HHS Public Access

Author manuscript

Accid Anal Prev. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Accid Anal Prev. 2016 November ; 96: 255–270. doi:10.1016/j.aap.2016.08.001.

Medication use and the risk of motor vehicle collisions among licensed drivers: A systematic review

Toni M. Rudisill[1], **Motao Zhu**[1,2,3], **George A. Kelley**[4], **Courtney Pilkerton**[1], and **Brandon R. Rudisill**[5]

[1] Department of Epidemiology, West Virginia University, PO BOX 9151, Morgantown, West Virginia, 26506, USA

[2] Center for Injury Research and Policy, The Research Institute at Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio, 43205, USA

[3] Injury Control Research Center, West Virginia University, PO BOX 9151, Morgantown, West Virginia, 26506, USA

[4]Department of Biostatistics, West Virginia University, PO BOX 9151, Morgantown, West Virginia, 26506, USA

[5]103 Sun Valley, Morgantown, West Virginia, 26508, USA

Abstract

Objectives—Driving under the influence of prescription and over-the-counter medication is a growing public health concern. A systematic review of the literature was performed to investigate which specific medications were associated with increased risk of motor vehicle collision (MVC).

Methods—The *a priori* inclusion criteria were: 1) studies published from English-language sources on or after January 1, 1960, 2) licensed drivers 15 years of age and older, 3) peer-reviewed publications, master's theses, doctoral dissertations, and conference papers, 4) studies limited to randomized control trials, cohort studies, case-control studies, or case-control type studies 5) outcome measure reported for at least one specific medication, 6) outcome measure reported as the odds or risk of a motor vehicle collision. Fourteen databases were examined along with hand-searching. Independent, dual selection of studies and data abstraction was performed.

Results—Fifty-three medications were investigated by 27 studies included in the review. Fifteen (28.3%) were associated with an increased risk of MVC. These included Buprenorphine, Codeine,

CORRESPONDING AUTHOR Motao Zhu, MD, MS, PhD, Center for Injury Research and Policy, The Research Institute at Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio, 43205, USA, Motao.Zhu@NationwideChildrens.org, Telephone: 614-355-6687.
trudisill@hsc.wvu.edu
gkelley@hsc.wvu.edu
cpilkerton@hsc.wvu.edu
brandonrudisill@gmail.com

Dihydrocodeine, Methadone, Tramadol, Levocitirizine, Diazepam, Flunitrazepam, Flurazepam, Lorazepam, Temazepam, Triazolam, Carisoprodol, Zolpidem, and Zopiclone.

Conclusions—Several medications were associated with an increased risk of MVC and decreased driving ability. The associations between specific medication use and the increased risk of MVC and/or affected driving ability are complex. Future research opportunities are plentiful and worthy of such investigation.

Keywords

Drugs; Driving; Review; Prescription; Ability

1. INTRODUCTION

While the number of motor vehicle collisions (MVC) and subsequent fatalities has steadily declined over the past decade among many high-income countries, MVC still remains one of the leading causes of mortality not just globally, but also within the United States (U.S.). [1-3] In 2010, this equated to approximately one death per collision every fifteen minutes in the U.S.[3] Besides the inherent risks to morbidity and mortality, MVCs are estimated to cost the U.S. over $300 billion dollars per year.[3]

While driving under the influence of alcohol is a well-documented area of study, driving under the influence of drugs (DUID) is also an emerging public health and traffic safety concern.[4-7] Driving under the influence of drugs entails the use of illicit drugs, i.e. drugs that are obtained illegally and with no real medical benefit, such as cocaine and methamphetamine. Driving under the influence of drugs can also entail the use of licit substances, such as common prescription or over-the-counter medications, whose effects impair the driver's ability to safely operate a motor vehicle from one destination to another. However, it's important to realize that while licit drugs can be obtained illegally, abused, or misused, the intent of use by the driver is often difficult to determine. In 2009, approximately 28% of all fatally injured U.S. drivers that were tested for either illicit or licit drugs tested positive for one or more of these substances.[8] In addition, recent research suggests that DUID is increasing nationally.[9]

Due to the complexity of DUID, the primary focus of this paper pertains to the association between licit drug use and MVC. However, one of the fundamental challenges to studying the effects of licit drugs on driving ability is that the relationship is not always as apparent when compared to alcohol.[8] For example, some drugs may not noticeably impair the skills (cognition, psychomotor function, physical ability) necessary to operate a motor vehicle.[10-13] Drugs that are perceived to affect the central nervous system may exhibit different effects among individuals; this may be attributed to the pharmacokinetic or pharmacodynamic properties of the drug,[14] the drug's half-life,[15] interactions with other consumed drugs,[16] tolerance, [17] drug elimination rate,[16] dosage,[15] route of administration,[16] solubility,[18] intestinal pH,[18] current health status of the individual,[16] genetics,[19] etc. It may also be difficult to partition out the effects of the licit drug and the medical condition for which it was taken to remedy.[16] For example, several medical conditions have been associated with an increased risk of MVC. These include, but are not necessarily limited to,

sleep apnea, [20] dementia, [21] arthritis, [22] diabetes, [23] epilepsy, [23] anxiety, [24] depression, [24] and Parkinson's disease.[25]

Numerous reviews and meta-analyses have investigated the association between licit drug use and MVC and/or driving ability. These reviews have focused predominately on opioids,[26-34] benzodiazepines,[29,31,35-38] antihistamines,[39,40] psychoactive drugs,[41-45] antidepressants,[36,46-49] hypnotics,[43,50] anxiolytics,[51,52] and sleep medications.[53-56] Some reviews have also examined multiple drug categories.[57-60] However, the majority of these studies have reviewed or analyzed licit drugs in broad groups.[27,29-31,36,37,42,48] There is the potential that if the drugs within these groups were reviewed individually, the outcome measures of interest may be varied as some drugs may be more or less driver-impairing than others. Therefore, the purpose of this study was to perform a systematic review of the literature to investigate which specific medications, including typical prescription or over-the-counter drugs, may be associated with an increased risk or odds of MVC and/or driving ability among licensed drivers 15 years of age and older.

2. MATERIALS AND METHODS

2.1 Study eligibility

The inclusion criteria for studies, which was defined *a priori*, were as follows: 1) English-language studies published on or after January 1, 1960, 2) licensed drivers 15 years of age and older, 3) studies published in a peer-reviewed journal or non-published (i.e. “grey literature”), which included master's theses, doctoral dissertations, and conference papers, 4) studies limited to randomized control trials, cohort studies, case-control studies, or case-control types of studies , i.e. case cross-over, case-time series, etc. 5) outcome measure reported for at least one specific medication, 6) outcome measure reported as the odds or risk of a motor vehicle collision or some affected aspect of driving ability during an on-road assessment or driving simulation (e.g. brake reaction time, weaving, standard deviation of lateral position, etc.). If the study reported outcome measures for both specific medications and illicit drugs or specific medications combined with alcohol, only outcome measures for specific medications alone were reported. A ‘medication’ was defined as a substance either available by prescription or over-the-counter to remedy a medical condition. Therefore, caffeine, nicotine, vitamins, and nutraceuticals were excluded. If the medication usage was combined with a medical procedure, then the study was excluded to avoid bias. While marijuana has been legalized for medicinal purposes in several states, it was not considered a medication in this analysis as it is still defined as an illegal substance by federal law. Because of the vast difference in the fidelity of driving simulators, a driving simulator must have consisted of a screen, pedals, and steering wheel. If the study did not specify the components of the simulator, an attempt was made to search the make and model of the simulator noted in the study to see if it was comprised of these constituents. The search date of January 1, 1960 was arbitrarily chosen as no DUID studies existed or were published prior to this time. Because of the complexity of the initial study question, it was decided *post-hoc* to only present the studies whose outcomes reported the association between a specific medication and the odds or risk of a motor vehicle collision.

2.2 Data sources

Studies were acquired from the following fourteen databases: 1) Medline (within EBSCO host), 2) PubMed, 3) Scopus, 4) International Pharmaceutical Abstracts (IPA), 5) Cochrane Central Register of Controlled Trials (CENTRAL), 6) CINAHL (within EBSCO host), 7) AgeLine, 8) Web of Science (WOS), 9) PsychInfo, 10) Transportation Research Information Services (TRID), 11) Academic Search Complete, 12) EconLit 13) SafetyLit, and 14) ProQuest Dissertations and Theses (ProQuest). All searches were performed by TMR with the assistance of a Health Sciences Librarian from West Virginia University. The last search was performed in June 2014. All searches were conducted using Medical Subject Headings (MESH) terminology. Each search contained the phrases, “drug”, “medication”, “traffic collision”, and “motor vehicle”. An example search strategy (ProQuest) is included in Appendix A.1. In addition to the fourteen databases, studies from TMR's personal library were also reviewed for eligibility. Hand searches from the reference lists of included studies were also examined. Government websites, such as the National Highway Traffic Safety Administration, were also searched for relevant government-performed studies.

2.3 Selection of studies

All included studies were independently selected by TMR and BR. Any discrepancies regarding the inclusion of studies were resolved through discussion. If a consensus could not be reached, MZ acted as the arbitrator. All studies, whether included or excluded in the review, were stored in EndNote, version X5, along with reasons for including or excluding the study.

2.4 Data abstraction

A codebook was developed by TMR in Microsoft Excel 2007. The codebook included variables regarding study characteristics (i.e. study design, year when published, etc.), study population (i.e. country of origin, ages/sex of participants, etc.), medications investigated, outcome measures, and study quality. All studies were coded by TMR and CP independent of one another. After coding was completed, both authors met to compare the entries for accuracy and/or precision. Any discrepancies were resolved through discussion. If disagreements could not be rectified, MZ acted as the arbitrator.

2.5 Study quality

The included studies were evaluated for quality by TMR and CP independent of one another. An abbreviated version of the checklist for measuring study quality designed by Downs and Black was used to score the studies for quality.[61] The original checklist designed by Downs and Black, which has been deemed both valid and reliable, is a 27 question, qualitative check-list to evaluate a study for internal and external validity, quality of reporting, and power; for every positive attribute/response, a study receives one point.[61] At the end of assessment, the points are tallied; the more points a study earns, the higher the study's quality.[61] Since not all questions in the Downs and Black scale were applicable to the review, the abbreviated checklist contained 5 measures of quality (i.e. a total of 5 possible points). It was determined *a priori* that if a study had less than 3 points, it would not be included in the review. After all coding and quality assessments were completed, the authors

met to compare their entries for accuracy and/or precision. Any discrepancies were resolved through discussion. If disagreements could not be reached, MZ acted as the arbitrator. No studies that met the eligibility criteria were excluded based on quality.

2.6 Data synthesis

All studies were synthesized qualitatively. No meta-analysis was performed given the *a priori* assumption that excessive statistical and/or methodological heterogeneity would be observed.[62] However, the overall odds or risk ratio for each medication and outcome was presented graphically and included the point estimate and corresponding 95% confidence intervals. *Post hoc,* it was realized that some included studies only presented crude estimates, [63-82] while others adjusted their outcome measures for various potential confounders such as age, gender, miles driven, day of the week, etc.[83-89] For those studies that presented adjusted estimates or did not include 95% confidence intervals for crude estimates, [83-89] then the adjusted point estimates and 95% confidence intervals for the population were reported. If a study's point estimate was greater than 1, this indicated that there was excess risk of collision; a point estimate less than 1 indicated that the medication use was associated with a decreased risk of collision (i.e. it was protective against MVC). Results were considered statistically significant if the 95% confidence intervals did not include 1.

3. RESULTS

3.1 Study characteristics

The search processes for the selection of studies, as well as reasons for excluding studies, are presented in Figure 1. Of the 6,516 records obtained, 208 studies met the original study question. Of these 208 studies, 27 pertained to the association of specific medications and the odds or risk of motor vehicle collision, while the others pertained to the association of specific medications and affected driving ability determined through the use of driving simulators (n=90) or actual driving assessments (n=91).

