Benzodiazepine Use and Driving: A Meta-Analysis

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Objective: The purpose of the present study was to examine the experimental and epidemiologic evidence linking benzodiazepine use to driving impairment.

Data Sources: We searched MEDLINE, PsycINFO, the Cochrane Collaboration, and EMBASE using the key terms (*"benzodiazepines"* OR *"exp benzodiazepines"*) AND (*"automobile driving"* OR *"accidents, traffic"* OR *"driving"* OR *"driver$"*) and limited the results to English citations from 1966 to August 5, 2005, with auto-updates for MEDLINE and PsycINFO to November 30, 2007.

Study Selection and Data Extraction: Experimental studies using driving simulators and on-road tests were sought, as were epidemiologic studies of a case-control or cohort design. Data were extracted by blinded raters and pooled using random-effects models. We excluded studies without control groups or without measures of driving or collisions. Studies with driving measures that could not be combined were also excluded.

Data Synthesis: Of 405 potential articles, 11 epidemiologic and 16 experimental studies were included in the meta-analysis. Associations between motor vehicle collisions (MVCs) and benzodiazepine use were found among 6 case-control studies (OR = 1.61, 95% CI = 1.21 to 2.13, $p < .001$), and 3 cohort studies (OR = 1.60, 95% CI = 1.29 to 1.97, $p < .0001$). Only 10 of 97 experimental driving variables could be pooled for analysis. While no consistent findings were observed in studies using driving simulators, increased deviation of lateral position was found on on-road driving tests (standardized mean difference = 0.80, 95% CI = 0.35 to 1.25, $p = .0004$).

Conclusions: Benzodiazepine users were found to be at a significantly increased risk of MVCs compared to nonusers, and these differences may be accounted for by a difficulty in maintaining road position.

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In studies conducted internationally, benzodiazepines are frequently detected drugs in people injured or killed in motor vehicle collisions (MVCs),[1] and the trends may be increasing.[2] Benzodiazepines act directly on the γ-aminobutyric acid (GABA) system, the major inhibitory neurotransmitter of the central nervous system. By enhancing GABA-ergic neurotransmission, they cause inhibition of the central nervous system in a manner similar to alcohol.[3] While the effects of alcohol on driving have been well-publicized and emphasized in transportation policies and legislation internationally, there has been less recognition of the potential negative effects of benzodiazepine use on road safety.[4]

There have been many studies published over the last 30 years attempting to discern the traffic risks associated with benzodiazepine use. Two complementary approaches, experimental and epidemiologic, provide the best information for understanding the relationship between drugs and MVCs or driving impairment.[1,4] The epidemiologic studies examine the risk of collisions associated with benzodiazepines "on the street" in the real world. Experimental studies examine the relationship

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between the administration of the benzodiazepines and driving behavior as measured by driving simulators or on-road driving tests. The purpose of the present study is to examine the association of benzodiazepine use with real-world MVCs in epidemiologic studies and with driving impairment in experimental studies.

METHOD

Identification of Studies

We searched MEDLINE, PsycINFO, the Cochrane Collaboration, and EMBASE using the key terms (*"benzodiazepines"* OR *"exp benzodiazepines"*) AND (*"automobile driving"* OR *"accidents, traffic"* OR *"driving"* OR *"driver$"*) and limited the results to English citations from 1966 to August Week 1, 2005, with auto-updates for MEDLINE and PsycINFO to November 30, 2007. Additional searches were conducted by listing individual benzodiazepines using the same strategy. Review articles and reference lists from the included articles were searched manually for published references pertaining to the topic. Authors of publications with missing data were contacted by mail.

Inclusion and Exclusion Criteria

We included English-language studies that examined real-world collisions in case-control or cohort studies, as well as studies examining driving behavior in a laboratory setting using either driving simulators or on-road driving tests. We excluded studies that did not examine benzodiazepines, those that only examined benzodiazepines in combination with other drugs or substances (i.e., not benzodiazepines in isolation), or studies lacking a control group not exposed to benzodiazepines. Studies of newer non-benzodiazepine sedative-hypnotics were excluded. We excluded experiments that examined psychomotor impairment on tests that did not have either a driving simulator or a road test. After a more detailed review of potential studies, we excluded duplicate publications and studies that employed a driving outcome measure in a manner that was unique to the individual study and could not be combined with other published studies.

Study Selection and Data Extraction

Articles were selected on the basis of inclusion and exclusion criteria. Data were extracted for each article by 2 investigators blinded with respect to authors, author affiliation, year, dates, location, and journal. The investigators extracted data concerning study design, inclusion and exclusion criteria, demographic information, methods of ascertainment of benzodiazepines, names and doses of benzodiazepines, category of driving impairment (simulated, on-road, or actual collisions), numbers of cases and controls, specific driving impairment measures, and outcomes. Discrepancies, where present, were resolved by consensus.

