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Impacts of alcohol and opioid polysubstance use on road safety: Systematic review

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ABSTRACT

Connections between substance use, impairment, and road safety have been frequently researched. Yet, little is known about how simultaneous use of opioids and alcohol affects road safety outcomes, which is an increasingly critical link within the current landscape of the substance use environment and public health. Lack of this understanding is partly due to testing complications and data limitations. We define polysubstance use here as alcohol and opioids consumed together or within a small-time window such that both are present in the system. This polysubstance use is on the rise and produces greater health risks than when the substances are consumed separately. Given the increasing rate of opioid use, high prevalence of alcohol use, and dangers of polysubstance use, we aim to synthesize literature on the prevalence and impact of this polysubstance on road safety-related outcomes. We performed a systematic review of studies published between 1974 and 2020 that examined opioid and alcohol use exposures and road safety-related outcomes. Out of 644 initial findings, 20 studies were included in this review. Outcomes included motor vehicle crash injuries, deaths, or driver culpability; suspected driving under the influence; and simulated driving performance. Evidence from multiple sources showed a significant rise, approximately 1% to 7%, in the prevalence of opioids among fatally injured drivers in the U.S. from 1995 to 2016. Information published on the simultaneous presence of opioids and alcohol in people involved in crashes was scarce. The limited available findings point toward an overlap where up to 30% of opioid-positive people involved in a crash were also positive for alcohol. Studies also suggest a possibly elevated risk presented by this polysubstance use relative to the substances used alone, though the majority of identified studies did not estimate this association. The synthesized research indicates that alcohol and opioid use is not uncommon and may be increasing among people involved in adverse driving events. More research and better data are needed to improve estimates of association with road traffic-related outcomes, potentially improving substance testing in current surveillance systems or using linked data sets and other novel data sources to improve estimates.

1. Introduction

The estimated age-standardized rate of global disability adjusted life years (DALYs) for opioid use disorder (OUD) increased by 6% from 2005 to 2015 (Kassebaum et al., 2016). Prescription opioid use has rapidly escalated over the last few decades, and despite reductions in opioid prescriptions, >153 million opioid prescriptions were provided to people in the U.S. in 2019, with a peak of 255 million in 2012 (Centers for Disease Control and Prevention, 2020). The burden of opioid use and dependence has not been isolated to just one U.S. state or county (Jalal et al., 2018). Beyond the U.S., the quantity of opiate production and seizures worldwide has remained high as of 2019 (United Nations, 2020). Approximately 57.8 million people globally used illicit opioids or misused prescription opioids in 2018 (United Nations, 2020).

At the same time, excessive alcohol consumption is common among the general population, and tied to countless negative health outcomes (World Health Organization, 2018). Alcohol-induced U.S. deaths increased an alarming 43% over twelve years, from 10.7 per 100,000

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people in 2006 to 15.3 per 100,000 people in 2018 (Spencer et al., 2020).

The consumption of opioids near or at the same time as alcohol represents a type of polysubstance use that has been increasing (Tori et al., 2020) and presents greater health risks than either substance alone (Witkiewitz and Vowles, 2018). The pharmacodynamic interactions between alcohol and opioids are problematic. Each substance operates as a central nervous system depressant, so the use of both simultaneously can result in substantial respiratory depression and elevates likelihood of an overdose (White and Irvine, 1999). Epidemiological evidence shows a trend toward the presence of multiple substances in opioid overdoses (Opioid Overdose Crisis Compounded by Polysubstance Use, 2020). Having a comorbid substance use disorder such as alcohol use disorder, in addition to opioid use disorder, is among the greatest risk factors for the occurrence of an opioid overdose (Lin et al., 2021; Betts et al., 2015; Bohnert et al., 2012; Kerr et al., 2007). Further, almost one quarter of people with an opioid use disorder have a concurrent alcohol use disorder (Hser et al., 2017).

The harmful effects of substance use on driving have been well established in the literature (Penning et al., 2010; Movig et al., 2004; Kelly et al., 2004). The existing literature has already documented the relationship between each of two substances – opioids (Chihuri and Li, 2017) and alcohol (Taylor et al., 2010; Taylor and Rehm, 2012) – with respect to their link to road safety outcomes. A topic that has received less attention is the specific impact that a rising and dangerous form of polysubstance use, i.e., combining opioids and alcohol, presents to driving-related outcomes.