The characteristics of the 27 studies included in this review are presented in Table 1. [63-89] The included studies spanned from 1992-2013. Of these studies, eight (29.6%) were conducted in Norway,[69,70,72,73,75,77,79,82] six (22.2%) in the United States,[63,64,81,83-85] five (18.5%) from Canada,[65,66,86-88] three (11.1%) from England,[71,74,76] three (11.1%) from France,[67,78,80] one (3.7%) from the Netherlands,[68] and one (3.7%) from Taiwan.[89] Eleven (40.7%) of these studies were cohort designs, while the rest consisted of case-control or variations of a case-control design. Only one study was limited to females.[63] Nine (33.3%) of the studies were limited to older adult drivers typically 60 years of age and older, nine (33.3%) included drivers aged approximately 18-70 years, and the remaining nine (33.3%) covered all licensed drivers from the country of origin. Three studies (11.1%) were doctoral dissertations, [63,66,81] one study (3.7%) was a conference paper, [68] and the remaining 23 studies (85.2%) were published in peer-reviewed journals. Among these studies, 53 specific medications were evaluated. Diazepam, Zolpidem, Zopiclone, and Insulin were the most commonly studied medications. With respect to study quality, 23 of the 27 studies (85.2%) received a score of 5 (Table 1). The studies that were scored 4 out of 5 typically did not

explain their statistical methodology in sufficient detail, i.e., did not mention or explain what types of regression they utilized to obtain study outcome measurements.[65,67,68]

3.2 Study outcomes

The medications that were investigated by the studies included in this review are presented by drug category in Figures 2-9. The drug categories consisted of analgesics, anticonvulsants, antidepressants, antihistamines, antihyperglycemics, benzodiazepines, and sleep-enhancing medications; if a drug could not be categorized into any of these groups, it classified as 'Other Medications'. Studies were adjusted by the original study authors for age and gender,[83] age, sex, gender, and annual mileage,[84] age, sex, gender, and days driven per week,[85] and age, gender, residence in the country, previous injurious MVC, chronic disease score, exposure to antidepressants, anti-epileptics, benzodiazepines, antipsychotics, anti-migraine, muscle relaxants, and narcotic analgesics.[86] Another study was adjusted for cardiac or stroke events within the past year as well as the following drug classes in the previous 60 days: antidepressants, anti-epileptics, benzodiazepines, antipsychotics, anti-migraine, narcotic analgesics, muscle relaxants.[87] Another study was adjusted for age, gender, previous MVC, and place of residence,[88] while another was adjusted for concomitant use of the following medications: Zolpidem, Zopiclone, long and short acting benzodiazepines, antihistamines, anticonvulsants, antidepressants, other sedatives/hypnotics, other psychoactive drugs, muscle relaxants, and opioid analgesics.[89]

3.2.1 Analgesics—Among the included studies, the associations between seven analgesic medications and the odds or risk of MVC were investigated (Figure 2). These medications included Aspirin[83] Buprenorphine,[80] Codeine,[68,72,74] Dihydrocodeine,[74] Methadone,[79,80] Morphine,[74] and Tramadol.[72,74] As shown in Figure 2, those taking Aspirin[83] and Morphine[74] did not experience a statistically significant increase in MVC; contrarily, those taking Buprenorphine,[80] Dihydrocodeine,[74] and Methadone[79,80] did experience an increase in MVC risk. The results for both Codeine and Tramadol were mixed. Three studies investigated the effects of Codeine on the risk of MVC; two of these studies reported a statistically significant increase in MVC, [72,74] while one study did not.[68] The study that did not report an association for the increased risk of MVC and Codeine may be because of sample size; [68] the study may not have had the statistical power to detect a difference. As for Tramadol, two studies investigated its effects and only one[74] reported a statistically significant increase in MVC. This, too, may have been attributed to sample size. Out of 181 collisions, only 20 people were found positive for Tramadol in the study conducted by Bachs et al.[72]

3.2.2 Anticonvulsants—Three studies investigated the effects of anticonvulsants, which included Carbamazepine,[86] Phenytoin,[63] and Valproate.[73] As seen in Figure 3, none of these medications were associated with a statistically significant increase of MVC.[63,73,86] Though not significant, Carbamazepine and Valproate were trending towards being protective against the risk of MVC.

3.2.3 Antidepressants—Antidepressant medications were the most studied class of drug. Twelve medications were investigated amongst three studies, which included

Amitriptyline,[74,76] Cetirizine,[74] Citalopram,[74,76] Dosulepin,[74,76] Escitalopram,[76] Fluoxetine,[74,76] Lofepramine,[74,76] Mirtazapine,[76] Paroxetine,[74,76] Sertraline,[76] Trazodone,[74,76,81] and Venlafaxine.[76] As seen in Figure 4, with the exception of one outcome for Dosulepin and two for Trazodone, virtually all of these medications were found to not be associated with a statistically significant increase of MVC. Though not significant, several of these medications were trending towards being protective against a MVC; this included Amitriptyline, Fluoxetine, Mirtazapine, Paroxetine, Sertraline, and Venlafaxine. In one study, Dosulepin was found protective[76] against MVC while another study[74] found no association. This may be attributed to the differences in study design or possibly the study population as the study that found Dosulepin protective was limited to older adult drivers.[76] All three studies investigated Trazodone and the findings for this medication were mixed. Two studies found Trazodone to not be statistically significant for the increased risk of MVC.[74,76] Hansen found that both new (HR=2.15; 95% CI 1.83-2.51) and prevalent users (HR=1.47; 95 % CI 1.18-1.85) of Trazodone to be at increased risk of MVC.[81] These differences may be attributed to the study population or possibly the study design.

3.2.4 Antihistamines—One study investigated the effects of nine antihistamines on the odds of MVC, which included Astemizole, Brompheniramine, Chlorphenamine, Desloratidine, Fexofenadine, Hydroxyzine, Levocitirizine, Loratadine, and Terfenadine.[74] As seen in Figure 5, only Levocitirizine was associated with an increased risk of MVC.[74]

3.2.5 Antihyperglycemics—Six studies investigated three antihyperglycemic medications which included Insulin, [66,71,75,84,85,88] Metformin, [88] and Sulfonylurea[88] (Figure 6). Of the six studies that reported outcome measures for Insulin, only two reported a statistically significant increase in MVC.[66,75] The other four studies reported no statistically significant associations.[71,84,85,88] This may be attributed to the adjustment of covariates. One study which included the odds of having any crash or a not-at-fault crash was adjusted for age, sex, race, and annual mileage,[84] while another study was adjusted for age, gender, and days driven per week.[85] Other studies were adjusted for age, sex, previous MVC, and place of residence,[88] or unadjusted but stratified by the following ages: <25, 25-44, 45-64, 65-74, and 75-84 years of age.[71] Since two studies were not adjusted and the other studies were adjusted or stratified by age, it is possible that these two studies were statistically significant because they were left unadjusted.[66,75] In addition, one study found that Metformin was not associated with an increased risk of crash, while Sulfonylurea was protective against MVC.[88]

3.2.6 Benzodiazepines—Nine benzodiazepines were investigated amongst seven studies which included Chlordiazepoxide,[74] Diazepam,[65,69,74,77,82] Flunitrazepam,[70] Flurazepam,[65] Lorazepam,[65] Nitrazepam,[70,74] Oxazepam,[65] Temazepam,[74,81] and Triazolam[65] (Figure 7). Chlordiazepoxide and Oxazepam were not found to be statistically significant for the increased risk of MVC.[65,74] Flunitrazepam, Flurazepam, Lorazepam, Temazepam, and Triazolam were found to be statistically significant for an increased risk of MVC.[65,70,74] The findings for Diazepam were slightly mixed. Of the five studies investigating the effects of Diazepam, four found a statistically significant increase in MVC[65,69,74,82] while only one did not.[77] Since the confidence intervals for one study was quite large, this estimate was

likely not precise.[77] The findings were also mixed for Nitrazepam. One study found it to be associated with an increased risk of MVC[70] while another did not.[74] It should be noted that the study that did not report a statistically significant increase in MVC trended towards an increased risk.[74] This discrepancy may have been attributed to different study designs.

3.2.7 Sleep Medications—Zolpidem and Zopiclone were the only two strictly sleep-enhancing medications to be investigated (Figure 8). Five studies explored Zolpidem's effects,[70,74,78,81,89] while six studies examined Zopiclone.[70,74,77,78,82,89] Both medications appeared to be associated with an increased risk of MVC. Four[70,78,81,89] of five studies found Zolpidem to be statistically significant for an increased risk of MVC. Two[70,77] of six studies found Zopiclone to be statistically significant for an increased risk of MVC, while the other four were trending towards an increased risk, but not statistically significant.[74,78,82,89]

3.2.8 Other Medications—Eight medications could not be grouped into any of the other drug categories (Figure 9). These included Atenolol (i.e. a beta-blocker),[74] Carisoprodol (i.e. a muscle relaxant),[69] Estrogen (i.e. a hormone),[85] Lithium (i.e. an antipsychotic),[73,86] Methyldopa (i.e. an antihypertensive)[63] Propranolol (i.e. a beta-blocker),[74] Salbutamol (i.e. an antispasmodic),[69] and Warfarin (i.e. an anticoagulant).[87] Of these medications, Carisoprodol was associated with a statistically significant increase in MVC.[69] The findings for Lithium and Warfarin were mixed. One study reported an increased risk of MVC for Lithium[86] while another reported no statistically significant association.[73] This may have been attributed to differences in study design or the age of the population. As for Warfarin, one study found that Warfarin was initially protective against MVC for new users, but if taken for an extended period of time, no association was found.[87] All other medications were not found to be statistically significant for the increased risk of MVC.

4. DISCUSSION

4.1 Findings

The principal finding of this study is that among the 53 specific medications investigated by the 27 studies included in this review, 15 medications (28.3%) were associated with an increased risk of motor vehicle collision. The medications that were associated with an increased risk of collision were: Buprenorphine, Codeine, Dihydrocodeine, Methadone, Tramadol, Levocitirizine, Diazepam, Flunitrazepam, Flurazepam, Lorazepam, Temazepam, Triazolam, Carisoprodol, Zolpidem, and Zopiclone. Two (3.8%) of the 53 medications, Sulfonylurea and Warfarin, may be protective against MVC. All other 36 medications (67.9%) were not significantly associated with MVC. The findings of this review illustrate that certain medications, even within the same class or drug category, may be more associated with crash risk than others.

These findings are consistent with the current literature. With the exception of Carisoprodol, Dihydrocodeine, and Tramadol, 12 of the 15 medications that were associated with increased MVC have also been studied in either driving simulations or actual driving assessments. Both types of studies use common measures to assess one's ability to safely navigate a vehicle; these measures include the ability to maintain position within the lane

[i.e. standard deviation of lateral position (SDLP)], tracking (i.e. following an object), missed instructions or directions, actual collisions with cars or objects, the ability to maintain constant speed, reactions or reaction time to stimuli, the ability to keep the vehicle on the road, steering wheel angle, divided attention (i.e. performing a task, such as acknowledging a sign or symbol, while driving), and gap acceptance (i.e. ability to judge distance between objects). There is evidence from both driving simulation and driving assessment studies that eight of these medications may also affect some aspects of driving ability; this includes Diazepam, Flunitrazepam, Flurazepam, Lorazepam, Temazepam, Triazolam, Zolpidem, and Zopiclone.

