

REVIEW

A systematic review of research examining benzodiazepine-related mortality

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SUMMARY

Purpose This paper will review literature examining the association of benzodiazepine use and mortality.

Methods An extensive literature review was undertaken to locate all English-language published articles that examine mortality risk associated with use of benzodiazepines from 1990 onwards.

Results Six cohort studies meeting the criteria above were identified. The results were mixed. Three of the studies assessed elderly populations and did not find an increased risk of death associated with benzodiazepine use, whereas another study of the general population did find an increased risk, particularly for older age groups. A study of a middle aged population found that regular benzodiazepine use was associated with an increased mortality risk, and a study of 'drug misusers' found a significant relationship between regular use of non-prescribed benzodiazepines and fatal overdose. Three retrospective population-based registry studies were also identified. The first unveiled a high relative risk (RR) of death due to benzodiazepine poisoning *versus* other outcomes in patients 60 or older when compared to those under 60. A positive but non-significant association between benzodiazepine use and driver-responsible fatalities in on-road motor vehicle accidents was reported. Drug poisoning deaths in England showed benzodiazepines caused 3.8% of all deaths caused by poisoning from a single drug.

Conclusion On the basis of existing research there is limited data examining independent effects of illicit benzodiazepine use upon mortality. Future research is needed to carefully examine risks of use in accordance with doctors' prescriptions and extra-medical use.

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KEY WORDS — benzodiazepines; mortality

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INTRODUCTION

Benzodiazepines have been widely used in clinical practice for over four decades and continue to be one of the most consumed and highly prescribed class of drugs available.¹ Chlordiazepoxide (Librium) was first introduced to the market in 1960, and because of the relative safety of benzodiazepines, these agents rapidly replaced barbiturates as the preferred sedative hypnotics.²

Most hypnotic drugs are consumed by chronic users who often take a sleeping pill nightly for many years.³

One study showed that in the USA, 65% of total hypnotic consumption was by individuals who took 30 doses or more per month, and the median usage was reported as 5 years.⁴ It has also been reported that the majority of hypnotics are used by persons over 60 years of age.³ Among this population, prevalence rates of benzodiazepine usage greater than 20% have been reported.^{3,5,6} In a study examined in more detail in this review, a prevalence of 30% was found among the elderly population in The Netherlands.⁷

Benzodiazepines promote the binding of the major inhibitory neurotransmitter γ -aminobutyric acid (GABA) to the GABAA subtype of GABA receptors in the central nervous system. Benzodiazepines are indicated for use in anxiety, insomnia, muscle

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spasticity including tetanus, acute behavioural disturbance, convulsive disorders, presurgical sedation, involuntary movement disorders, and detoxification from alcohol and other substances.^{8,9}

Benzodiazepines can be expected to cause varying degrees of drowsiness, light-headedness, lassitude, increased reaction time, dysarthria, ataxia, motor incoordination, impairment of mental and motor functions, confusion, depression and anterograde amnesia. When the drug is given at the intended time of sleep, the persistence of these effects during the waking hours is adverse. Studies of the psychomotor effects suggest that benzodiazepines slow reaction time and impair driving skills, increasing the risk of motor vehicle accidents in patients who are taking these agents.^{2,10–16} Among the elderly, a relationship between falls, hip fractures and benzodiazepine use has also been described, and is explained by the negative effect these drugs have on balance.^{17–22} These dose-related residual effects can be insidious because most subjects underestimate the degree of their impairment.^{23–25}

Benzodiazepines alone cause significantly less respiratory depression than barbiturates and even large doses are rarely fatal in acute situations. However, when other central nervous system (CNS)-depressants, such as opioids, hypnotics, sedating antidepressants, neuroleptics, anticonvulsants, antihistamines and alcohol, are taken concomitantly, deaths involving benzodiazepines become more common place.^{2,23,26,27} The intensity and incidence of CNS toxicity generally increase with age; both pharmacokinetic and pharmacodynamic factors are involved.¹⁹