Data Analysis

For the experimental studies using different benzodiazepines, the individual doses were converted into diazepam equivalents.[5,6] The raw data from each study were extracted and entered into RevMan, Version 4.2 (The Cochrane Collaboration, Copenhagen, Denmark). The standardized mean difference (SMD) of scores on the laboratory tests between subjects taking benzodiazepines and controls was calculated. Odds ratios and relative risks were calculated for the case-control and cohort studies, respectively. The risk among older adults (in subgroups age 60 years and over or 65 years and over) was calculated when possible in subgroup analyses. Heterogeneity was estimated, and significance was assessed using χ^2 and I^2. Outcomes were pooled across the studies with the random-effects meta-analytic model developed by Cochrane, which weights each study's effect size by its sample size and by the between-study variance.[7] The random-effects model gives a more conservative estimate of the effect size than a fixed-effects model and is more appropriate when one cannot assume the studies estimate a common effect size or are representative of all studies.[7] In order to assess the impact of publication bias, the Begg method[8] was used for the case-control studies, calculating a Spearman correlation between sample size and odds ratio. The Begg method could not be used for the other outcomes because each had 3 or fewer studies. The number needed to harm (NNH) for the case-control studies was calculated as $1 + [CER \times (OR–1)]/[(1–CER) \times (CER) \times (OR–1)]$,[9] with CER representing the control event rate (i.e., the event rate in the control group).

RESULTS

Studies

Using the search strategy, a total of 405 articles were obtained. Of those identified, 378 were excluded, and 27 were included (Figure 1). Reasons for initial exclusion (N = 335) were not matching search criteria (N = 98), no benzodiazepines-only group (N = 43), reviews or editorials (N = 62), no control group (N = 75), and nondriving psychomotor tests (N = 57). A further 43 were excluded after more detailed review because of duplicate publication or population (N = 5) and the use of unique outcomes or measures that could not be combined for meta-analysis (N = 38) (Appendix 1).

Letters were sent to 22 authors of studies in which data were missing. Data were provided from 1 author, 4 authors replied that data were unavailable, 5 letters were "returned to sender," and the remainder did not reply after a second follow-up letter.

The initial literature search revealed a total of 97 outcome measures used in the various experimental studies. Only 10 outcome measures were used in more than 1 study in a comparable manner, and only studies incorpo-

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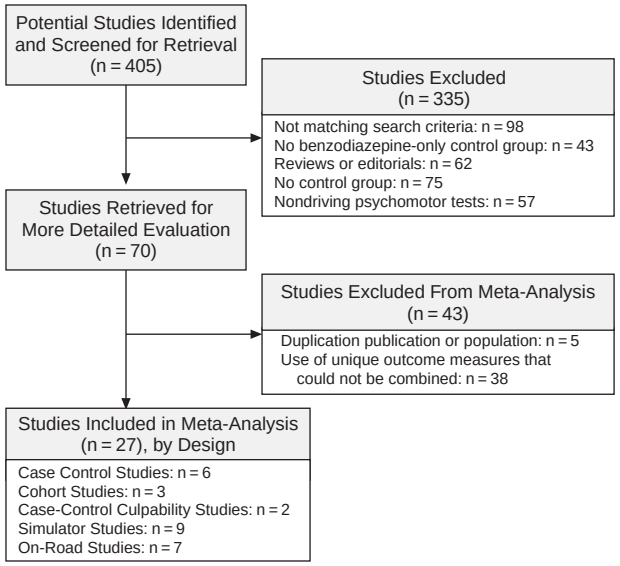
Figure 1. Flow Diagram for Studies Included and Excluded From Meta-Analysis



rating these measures were included in the analyses. The common outcome measures using driving simulators were brake reaction time, standard deviation of lateral position, absolute speed deviation, deviation from instructed speed, number of collisions, and a tracking error severity index. The common outcome measures of studies using an on-road driving study were brake reaction time, standard deviation of lateral position, mean speed, and deviation from instructed speed.

The 11 epidemiologic studies included 6 case-control studies[10–15] (Table 1), 3 cohort studies[16–18] (Table 2), and 2 "case-control culpability" studies.[19,20] In the case-control culpability studies, all subjects were involved in a MVC, and the relationship between their drug use and culpability for the MVC was assessed. We included 15 publications that incorporate 16 experimental studies: there were 9 reports using computer-simulated driving tests[21–29] (Table 3) and 8 using an on-road driving test[29–36] (Table 4).

Epidemiologic Studies

Case-control studies. Among the 6 case-control studies[10–15] (see Table 1), one study by Hemmelgarn et al.[15] divided benzodiazepine exposure to short-acting and long-acting benzodiazepines, and exact data were not available for "any benzodiazepine" exposure. In that study, long-acting benzodiazepine exposure but not short-acting exposure was associated with MVC. Combining the 6 case-control studies using the long-acting benzodiazepines from the former study yielded an OR of 1.61 (95% CI = 1.21 to 2.13, $p < .001$) (Figure 2). Correspondingly, the NNH for the risk of MVCs with benzodiazepines was 25.5 (95% CI = 14.3 to 72.0). Analysis of publication bias indicated that there was no association between sample size and odds ratio (Spearman $r = –0.086$, $p = .87$). While using short-acting benzodiazepines from the study by Hemmelgarn et al.[15] also yielded an OR of 1.59 (95% CI = 1.05 to 2.39, $p = .03$) in the meta-analysis, there was substantial heterogeneity ($\chi^2 = 19.45$, $df = 5$, $p = .002$, $I^2 = 74.3\%$). Because the Hemmelgarn et al. study[15] did not have data for "any benzodiazepine exposure," we also repeated the meta-analysis excluding that study and found a comparable OR of 1.88 (95% CI = 1.20 to 2.94, $p = .006$), with reasonable homogeneity ($\chi^2 = 7.50$, $df = 4$, $p = .11$, $I^2 = 46.6\%$).