Diazepam, an anxiolytic, has been studied more extensively than any other of the medications. Six driving assessments[90-95] and ten simulation studies [96-105] have investigated its effects on driving ability. The majority of studies have been randomized, double-blind, and cross-over by design. Participants in these studies have involved both genders of different age ranges. Professional drivers have also been used to study its effects.[93] Diazepam has been shown to negatively affect driving ability in virtually all the studies whether the source is an actual driving assessment or driving simulation. Collectively, Diazepam has affected nearly every aspect of driving ability including braking, SDLP, incidence of collisions, driver behavior, tracking, steering, car following, and reaction time, compared to placebo conditions.[90-105]

Flunitrazepam, a benzodiazepine, has been studied in one simulation[106] and one driving assessment.[107] In the simulation study, 16 healthy subjects underwent a double blind cross-over study where they took Flunitrazepam the night before than completed the simulation the next morning to assess residual effects of the drug. Participants tended to speed when taking Flunitrazepam.[106] In the driving assessment, 32 outpatients with sleep disorders received either 2 mg of Flunitrazepam or 20 mg of Temazepam daily for seven days and partook in a driving test on day one and day seven.[107] Steering, lateral acceleration, and velocity were used to assess driving ability. Those taking Flunitrazepam experienced greater decreases in steering ability compared to Temazepam.[107]

Flurazepam, a benzodiazepine derivative, has been investigated in two driving assessments[108,109] and two simulations.[105,110] In a blinded, cross-over trial, 12 female volunteers received placebo or Flurazepam the night before and then drove a course the following morning. Under Flurazepam, participants incorrectly performed passable gaps.[108] In another double-blind, cross-over study, 16 patients treated for insomnia performed a 75km driving assessment. When treated with Flurazepam, SDLP was decreased, but was more pronounced in female subjects during morning assessments.[109] In a double-blind, cross-over simulation using 12 healthy volunteers, general reaction time to signals was impaired under Flurazepam compared to control periods.[110] In another placebo-controlled, double-blind simulation using 54 healthy volunteers, executed tasks while driving were decreased in those taking Flurazepam compared to placebo periods.[105]

Lorazepam, a benzodiazepine, has been evaluated in seven driving assessments[94,111-116] and one simulation.[117] All of the studies were randomized, double-blind, and cross-over by design. Four of the driving assessments were limited to males,[111,114-116] two to

females,[112,113] and one to a group of clinically anxious and non-anxious participants of mixed gender.[94] The simulation study encompassed healthy volunteers.[117] Driving ability (i.e. SDLP, inappropriate line crossings, car handling, lane-keeping, speed, following distance, and tracking) was affected in all driving assessments and simulations.[94,111-117]

Temazepam, a benzodiazepine prescribed to treat short-term insomnia, has been evaluated in five driving assessments[107,108,118-120] and one simulation study.[121] All of the driving assessments and simulations were randomized, double-blind, and cross-over by design. The driving assessments used female volunteers in two studies,[108,120] one used rotating shift workers,[119] one used healthy volunteers,[118] and one used insomniacs.[107] The driving simulation used only female participants.[121] Temazepam affected driving ability (i.e. participants hit more bollards) in only one study, but none of the others.[108]

Triazolam, a sedating benzodiazepine used to treat severe insomnia, has been studied in three driving assessments[119,122,123] and three driving simulations.[15,124,125] All three driving assessments were randomized, double-blind, and cross-over by design.[119,122,123] Two of the studies used rotating shift workers[119,123] while the third used healthy volunteers.[122] In the two driving assessments using shift workers, Triazolam severely affected driving ability;[119,123] driving performance was not as affected among the healthy volunteers.[122] In the simulation studies, all three were similar in design and used commercial bus drivers as the study population.[15,124,125] Driving ability (i.e. lane keeping, driving path, steering, braking, and SDLP) was affected in all of the simulation studies simulations.[15,124,125]

Zolpidem and Zopiclone, two sleep-promoting medications, were evaluated simultaneously in two driving assessments[126,127] and four driving simulations.[106,128-130] The two driving assessments were randomized, double-blind, and cross-over by design that used healthy participants of all age ranges.[126,127] In both studies, Zopiclone and Zolpidem affected driving ability. In the simulation studies, all four were randomized, double-blind, and cross-over by design; three studies used participants 55 years of age and older, [106,128,130] while the mean age in the fourth study was 38 years.[129] Zopiclone affected driving ability in all four simulations; [106,128-130] Zolpidem affected driving ability in three simulations, [106,129,130] but not in the fourth.[128] Zolpidem and Zopiclone were studied individually in three additional studies each. Zolpidem affected driving ability in all three studies, [121,131,132] while Zopiclone affected driving ability in two of the three studies.[118,133,134]

In addition to the eight medications described, four of the other 15 medications associated with increased risk of MVC have not been associated with affected driving ability during driving assessments or simulation studies; this includes Buprenorphine, Methadone, Levocitirizine, and Codeine. One driving simulation study investigated the effects of Buprenorphine and Methadone in a group of former heroin addicts whom were stabilized for at least three months and compared them to a group of healthy controls.[135] SDLP, speed, steering wheel angle, and reaction time were used to assess driving ability. There was no difference in driving ability between the placebo group and those treated with either Buprenorphine or Methadone.[135] Another study investigated the effects of Levocitirizine through an on-the-road assessment, which measured SDLP and speed to evaluate driving ability.[136] No difference in performance was detected among those treated with

Levocitirizine and the control group.[136] Codeine has been studied in three driving simulations.[96,137,138] A randomized, double-blind, placebo-controlled, crossover study of 13 healthy volunteers were administered therapeutic levels of Codeine and assessed on SDLP and time to collision under simulation. There were no differences between exposure and control periods.[137] In another simulation study, 70, 16-22 year old professional drivers from the Finnish Army were randomized to various treatment and control groups and assessed on numerous factors during simulation.[96] The only difference among the Codeine treated group was that they caused slightly more collisions.[96] In another simulation study, which compared chronic pain users with Codeine, chronic pain users not using Codeine, and placebo group of healthy controls, participants were assessed on reaction time and missed reactions.[138] No differences were detected in the Codeine treated group.[138]

While the remaining three medications, Carisoprodol, Dihydrocodeine, and Tramadol, have not been evaluated in driving assessments or driving simulations, their effects on psychomotor performance and/or cognition have been evaluated in laboratory settings. Carisoprodol, a muscle relaxant, can cause users to feel sedated, sluggish, and distracted, especially at high dosages.[139,140] At therapeutic doses, Carisoprodol users often report feeling no effects of the medication even though their psychomotor functioning is decreased; this situation may cause users of this medication to underestimate its effects and partake in behaviors, such as driving, when they may be impaired.[140] Dihydrocodeine, an opioid prescribed for mild to moderate pain, is known to cause dizziness and mild euphoria especially in new users,[141] which may interfere with their ability to drive. Tramadol, an opioid for mild to moderate pain, has been shown to be fairly safe in respect to cognition and psychomotor function, though at higher doses, Tramadol has been linked to the worsening of balance.[142] It should be noted that poor balance has been linked to higher incidences of MVC.[143]

4.1 Implications for research

From these findings, it is apparent that some medications that are associated with an increased risk of MVC do not appear correlated with decreased driving ability. Conversely, while the majority of the medications included in this review were not found to be statistically associated with increased risk of MVC, the inference that these medications are innocuous on one's ability to drive is not advised. There are several plausible reasons why the association between MVC and driving ability were not congruent with all medications presented in this review. First, this incongruence may be attributed to study design. The 27 studies investigating the risk or odds of MVC were observational in nature, whereas the studies investigating driving ability were all randomized control trials (RCT) and therefore, experimental. The studies investigating driving ability were comprised of small sample sizes and were occasionally limited to certain age groups or genders. Therefore, the findings of the RCTs may not be generalizable to the entire population, which is a known limitation of this type of study design.[144] In addition, the observational studies may not have been adjusted for key confounders whereas this would not have affected the RCTs results if participants were randomized properly.[144] Also, most of the RCTs only investigated one or two aspects of driving ability. The act of driving is quite complex in nature. It is possible that other aspects of driving ability may not have been affected by the medication being

investigated. It is also plausible that even if driving ability is partially affected by a medication, some drivers may compensate their driving behaviors to avoid a potential collision, which is a known phenomenon.[145-147] Second, epidemiological research investigating the associations between specific medications and MVC is lacking; this is evident by the number of studies included in this review. Some medications that have been studied via RCTs may not have been investigated observationally in larger populations. Third, many of the RCTs used healthy volunteers. This is problematic as disease-medication relationships are often difficult to distinguish. It is entirely possible that the disease in which the medication is prescribed is affecting an individual's ability to drive or their risk of MVC. It is also possible that driving ability is only affected for a short period of time and that an individual who takes a medication for an extended period of time develops a tolerance. This may not have been detected as the RCTs were often short in duration.

4.2 Implications for clinical practice

The findings of this review have several key clinical implications. First, the association between a specific medication and increased risk of MVC and decreased driving ability is not always clear. There are some specific medications that are most likely driver-impairing as both experimental and observational research has associated them with decreased driving ability and increased risk of MVC, respectively. These include Diazepam, Flunitrazepam, Flurazepam, Lorazepam, Temazepam, Triazolam, Zolpidem, and Zopiclone. For other medications, such as Buprenorphine, Codeine, Methadone, and Levocitirizine, there appears to be an association between them and increased risk of MVC, but not driving ability. As for Tramadol, Carisoprodol, and Dihydrocodeine, they appear to be associated with increased risk of MVC, but have not been evaluated in driving assessments or simulations. Secondly, some specific medications belonging to the same category or class may be more detrimental than others. For example, among the ‘Other Medications” included in this review, Carisoprodol had a strong association with MVC while the other medications in this category did not. Thirdly, some of these medications are widely prescribed. For example, Buprenorphine was the 39th most sold drug in the United States during the fourth quarter of 2013.[148] Therefore, careful consideration of the patient and their lifestyle must be given when these medications are prescribed. Possible alternatives within a drug category or class should be considered for patients that frequently drive as certain medications may be more driver-impairing than others. Education efforts are needed to ensure that patients are aware that certain medications may increase their risk of MVC.

4.3 Strengths and limitations of this review

The strengths of this review are that over 50 years of data among fourteen different databases were searched for potential studies. This review also included relevant ‘grey literature’ as evidenced by the inclusion of three doctoral dissertations and one conference paper. Despite its strengths, this review is not without its limitations. For example, publication bias is a known limitation of systematic reviews.[144] It is also possible that some studies may have been missed despite two authors independently reviewing studies for inclusion. As much of the DUID research arises from Europe, [59] it is likely that several studies were not included or missed as they were not available in the English language, a requirement of the *a priori* inclusion criteria. In some instances, only abstracts and not

complete studies could be retrieved, especially with reports or conference papers that were dated. Also, some studies were adjusted for potential confounders, while others were crude estimates. The findings of this review also indicate that future research opportunities in this area of study are plentiful. Future research could entail, 1) RCTs of medications found to be associated with increased risk of MVC that were never evaluated in a driving assessment or simulation, 2) epidemiological studies investigating the effects of other medications or new medications that may be driver-impairing, 3) investigating different methods of measuring driving ability in simulations and actual assessments, and 4) pursuing patient or clinician educational efforts to raise awareness about the possible effects of specific medications on MVC or affected driving ability.

4.4 Conclusions

This systematic review sought to determine which specific medications were associated with increased risk of motor vehicle collision among licensed drivers. While the majority of medications investigated were found to not be significantly associated with increased MVC, several medications were associated with such risks. It was also determined that some medications may be more driver-impairing than others. These findings pose numerous clinical implications. Due to the increasing public health and traffic safety concerns regarding driving under the influence of drugs, future research in this area of study is worthy of investigation as the associations between specific medication use and the increased risk of motor vehicle collision or affected driving ability are complex and not always lucid.

ACKNOWLEDGEMENTS

The authors would like to thank Jean Siebert of the West Virginia University Health Sciences Library for her assistance with the search process. MZ and TMR received support from grants (R01HD074594 from the National Institutes of Health, National Institute of Child Health & Human Development; R21CE001820 from the Centers for Disease Control and Prevention, National Center for Injury Prevention and Control). GAK was partially funded by the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) under award number U54GM104942. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

APPENDIX A.1

APPENDIX 1

Example search strategy for one database (PROQUEST)

Database	**PROQUEST**
Search Date	4/14/2014
Searches	
#1	all((‘motor vehicle’ OR automo* OR vehic*)) AND all((medication OR prescription OR drug*)) AND all((collision OR accident OR crash))
#2	(“motor vehicles” OR “automobiles” OR “automobile driving”) AND (“prescriptions” OR “pharmaceutical preparations” OR “drug prescriptions” OR “nonprescription drugs”) AND (“accidents, traffic”)
#3	all((‘motor vehicle’ OR automo* OR vehic*)) AND all((medication OR prescription OR drug*)) AND all((‘driving ability’ OR ‘driving test’ OR ‘driving simulator’ OR ‘on-the-road’ OR ‘standard deviation of lateral position’ OR ‘SDLP’ OR weav* OR ‘driving skills’ OR ‘gap acceptance’ OR ‘emergency avoidance’ OR ‘evasive lane change’ OR simulation OR ‘divided attention’ OR tracking OR cognition OR psychomotor OR ‘reaction time’))
Total Retrieved	170