The specific concerns about the long-term use of benzodiazepines vary and include tolerance development and dose escalation, dependency, medication abuse and withdrawal difficulties, and an increased risk of death.²⁵ Tolerance develops quickly to benzodiazepines, and can limit long term efficacy in some clinical conditions such as seizures. Chronic benzodiazepine use poses a real risk for development of physiological and psychological dependence and abuse based on the drug's dosage, duration of therapy and potency.^{2,25} Both tolerance and dependence can lead to dose escalation and compounding of adverse events. Of significance is an association noted between benzodiazepine use and depressive symptoms and, in some cases, the intent or act of suicide.^{28–30} Furthermore, other paradoxical reactions, such as behavioural disinhibition and aggression, can also occur with the use of benzodiazepines.^{23,31}

All of these adverse effects have created concern amongst the medical profession to some degree. Logic tells us that risks of impaired driving and falls in the elderly have the potential to create serious public

health issues. But questions remain: are we underestimating the adverse effects of benzodiazepine use? Is there a link between benzodiazepine use and increased mortality? Historically, most of our knowledge about the long-term risks of hypnotic medications comes from voluntary reporting. Unfortunately, these sources are unreliable and we are left with examining clinical case series data to provide information on the long-term use of hypnotic medication.

The Global Burden of Disease (GBD), Injuries and Risk Factors Study (GBD Study 2005) is a follow-up from the original GBD Study of 1990.^{32,33} It involves a systematic assessment of the data on all diseases and injuries and will produce comprehensive and comparable estimates of the burden of diseases, injuries and risk factors across the globe. As part of this process, a systematic review was undertaken to determine the existing evidence of mortality risk for extra-medical illicit benzodiazepine use—that is, use *outside* the advice of a doctor or allied health professional. This was intended to inform decisions about the strength and quality of evidence for the conduct of estimates of the global burden of disease attributable to illicit benzodiazepine dependence.¹

Due to a dearth in literature and difficulties in distinguishing between illicit and non-illicit use of a widely used prescription medication, this systematic review was extended to include both prescription and non-prescription use, and both illicit and licit use. This paper aims to

1. Examine whether there is evidence of elevated mortality risk among heavy or dependent benzodiazepine users;
2. Examine whether there is sufficient evidence of elevated risk of adverse outcomes of benzodiazepine use, such as deaths due to injuries, which might be examined as part of the 'comparative risk assessment' component of the Global Burden of Disease project.²

METHODS

An extensive literature review was undertaken utilizing Embase, PsycInfo and Medline databases to locate all english-language published articles that examine mortality risk associated with use of benzodiazepines from 1990 onwards (see Annex 1 for search terms used). Studies were graded (see Annex 2) to determine the quality of the research. A number of case-series studies present crude data from various sources that can provide useful sources for discussion.^{34–48} However, it

¹Refer to GBD website <http://www.gbd.unsw.edu.au>.

²Comparative risk assessment allows the evaluation of the changes in population health which would result from modifying the population distribution of exposure to a risk factor or a group of risk factors

Table 1. Population-based registry studies of benzodiazepine-associated mortality

Reference	Location	Quality score	Sample population	Sample size	Period of follow-up	Definition of use	Estimate		
Rogers <i>et al.</i> 2007	USA	8	All adult patients ≥ 20 years old on the Toxic Exposure Surveillance System (TESS) database	72 694	1995–2002	Benzodiazepines (no other substances) present in toxicology screen	Acute poisoning mortality in 60 or older compared < 60 , unadjusted RR = 7.1 (95%CI = 3.2–15.5). Adjusted OR for each 10-year increase in age = 1.7 (95%CI = 1.4–2.0)		
Drummer <i>et al.</i> 2004	Vic, NSW and WA, Australia	9	Drivers killed in on-road motor vehicle crashes	3389	1990–1999	Benzodiazepines (no other drugs or alcohol) present in toxicology screen	Driver culpability OR = 1.27 (95%CI = 0.5–3.3)		
Shah <i>et al.</i> 2001	UK	12	Deaths from drug poisoning	15 720 deaths due to poisoning, of which 1667 were due to benzodiazepines (alone or in combination with another substance)	1993–1998	Presence of benzodiazepines mentioned in deaths from overdose and poisoning database.	Age-standardized mortality rates (per million)		
								Males	Females
							1993	7.1	4.1
							1994	7.3	3.9
							1995	6.7	3.4
							1996	6.8	2.4
							1997	7.0	2.8
1998	6.6	2.4							