Three of the case-control studies did not perform subanalyses.[10,11,13] Leveille et al.[14] demonstrated no differences in risk based on quantity of benzodiazepines prescribed or on whether the use was "current or past." Hemmelgarn and colleagues' study[15] demonstrated that the risk of collision was associated with long-acting benzodiazepine use in the first 7 days after prescription and for use between 61 and 365 days after prescription, but not for use between 8 and 60 days after prescription. They also reported no increased risk of collisions with short-acting benzodiazepines regardless of when prescribed in relation to the collision. McGwin et al.[12] found an increased risk of benzodiazepine exposure when comparing at-fault collisions vs. no collisions, and when comparing at-fault versus not-at-fault collisions. Meta-analysis of these subanalyses was not possible.

Two case-control culpability studies were found,[19,20] in which all subjects were involved in collisions. In these studies, subjects who were found culpable for the collisions and those found not culpable were compared for benzodiazepine exposure. One of these studies reported an association between culpability for collision and benzodiazepine exposure,[20] while the other did not.[19] Heterogeneity precluded meta-analysis ($\chi^2 = 12.08$, $df = 1$, $p = .0005$, $I^2 = 91.7\%$).

Cohort studies. Three cohort studies were examined in which subjects exposed to benzodiazepines were compared with controls for risk of MVC[16–18] (Table 2). The study by Neutel[17] subdivided benzodiazepine exposure into hypnotics and anxiolytics, but exact data were not available for "any benzodiazepine." Combining the data regarding anxiolytics from that study with the other 2, we found a relative risk (RR) of 1.60 (95% CI = 1.29 to 1.97, $p < .0001$) (Figure 3), but data were heterogeneous when analyzed with the hypnotics ($\chi^2 = 7.96$, $df = 2$, $p = .02$, $I^2 = 74.9\%$). Analysis of the data from the 2 studies[16,18] excluding the Neutel study[17] yielded a comparable RR of 1.59 (95% CI = 1.42 to 1.77, $p < .00001$) with reasonable homogeneity ($\chi^2 = 1.32$, $df = 1$, $p = .25$, $I^2 = 24.2\%$).

Subanalyses were done by the authors of the cohort studies, but these could not be subjected to meta-analysis. A dose-response relationship indicating increased risk of

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Table 1. Case-Control Studies Included in the Meta-Analysis of the Association of Benzodiazepine Use With Real-World Motor Vehicle Collisions (MVCs)

Study, Country	Case Identification	Control Identification	Benzodiazepine Ascertainment	Timing of Benzodiazepine Ascertainment	Subgroups
Honkanen et al, 1980, Finland[10]	Drivers who arrived at one of 5 public emergency departments within 6 hours of injury	Randomly selected car drivers at 10 petrol stations during the same sampling period; matched to weekday, hour, and location	Blood screen	Time of ER visit	None
Mura et al, 2003, France[11]	Drivers involved in a nonfatal road accident and admitted in emergency units of 6 hospitals	900 patients having a driver's license who attended for any nontraumatic reason the same emergency unit as the cases; matched for sex and age ± 1 year	Blood screen	Time of ER visit	Benzodiazepines only, excluding hypnotic benzodiazepines (hypnotics assessed separately, but not exclusively benzodiazepines; these data are not incorporated into the meta-analysis)
McGwin et al, 2000, United States[12]	Drivers in MVCs identified by database; of 1507 drivers, 560 were selected for whom phone numbers were available, 79.8% of whom agreed to be interviewed	Random sample of 1900 controls selected, of whom 647 were selected who matched cases on age (± 1 year) and sex	Interview	Currently taking	Fault, no fault
Skegg et al, 1979, United Kingdom[13]	Hospital admissions or deaths among a population of 43,117 patients registered with 16 GPs	For each patient, 25 controls from same practice, matched on sex and year of birth	Prescriptions issued or dispensed	3 months before injury or reference date	None; note "minor tranquillizers" (eg, benzodiazepines)
Hemmelgarn et al, 1997, Canada[15]	Nested case-control population of drivers aged 67 to 84 years; collisions involving injury identified on a collision database	20 controls per case, selected randomly, not matched for gender or age, but adjusted	Prescription database	Current use (exposure on the index date)	Long $t_{1/2}$, short $t_{1/2}$ reported separately; duration of exposure assessed but not incorporated into meta-analysis
Leveille et al, 1994, United States[14]	Older drivers aged 65+ years who were enrollees of a large health maintenance organization and who sought treatment for MVC injuries within 7 days of injury	Two controls per case selected at random from enrollment files, and matched for age, gender, and county	Computerized pharmacy database	6 months before injury or reference date	By tertile of probability quotient, current or past exposure; examined current exposure only

Abbreviations: ER = emergency room, GP = general practitioners, $t_{1/2}$ = half-life.