REFERENCES

1. Sise RG, Calvo RY, Spain DA, Weiser TG, Staudenmayer KL. The epidemiology of trauma-related mortality in the United States from 2002 to 2010. The journal of trauma and acute care surgery. Apr; 2014 76(4):913–919. discussion 920. [PubMed: 24662852]
2. Rockett IR, Regier MD, Kapusta ND, et al. Leading causes of unintentional and intentional injury mortality: United States, 2000-2009. Am J Public Health. Nov; 2012 102(11):e84–92. [PubMed: 22994256]
3. Oster CV, Strong J. Analyzing road safety in the United States. Res. Transp. Econ. 2013; 43:98–111.
4. Hayman AV, Crandall ML. Deadly partners: interdependence of alcohol and trauma in the clinical setting. Int J Environ Res Public Health. Dec; 2009 6(12):3097–3104. [PubMed: 20049248]
5. Morland J. Driving under the influence of non-alcohol drugs. Forensic Sci.Rev. 2000; 12:80–105.
6. Movig KLL, Mathijssen MPM, Nagel PHA, et al. Psychoactive substance use and the risk of motor vehicle accidents. Accident Analysis & Prevention. 2004; 36(4):631. [PubMed: 15094417]
7. Walsh JM, de Gier JJ, Christopherson AS, Verstraete AG. Drugs and driving. Traffic Inj Prev. Sep; 2004 5(3):241–253. [PubMed: 15276925]
8. National Highway Traffic Safety Administration. Drug Involvement of Fatally Injured Drivers. Traffic Safety Facts Vol November. United States Department of Transportation. , editor. DOT HS 811 415 ed2010:1-3
9. Wilson FA, Stimpson JP, Pagan JA. Fatal crashes from drivers testing positive for drugs in the U.S., 1993-2010. Public health reports (Washington, D.C. : 1974). Jul-Aug;2014 129(4):342–350.
10. Coopersmith HG, Korner-Bitensky NA, Mayo NE. Determining medical fitness to drive: physicians' responsibilities in Canada. CMAJ : Canadian Medical Association journal. Feb 15; 1989 140(4):375–378. [PubMed: 2914258]
11. Carr DB. The older adult driver. Am Fam Physician. Jan 1; 2000 61(1):141–146, 148. [PubMed: 10643955]
12. Carr DB, Duchek JM, Meuser TM, Morris JC. Older adult drivers with cognitive impairment. Am Fam Physician. Mar 15; 2006 73(6):1029–1034. [PubMed: 16570737]
13. Cheung I, McCartt AT. Declines in fatal crashes of older drivers: changes in crash risk and survivability. Accid Anal Prev. May; 2011 43(3):666–674. [PubMed: 21376853]
14. Jusko WJ. Moving from basic toward systems pharmacodynamic models. Journal of pharmaceutical sciences. Sep; 2013 102(9):2930–2940. [PubMed: 23681608]
15. Brown, T.; Milavetz, G.; Murry, DJ. Alcohol, drugs and driving: Implications for evaluating driver impairment.. Paper presented at: 57th Annual Scientific Conference of the Association for the Advancement of Automotive Medicine; Quebec City, QC.. 2013;
16. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. Clinical interventions in aging. 2008; 3(2):383–389. [PubMed: 18686760]
17. Stein C, Baerwald C. Opioids for the treatment of arthritis pain. Expert opinion on pharmacotherapy. Feb; 2014 15(2):193–202. [PubMed: 24283649]
18. Augustijns P, Wuyts B, Hens B, Annaert P, Butler J, Brouwers J. A review of drug solubility in human intestinal fluids: implications for the prediction of oral absorption. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. Jun 16.2014 57:322–332. [PubMed: 23994640]
19. Daly AK. Is there a need to teach pharmacogenetics? Clin Pharmacol Ther. Mar; 2014 95(3):245–247. [PubMed: 24548988]
20. Ellen RL, Marshall SC, Palayew M, Molnar FJ, Wilson KG, Man-Son-Hing M. Systematic review of motor vehicle crash risk in persons with sleep apnea. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. Apr 15; 2006 2(2):193–200. [PubMed: 17557495]
21. Brown LB, Ott BR. Driving and dementia: a review of the literature. Journal of geriatric psychiatry and neurology. Dec; 2004 17(4):232–240. [PubMed: 15533995]

22. Cross JM, McGwin G Jr. Rubin GS, et al. Visual and medical risk factors for motor vehicle collision involvement among older drivers. The British journal of ophthalmology. Mar; 2009 93(3):400–404. [PubMed: 19019937]

23. Hansotia P, Broste SK. The effect of epilepsy or diabetes mellitus on the risk of automobile accidents. The New England journal of medicine. Jan 3; 1991 324(1):22–26. [PubMed: 1984160]

24. Sagberg F. Driver health and crash involvement: a case-control study. Accid Anal Prev. Jan; 2006 38(1):28–34. [PubMed: 16054104]

25. Uc EY, Rizzo M, Anderson SW, Sparks JD, Rodnitzky RL, Dawson JD. Driving with distraction in Parkinson disease. Neurology. Nov 28; 2006 67(10):1774–1780. [PubMed: 17130409]

26. Borgeat A. Do Opioids Affect the Ability to Drive Safely? Journal of Pain & Palliative Care Pharmacotherapy. 2010; 24(2):167–169. [PubMed: 20504144]

27. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Can patients taking opioids drive safely? A structured evidence-based review. J Pain Palliat Care Pharmacother. 2002; 16(1):9–28. [PubMed: 14650448]

28. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Are Opioid-Dependent/Tolerant Patients Impaired in Driving-Related Skills? A Structured Evidence-Based Review. Journal of Pain & Symptom Management. 2003; 25(6):559. [PubMed: 12782437]

29. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug Alcohol Depend. Sep 1; 2012 125(1-2):8–18. [PubMed: 22857878]

30. Kress HG, Kraft B. Opioid medication and driving ability. European Journal Of Pain (London, England). 2005; 9(2):141–144.

31. Leung SY. Benzodiazepines, opioids and driving: An overview of the experimental research. Drug & Alcohol Review. 2011; 30(3):281–286. [PubMed: 21545558]

32. Mailis-Gagnon A, Lakha SF, Furlan A, Nicholson K, Yegneswaran B, Sabatowski R. Systematic review of the quality and generalizability of studies on the effects of opioids on driving and cognitive/psychomotor performance. Clinical Journal of Pain. 2012; 28(6):542–555. [PubMed: 22673489]

33. Soyka M. Opioids and Traffic Safety - Focus on Buprenorphine. Pharmacopsychiatry. 2014; 47(1): 7–17. [PubMed: 24222013]

34. Strand MC, Fjeld B, Arnestad M, Mørland J. Can patients receiving opioid maintenance therapy safely drive? A systematic review of epidemiological and experimental studies on driving ability with a focus on concomitant methadone or buprenorphine administration. Traffic Injury Prevention. 2013; 14(1):26–38. [PubMed: 23259516]

35. van Laar MW, Volkerts ER. Driving and Benzodiazepine Use: Evidence That They Do Not Mix. CNS Drugs. 1998; 10(5):383–396.

36. Dassanayake T, Michie P, Carter G, Jones A. Effects of Benzodiazepines, Antidepressants and Opioids on Driving. Drug Safety. 2011; 34(2):125–156. [PubMed: 21247221]

37. Rapoport MJ, Lanctôt KL, Streiner DL, et al. Benzodiazepine use and driving: A meta-analysis. Journal of Clinical Psychiatry. 2009; 70(5):663–673. [PubMed: 19389334]

38. Smink BE, Egberts A, Lusthof KJ, Uges DRA, de Gier JJ. The Relationship between Benzodiazepine Use and Traffic Accidents: A Systematic Literature Review. CNS Drugs. 2010; 24(8):639–653. [PubMed: 20658797]

39. Popescu FD. H1 antihistamines and driving. Journal of medicine and life. 2008; 1(3):262–268. [PubMed: 20108503]

40. Roberts DJ. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. Mar; 2005 94(3):407–409. author reply 409-410.

41. Cooper L, Meuleners LB, Duke J, Jancey J, Hildebrand J. Psychotropic medications and crash risk in older drivers: A review of the literature. Asia-Pacific Journal of Public Health. 2011; 23(4):443–457. [PubMed: 21768133]

42. Joris CV, Monique Anna Johanna M. Psychoactive medication and traffic safety. International Journal of Environmental Research and Public Health. 2009; 6(3):1041–1054. [PubMed: 19440432]

43. Krueger GP. Psychoactive Medications, Stimulants, Hypnotics, and Nutritional Aids: Effects on Driving Alertness and Performance. Journal of the Washington Academy of Sciences. 2010; 96(3): 51–85.
44. Rapoport MJ, Baniña MC. Impact of Psychotropic Medications on Simulated Driving: A Critical Review. CNS Drugs. 2007; 21(6):503. [PubMed: 17521229]
45. Verster JC, Mets MAJ. Psychoactive medication and traffic safety. International Journal Of Environmental Research And Public Health. 2009; 6(3):1041–1054. [PubMed: 19440432]
46. Brunnauer A, Laux G. The effects of most commonly prescribed second generation antidepressants on driving ability: a systematic review : 70th Birthday Prof. Riederer. Journal Of Neural Transmission (Vienna, Austria: 1996). 2013; 120(1):225–232.
47. Ramaekers JG. Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. The Journal of clinical psychiatry. Jan; 2003 64(1):20–29. [PubMed: 12590619]
48. Ravera S, Ramaekers JG, de Jong-van den Berg LTW, de Gier JJ. Are Selective Serotonin Reuptake Inhibitors Safe for Drivers? What is the Evidence? Clinical Therapeutics. 2012; 34(5): 1070–1083. [PubMed: 22554974]
49. Verster JC, Ramaekers JG. Antidepressants and Traffic Safety. 2009:307–313.
50. Verster JC, Veldhuijzen DS, Patat A, Olivier B, Volkerts ER. Hypnotics and driving safety: meta-analyses of randomized controlled trials applying the on-the-road driving test. Current Drug Safety. 2006; 1(1):63–71. [PubMed: 18690916]
51. Vermeeren A, Leufkens TRM, Verster JC. Effects of Anxiolytics on Driving. 2009:289–305.
52. Verster JC, Veldhuijzen DS, Volkerts ER. Is it Safe to Drive a Car when Treated with Anxiolytics? Evidence from onthe- Road Driving Studies During Normal Traffic. Current Psychiatry Reviews. 2005; 1(2):215–225.
53. Gunja N. In the Zzz zone: the effects of Z-drugs on human performance and driving. Journal Of Medical Toxicology: Official Journal Of The American College Of Medical Toxicology. 2013; 9(2):163–171. [PubMed: 23456542]
54. Leufkens TRM, Vermeeren A. Zopiclone's Residual Effects on Actual Driving Performance in a Standardized Test: A Pooled Analysis of Age and Sex Effects in 4 Placebo-Controlled Studies. Clinical Therapeutics. 2014; 36(1):141–150. [PubMed: 24360801]
55. Verster JC, Volkerts ER, Olivier B, Johnson W, Liddicoat L. Zolpidem and Traffic Safety - The Importance of Treatment Compliance. Current Drug Safety. 2007; 2(3):220–226. [PubMed: 18690971]
56. Verster JC, Volkerts ER, Spence DW, Alford C, Pandi-Perumal S. Effects of Sleep Medications on Cognition, Psychomotor Skills, Memory and Driving Performance in the Elderly. Current Psychiatry Reviews. 2007; 3(4):281–292.
57. Amanda H, David B. C. Medications and impaired driving: A review of the literature. Annals of pharmacotherapy. 2014 ePub(ePub):ePub-ePub.
58. Elvik R. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. Accident Analysis & Prevention. 2013; 60:254–267. [PubMed: 22785089]
59. Kelly E, Darke S, Ross J. A review of drug use and driving: epidemiology, impairment, risk factors and risk perceptions. Drug & Alcohol Review. 2004; 23(3):319–344. [PubMed: 15370012]
60. Orriols L, Salmi LR, Philip P, et al. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. Pharmacoepidemiology and drug safety. Aug; 2009 18(8):647–658. [PubMed: 19418468]
61. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and nonrandomised studies of health care interventions. Journal of epidemiology and community health. Jun; 1998 52(6):377–384. [PubMed: 9764259]
62. Purgato M, Adams CE. Heterogeneity: the issue of apples, oranges and fruit pie. Epidemiology and psychiatric sciences. Mar; 2012 21(1):27–29. [PubMed: 22670409]
63. Nelson, RC. Psychotherapeutic drugs, mental disorders and automobile crashes: A case control study of 1308 females. (Volumes I and II) [Ph.D.]. University of Minnesota; 1992.

64. Koepsell TD, Wolf ME, McCloskey L, Buchner DM, Louie D. Medical conditions and motor vehicle collision injuries in older adults. Journal of the American Geriatrics Society. 1994; 42(7): 695–700. [PubMed: 8014341]

65. Neutel I. Benzodiazepine-related traffic accidents in young and elderly drivers. Human Psychopharmacology: Clinical & Experimental. 1998; 13:S115–S123.

66. Cui, X. Injurious crash risk and medical condition and medication use among senior drivers [Ph.D.]. University of Alberta (Canada); Ann Arbor: 2001.

67. Mura P, Kintz P, Ludes B, et al. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: Results of a French collaborative study. Forensic Science International. 2003; 133(1-2):79–85. [PubMed: 12742692]

68. Mathijssen, MPM. The risk of drink and drug driving--results of a case-control study conducted in the Netherlands. 2006.