was decided crude data does not provide significantly useful insight into the real impact of benzodiazepine use on mortality within a population and therefore these studies were excluded from the presented results. From 9159 publications retrieved from the search, nine studies were included in the present review (Figure 1).

RESULTS

Population-based registry studies

Three retrospective population-based registry studies, all from high income countries, were identified from the literature search. All three studies used differing types of estimates in their data analysis. Rogers *et al.* examined a national database of calls received by US poison centres regarding poisoning and exposure cases and unveiled an extraordinarily high relative risk (RR) of death due to benzodiazepine poisoning *versus* other outcome in patients 60 or older when compared to under 60 (RR = 7.1, 95%CI = 3.2–15.5). The adjusted odds ratio (OR) of death for each 10-year increase in age was 1.7 (95%CI = 1.4–2.0).⁴⁹

Using case-control responsibility analysis, Drummer *et al.* examined the role of benzodiazepines in driver fatalities in on-road motor vehicle accidents. Benzodiazepines showed a positive association with driver-responsible fatalities (OR = 1.27, 95%CI = 0.5–3.3). However, because other drugs were detected post-mortem, the power of the study was reduced and the

estimate was non-significant when presence of other drugs was controlled for.⁵⁰

Lastly, Shah *et al.* found some interesting age-standardized benzodiazepine associated mortality rates. Most deaths associated with benzodiazepine poisoning involved additional substances (71%), particularly opioids, but this study found that benzodiazepines caused 3.8% of all deaths caused by poisoning from a single drug. The age-standardized mortality rate (per million population) for males ranged from 7.1 in 1993 to 6.6 in 1998. For females, the rate ranged from 4.1 in 1993 to 2.4 in 1998.⁵¹

Cohort studies

Six prospective cohort studies meeting criteria were identified and are presented in Table 2. All studies were from high-income countries within Europe and North America.

Vinkers *et al.* found RR of all-cause mortality was not increased in elderly users of benzodiazepines both before and after adjustment for confounding factors; RR were 0.77 (95%CI = 0.51–1.17), and 0.68 (95%CI = 0.44–1.04), respectively. However, an increase in fracture-related mortality was inferred, but not significant, with a hazard ratio (HR) of 2.71 (95%CI = 0.37–19.76). This finding is consistent with results from previous cross-sectional studies and highlights concerns about fracture-related mortality among the elderly.⁷