Table 2. Cohort Studies Included in the Meta-Analysis of the Association of Benzodiazepine Use With Real-World Motor Vehicle Collisions (MVCs)

Study, Country	Case Identification	Control Identification	MVC Identification	How Reported
Oster et al, 1987, United States[16]	Prescription claim via managed-care plan	Nonusers, matched on age and sex	Hospitalization, health care utilization	Annualized average no. of hospital admissions; converted to no. per person-year.
Neutel, 1995, Canada[17]	Prescriptions from Saskatchewan health database; total group and aged 60+ y group	Nonexposed	Within 2 months after the index benzodiazepine prescription; hospitalization	No. in collisions within two months; converted to no. per person-year
Ray et al, 1992, United States[18]	Aged 65 to 94 years enrolled in Tennessee Medicaid with valid driver's license; current use of benzodiazepines (except flurazepam and triazolam)	No use of benzodiazepine	5-year prospective reported injurious MVCs based on Tennessee Department of Safety	Event per person-year

Table 3. Experimental Studies Using Driving Simulators

Study	Subjects	Task	Drug, Dose, and Time	Timing of Testing Postdose	Design
Mattila, 1988[25]	9 healthy volunteers	Tracking errors and severity (percent of time driven off the road) during a task of simple tracking and tracking while distracted by choice reaction stimuli	Diazepam 10 mg hs	1.5 h and 3 h	Double-blind crossover
Mattila et al, 1998[26]	12 healthy volunteers	Same as in Mattila[25]	Diazepam 15 mg	1 h and 3.5 h	Double-blind crossover
Dureman and Norrman, 1975[22]	54 healthy volunteers, 6 per group	Simulator brake reaction time, not described in detail in the text; absolute speed deviation also assessed	Diazepam 5 mg, 10 mg, 20 mg; clorazepate 10 mg, 20 mg, 40 mg; two consecutive nights	2 h	Double-blind parallel groups
Dureman et al, 1978[21]	12 male anxious patients	Simulator brake reaction time, not described in detail in the text	Clorazepate 20 mg hs (or 5 mg bid and 10 mg hs) for 17 days; testing on days 3, 10, and 17	8 h	Double-blind crossover
Friedel et al, 1991[23]	60 healthy male volunteers	Daimler-Benz driving simulator—real vehicle in a simulated environment, 180 degree panoramic image; 20 min drive on standardized scenarios; brake reaction time	Diazepam 0.11 mg/kg (average 7 mg) or 0.22 mg/kg (approx 14 mg), 1 dose	Shortly after	Double-blind parallel groups
Volkerts et al, 1992[29]	18 healthy male volunteers	Driving simulator ("model TS2"); respond as quickly as possible to random illumination of brake lamps	Lormetazepam 1 mg; oxazepam 50 mg on 2 consecutive nights	7 h (am) and 16 h (pm)	Double-blind crossover
Partinen et al, 2003[27]	19 women with insomnia	STISim driving simulator, deviation from instructed speed on 100 km simulated driving task; monotonous drive; deviation from instructed speed	Single doses of temazepam 20 mg or placebo at 2:00 am	5.5 h postdose; 7:30 am	Double-blind crossover
Staner et al, 2005[28]	23 patients with insomnia	Faros driving simulator, 120 degree visual field, monotonous drive for 60 min; deviation from instructed speed, absolute speed deviation, and no. of collisions	Single and repeated (7 d) doses of lormetazepam 1 mg or placebo at 10:30 pm	9–11 h postdose; 7:30–9:30 am	Double-blind crossover
Linnoila and Hakkinen, 1974[24]	70 drivers	No. of collisions on a 40 min simulated drive	Diazepam 25 mg	30 min	Double blind parallel groups

MVCs with higher doses was demonstrated by Ray et al.,[18] in which the RR increased from 1.1 (95% CI = 0.5 to 2.2) for the equivalent of 4 mg of diazepam or less to 2.4 (95% CI = 1.3 to 4.4) for 20 mg or more (p = .05). They also reported that the risk was significantly higher for the use of more than 1 benzodiazepine (RR = 4.8, 95% CI = 1.6 to 14.5) as compared with single benzodiazepines (RR = 1.5, 95% CI = 1.1 to 2.0, p = .05). Duration of use did not vary the risk in the study by Ray et al.,[18] but Neutel, in a publication of subanalyses,[37] reported that the risk of collisions increased for hypnotics in the first 14 days of use, but not subsequently, and that new users had an increased risk but repeat users did not. Oster et al.[16] found that benzodiazepines of both short and long duration increased risks of collisions.

Older adult subgroup analysis. Subgroup analysis of the 3 case-control studies that examined data for subjects aged 65 years and older[12,14] or aged 67 to 84 years[15] (using the long-acting benzodiazepine subgroup of Hemmelgarn et al.[15] as described previously) was homogeneous ($\chi^2 = 2.33$, df = 2, p = .31, $I^2 = 14.1\%$) and revealed an OR of 1.35 (95% CI = 1.09 to 1.69, p = .007). Subgroup analysis of the 2 cohort studies that examined data for subjects aged 60 years and older[17] or aged 65 to 94 years[18] (using the anxiolytic subgroup from the Neutel study[17] as described previously) was also homogeneous ($\chi^2 = 1.06$, df = 1, p = .30, $I^2 = 5.6\%$) and revealed an OR of 1.41 (95% CI = 1.03 to 1.93, p = .03).