69. Bramness JG, Skurtveit S, Morland J, Engelund A. The risk of traffic accidents after prescriptions of carisoprodol. Accident Analysis & Prevention. 2007; 39(5):1050–1055. [PubMed: 17854578]

70. Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Mørland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. Sleep Medicine. 2008; 9(8):818–822. [PubMed: 18226959]

71. Lonnen KF, Powell RJ, Taylor D, Shore AC, MacLeod KM. Road traffic accidents and diabetes: insulin use does not determine risk. Diabetic Medicine. 2008; 25(5):578–584. [PubMed: 18445171]

72. Bachs LC, Engeland A, Mørland JG, Skurtveit S. The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol. Clinical Pharmacology and Therapeutics. 2009; 85(6):596–599. [PubMed: 19279562]

73. Bramness JG, Skurtveit S, Neutel CI, Mørland J, Engeland A. An increased risk of road traffic accidents after prescriptions of lithium or valproate? Pharmacoepidemiol. Drug Saf. 2009; 18(6): 492–496. [PubMed: 19326366]

74. Gibson JE, Hubbard RB, Smith CJ, Tata LJ, Britton JR, Fogarty AW. Use of Self-controlled Analytical Techniques to Assess the Association Between Use of Prescription Medications and the Risk of Motor Vehicle Crashes. American Journal of Epidemiology. 2009; 169(6):761–768. [PubMed: 19181876]

75. Skurtveit S, Strøm H, Skrivarhaug T, Mørland J, Bramness JG, Engeland A. Road traffic accident risk in patients with diabetes mellitus receiving blood glucose-lowering drugs. Prospective follow-up study. Diabetic Medicine. 2009; 26(4):404–408. [PubMed: 19388971]

76. Coupland CAC, Dhiman P, Barton G, et al. A study of the safety and harms of antidepressant drugs for older people: A cohort study using a large primary care database. Health Technol. Assess. 2011; 15(28):5–218.

77. Gjerde H, Normann PT, Christophersen AS, Samuelsen SO, Morland J. Alcohol, psychoactive drugs and fatal road traffic accidents in Norway: A case-control study. Accident Analysis & Prevention. 2011; 43(3):1197–1203. [PubMed: 21376919]

78. Orriols L, Philip P, Moore N, et al. Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. Clinical Pharmacology and Therapeutics. 2011; 89(4):595–601. [PubMed: 21368756]

79. Bramness JG, Skurtveit S, Mørland J, Engeland A. An increased risk of motor vehicle accidents after prescription of methadone. Addiction. 2012; 107(5):967–972. [PubMed: 22151376]

80. Corsenac P, Lagarde E, Gadegbeku B, et al. Road traffic crashes and prescribed methadone and buprenorphine: A french registry-based case–control study. Drug & Alcohol Dependence. 2012; 123(1-3):91–97. [PubMed: 22104480]

81. Hansen, RN. Investigating the Association Between Sedative Hypnotic Prescription Exposures and Motor Vehicle Crashes [Ph.D.]. University of Washington; Ann Arbor: 2012.

82. Gjerde H, Christophersen AS, Normann PT, Mørland J. Associations between substance use among car and van drivers in Norway and fatal injury in road traffic accidents: A case-control study. Transportation Research: Part F. 2013; 17:134–144.

83. Foley DJ, Wallace RB, Eberhard J. Risk factors for motor vehicle crashes among older drivers in a rural community. J Am Geriatr Soc. Jul; 1995 43(7):776–781. [PubMed: 7602030]

84. McGwin G Jr. Sims RV, Pulley L, Roseman JM. Relations among chronic medical conditions, medications, and automobile crashes in the elderly: a population-based case-control study. Am J Epidemiol. Sep 1; 2000 152(5):424–431. [PubMed: 10981455]
85. Sims RV, McGwin G Jr. Allman RM, Ball K, Owsley C. Exploratory study of incident vehicle crashes among older drivers. Journals of Gerontology: Series A: Biological Sciences and Medical Sciences. 2000; 55A(1):M22–M27.
86. Etminan M, Hemmelgarn B, Delaney JAC, Suissa S. Use of lithium and the risk of injurious motor vehicle crash in elderly adults: case-control study nested within a cohort. BMJ: British Medical Journal (International Edition). 2004; 328(7439):558–559.
87. Delaney JAC, Opatrny L, Suissa S. Warfarin use and the risk of motor vehicle crash in older drivers. British Journal of Clinical Pharmacology. 2006; 61(2):229–232. [PubMed: 16433878]
88. Hemmelgarn B, Lévesque LE, Suissa S. Anti-diabetic drug use and the risk of motor vehicle crash in the elderly. Canadian Journal of Clinical Pharmacology. 2006; 13(1):e112–e120. [PubMed: 16585812]
89. Yang YH, Lai JN, Lee CH, Wang JD, Chen PC. Increased risk of hospitalization related to motor vehicle accidents among people taking zolpidem: A case-crossover study. J. Epidemiol. 2011; 21(1):37–43. [PubMed: 21030794]
90. Biehl B. Studies of clobazam and car-driving. British Journal Of Clinical Pharmacology. 1979; 7(Suppl 1):85S–90S. [PubMed: 35213]
91. De Gier JJ. Driving tests with patients. British Journal of Clinical Pharmacology (England). 1984; 18(Suppl. 1):103–108.
92. De Gier JJ, t Hart BJ, Nelemans FA, Bergman H. Psychomotor performance and real driving performance of outpatients receiving diazepam. Psychopharmacology. 1981; 73(4):340–344. [PubMed: 6789355]
93. O'Hanlon JF, Haak TW, Blaauw GJ, Riemersma JBJ. Diazepam impairs lateral position control in highway driving. Science. 1982; 217(4554):79–81. [PubMed: 7089544]
94. O'Hanlon JF, Vermeeren A, Uiterwijk MM, van Veggel LM, Swijgman HF. Anxiolytics' effects on the actual driving performance of patients and healthy volunteers in a standardized test. An integration of three studies. Neuropsychobiology. 1995; 31(2):81–88. [PubMed: 7760989]
95. van Laar MW, Volkerts ER, van Willigenburg AP. Therapeutic effects and effects on actual driving performance of chronically administered buspirone and diazepam in anxious outpatients. Journal Of Clinical Psychopharmacology. 1992; 12(2):86–95. [PubMed: 1573045]
96. Linnoila M, Hakkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. Clin Pharmacol Ther. Apr; 1974 15(4):368–373. [PubMed: 4595291]
97. Friedel B, Joo S, Reker K, Hartmann R. TESTING DRIVERS TAKING DIAZEPAM IN THE DAIMLER-BENZ DRIVING SIMULATOR. J. Traffic Med. 1991; 19(1.2):15–27.
98. Kuitunen T. Drug and ethanol effects on the clinical test for drunkenness: single doses of ethanol, hypnotic drugs and antidepressant drugs. Pharmacology & Toxicology. 1994; 75(2):91–98. [PubMed: 7971743]
99. Moskowitz H, Smiley A. Effects of chronically administered buspirone and diazepam on driving-related skills performance. Journal of clinical psychiatry. 1982; (12 Pt 2):45–55. [PubMed: 6130073]
100. Smiley A, Moskowitz H. Effects of long-term administration of buspirone and diazepam on driver steering control. Am J Med. Mar 31; 1986 80(3B):22–29. [PubMed: 3963031]
101. Takahashi M, Iwamoto K, Kawamura Y, et al. The effects of acute treatment with tandospirone, diazepam, and placebo on driving performance and cognitive function in healthy volunteers. Human psychopharmacology. 2010; (3):260–267. [PubMed: 20373478]
102. Tamaji A, Iwamoto K, Kawamura Y, et al. Differential effects of diazepam, tandospirone, and paroxetine on plasma brain-derived neurotrophic factor level under mental stress. Human psychopharmacology. 2012; (3):329–333. [PubMed: 22344744]
103. Vanakoski J, Mattila MJ, Seppälä T. Driving under light and dark conditions: effects of alcohol and diazepam in young and older subjects. European journal of clinical pharmacology. 2000; (6-7):453–458. [PubMed: 11049006]

104. Willumeit HP, Ott H, Neubert W, Hemmerling KG, Schratzer M, Fichte K. Alcohol interaction of lormetazepam, mepindolol sulphate and diazepam measured by performance on the driving simulator. Pharmacopsychiatry. 1984; 17(2):36–43. [PubMed: 6145169]

105. Willumeit HP, Ott H, Neubert W. Simulated car driving as a useful technique for the determination of residual effects and alcohol interaction after short- and long-acting benzodiazepines. Psychopharmacology. Supplementum. 1984; 1:182–192. [PubMed: 6147840]

106. Meskali M, Berthelon C, Marie S, Denise P, Bocca ML. Residual effects of hypnotic drugs in aging drivers submitted to simulated accident scenarios: An exploratory study. Psychopharmacology. 2009; 207(3):461–467. [PubMed: 19798483]

107. Schmidt U, Brendemühl D, Rüther E. Aspects of driving after hypnotic therapy with particular reference to temazepam. Acta psychiatrica Scandinavica. Supplementum. 1986:112–118. [PubMed: 2883818]

108. Betts TA, Birtle J. Effect of two hypnotic drugs on actual driving performance next morning. British Medical Journal (England). 1982; 285:852. Sep 25.

109. Brookhuis KA, Volkerts ER, O'Hanlon JF. Repeated dose effects of lormetazepam and flurazepam upon driving performance. European Journal Of Clinical Pharmacology. 1990; 39(1):83–87. [PubMed: 1980464]

110. Willumeit HP, Neubert W, Ott H, Hemmerling KG. Driving ability following the subchronic application of lormetazepam, flurazepam and placebo. Ergonomics. 1983; 26(11):1055–1061. [PubMed: 6662099]

111. Daurat A, Sagaspe P, Moták L, et al. Lorazepam impairs highway driving performance more than heavy alcohol consumption. Accident Analysis & Prevention. 2013; 60:31–34. [PubMed: 24007754]

112. Hindmarch I, Gudgeon AC. The effects of clobazam and lorazepam on aspects of psychomotor performance and car handling ability. British Journal Of Clinical Pharmacology. 1980; 10(2): 145–150. [PubMed: 6107116]

113. Irving A, Jones W. Methods for testing impairment of driving due to drugs. European Journal Of Clinical Pharmacology. 1992; 43(1):61–66. [PubMed: 1505611]

114. Mercier-Guyon C, Lejay J, Choay P. Comparative Study of the Effects of Captodiamine and Lorazepam on Car Driving Ability. Clinical Drug Investigation. 1999; 17(6):451–459.

115. Moták L, Bayssac L, Taillard J, et al. Naturalistic conversation improves daytime motorway driving performance under a benzodiazepine: A randomised, crossover, double-blind, placebo-controlled study. Accident Analysis and Prevention. 2014; 67:61–66. [PubMed: 24631977]

116. van Laar M, Volkerts E, Verbaten M. Subchronic effects of the GABA-agonist lorazepam and the 5-HT2A/2C antagonist ritanserin on driving performance, slow wave sleep and daytime sleepiness in healthy volunteers. Psychopharmacology (Berl). Mar 1; 2001 154(2):189–197. [PubMed: 11314681]

117. Mattila MJ, Kuitunen T, Veilahti J. RELATED COORDINATIVE, REACTIVE AND COGNITIVE PERFORMANCES AS IMPAIRED BY DRUGS AND ALCOHOL: COMPARISON WITH CLINICAL TEST FOR DRIVING FITNESS. J. Traffic Med. 1993; 21(3):101–114.

118. Leufkens TRM, Vermeeren A. Highway driving in the elderly the morning after bedtime use of hypnotics: A comparison between temazepam 20 mg, zopiclone 7.5 mg, and placebo. Journal of Clinical Psychopharmacology. 2009; 29(5):432–438. [PubMed: 19745642]

119. Riedel WJ, Quasten R, Hausen C, O'Hanlon JF. A Study Comparing the Hypnotic Efficacies and Residual Effects on Actual Driving Performance of Midazolam 15 mg, Triazolam 0.5 mg, Temazepam 20 mg and Placebo in Shift Workers on Night Duty. 1988:9051470061.