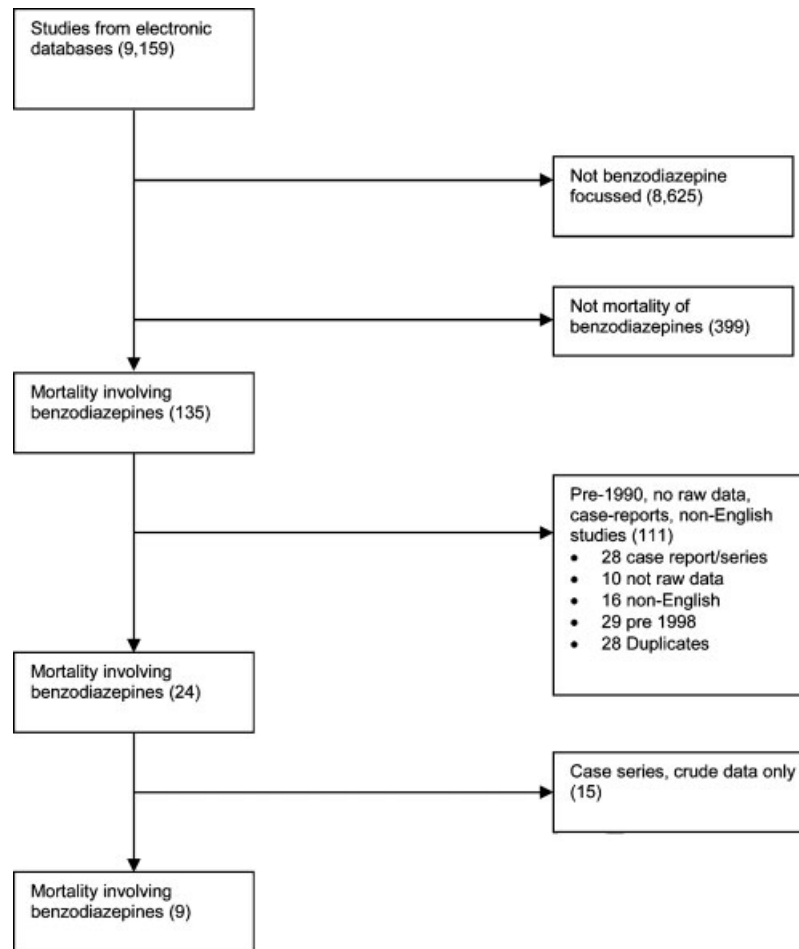


Figure 1. Search results

Another European study by Hausken *et al.* supports an increased risk of mortality with daily use of benzodiazepines among those aged 40–42 (at baseline). Increased HRs persisted for females after even the most comprehensive adjustment for confounding variables (RR = 1.5 [95%CI = 0.9–2.7] for men and 1.7 [95%CI = 1.1–2.6] for women). A dose-response relationship was observed with regular use being the highest risk for mortality.⁵²

A third cohort study by Hogan *et al.* that examined an elderly population found no significant differences in mortality between users (54.8%) versus non-users (53.2%)⁵³ This study did not provide standardized estimates and thus did not meet the quality index criteria but was included for interest's sake given the limited number of studies available.

The paper by Gossop *et al.* found a significant relationship between regular use of non-prescribed benzodiazepines and fatal overdose amongst 'drug misusers' (OR = 3.32, 95%CI = 1.58–6.97). It should

be noted that typically more than one drug was detected at post-mortem. However, after adjustment for confounding effects of use of other substances the relationship held (OR = 2.86, 95%CI = 1.32–6.16).⁵⁴

In 1998, Kripke *et al.*⁴ showed an association between prescription sleeping pill use and an increased risk of death within 6 years. The standardized mortality ratio (SMR) for men and women using at least 30 sleeping pills per month, adjusted for age, was 3.18 and 2.82, respectively ($p < 0.001$). After adjusting for a further 14 variables, the SMR for males and females was reduced to 1.17 (not significant) and 1.41 ($p < 0.001$), respectively. HRs associated with use of sleeping pills at least 30 times per month, adjusted for over 30 variables, were significant among older age groups. This built on findings from previous research,^{55–57} but used a more robust prospective cohort study-design which controlled for multiple variables. Among some age groups, the HRs associated with regular sleeping pill use was similar to the HRs of