Given the increase in opioid use, high prevalence of alcohol consumption, and the dangers inherent to rising polysubstance use of these two substances, it is important to understand the transportation risks associated with simultaneous alcohol and opioid use. Greater clarity regarding the extent and landscape of the problem can help practitioners and the public understand its risks and can inform policymakers as they strategize solutions and optimal allocation of research funding. Therefore, we aimed to synthesize and critically examine existing research on the prevalence of polysubstance involvement in harmful road traffic outcomes and the association between polysubstance impaired driving and road safety-related outcomes.

2. Methods

2.1. Search strategy and selection criteria

We conducted a systematic search and review consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Moher et al., 2009). Explicit search terms chosen based on their relevance to road safety, opioid use, and alcohol use were run through PubMed Central and MEDLINE databases—see Appendix for search terms. In our review, we define the term "opioid," to be inclusive of prescription as well as illicit opioids. Inclusion was not restricted by time frame of study data nor publication date. Titles and abstracts were screened in Rayyan (Ouzzani et al., 2016). Articles were excluded if they were not a peer-reviewed English research article. Despite the language limitation, the search was designed to include both U.S. and international studies in order to produce a broad set of findings. Animal studies, articles that failed to establish temporality between polysubstance use and a safety-related outcome when examining impacts, or those that included qualitative data only were also excluded.

To calibrate a consistent inclusion/exclusion coding, two researchers (GD, LW) separately reviewed the titles and abstracts of 30 randomly selected articles and then discussed decisions with two additional researchers (MJ, RN). The reviewers repeated the same process to screen the full-text version of articles in the subsequent review stage.

2.2. Data extraction

After screening, the research team collaboratively developed a data extraction tool. Extracted elements included authors' disciplines, the primary study aim(s), study design, details on exposure and outcome assessment, data sources, sample size, analytic approach and covariates included in analyses, and key results, estimates, and conclusions. Studies varied in their definition of "opioid" and we preserve their respective terms in the data extraction. See Table S2 for full details on extraction elements. Two reviewers (GD, LW) extracted the data and performed a cross-check process such that each item was entered by one reviewer and that content was reviewed by the other reviewer.

2.3. Quality assessment

To assess the methodological quality of studies, the reviewers used critical appraisal checklists. Three different checklists were used, corresponding to the three different study types represented in this review (i.e., randomized control trial (RCT) (Tufanaru et al., 2020), case control (Moola et al., 2020), and cross-sectional study (Moola et al., 2020). These checklists are widely cited in assessments of epidemiological studies (e.g., (Pramukti et al., 2020; Tougas et al., 2021; Trippella et al., 2020)). Each checklist contains a list of quality assessment items. The checklist corresponding to the appropriate study type was completed, where the reviewer evaluated whether each quality criterion was satisfied by a given study, and assigned a score of "yes," "no," or "unclear." A detailed explanation of how to assess each appraisal item was made available to the reviewers to ensure consistent application of the criteria. Checklist items were completed for each study by a primary reviewer (GD, LW) and cross-checked by the other reviewer (GD, LW). Upon completion of both initial review and cross-checking processes, scores were summarized for each study as the percentage of checklist items which were fully satisfied. Quality assessment findings are summarized in Table S4.

3. Results

3.1. Study selection

Figure 1 reports details on the search strategy stages from the database search through full eligibility screening. The search process produced 20 articles for final inclusion.

We summarize the extracted information by key items below, organized first for descriptive characteristics of studies, then by analytic characteristics, and finally by study findings. Table 1 reports main results from the data extraction process; Table S1 defines a full list of acronyms that appear in the extraction tables; and Table S3 contains additional extracted details.

3.2. Descriptive characteristics of study design and measures

The objectives of the 20 studies fall within one or more of the following broad categories: describing and comparing epidemiological records of polysubstance use among populations experiencing adverse road safety-related outcomes; describing trends over time of said polysubstance involvement; and estimating associations between polysubstance use and road safety-related outcomes.