Experimental Studies

Simulator. Mattila[25] and Mattila et al.[26] published 2 studies, one in 1988[25] and one in 1998,[26] in which healthy volunteers were entered into double-blind randomized crossover studies of diazepam compared with placebo. At 1 or 1.5 hours and 3 or 3.5 hours postdose, subjects were tested on their ability to maintain a set road position on a test of simulated driving on a tracking task and while distracted by choice reaction stimuli. The percentage of time driven off the path was calculated as a tracking error severity index. The 1988 publication used a single 10-mg dose of diazepam, while the 1998 publication used 15 mg. The analysis revealed no increase

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Table 4. Experimental Studies Using On-Road Driving Tests

Study	Subjects	Task	Drug, Dose, and Time	Timing of Testing Postdose	Design
O'Hanlon, 1984[33]	24 female former hypnotic drug users	SDLP	Flurazepam 15 mg and 30 mg hs on 2 consecutive nights	10–11 h (am) and 16–17 h (pm)	Double-blind crossover
O'Hanlon, 1984[33]	16 female former hypnotic drug users	SDLP	Loprazolam 1 mg hs; Flunitrazepam 2 mg hs on 2 consecutive nights	10–11 h (am) and 16–17 h (pm)	Double-blind crossover
Verster et al, 2002[36]	20 healthy volunteers	SDLP; mean speed deviation from instructed speed	Alprazolam 1 mg, 1 dose only	1 h	Double-blind crossover
Volkerts et al, 1992[29]	18 healthy male volunteers	SDLP	Lormetazepam 1 mg; oxazepam 50 mg on 2 consecutive nights	7 h (am) and 16 h (pm)	Double-blind crossover
O'Hanlon et al, 1995[34]	16 healthy volunteers	SDLP	Diazepam 5 mg po tid x 8 d (lorazepam 0.5 mg tid in another group of 19)	1–2 h postdose on days 1 and 8	Double-blind crossover
Hindmarch and Subhan, 1983[31]	8 healthy female controls	Brake reaction time with cruise control maintaining constant speed of 45 mph	Midazolam 15 mg, 1 dose	10 h	Double-blind crossover
Harrison et al, 1985[30]	10 healthy female controls	Brake reaction time with cruise control maintaining constant speed of 45 mph	Lormetazepam 1 mg; triazolam 0.25 mg; flunitrazepam 1 mg given at hs; one dose	10 h	Double-blind crossover
Moore, 1977[32]	14 anxious patients	Brake reaction time; driving a prepared car, respond to emergency stop	Medazepam average dose 16.5 mg for 3 wk, dose ranged from 5–30 mg/d	Various	Double-blind crossover
van Laar et al, 1992[35]	24 patients with generalized anxiety	Mean speed deviation from instructed speed	Diazepam 5 mg tid for 4 wk after 1-week placebo lead-in	1.5 h	Double-blind parallel groups, with placebo lead-in

Abbreviation: SDLP = standard deviation of lateral position.

in tracking errors when tested at 3 or 3.5 hours postdose (SMD = 0.79, 95% CI = –0.23 to 1.81), but heterogeneity precluded combining results of testing less than 1.5 hours postdose (χ^2 = 5.39, df = 1, p = .02, I^2 = 81.4%).

Four studies of brake reaction time[21–23,29] were homogeneous when stratified for dose (χ^2 = 1.35, df = 2, p = .51, I^2 = 0% for 3 experiments with 5 mg diazepam equivalents or less,[22,23,29] and χ^2 = 1.89, df = 2, p = .39, I^2 = 0% for 3 experiments with 10 mg or more[21–23]) but no differences were found between benzodiazepine and placebo (SMD = –0.13, 95% CI = –0.50 to 0.24, p = .50). The 2 studies of deviation from instructed speed[27,28] were homogeneous (χ^2 = 0.85, df = 1, p = .36, I^2 = 0%), but also showed no increase with benzodiazepines (SMD = –0.05, 95% CI = –0.49 to 0.40, p = .84). Heterogeneity among studies assessing number of collisions on a simulator[24,28] (χ^2 = 3.44, df = 1, p = .06, I^2 = 70.9%) and absolute speed deviation[22,28] (χ^2 = 13.09, df = 1, p < .0003, I^2 = 92.4%) precluded meta-analysis.

On-Road. Four reports, including 5 experiments using on-road assessment of subjects entered into double-blind placebo-controlled crossover studies of the effects of benzodiazepines on deviation of road position, were combined for meta-analysis.[29,33,34,36] In each of the studies, the task of subjects was to drive an instrumented vehicle around a 100-km primary highway circuit while maintaining constant speed (95 km/h) and steady lateral position. Standard deviation of lateral position (SDLP) was calculated using an on-board computer. Four of the studies assessed healthy volunteers as subjects,[29,33,34,36] and 1 study assessed former hypnotic drug users.[34] When analyzed together, the results were heterogeneous (χ^2 = 157.02, df = 3, p < .00001, I^2 = 98.1%). Studies were then stratified by dosage and timing. Increased deviation of lateral position was found in 2 studies using benzodiazepine equivalents of 5 mg of diazepam or less tested the morning after bedtime dosing[29,33] (SMD = 0.80, 95% CI = 0.35 to 1.25, p = .0004), but not among 2 studies from the same reports testing impairment in the afternoon after bedtime dosing.[29,33] The effect on SDLP was more marked at doses of 10 mg of diazepam equivalents or more but was associated with substantial heterogeneity (χ^2 = 45.94, df = 2, p < .00001, I^2 = 95.6%)[33,34,36] (Figure 4).