Table 2. Cohort studies examining benzodiazepine-associated mortality

Reference	Location	Quality score	Sample population	Sample size	Period of follow-up	Definition of use	Estimate
Hausken <i>et al.</i> 2007	Østfold and Aust-Agder, Norway	8	General population aged between 40 and 42 years of age	14 951	T1 = 1985–1989, follow-up = 18 years	Daily use in past month	All-cause mortality, adjusted HR = 1.5 (95%CI = 0.9–2.7) for men and 1.7 (95%CI = 1.1–2.6) for women
Vinkers <i>et al.</i> 2003	Leiden, The Netherlands	7	All inhabitants of Leiden >85 years of age	599	1997–2002	Use for more than half of the 3 month assessment period	All-cause mortality, adjusted RR = 0.68 (95%CI = 0.44–1.04). Fracture-related mortality, unadjusted RR = 2.71 (95%CI = 0.37–19.76)
Hogan <i>et al.</i> 2003	Canada	6	General population >65 years of age	2914	1990–1996	Current use	All-cause mortality of users (54.8%) versus non-users (53.2%) at baseline ($p = 0.48$)
Gossop <i>et al.</i> 2001	United Kingdom	8	Drug misusers in 54 treatment centres	1075	1995–1999	Weekly or more frequent use	Regular (weekly or more frequent) use of non-prescribed benzodiazepines associated with fatal overdose, adjusted OR = 2.86 (95%CI = 1.32–6.16)
Kripke <i>et al.</i> 1998	United States of America	10	General population (not necessarily representative)	1 099 830	1982–1988	Daily use in past month	Standardized mortality ratios for use of sleeping pills 30+ times per month: Adjusted for age 3.18 for males and 2.82 for females ($p < 0.001$). Adjusted for 15 variables 1.17 for males (ns) and 1.41 for females ($p < 0.001$)
Rumble & Morgan 1992	England	6	General population, elderly (≥ 65 years of age)	1042	1985–1990	Use of hypnotic drugs 'sometimes' or more often	Mortality of hypnotic users, odds ratio, adjusted for sex, health risk and usual sleep duration: 1.20 (95%CI = 0.83–1.73)

smoking 1–2 packs of cigarettes per day.^{3,4} It should be noted that this study did not specify which sleeping pills in particular were associated with increased mortality, so it is not known whether there was an increased risk of death associated with benzodiazepines in particular. Furthermore, separate analyses were conducted for two common types of benzodiazepines (diazepam and chlorthalidone), and did not find increased mortality associated with these particular drugs. Despite acknowledgement of bias and limitations, this study along with previous work propelled a debate regarding the real safety of benzodiazepines.²⁵

A study by Rumble and Morgan⁵⁷ assessing an elderly cohort from the general population did not find an increased risk of mortality among ‘hypnotic’ drug users. Although an initial association was found between increased mortality and the use of medication to aid sleep, once this category was broken down into ‘hypnotic’ medication (mainly benzodiazepines) and ‘other’ sleep medication, only the ‘other’ category persisted to be associated significantly with mortality. It should be noted that this study did not distinguish between those who used benzodiazepines infrequently and frequently.

A recent study assessing benzodiazepine-related mortality among dialysis patients in the United States did not meet criteria for inclusion in this review, as it is sampled a very specific patient population.⁵⁸ However, it is worth mentioning that although this study found a slightly increased risk of mortality associated with benzodiazepine use (HR = 1.15, 95%CI = 1.02–1.31), further analysis revealed that this excess mortality was only present for those with chronic obstructive pulmonary disease. Benzodiazepine use was not associated with a greater risk of hip fracture.

DISCUSSION

Six prospective cohort studies assessing the mortality risk of benzodiazepine use meeting the inclusion criteria were identified. The populations studied varied and included elderly populations, a middle-aged population, a general population sample and ‘drug misusers’. All studies were from high-income countries within Europe and North America. None of the studies specifically examined *illicit* benzodiazepine use.

The results from the cohort studies are mixed and inconclusive; Vinkers *et al.* Rumble and Morgan and Hogan *et al.* found no increased mortality among elderly users of benzodiazepines, whilst Hausken *et al.* showed a positive association among females in a middle-aged population, and Kripke *et al.* found

significant relationships between mortality and sleeping pill use, particularly among older groups. A dose-response relationship with frequency of use of benzodiazepines was also found in one study which supports the previous finding by Kripke *et al.*^{4,52} Rogers *et al.* believes the large increased mortality in those over 60 years of age, compared to younger people, highlights the importance of increased effects and toxicity of benzodiazepines in the elderly, as described earlier.⁴⁹

In contrast to previous research,^{59,60} benzodiazepines did not show a strong positive association with driver culpability in fatal road accidents. However, this lack of an association may have been due to this study’s lack of power to address the issue; benzodiazepines have been shown to increase crash risk in a number of epidemiological studies.^{10,11,60–62} While the rates in Shah *et al.* are relatively low, it does highlight the fact that benzodiazepines do pose a risk and their safety should not be overestimated.