Three study designs were represented: fifteen cross-sectional studies (Conner et al., 2017; Augsburger and Rivier, 1997; Chihuri and Li, 2017; Duren et al., 2019; Favretto et al., 2018; Palmentier et al., 2009; Pelletti et al., 2019; Romano and Pollini, 2013; Christophersen et al., 1999; Schwilke et al., 2006; Valen et al., 2019; Budd et al., 1989; Fitzpatrick et al., 2006; Jones and Holmgren, 2012; Li and Chihuri, 2020); three case-control studies (Chihuri and Li, 2019; Li and Chihuri, 2019; Jones et al., 2012); and two RCTs (Lenné et al., 2003; Linnoila and Häkkinen, 1974). All studies included opioid and alcohol use. Opioid and alcohol

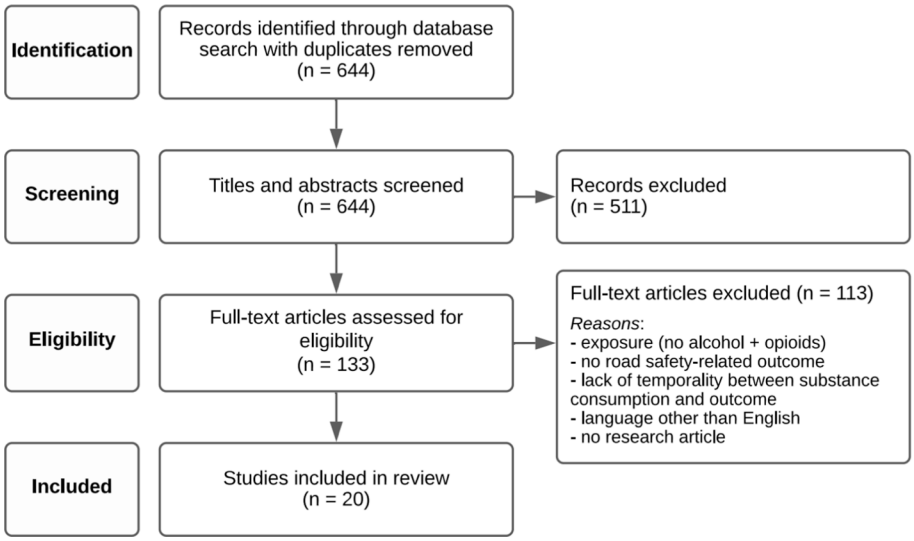

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.

use was assessed through toxicology testing (i.e., laboratory analysis of blood and/or urine samples or immunological methods testing (n = 12) (Fitzpatrick et al., 2006; Chihuri and Li, 2019; Li and Chihuri, 2019; Conner et al., 2017; Augsburger and Rivier, 1997; Chihuri and Li, 2017; Duren et al., 2019; Favretto et al., 2018; Pelletti et al., 2019; Romano and Pollini, 2013; Christophersen et al., 1999; Schwilke et al., 2006); gas or liquid chromatography, mass spectrometry, or radioimmunoassay techniques (n = 6) (Palmentier et al., 2009; Valen et al., 2019; Budd et al., 1989; Jones and Holmgren, 2012; Li and Chihuri, 2020; Jones et al., 2012) (sometimes in addition to immunological methods); or experimental manipulation in studies of simulated rather than real-world outcomes (n = 2) (Lenné et al., 2003; Linnoila and Häkkinen, 1974). Reported outcomes varied. Many articles combined motor vehicle crash (MVC) death, MVC injury, or both MVC death and injury as the outcome (n = 9) (Conner et al., 2017; Chihuri and Li, 2017; Duren et al., 2019; Romano and Pollini, 2013; Li and Chihuri, 2020; Li and Chihuri, 2019; Schwilke et al., 2006; Valen et al., 2019; Budd et al., 1989). Other studies considered safe driving indicators or driving skill (Lenné et al., 2003; Linnoila and Häkkinen, 1974); culpability in the fatal MVC (Chihuri and Li, 2019); and erratic driving where the influence of drugs or alcohol was suspected (n = 4) (Christophersen et al., 1999; Fitzpatrick et al., 2006; Jones and Holmgren, 2012; Jones et al., 2012).