Three double-blind placebo-controlled crossover studies assessing the impact of benzodiazepines on on-road driving among healthy controls[30,31] or anxious patients[32] were homogeneous (χ^2 = 0.17, df = 2 p = .92, I^2 = 0%) but showed no impact on brake reaction time (SMD = 0.05, 95% CI = –0.44 to 0.54, p = .84).

Heterogeneity precluded pooling of 2 studies[35,36] that assessed mean speed (χ^2 = 13.07, df = 1, p < .00003, I^2 = 92.3%) and deviation from instructed speed (χ^2 = 17.44, df = 1, p < .0001, I^2 = 94.3%) on on-road driving tests.

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Figure 2. Case-Control Studies of Risk of Exposure to Benzodiazepines Associated With Motor Vehicle Collisions

Study or Subcategory	Treatment Group (n/N)	Control Group (n/N)	OR (random), 95% CI	Weight, %	OR (random), 95% CI
Hemmelgarn et al (1997)[15] long-acting	387/3817	2911/38,511		41.07	1.38 (1.23 to 1.54)
Honkanen et al (1980)[10]	10/201	7/325		6.90	2.38 (0.89 to 6.35)
Leveille et al (1994)[14]	22/234	40/447		16.53	1.06 (0.61 to 1.82)
Mura et al (2003)[11]	85/900	52/900		25.64	1.70 (1.19 to 2.43)
Skegg et al (1979)[13]	5/57	32/1425		6.90	4.19 (1.57 to 11.18)
McGwin et al (2000)[12]	7/447	2/454		2.96	3.60 (0.74 to 17.40)
Total (95% CI)	5656	42,062		100.00	1.61 (1.21 to 2.13)
Total events: 516 (treatment group), 3044 (control group)					
Test for heterogeneity: $\chi^2 = 9.40$, df = 5 (p = .09), $I^2 = 46.8\%$					
Test for overall effect: Z = 3.30 (p =.0010)					

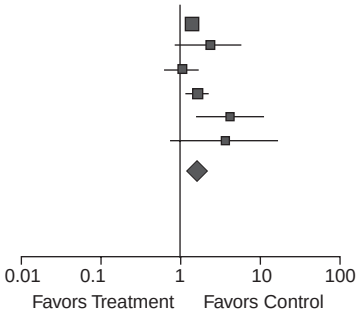


Figure 3. Cohort Studies of Risk of Exposure to Benzodiazepines Associated With Motor Vehicle Collisions

Study or Subcategory	Treatment Group (n/N)	Control Group (n/N)	OR (random), 95% CI	Weight, %	OR (random), 95% CI
Oster et al (1987)[16]	233/7271	1309/65,439		56.23	1.60 (1.40 to 1.84)
Ray et al (1992)[18]	46/2978	245/21,578		27.95	1.31 (0.96 to 1.79)
Neutel (1995)[17] anxiolytic	77/24,284	23/16,087		15.82	2.22 (1.39 to 3.53)
Total (95% CI)	34,533	103,104		100.00	1.60 (1.29 to 1.97)
Total events: 356 (treatment group), 1586 (control group)					
Test for heterogeneity: $\chi^2 = 3.45$, df = 2 (p = .18), $I^2 = 41.9\%$					
Test for overall effect: Z = 4.39 (p < .0001)					

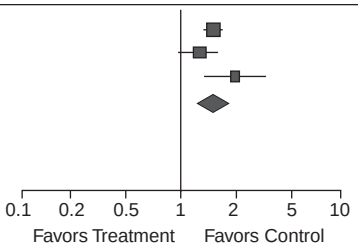
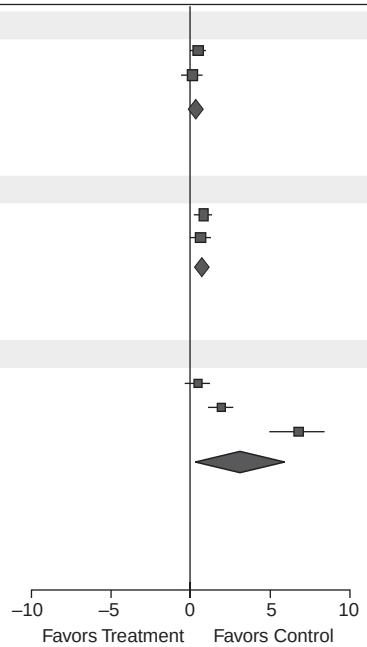