Increased mortality associated with benzodiazepine use has been clearly documented among ‘drug misusers’. In a sample of injecting drug misusers, non-opiate drugs were involved in approximately half of fatal overdoses along with opiate drugs, and benzodiazepines made up the majority of this ‘non-opiate’ category.²⁷ Other studies have found similar results.²⁶

Limitations

All studies to date, including Kripke *et al.* acknowledge serious limitations in their design and data. Perhaps the most significant and most difficult to overcome is the accurate certification of cause of death. In some of these papers no standardized system of identifying cause of death is obvious. This creates inherent problems with misclassification.⁵⁴ Some of the studies listed a standardized system as the method of diagnosing cause of death. But even an internationally standardized system such as International Classification of Diseases ICD has limitations. Small changes in coding of deaths over time create inconsistencies during observations of longitudinal trends.⁴⁸ The skills of those who are assessing cause of death is a significant limitation and it appears reproducibility of diagnosis is often not proven.

It has not been established whether it is appropriate to consider all benzodiazepines as a class or whether there are differing risks associated with individual drugs. Whereas Kripke *et al.* found an increased risk of mortality among those who used sleeping pills, it is not clear whether the increased risk was associated with benzodiazepines in particular. Additionally, this study failed to find an increased risk of mortality associated

with two commonly prescribed benzodiazepines. Another limitation of this study, which is a limitation of these cohort studies generally, is that it was unknown whether those who died had continued to use sleeping pills in the follow-up period, or whether those that did not die initiated use of sleeping pills during the follow-up period.

Many of the sample populations used, particularly for retrospective analysis, are obtained through convenience sampling methods. These samples are usually not representative of the general population. Questionnaires and databases may be incomplete due to non-response, underreporting or incomplete follow-up.^{49,52} It is plausible that the increased rates of mortality associated with violent or reckless behaviour, such as that involved in driving, among benzodiazepine users may also be due to confounding by indication.

A further difficulty lies in the definitions of users and non-users of benzodiazepines. This review has not noted any significant consistency in these definitions. Vinkers *et al.* description of a user was based on prescription duration of more than half of the study period,⁷ whilst Hausken *et al.* classified a user as someone who reported using benzodiazepines in the last month.⁵² Stratification was done during analysis in some studies but was also extremely varied; for example, by number and/or type of benzodiazepine,⁷ and by frequency of use.⁵⁴ It appears commonplace for the definition to be made at post-mortem through toxicology investigations. However a wide range of blood concentrations and a lack of clarity in what are 'toxic' blood levels of benzodiazepines make it difficult to assess the contribution of benzodiazepines in death. Furthermore, post-mortem drug concentrations are difficult to interpret and cannot be compared with single dose or steady-state concentrations in plasma.

In death among both benzodiazepine users and 'misusers', polydrug use has been identified again confusing the explicit role of benzodiazepines in the cause of death. The contributory effects of other drugs such as alcohol and opioids have been well documented.⁵⁴ This is merely one confounding factor creating an enormous complexity in the research.