3.3. Analytic characteristics of studies

Studies included data from government agencies and other surveillance databases (n = 13) (Conner et al., 2017; Chihuri and Li, 2017; Duren et al., 2019; Romano and Pollini, 2013; Schwilke et al., 2006; Valen et al., 2019; Budd et al., 1989; Fitzpatrick et al., 2006; Jones and Holmgren, 2012; Li and Chihuri, 2020; Chihuri and Li, 2019; Li and Chihuri, 2019; Jones et al., 2012), frequently using the U.S. Fatality Analysis Reporting System (FARS). Experimental studies internally generated data from simulated trials (n = 2) (Lenné et al., 2003; Linnoila and Häkkinen, 1974). Data ranged in time from 1973 to 2018 and in geography from North America (n = 10) (Conner et al., 2017; Chihuri and Li, 2017; Duren et al., 2019; Palmentier et al., 2009; Romano and Pollini, 2013; Schwilke et al., 2006; Budd et al., 1989; Li and Chihuri, 2020; Chihuri and Li, 2019; Li and Chihuri, 2019) to Europe (often Scandinavian countries) (n = 9) (Augsburger and Rivier, 1997; Favretto et al., 2018; Pelletti et al., 2019; Christophersen et al., 1999; Valen et al., 2019; Fitzpatrick et al., 2006; Jones and Holmgren, 2012; Jones et al., 2012; Linnoila and Häkkinen, 1974) and Australia (n = 1) (Lenné et al., 2003).

Sample sizes of the studies ranged from 55 to over 100,000 participants. Samples were typically not restricted to age groups or genders, though these subgroups were sometimes explored in post-hoc analyses. Researchers often performed descriptive analyses. Studies which included estimates of association (n = 7) (Conner et al., 2017; Valen et al., 2019; Fitzpatrick et al., 2006; Li and Chihuri, 2020; Chihuri and Li, 2019; Lenné et al., 2003; Linnoila and Häkkinen, 1974) leveraged multivariable regression frequently (n = 6) (Chihuri and Li, 2017; Romano and Pollini, 2013; Fitzpatrick et al., 2006; Li and Chihuri, 2020; Chihuri and Li, 2019; Li and Chihuri, 2019) and often in addition to other tools of statistical analysis such as hypothesis testing with t-tests, Chi-squared tests, McNemar tests, and ANOVA. Covariates considered in models included sex, age, race/ethnicity, geographic region, prescription opioid and other drug test results, blood alcohol content (BAC) results, and details surrounding the MVC (e.g., time of day; age of vehicle involved; presence of speeding).

3.4. Study findings

While the heterogeneity of studies precluded a meta-analysis, we synthesized results based on type of analysis and reported outcomes. We first summarize descriptive statistics on the prevalence of polysubstance involvement in harmful road safety outcomes, both from a cross-sectional and time trend point of view. We then summarize findings for estimated measures of association between opioids- and alcohol-attributed impaired driving and road safety-related outcomes. Finally, we discuss subgroup findings. To be included in the review, studies needed alcohol and opioids as the exposure; however, estimates of their simultaneous use was not an inclusion criterion for the review, and was not consistently reported across studies. While many studies were well-powered to detect associations and provide prevalence estimates with reasonable precision, some studies included smaller study populations. Table 1 includes sample sizes for all studies, and when estimates presented below are based on relatively small sample sizes (n < 500), we specifically note the sample size.

Six studies (Conner et al., 2017; Chihuri and Li, 2017; Duren et al., 2019; Romano and Pollini, 2013; Schwilke et al., 2006; Budd et al., 1989) reported findings that described the presence of alcohol and drugs in fatal MVCs. Four studies (Augsburger and Rivier, 1997; Favretto et al., 2018; Palmentier et al., 2009; Pelletti et al., 2019) reported on a group of fatal and non-fatal crashes, and six studies (Augsburger and Rivier, 1997; Palmentier et al., 2009; Christophersen et al., 1999; Fitzpatrick

Table 1
Characteristics and findings of reviewed studies.