Figure 4. Standard Deviation of Lateral Position (SDLP) in On-Road Studies

Study or Subcategory	N	Treatment Group, Mean (SD)	N	Control Group, Mean (SD)	SMD (random), 95% CI	Weight, %	SMD (random), 95% CI
SDLP on road at dose equivalent ≤ 5 mg diazepam tested in pm							
O'Hanlon (1984)[a]	24	21.20 (4.00)	24	19.00 (4.00)		15.35	0.54 (–0.04 to 1.12)
Volkerts et al (1992)[b]	18	17.76 (2.73)	18	17.56 (2.82)		15.08	0.07 (–0.58 to 0.72)
Subtotal (95% CI)	42		42			30.43	0.33 (–0.13 to 0.79)
Test for heterogeneity: $\chi^2 = 1.12$, df = 1 (p = .29), $I^2 = 10.6\%$							
Test for overall effect: Z = 1.42 (p = .16)							
SDLP at dose equivalent ≤ 5 mg diazepam tested in am							
O'Hanlon (1984)[c]	24	22.50 (3.00)	24	19.00 (4.50)		15.28	0.90 (0.30 to 1.50)
Volkerts et al (1992)[d]	18	18.76 (2.53)	18	17.10 (2.27)		15.00	0.68 (0.00 to 1.35)
Subtotal (95% CI)	42		42			30.28	0.80 (0.35 to 1.25)
Test for heterogeneity: $\chi^2 = 0.24$, df = 1 (p = .62), $I^2 = 0\%$							
Test for overall effect: Z = 3.52 (p = .0004)							
SDLP at dose equivalent ≥ 10 mg diazepam							
O'Hanlon (1984)[e]	16	21.10 (2.20)	16	19.00 (4.50)		14.87	0.58 (–0.13 to 1.29)
O'Hanlon et al (1995)[f]	16	24.60 (1.40)	16	22.00 (1.00)		14.15	2.08 (1.20 to 2.96)
Verster et al (2002)[gAllALLA]	20	30.60 (1.60)	20	21.20 (1.00)		10.28	6.91 (5.20 to 8.62)
Subtotal (95% CI)	52		52			39.29	3.07 (0.30 to 5.83)
Test for heterogeneity: $\chi^2 = 45.94$, df = 2 (p = .00001), $I^2 = 95.6\%$							
Test for overall effect: Z = 2.17 (p = .03)							



[a]O'Hanlon (1984)[33]: flurazepam 15 mg tested in p.m.
[b]Volkerts et al. (1992)[29]: lormetazepam 1 mg tested in p.m.
[c]O'Hanlon (1984)[33]: flurazepam 15 mg tested in a.m.
[d]Volkerts et al. (1992)[29]: lormetazepam 1 mg tested in a.m.
[e]O'Hanlon (1984)[33]: flunitrazepam 2 mg tested in a.m.
[f]O'Hanlon et al. (1995)[34]: diazepam 15 mg.
[g]Verster et al. (2002)[36]: alprazolam 1 mg tested 1 hour postdose.

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DISCUSSION

The present meta-analysis revealed a consistent 60% increase of MVC risk associated with benzodiazepine use, using case-control and cohort studies. The magnitude of risk was comparable to that found in recent meta-analyses showing associations of benzodiazepines with adverse effects, especially drowsiness and dizziness, among mixed-age groups (OR = 1.8, 95% CI = 1.4 to 2.4),[38] and with falls among older adults (OR = 1.48, 95% CI = 1.23 to 1.77).[39] We had anticipated that the risks might be particularly salient in older subjects, a vulnerable group to whom benzodiazepines are frequently prescribed.[40,41] Another recent meta-analysis of benzodiazepines in those aged 60 years and older revealed more than a 3-fold increase in risk of daytime fatigue (OR = 3.82, 95% CI = 1.88 to 7.80), in addition to increased risk of adverse cognitive events (OR = 4.78, 95% CI = 1.47 to 15.47).[42] In the present meta-analysis, the risk estimates for subgroups of older adults were similar to that in mixed-age groups, with the older adults' midpoint estimate within the mixed-age confidence intervals, suggesting that perhaps other patient-related factors beyond benzodiazepines may be playing a role in the phenomenon of MVCs among mixed-age groups. For example, older adults may engage in less frequent or less risky driving.

A prior systematic review of the epidemiologic literature on benzodiazepines and collisions indicated an OR ranging from 1.45 to 2.40 for mortality and emergency admissions among 6 case-control studies,[43] but meta-analysis was not conducted. Limitations exist because of the variability of method of drug ascertainment and with the interpretation of causality in these epidemiologic studies.[1,44] Other factors, such as a sensation-seeking personality, may explain both drug use and high-risk driving. In the present meta-analysis, while the ORs may be sensitive to the high prevalence of benzodiazepine use and motor vehicle collisions and may overestimate RRs, the summary ORs found in the case-control studies were very similar to the RRs in the cohort studies.

Psychomotor impairment has consistently been found to be associated with use of benzodiazepines,[45–47] and yet the mechanism for impaired driving ability and subsequent collision risk remains unclear even with the present meta-analysis of the experimental studies. Studies using simulators and on-road design showed no delay or slowing of brake reaction time. A nondriving study previously demonstrated that simple motor reaction time is less affected by benzodiazepines than complex reaction time tests requiring decisions.[47] The tasks assessing brake reaction time in the controlled settings described in the studies in the present meta-analysis did not assess the phenomenon of braking in the face of routine driving distractions. A previous systematic review of the literature on the effect of psychotropic medication on computer-simulated driving tests revealed inconsistent patterns of impairment in reaction time, tracking, and coordination after acute doses, but few residual effects on driving testing the morning after acute doses, particularly since the studies of residual effects did not utilize longer-acting benzodiazepines.[48] The external validity of driving simulators in assessing road safety has yet to be established.[49] Furthermore, the impact of the experimental findings of drug-induced driving changes in the on-road studies occurs in a controlled laboratory environment that may not translate to the real world. The only experimental finding that was significantly associated with benzodiazepines in the present report was the ability to maintain road position, as measured by SDLP in the on-road studies. A prior meta-analysis limited to SDLP studies of the effect of benzodiazepines on driving the morning following nocturnal treatment similarly found strong effects.[50] Heterogeneity and inconsistencies in study design precluded detailed assessment of many of the other experimental driving variables, including the tracking error severity index, a simulator task analogous to the SDLP on-road task. Thus, while the mechanism by which benzodiazepines increase the risk of collisions appears to be related to ability to maintain a proper road position but not brake reaction time, other variables have not been assessed in a way that allows for meta-analytic study.