The interplay of psychosocial, social, economic, biological and other variables complicates the relationship between benzodiazepine use and mortality.^{52,54} Benzodiazepines are psychoactive drugs and are often used in populations who suffer from comorbidity.⁶³ Exacerbation of sleep apnea, sedation, suppression of self-care functions, confusion, amnesia and disinhibition are suggested as possible psychopathological risks, which might help explain the increase in mortality.⁵²

Users often also use other drugs or medication and may be more likely to be smokers or to be physically inactive.⁶³ Perhaps benzodiazepine use is merely a proxy for other risk factors associated with mortality. Confounding factors have been discussed at length by many studies and attempts to control for known or potential factors have been done on occasions. However, large variations in controlling for confounding factors was found between studies with some only adjusting for age and/or sex, whilst others for multiple variables.^{7,52}

All these factors make it extremely difficult to show a cause and effect relationship between benzodiazepine consumption and mortality and to date the findings from available literature cannot be considered anything more than exploratory. The true relationship between benzodiazepine use and increased mortality (and indeed other outcomes not discussed in this article) is still very unclear. Research has also yet to differentiate between different types of benzodiazepines. Currently we do not know whether or not some benzodiazepines carry measurable mortality risk whilst others do not. If there is in fact an increased mortality risk, it is not known whether this risk is carried by certain 'at risk' populations who may have coexisting risk factors.⁴

Well-designed cohort and case-control studies can identify significant associations between various factors and outcomes, however, in concurrence with other authors, there is a need for long-term randomized, double-blind, parallel group, controlled trials of hypnotics. Only randomized controlled trials can control for the complexity of confounding factors to provide conclusive evidence of cause and effect. The necessity for a placebo control is of particular importance.²⁵ A future research agenda should include a long-term controlled trial in users and non-users of benzodiazepines. It could be useful to include a third arm in the study for comparison with other hypnotic-sedative drugs. The sample population should be large and represent a large diversity of characteristics to assist in identification and controlling of confounders and subgroup analysis. Given the widespread use of benzodiazepines and the possible effects of confounding social and economic factors, it is also important to represent a diversity of countries. An international multi-centre trial including low- and middle-income countries, rather than only high-income countries, will be important, particularly as use and abuse of benzodiazepines in these countries can be expected to increase.⁶⁴

Although the primary objective of this paper was to examine the link between benzodiazepine use and mortality in the general population, the majority of the

KEY POINTS

- There is some evidence of increased mortality in regular benzodiazepine users and among 'drug misusers'.
- There is no strong positive association between benzodiazepine use and driver culpability in fatal road accidents.
- Overall, results of cohort studies are mixed and inconclusive.
- There is an absence of data specific to illicit benzodiazepine use/dependence in the general population.

studies presented have examined the link in more 'at risk' populations such as injecting drug users, drivers, non-intentional fatal poisonings, suicide and the elderly. Such targeted research and demographic profiling of those at risk also remains to be critical so that information can be obtained and incorporated into targeted public health programs. Finally, published case-series literature will continue to provide further direction for future research.

CONCLUSIONS

The limited data suggesting elevated overall mortality among benzodiazepine users has not carefully examined whether users were taking medication as directed, or outside the directions of a medical professional. Guidelines for the use of benzodiazepines acknowledge adverse effects and inappropriate prescribing but there are many questions unanswered and recommendations are at times based on research of inadequate quality.^{51,65,66}

On the basis of existing research there is insufficient data to conduct a comparative risk assessment for benzodiazepine use. There are too few studies that report on specific causes of death and examine the risk of such causes of death relative to people who are not using benzodiazepines in an extra-medical manner.

The popularity of benzodiazepines among prescribers and patients should provide impetus for a thorough and conclusive investigation of benzodiazepine-associated mortality risk to prevent avoidable burden of disease and negative public health outcomes.

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ANNEX 1: SEARCH STRATEGY

Databases included were Embase, PsycInfo and Medline.

Search terms:

Mortality

Mortal\$ or fatal\$ or death\$
exp DEATH/or exp 'CAUSE OF DEATH'/or exp SUDDEN DEATH/or exp Mortality/or exp Hospitalization/or exp Fatal Outcome/