120. O'Hanlon JF, Volkerts ER. Hypnotics and actual driving performance. Acta Psychiatrica Scandinavica. Supplementum. 1986; 332:95–104. [PubMed: 3554901]

121. Partinen M, Hirvonen K, Hublin C, Halavaara M, Hiltunen H. Effects of after-midnight intake of zolpidem and temazepam on driving ability in women with non-organic insomnia. Sleep Medicine. 2003; 4(6):553. [PubMed: 14607350]

122. Laurell H, Tornros J. The carry-over effects of triazolam compared with nitrazepam and placebo in acute emergency driving situations and in monotonous simulated driving. Acta Pharmacol Toxicol (Copenh). Mar; 1986 58(3):182–186. [PubMed: 3716812]

123. Riedel WJ, et al. Eye movements, expert ratings, weaving, and time-to-licne crossing as measures of driving performance and driving performance impairment. Vision in Vehicles—III/ Edited by A.G. Gale; Co-edited by I.D. Brown. 1991

124. Deits C, Boyle L, Morrison J. Driving Performance of Drug-Impaired Bus Drivers in Work Zone Areas. 2011

125. Morrison JB, Boyle LN, Deitz C. PATH - Post-Accident Testing Heuristics. 2011

126. Leufkens TRM, Lund JS, Vermeeren A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. Journal Of Sleep Research. 2009; 18(4):387–396. [PubMed: 19552733]

127. Verster J, Bervoets A, Klerk S, Roth T. Lapses of attention as outcome measure of the on-the-road driving test. Psychopharmacology. 2014; 231(1):283–292. [PubMed: 23975036]

128. Bocca ML, Le Doze F, Etard O, Pottier M, L'Hoste J, Denise P. Residual effect of zolpidem 10 mg and zopiclone 7.5 mg versus flunitrazepam 1 mg and placebo on driving performance and ocular saccades. Psychopharmacology. 1999; 143(4):373–379. [PubMed: 10367554]

129. Staner L, Ertlé S, Boeijinga P, et al. Next-day residual effects of hypnotics in DSM-IV primary insomnia: a driving simulator study with simultaneous electroencephalogram monitoring. Psychopharmacology. 2005; (4):790–798. [PubMed: 16025317]

130. Bocca ML, Marie S, Lelong-Boulouard V, et al. Zolpidem and zopiclone impair similarly monotonous driving performance after a single nighttime intake in aged subjects. Psychopharmacology. 2011; (3):699–706. [PubMed: 21086117]

131. Verster JC, Volkerts ER, Schreuder A, et al. Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. Journal of Clinical Psychopharmacology. Dec; 2002 22(6):576–583. [PubMed: 12454557]

132. Otmani S, Demazières A, Staner C, et al. Effects of prolonged-release melatonin, zolpidem, and their combination on psychomotor functions, memory recall, and driving skills in healthy middle aged and elderly volunteers. Human psychopharmacology. 2008; (8):693–705. [PubMed: 18763235]

133. Mets MA, Vries JM, Senerpont Domis LM, Volkerts ER, Olivier B, Verster JC. Next-day effects of ramelteon (8 mg), zopiclone (7.5 mg), and placebo on highway driving performance, memory functioning, psychomotor performance, and mood in healthy adult subjects. Sleep. 2011; (10): 1327–1334. [PubMed: 21966064]

134. Vermeeren A, Riedel WJ, Boxtel MP, Darwish M, Paty I, Patat A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. Sleep. 2002; (2):224–231. [PubMed: 11905433]

135. Lenné MG, Dietze P, Rumbold GR, Redman JR, Triggs TJ. The effects of the opioid pharmacotherapies methadone, LAAM and buprenorphine, alone and in combination with alcohol, on simulated driving. Drug and alcohol dependence. 2003; (3):271–278. [PubMed: 14643944]

136. Verster JC, Weert AM, Bijtjes SI, et al. Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: a randomized, double-blind, placebo-controlled trial. Psychopharmacology. 2003; (1):84–90. [PubMed: 12721777]

137. Leung S, Chapman R, Bruno R, Lenne M, Haber P, Lintzeris N. Medicinal drug use and driving. 2013

138. Nilsen HK, Landr NI, Kaasa S, Jenssen GD, Fayers P. Driving Functions in a Video Simulator in Chronic Non-malignant Pain Patients Using and Not Using Codeine. European Journal of Pain. 2011; 15(4):409–415. [PubMed: 20947399]

139. Zacny JP, Paice JA, Coalson DW. Characterizing the subjective and psychomotor effects of carisoprodol in healthy volunteers. Pharmacol Biochem Behav. Nov; 2011 100(1):138–143. [PubMed: 21884720]

140. Zacny JP, Paice JA, Coalson DW. Subjective and psychomotor effects of carisoprodol in combination with oxycodone in healthy volunteers. Drug Alcohol Depend. Jan 1; 2012 120(1-3): 229–232. [PubMed: 21840651]

141. Ammon S, Hofmann U, Griese EU, Gugeler N, Mikus G. Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple oral dosing. Br J Clin Pharmacol. Sep; 1999 48(3):317–322. [PubMed: 10510141]

142. Mintzer MZ, Lanier RK, Lofwall MR, Bigelow GE, Strain EC. Effects of repeated tramadol and morphine administration on psychomotor and cognitive performance in opioid-dependent volunteers. Drug Alcohol Depend. Oct 1; 2010 111(3):265–268. [PubMed: 20538418]

143. Huisingh C, McGwin G Jr. Orman KA, Owsley C. Frequent Falling and Motor Vehicle Collision Involvement of Older Drivers. J Am Geriatr Soc. Nov 26.2013

144. Rothman, KJ.; Greenland, S.; Lash, TL. Modern Epidemiology. Second ed.. Lippincott Williams & Williams; Philadelphia: 2008.

145. Marottoli RA, Ostfeld AM, Merrill SS, Perlman GD, Foley DJ, Cooney LM Jr. Driving cessation and changes in mileage driven among elderly individuals. Journal of gerontology. Sep; 1993 48(5):S255–260. [PubMed: 8366274]

146. Martinez R. Older drivers and physicians. JAMA : the journal of the American Medical Association. Oct 4.1995 274(13):1060. [PubMed: 7563458]

147. Kelly R, Warke T, Steele I. Medical restrictions to driving: the awareness of patients and doctors. Postgrad Med J. Sep; 1999 75(887):537–539. [PubMed: 10616686]

148. IMS Health. [10/1/2014] U.S. pharmaceutical sales-Q4 2013. 2014. http://www.drugs.com/stats/top100/sales.

HIGHLIGHTS

- Of the 27 studies included in this review, 53 medications were investigated
- 15 medications (28.3%) were associated with motor vehicle collision risk
- As these drugs are widely prescribed, clinical and research implications exist

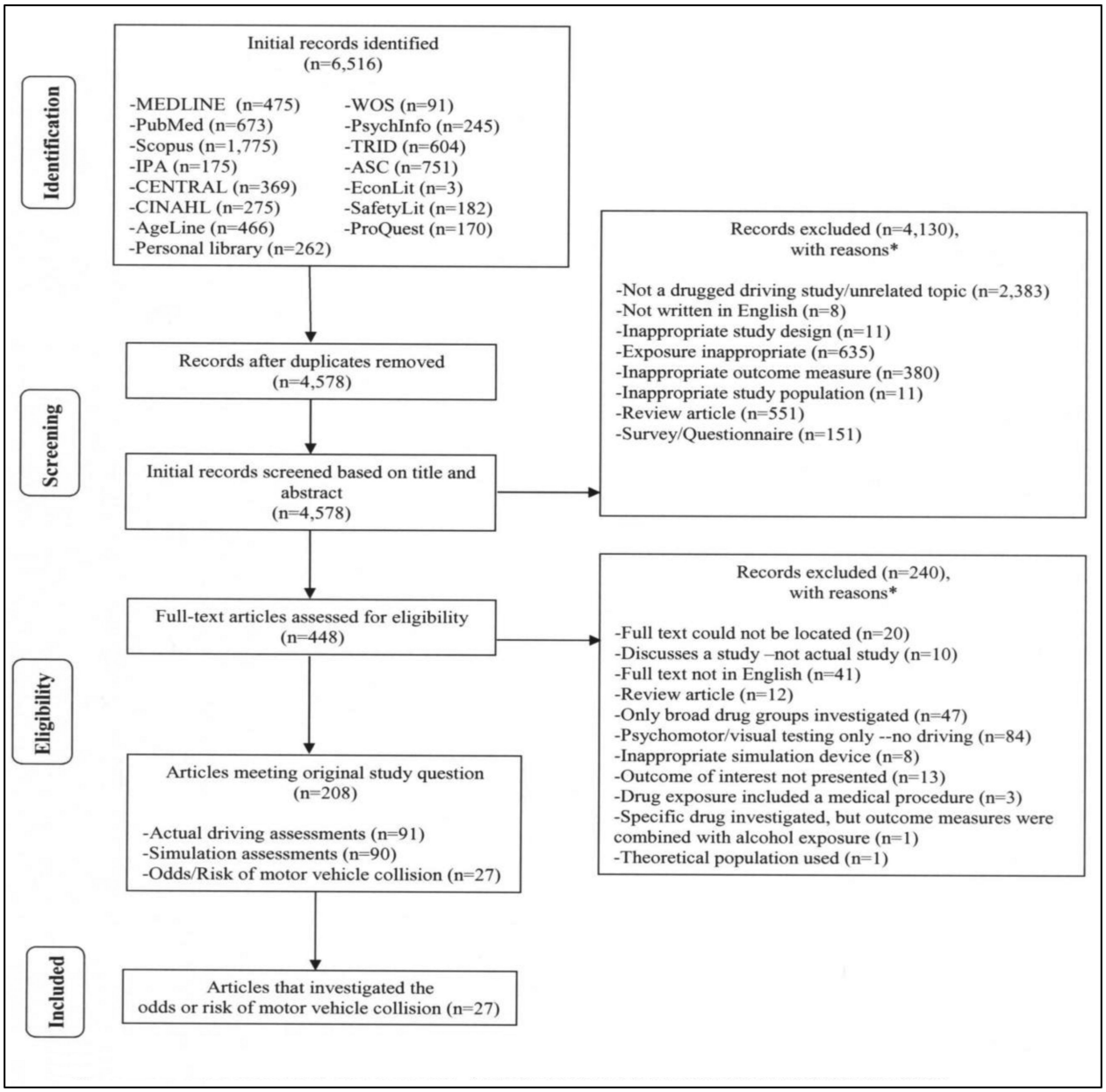

Figure 1.

Flow chart for the selection of studies.*, studies could have been excluded for multiple reasons

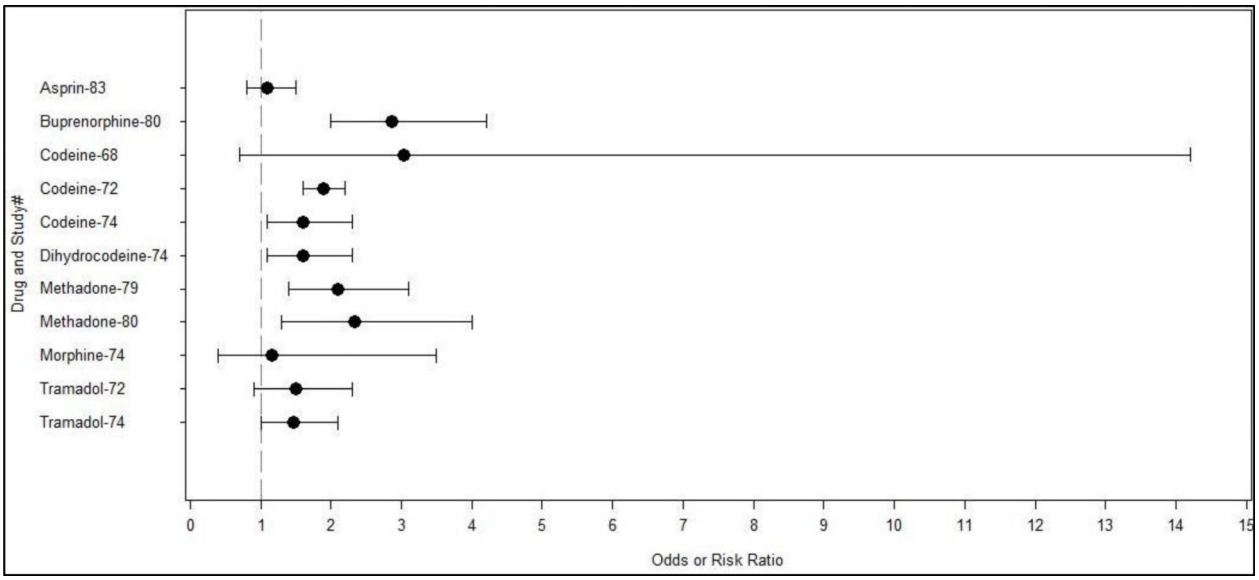

Figure 2.