The most important limitation of the present meta-analysis of experimental data is that, although we found 97 different outcome measures in the experimental studies reviewed, only 10 outcome measures were assessed in a manner consistent enough to be combined for the purpose of meta-analysis. Furthermore, studies using 4 of the 10 experimental outcome measures had heterogeneous results that precluded meta-analysis. Thus, only 6 of 97 outcome measures had data sufficient for analysis in the present report, limiting the generalizability of our findings to the entire experimental literature on benzodiazepines and driving. Caution should also be taken when interpreting these results because of the fact that the tracking error severity index studies and SDLP studies were conducted at 1 research center each, and the external validity of these protocols has yet to be established. Hence, even for the 2 experimental driving measures that were consistently impaired in this meta-analysis, generalizability is limited.

Publication bias is a potential limitation to the present meta-analysis.[51] In the prior meta-analysis of SDLP and driving while using benzodiazepines,[50] 3 of the 14 studies examined were not published in the literature. Nonetheless, publication bias did not seem to affect the case-control findings in our analysis using the Begg method. Other limitations of this meta-analysis are the small sample sizes and the use of healthy controls in most of the experimental studies. The assessment of risk of benzodiazepine use among patients is considerably more

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complex, as insomnia and underlying sleep disorders are well documented to be associated with road hazards.[52,53] Given the limitations of the randomized controlled experimental data thus far, one must be particularly cautious in interpreting the observational data derived from the epidemiologic literature, in which the relative impact of the drugs and the conditions that they treat remain unexplored.

Because of the variability of the studies in this area, conclusions could not be made about clinically important questions that remain. Insufficient information is available in a consistent manner to address the impacts of dose, timing following dose, age, duration of treatment, or the impact of concomitant medications in this meta-analysis. As benzodiazepines are often prescribed for long durations, more information is also needed on the impact on driving beyond the acute period. Furthermore, the effects of these medications on patients with significant anxiety disorders as compared to controls has not been systematically assessed—it is possible that, for some patients, the anxiety itself may impact more negatively on driving than the pharmacotherapy. The interaction of benzodiazepines with alcohol is a clinically important problem when it comes to road safety, but this was outside the scope of the present review.

Since patients often receive long-term treatment with low doses of benzodiazepines, further work is particularly needed to establish whether lower doses of benzodiazepines impair driving. The on-road data presented revealed tracking difficulties the morning after a low dose of benzodiazepine, but not the afternoon after that same dose, and one of the cohort studies[18] found no increase in risk of collisions associated with lower doses of benzodiazepines.

The ideal randomized controlled trial exploring the effects of benzodiazepine use on driving in the real world among patients would be unethical. However, future experimental studies should be done with patient rather than healthy control populations and with more consistent methodologies using typical clinical doses in order to better ascertain the degree and mechanism of driving impairment. Future research is also needed to determine whether informing patients of road risks and monitoring for sedation with benzodiazepines prior to driving would have a significant impact on this risk.

CONCLUSIONS

Given the large numbers of drivers prescribed benzodiazepines, and the significant increase in MVC risk found in this meta-analysis and in the previous systematic review,[43] calls to limit prescriptions for benzodiazepines because of other adverse effects are warranted. Estimates indicated that 1.2 million people worldwide are killed in MVCs annually, with up to an additional 50 million injured.[54] Five benzodiazepines were listed among the top 50 drugs prescribed in the United States in 2005,[55] and these drugs are prescribed for more than 15% of older adults in Ontario, Canada.[41] The present meta-analysis demonstrated that the NNH for MVCs with benzodiazepines is approximately 26, which is particularly concerning given the high prevalence of these drugs in the community. More research is needed to address the relative role of anxiety, insomnia, other psychiatric illness, and low doses of benzodiazepines on road risk. Nonetheless, clinicians must consider and inform patients about the impact of benzodiazepines on driving ability. Guidelines recommending short-term use only may help limit the risks, but are likely insufficient as evidence suggests that the risk may be highest within the first month of prescription.[17] Clinical approaches will, however, not be sufficient, as an estimated 7.8% of U.S. college students have a lifetime prevalence of nonprescription benzodiazepine use.[56] Policy makers should consider making these risks better known to the public, and legislative changes may be required to better deal with drivers under the influence of drugs such as benzodiazepines.[4]

Drug names: alprazolam (Xanax, Niravam, and others), clorazepate (Gen-Xene, Tranxene, and others), diazepam (Diastat, Valium, and others), flurazepam (Dalmane and others), lorazepam (Ativan and others), temazepam (Restoril and others), triazolam (Halcion and others).

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Appendix 1. Articles Excluded From Meta-Analysis

A. Articles excluded because of duplicate publication or population

1. Longo MC, Lokan RJ, White JM. The relationship between blood benzodiazepine concentration and vehicle crash culpability. J Traffic Med 2001;29(1–2):36–43
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B. Articles excluded for the use of unique outcomes or measures which could not be combined for meta-analysis

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