	Characteristics	Results	Conclusions and implications
Augsburger and Rivier (1997) (Augsburger and Rivier, 1997)	**Aim:** Examine epidemiological and analytical laboratory records of living drivers suspected of DUID from 1982 to 1994 **Study design; data sources**: Cross sectional; epidemiological and analytical laboratory records **Exposure**: drivers suspected of DUID **Outcome**: traffic crash, erratic driving **Sample Size; location**: N = 641 records; Switzerland **Year(s) of data:** 1982–1994	• Traffic crashes occurred in 254 (39.6%) of records; crashes were the most frequent circumstance involving requests for toxicological analyses 273 (43%) were suspected of DUID during police controls, 95 (15%) suspected of DUID due to erratic driving 1 + psychoactive drug found in 93% of samples Opiates found in 36%, ethanol in 36%, methadone in 10%	• Police suspicion about DUI was highly correlated with positive drug tests Driving impairment of patients taking methadone-substitution medication should be carefully evaluated Essential need for educational programs for prescribers and consumers
Budd et al. (1989) (Budd et al., 1989)	**Aim:** Examine the use of barbiturates, cocaine, PCP, opiates, marijuana and ethanol in LAC fatally injured drivers **Study design; data sources**: Cross sectional; LAC medical examiner data. Small preliminary study with follow-up study conducted one year later using expanded sample size **Exposure**: use of alcohol or drugs in fatally injured drivers **Outcome**: fatal crash injury **Sample Size; location**: N = 102 in preliminary study; N = 492 in follow-up study; U.S. (LAC) **Year(s) of data:** Preliminary study in winter of 1985 – 1986, follow-up study from May 1987 - May 1988.	• 65 (64%) out of 102 fatally injured drivers had used alcohol and/or another drug: 34 (33%) had used alcohol only, 12 (12%) had used 1 + drugs, 19 (19%) had used alcohol in combination with another drug Codeine + alcohol found in 1 (0.9%) driver in preliminary study Preliminary study was short and took place during the Christmas/New-Year holiday period where alcohol and drug intake increases; Longer follow-up study was conducted to address this potential confounder Of 492 new subjects in follow-up study, 41% were positive for ethanol No opiates detected in follow-up study	• There is extensive use of ethanol, marijuana, and cocaine among fatally injured drivers Nationwide, coroners should conduct blood tests for ethanol and marijuana in fatally injured drivers
Chihuri and Li (2017) (Chihuri and Li, 2017)	**Aim:** Assess time trends in PO among fatally injured drivers **Study design; data sources**: Cross sectional; FARS **Exposure**: PO use in fatally injured drivers **Outcome**: fatal crash injury **Sample Size; location**: N = 36,729 drivers who died within 1 h of crash with available toxicological data; U.S. **Year(s) of data:** 1995–2015	• % positive: 39% for alcohol; 24% for nonalcohol drugs; 3% for Rx opioids Prevalence of PO detected in fatally injured drivers increased from 1% (95% CI: 0.5–1.4) in 1995 to 7% (95% CI: 5.7–8.8) in 2015 (Z = –9.04; $p < 0.001$) PO prevalence was higher in female than in male drivers (4% vs 3%; $p < 0.001$)Of the 1,194 drivers testing positive for PO, 42% tested positive for hydrocodone, 22% for morphine, and 16% for oxycodone; 30% had elevated BAC (‡ 0.01 g/dL), and 68% tested positive for other drugs	• Prevalence of PO use in fatally injured drivers has increased over the past 2 decades Urgent need to assess the effect of increased PO use on traffic safety Future research needed for role of PO in MVCs and effectiveness of PDMPs and other intervention programs in reducing drugged driving and traffic crashes