Odds or risk ratios with corresponding 95% confidence intervals from included studies that investigated the association between specific analgesic medications and MVC. Estimates by Foley et al[83] were adjusted for age and gender; all other estimates presented are unadjusted.

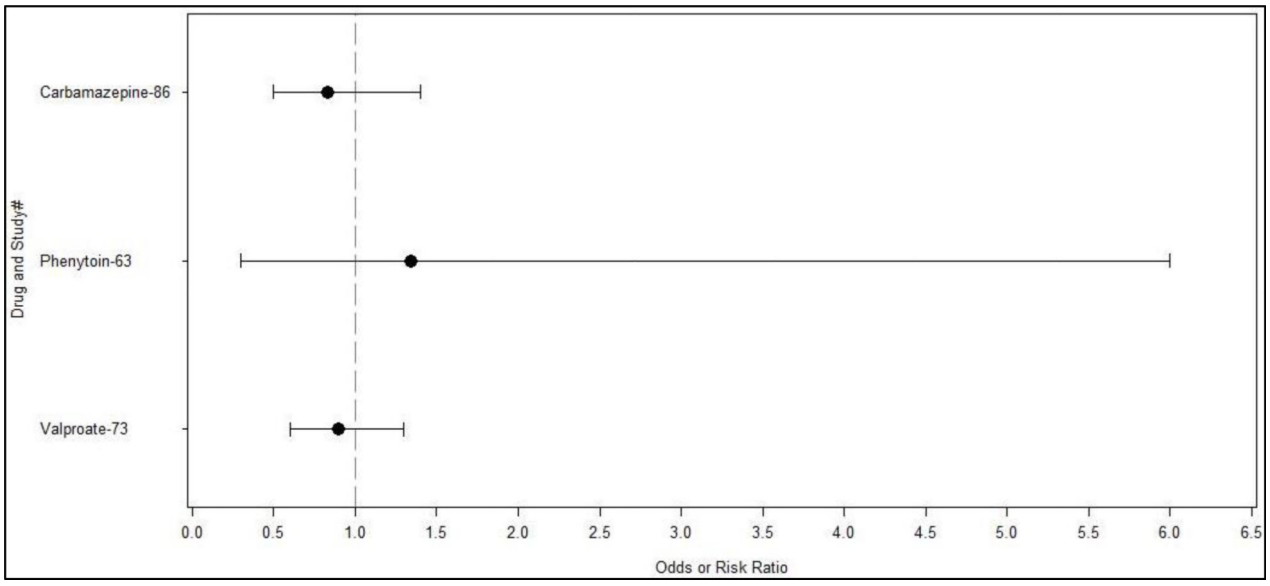

Figure 3.

Odds or risk ratios with corresponding 95% confidence intervals from included studies that investigated the association between specific anticonvulsant medications and MVC. The study by Etminan et al.[86] was adjusted for age, sex, residence, previous MVC, chronic disease score, and exposure to antidepressants, antiepileptic, benzodiazepines, antipsychotics, antimigraine, muscle relaxants, and/or narcotic analgesics. All other estimates are unadjusted.

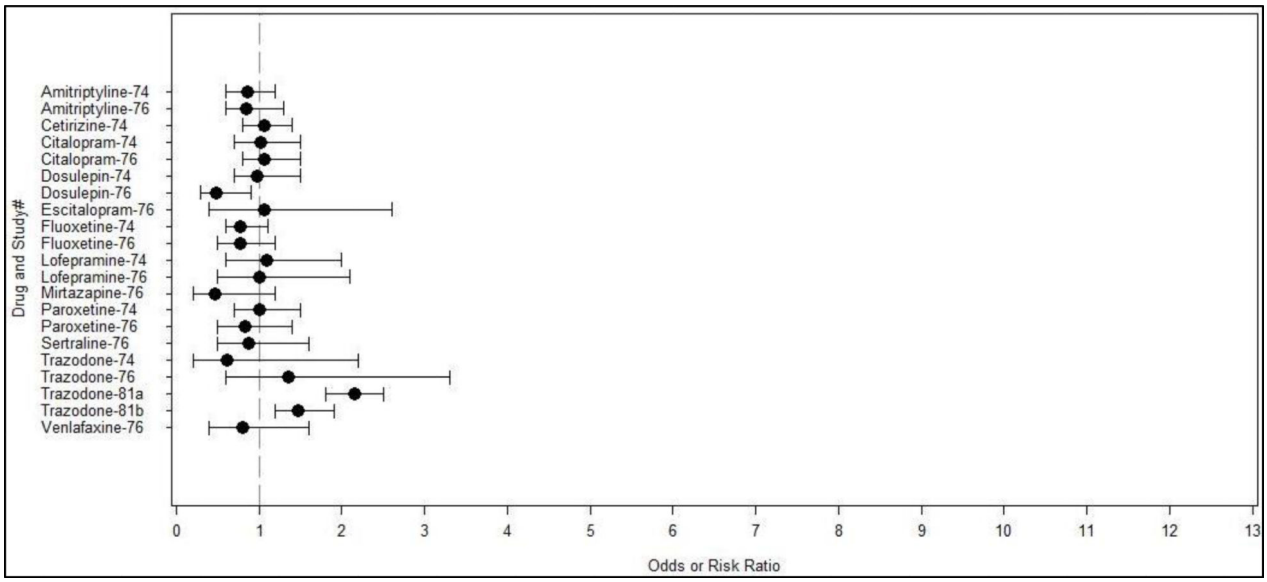

Figure 4.

Odds or risk ratios with corresponding 95% confidence intervals from included studies that investigated the association between specific antidepressant medications and MVC. The study by Hansen[81] provided two estimates. The first estimate (81a) corresponds to new users of Trazodone while the second (81b) corresponds to prevalent users of Trazodone.

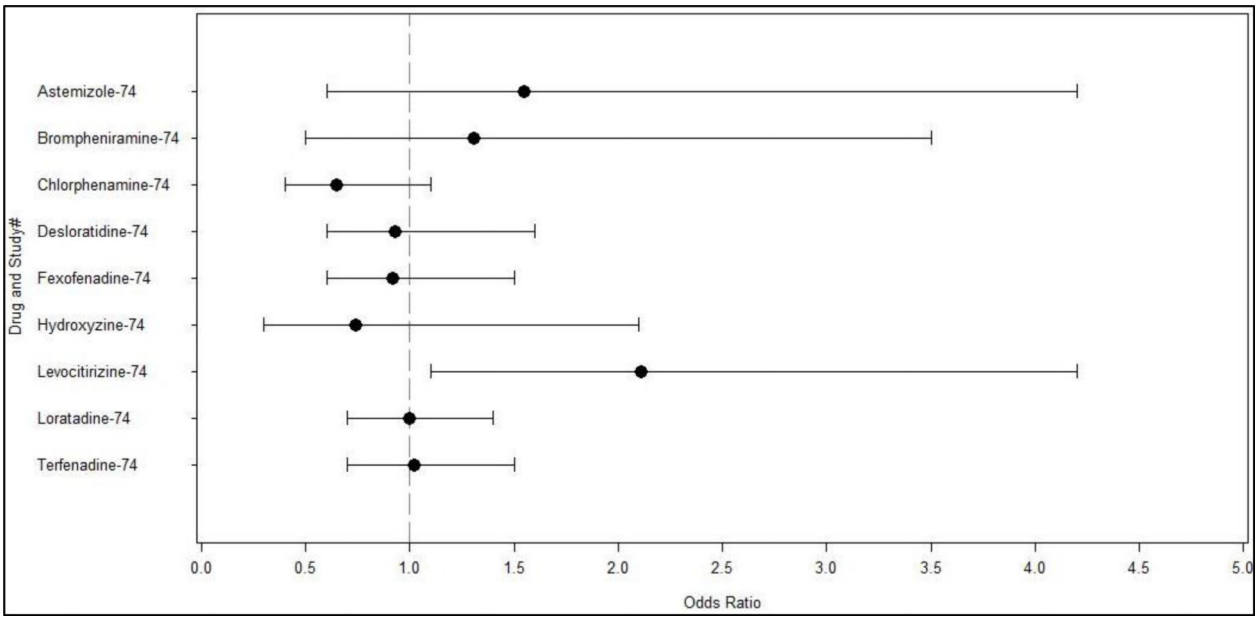

Figure 5.

Odds or risk ratios with corresponding 95% confidence intervals from included studies that investigated the association between specific antihistamine medications and MVC

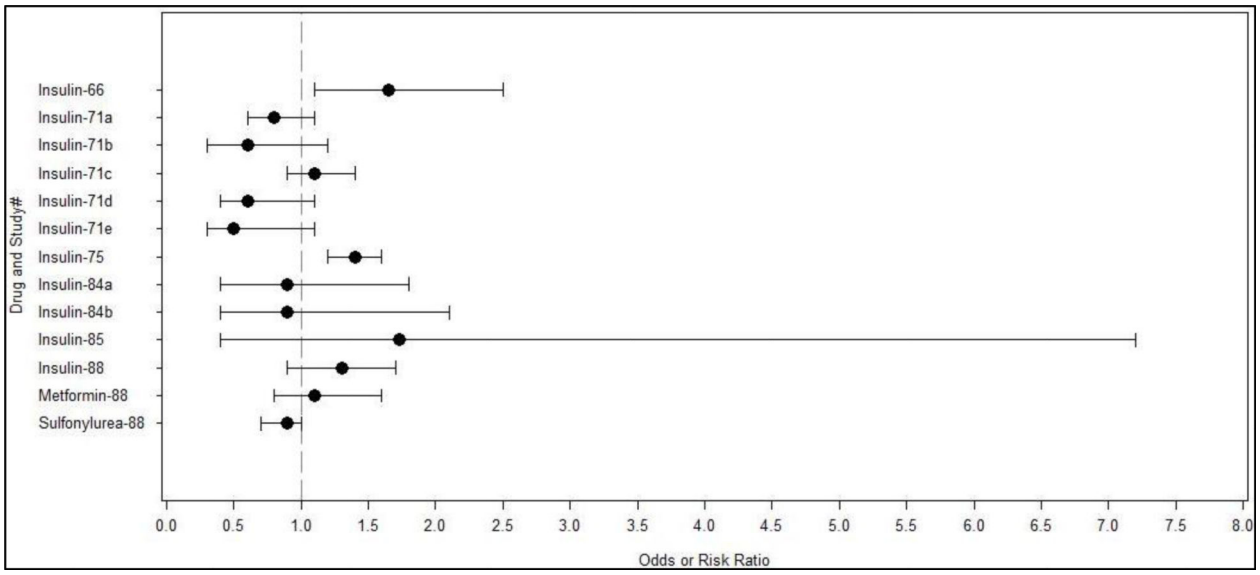

Figure 6.

Odds or risk ratios with corresponding 95% confidence intervals from included studies that investigated the association between specific antihyperglycemic medications and MVC. The study by Lonnen et al[71] provided five estimates of risk (71a-e). These correspond to the risk of MVC for the following age groups respectively, <25, 25-44, 45-64, 65-74, and 75-84 years of age. The study by Mcgwin et al[84] provided two estimates of risk (84a-b), which correspond with the odds of having any crash or a not-at-fault crash, respectively. The study by Mcgwin et al[84] was adjusted for age, sex, and annual miles driven. The study by Sims et al[85] was adjusted for sex, age, and days driven per week. The study by Hemmelgarn et al.[88] was adjusted for age, gender, previous MVC, and place of residence. All other estimates are unadjusted.

