only two studies of older adults suggest that cyclic antidepressants may double crash risk while oral opioids and antihistamines do not increase risk.

But there is still a great deal we need to know about this issue. In order to accurately estimate risk, we need to precisely determine exposure. Many psychoactive drugs are prescribed on an "as needed" basis so studies using records and dates for prescriptions may not accurately reflect use. Other drugs, like antihistamines, are available over-the-counter so it is difficult to get accurate data about use. Unlike alcohol, we cannot use blood levels of drugs that are fat soluble to measure impairment. We need better ways to ascertain what drug or drugs are taken, at what time of day, and at what dosage and then to link this information with data on motor vehicle crashes.

We need to conduct additional epidemiologic studies of BZDs to clarify the differences in risks for long- and short-acting medications, to study the risks associated with hypnotic and anxiolytic BZDs, and to look at risk for short- and long-term use of these drugs. We need further study of antidepressants among people of all ages. And we need to study additional prescription and over-the-counter medications that may impair drivers, such as codeine cough medicines and antihistamines, to see if these also may contribute to an increased risk of motor vehicle crashes.

Studies need to be broadened to include drivers of all ages, to assess whether alcohol in combination with some medications is a significant factor, and to take into account the metabolic effects of aging on drug metabolism and tolerance. We need to know whether

impairment differs by gender. We need to understand whether long-term use of some medications increases or decreases risks. And we need to learn more about conditions, such as depression, that may influence the relationship between driving ability and the likelihood of taking medications.

To answer these questions, we will need to develop more complete and complex data bases. We will also need to develop new and creative approaches to obtaining detailed information about the use of prescription and over-the-counter medications that may impair drivers. Finally, this information needs to be linked to comprehensive data about motor vehicle crashes.

In summary, these population-based epidemiologic studies have provided us with basic information about the risks of traffic crashes associated with BZDs. However, further research is needed to provide clear and comprehensive answers about the impact of all types of medications on transportation safety in the United States.

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