Chihuri and Li (2019) (Chihuri and Li, 2019)	**Aim**: Assess the association between drivers' PO use and risk of culpability of crash initiation in fatal 2-vehicle crashes **Study design; data sources**: Case control; FARS **Exposure**: PO and alcohol use **Outcome**: culpability of crash initiation **Covariates**: Driver characteristics **Sample size; location**: *N* = 36,642 drivers (18,321 fatal crashes); U.S. **Year(s) of data:** January 1, 1993 - December 31, 2016	• Drivers culpable of initiating crashes were more likely than their nonculpable counterparts to test positive for PO (5.0% vs. 3.0%; $p < 0.001$), alcohol (28.7% vs. 9.9%; $p < 0.001$), and both substances (1.0% vs. 0.3%; $p < 0.001$) AOR of crash initiation: 2.18 (95% CI: 1.91–2.48) for drivers using PO vs. those who were not AOR increased with BAC: BAC 0.01–0.07 g/dL: AOR 1.97 (95% CI: 1.75–2.22); BAC ≥ 0.08 g/dL: AOR 8.20 (95% CI: 7.42–9.07) compared with BAC < 0.01 g/dL No significant interaction effect on crash initiations between PO use and alcohol use	• Use of PO was associated with initiation of 2-vehicle crashes, independent of alcohol use Prescribing clinicians must be more aware of opioids' effects on safe driving
Christophersen et al. (1999) (Christophersen et al., 1999)	**Aim:** Compare the high incidence of drugged driving in Norway to that of other Nordic countries **Study design; data sources**: Cross sectional; Blood samples of drivers from Denmark, Finland, Iceland, Sweden, and Norway suspected of DUI **Exposure**: use of drugs and/or alcohol in drivers **Outcome**: prevalence of drugs and/or alcohol **Sample Size; location**: N = 255 blood samples from Denmark; N = 270 Finland; N = 40 Iceland; N = 86 Sweden; N = 149 Norway **Year(s) of data:** Blood Samples Collected during Week 10 of 1996	• Opiates (morphine or codeine) were detected in 6 and 5% of the Norwegian and Swedish samples, respectively, three samples (1%) from Denmark, one from Iceland and none from Finland contained opiates in addition to BAC over legal limit Frequencies of drugs (19–22%) in samples with BAC's above legal limits, were not significantly different in the different countries (x^2, P =.96)	• Authorities and police and health personnel must focus on work involving drugs and driving Drivers should be more informed; medical doctors and pharmacists must give warnings; police should have more training to discover drugs; and drug screening devices should be used by police at roadside
Conner et al. (2017) (Conner et al., 2017)	**Aim:** Compare postmortem toxicology results for alcohol and nonalcohol drugs, alone and in combination, in suicide decedents and MVCs **Study design; data sources**: Cross sectional; New Mexico medical examiner system **Exposure**: presence of alcohol and non-alcohol	• Alcohol + Drug was more likely in suicide decedents as compared to non-suicide MVC decedents, AOR 4.33 (95% CI: 1.70–11.03) Drug prevalence in suicides: alcohol + drug = 13%, alcohol = 40%, drug = 5%, none = 42% Drug prevalence in MVCs: alcohol + drug =	• Combination of alcohol and 1 + drugs, particularly cocaine, may be more likely in suicides versus MVCs Results may inform prevention efforts targeting specific substances and types of injury