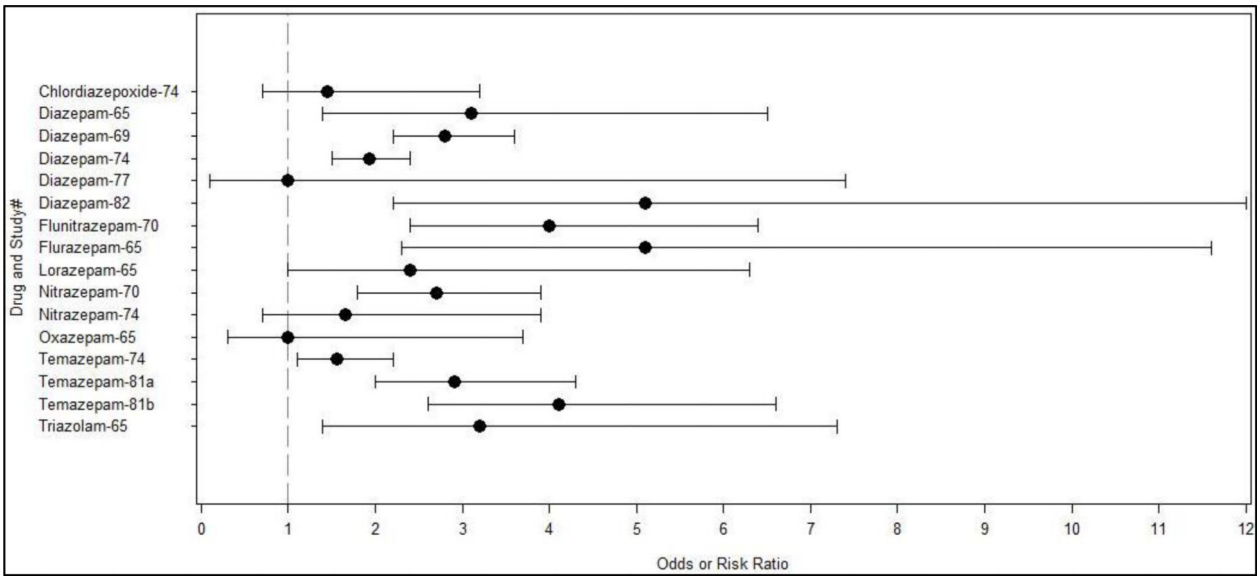

Figure 7.

Odds or risk ratios with corresponding 95% confidence intervals from included studies that investigated the association between specific benzodiazepine medications and MVC. Hansen[81] provided two estimates of risk (81a-b) which correspond to new and prevalent users of Temazepam, respectively.

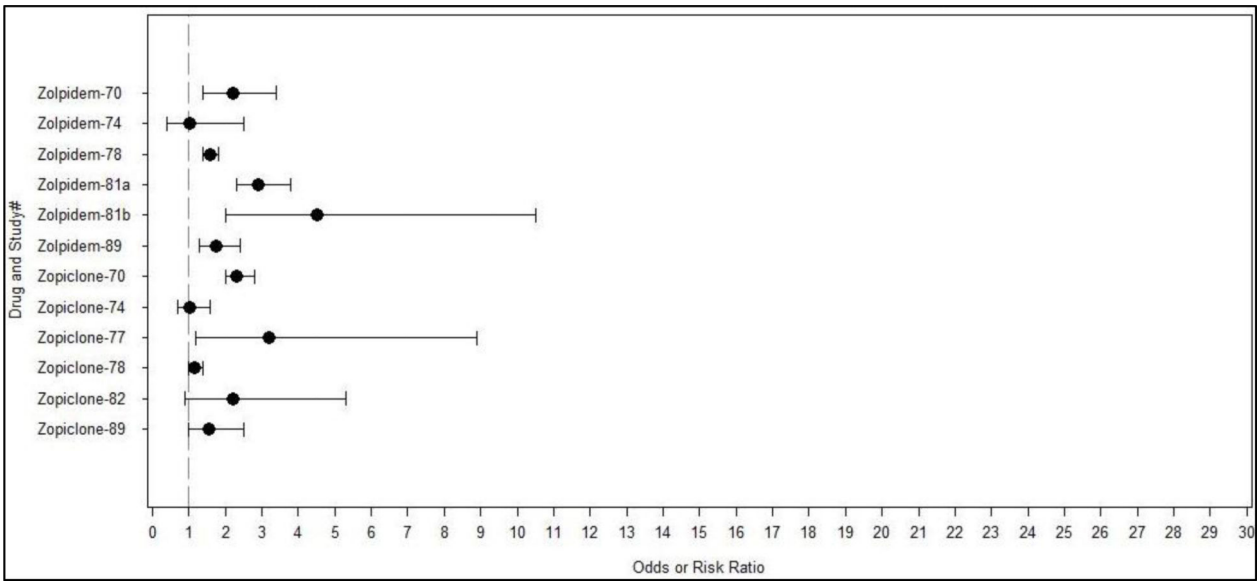

Figure 8.

Odds or risk ratios with corresponding 95% confidence intervals from included studies that investigated the association between specific sleep-promoting medications and MVC. Hansen[81] provided two estimates of risk (81a-b) which correspond to new and prevalent users of Zolpidem, respectively. The estimates provided by Yang et al.[89] were adjusted for concomitant use of the following medications: Zolpidem, Zopiclone, long and short acting benzodiazepines, antihistamines, anticonvulsants, antidepressants, other sedatives/hypnotics, other psychoactive drugs, muscle relaxants, and opioid analgesics. All other estimates are unadjusted.

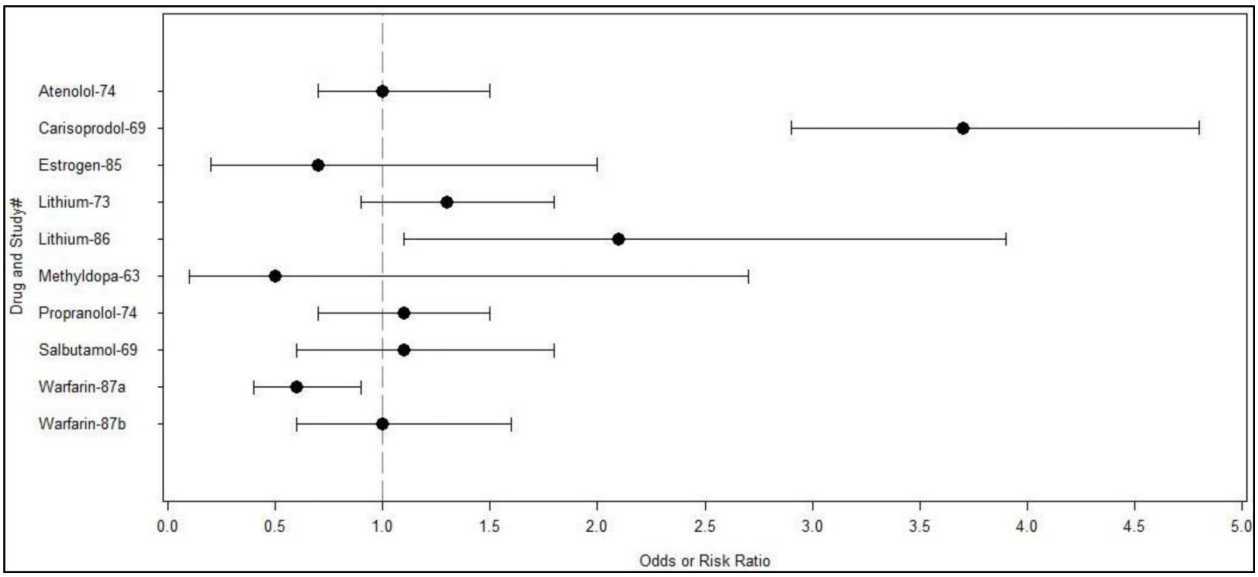

Figure 9.

Odds or risk ratios with corresponding 95% confidence intervals from included studies that investigated the association between MVC and specific medications that could not be grouped into the other drug categories. Delaney et al[87] provided two estimates of risk (87a-b) which correspond to both new and prevalent users, respectively, of Warfarin. The study by Sims et al.[85] was adjusted for sex, age, and days driven per week. The study by Etminan et al.[86] was adjusted for age, sex, residence, previous MVC, chronic disease score, and exposure to antidepressants, antiepileptic, benzodiazepines, antipsychotics, antimigraine, muscle relaxants, and/or narcotic analgesics. The study by Delaney et al.[87] was adjusted for cardiac or stroke events within the past year and the following drug classes in the previous 60 days: antidepressants, anti-epileptics, benzodiazepines, antipsychotics, anti-migraine, narcotic analgesics, muscle relaxants. All other estimates are unadjusted.

Table 1

Characteristics of included studies that investigated the risk or odds of motor vehicle collision and specific medication (s)

Author	Year	Country	Study Design	Outcome Measure	Population[a] Characteristics	Medications Investigated	Source[b]
Nelson[63]	1992	U.S.	Case-Control	Odds Ratio	30-65 yrs, females	Methyldopa, Phenytoin	R
Koepsell et al.[64]	1994	U.S.	Case-Control	Odds Ratio	≥65 yrs, both genders	Insulin	R
Foley et al.[83]	1995	U.S.	Cohort	Relative Risk	≥65 yrs, both genders	Aspirin	S
Neutel[65]	1998	Canada	Case-Control	Odds Ratio	≥20 yrs, both genders	Diazepam, Flurazepam, Lorazepam, Oxazepam, Triazolam	R
McGwin et al.[84]	2000	U.S.	Case-Control	Odds Ratio	≥65 yrs, both genders	Insulin	S
Sims et al.[85]	2000	U.S.	Cohort	Relative Risk	≥55 yrs, both genders	Estrogen, Insulin	S
Cui[66]	2001	Canada	Case-Control	Odds Ratio	≥65.5 yrs, both genders	Insulin	R
Mura et al.[67]	2003	France	Case-Control	Odds Ratio	≥18 yrs, both genders	Morphine	L
Etminan et al.[86]	2004	Canada	Case-Control	Odds Ratio	67-84 yrs, both genders	Carbamazepine, Lithium	R
Delaney et al.[87]	2006	Canada	Case-Control	Odds Ratio	67-84 yrs, both genders	Warfarin	R
Hemmelgarn et al.[88]	2006	Canada	Case-Control	Odds Ratio	67-84 yrs, both genders	Insulin, Metformin, Sulfonylurea	R
Mathijssen et al.[68]	2006	Netherlands	Case-Control	Odds Ratio	≥18 yrs, both genders	Codeine	L
Bramness et al.[69]	2007	Norway	Cohort	Relative Risk	18-69 yrs, both genders	Carisoprodol, Diazepam, Salbutamol	R
Gustavsen et al.[70]	2008	Norway	Cohort	Relative Risk	18-69 yrs, both genders	Flunitrazepam, Nitrazepam, Zolpidem, Zopiclone	R
Lonnen et al.[71]	2008	England	Cohort	Relative Risk	≥15 yrs, both genders	Insulin	R
Bachs et al.[72]	2009	Norway	Cohort	Relative Risk	18-70 yrs, both genders	Codeine, Tramadol	R
Bramness et al.[73]	2009	Norway	Cohort	Relative Risk	18-69 yrs, both genders	Lithium, Valproate	R
Gibson et al.[74]	2009	England	Case-Control	Odds Ratio	18-74 yrs, both genders	Amitryptyline, Astemizole, Atenolol, Brompheniramine, Cetirizine, Chlordiazepoxide Chlorphenamine Citalopram Codeine, Desloratidine, Diazepam, Dihydrocodeine, Dosulepin, Fexofenadine, Fluoxetine, Hydroxyzine, Levocitirizine,, Lofepramine, Loratadine, Morphine, Nitrazepam, Paroxetine, Propranolol, Temazepam, Terfendine, Tramadol, Trazodone, Zopiclone, Zolpidem	R
Skurtveit et al.[75]	2009	Norway	Cohort	Relative Risk	18-69 yrs, both genders	Insulin	R
Coupland et al.[76]	2011	England	Cohort	Relative Risk	≥65 yrs, both genders	Amitiptyline, Citalopram, Dosulepin, Escitalopram, Fluoxetine, Lofepramine, Mirtazapine, Paroxetine, Sertraline, Trazodone, Venlafaxine	R
Gjerde et al.[77]	2011	Norway	Case-Control	Odds Ratio	Both genders	Diazepam, Zopiclone	L
Orriols et al.[78]	2011	France	Case-Control	Odds Ratio	Both genders	Zopiclone, Zolpidem	R
Yang et al.[89]	2011	Taiwan	Case-Crossover	Odds Ratio	≥18 yrs, both genders	Zopiclone, Zolpidem	R
Bramness et al.[79]	2012	Norway	Cohort	Relative Risk	18-69 yrs, both genders	Methadone	R
Corsenac et al.[80]	2012	France	Case-Control	Odds Ratio	Both genders	Buprenorphine, Methadone	R

Author	Year	Country	Study Design	Outcome Measure	Population[a] Characteristics	Medications Investigated	Source[b]
Hansen.[81]	2012	U.S.	Cohort	Relative Risk	21-79 yrs, both genders	Temazepam, Trazodone, Zolpidem	R
Gjerde et al.[82]	2013	Norway	Case-Control	Odds Ratio	Both genders	Diazepam, Zopiclone	L

[a]Yrs=years; if age is not specified, the population came from a registry of drivers in the country of origin

[b]Source indicates how prescription drug information was collected in each of the studies. R=medical/dispensing/insurance records or registry; L=laboratory test, S=self-report