And

Benzodiazepines

Benzodiazepine\$ OR benzo OR Benzos OR alprazolam OR anthramycin OR benzodiazepinones OR brotizolam OR bromazepam OR camazepam OR chlordiazepoxide OR cinolazepam OR clonazepam OR clorazepate OR clorazepate dipotassium OR clotiazepam OR cloxazolam OR delorazepam OR devazepide OR diazepam OR etizolam OR estazolam OR fludiazepam OR flumazenil OR flunitrazepam OR flurazepam OR halazepam OR haloxazolam OR ketazolam OR loprazolam OR lorazepam OR lormetazepam OR medazepam OR midazolam OR nimetazepam OR nitrazepam OR nordazepam OR oxazolam OR oxazepam OR phenazepam OR pinazepam OR pirenzepine OR prazepam OR quazepam OR temazepam OR tetrazepam OR tofisopam OR triazolam OR Xanax OR Lexomil OR Valium OR Ativan OR Klonopin OR Restoril OR Serax OR Rohypnol OR Halcion OR Librium OR Dalmane OR ProSom OR Mogadon
exp 'hypnotics and sedatives'/or exp anti-anxiety agents/or exp benzodiazepines/or exp benzodiazepinones/or exp alprazolam/or exp bromazepam/or exp chlordiazepoxide/or exp clonazepam/or exp clorazepate dipotassium/or exp devazepide/or exp diazepam/or exp estazolam/or exp flumazenil/or exp flunitrazepam/or exp flurazepam/or exp lorazepam/or exp medazepam/or exp midazolam/or exp nitrazepam/or exp nordazepam/or exp oxazepam/or exp pirenzepine/or exp prazepam/or exp temazepam/or exp triazolam/

ANNEX 2: QUALITY INDEX

Variable name	Description	Options	Score
Case ascertainment	How representative are the cases chosen?	All cases from a geographically defined population (e.g. all heroin users in treatment in a state or country)	3
		Random, but representative sample of a population (e.g. X number of treatment centres, which are representative of state or country)	2
		Sample restricted to one city (e.g. multiple treatment centres in a city)	1
		Convenience sample, where the representativeness of the sample is unclear	0
		Dependence assessed via structured interview, or in treatment for dependence	2
Measurement	Measurement instrument to determine use or dependence.	Diagnosis from chart/drug use (without formal assessment)	1
		Not specified	0
		Any diagnostic system reported for drug dependence or abuse/dependence inferred from type of sample population	2
Diagnosis	Indicates whether dependence was diagnosed.	Drug use/own system/symptoms described	1
		Not reported	0
Estimate	Type of estimate	Crude mortality rate	
		Yes	1
		No	0
		Standardized mortality ratio	
		Yes	1
Num/Den	Was the numerator <i>and</i> denominator presented for the estimates?	No	0
		Crude mortality rate: person years follow-up reported (denominator)?	
		Yes	1
		No	0

(Continues)

ANNEX (Continued)

Variable name	Description	Options	Score
		Standardized mortality ratio: expected deaths reported (denominator)?	
		Yes	1
		No	0
Num/Den Area/Epoch	Were the numerator and denominator based on identical epochs and identical catchment areas for estimate of interest?	Yes (for CMRs, the estimate will by definition be of the same epoch and catchment area, for SMRs, the expected deaths need to be for the same catchment area and epoch)	1
		No	0
Completeness	Captures response rates and attrition rates	High response rate/follow-up rate (>80%)	2
		Moderate response rate (60–79%)	1
		Exclusions poor response rate (<60%)made	0
Variable name	Description	Options	Score
Representativeness	Determines generalizability of the sample to the population	Well represented/national registers/multiple institutions across states	2
		Small area/not representative of nation/one treatment centre/registers of specific populations	1
		Convenience sampling/not reported	0
Age/sex	Identifies whether age and/or sex specific values were reported.	Yes	2
		Some (e.g. sex and 2 broad age ranges only)	1
		No	0
Qualitative information (free text)			
Quality	To capture methods that were not reported on by other variables (free text)		
Duration FU	To obtain more information about follow-up periods and sample sizes when doing so (free text)		
Quality Index Notes	Insert any other quality information that has not been captured by other variables. For example, note whether the study is one that uses indirect prevalence methods, and state which data sources were used for this.		
Total score			
Out of a possible 18			