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Table 1 (*continued*)

	Characteristics	Results	Conclusions and implications
	drugs **Outcome**: suicide or MVC death **Covariates:** sex (male, female), age (18–34, 35–54), race/ethnicity (Hispanic, American Indian/Alaskan Native [AI/AN], white non-Hispanic) **Sample Size; location**: N = 185 suicides; N = 161 MVCs; U.S. **Year(s) of data:** 2012	4%, alcohol = 44%, drug = 5%, none = 47% OR (95% CI) for alcohol + drug: 3.34 (1.36, 8.21); alcohol alone 1.02 (0.64, 1.60); drug alone 1.22 (0.46, 3.25), as compared to the no drug or alcohol reference group	
Duren et al. (2019) (Duren et al., 2019)	**Aim:** Describe opioid prevalence trends in driver fatalities and examine geographic variation in opioid-involved crashes among counties **Study design; data sources**: Cross sectional; Toxicological data from Office of the Chief Medical Examiner in Maryland, US census data, Maryland highway safety office, CDC data **Exposure**: opioid use in drivers **Outcome**: driver fatality **Sample Size; location**: N = 3,149 fatally injured drivers; U.S. **Year(s) of data:** 2006–2017	• Opioid-involved crash deaths accounted for 10.0% of all driver deaths during study period Statistically significant difference in distribution of opioid-involved crashes by racial category ($p < 0.001$) (Caucasians were in 81.6% of opioid-involved crashes) Prevalence of opioids detected in fatally injured drivers increased from 8.3% in 2006 to 14.1% in 2017, ($Z = -1.9$, $p < 0.05$) Of the drivers testing positive for opioids, 28% had elevated BAC (‡ 0.01 g/dL), and 45% tested positive for other drugs Counts of opioid-involved crash deaths by county are strongly correlated to counts of overall opioid overdose deaths in counties (Spearman's rho - 0.77, p < 01)	• Prevalence and characteristics of opioid-involved MVCs are under-examined in literature Opioid-involved driver fatalities largely reflect broader patterns of opioid deaths Opioid-involved crash deaths are increasing, with an over-representation of White, middle-aged, older adults living in rural counties Data can aid with trend monitoring of opioid-involved MVCs, targeted prevention, and enhanced enforcement efforts
Favretto et al. (2018) (Favretto et al., 2018)	**Aim:** Present the prevalence and concentrations of drugs in blood samples of drivers involved in RTCs; discuss the effects of concentration cutoff values in European countries on DUID offenses **Study design; data sources**: Cross-Sectional; blood samples from drivers involved in RTCs in Padova province hospital **Exposure**: Driving under the influence of drugs and/or alcohol (cannabinoids, cocaine, benzodiazepines, opiates/opioids, amphetamines, barbiturates, ketamine, alcohol) **Outcome:** RTCs **Sample Size; location**: N = 4,443 (378 samples analyzed exclusively for the presence of alcohol; 4,065 for alcohol and other substances); Italy **Year(s) of data:** 2014–2017	• Of the 4,443 blood samples analyzed, 23.7% were positive for alcohol and psychoactive drugs Opiates were detected in 1.9% of blood samples and other opioids were detected in 1.7% of blood samples. 12% of opiate-positive and 24% of opioid-positive samples were also positive for alcohol	• High analytical limits based on impairing concentrations in the Italian legislation could result in the prosecution of a much lower number of drugged drivers involved in RTCs, with a decrease from 25% to>80% The different per se limits (either analytical or based on impairing concentrations), applied in different legislation, have a role in the estimation of drugged driving prevalence and in the number of the DUID offenses.
Fitzpatrick et al. (2006) (Fitzpatrick et al., 2006)	**Aim:** Examine the prevalence of drug positivity among drivers suspected of driving under the influence of an intoxicant, and consequently apprehended by the police in Ireland **Study design; data sources**: Cross sectional; Medical Bureau of Road Safety **Exposure**: Exposure to drugs and/or alcohol (alcohol, cannabinoids, amphetamine, m-amphetamine, opiates, cocaine, methadone, benzodiazepines) **Outcome:** Drivers selected for testing by police officers who had clear evidence of aberrant driving behavior **Covariates:** time **Sample Size; location:** N = 2,000; Ireland **Year(s) of data:** circa 2003–2005	• 33% of drivers under the legal limit for alcohol tested positive for one or more drugs; corresponding figures of drivers over the limit was 14%. Using weighted analysis, this corresponds to 16% of tested drivers (16% in men, 15% in women). Among drivers who had minimal blood alcohol levels, 68% were taking at least one type of drug. Prevalence of taking drugs reduced steadily as alcohol concentrations increased, but still remained as high as 11% Being under the limit for alcohol, stopped in a city area, stopped between 6 am and 4 pm, or 4 pm and 9 pm, and being of a younger age were each independently associated with drug positivity 7% under the alcohol BAC limit tested positive for opiates 0.8% over the alcohol BAC limit tested positive for opiates	• For the evidential breath alcohol program and for checkpoints; in the event of a nil or low alcohol reading being obtained, a separate blood or urine specimen should be sought for analysis (currently non-routine) Role of drugs in injuries caused by road traffic is likely to be underestimated internationally
Jones et al. (2012) (Jones et al., 2012)	**Aim:** Compare the concentrations of free-morphine in femoral blood in heroin-related deaths with the concentrations of this opiate in venous blood from people arrested by the police for impaired driving. **Study design; data sources**: Case-Control; TOXBASE **Exposure**: Exposure to heroin and/or alcohol (ethanol 6-MAM (heroin), benzodiazepine, morphine, codeine) **Outcome:** Drivers arrested by police for suspected driving under the influence of drugs/alcohol	• Concentration of morphine in drug overdose deaths (median 0.25 mg/L, N = 669) was about the same as in traumatic deaths among heroin users (0.23 mg/L, N = 97). However, the concentration of morphine was lower when the deceased had consumed alcohol (0.18 mg/L, N = 104) compared with taking a benzodiazepine (0.32 mg/L, N = 94). Concentration distributions of free- morphine in blood in heroin-related deaths overlapped with the concentrations in impaired drivers, which makes the interpretation of toxicology	• Concentrations of free-morphine in blood in heroin-related deaths was similar to that of impaired drivers; interpretation of the levels is complicated without knowledge of the person's past drug experience and tolerance to opiates Autopsy findings, the police investigation, the death scene, eye-witness statements, and knowledge about prior use and abuse of illicit drugs all need consideration when the cause and manner of death are determined.

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Table 1 (*continued*)

	Characteristics	Results	Conclusions and implications
	Covariates: Age, gender **Sample Size; location**: N = 766; Sweden **Year(s) of data:** 1992–2009	results difficult without knowledge about tolerance to opiates in any individual case.	
Jones and Holmgren (2012) (Jones and Holmgren, 2012)	**Aim:** Document the types of drugs used by apprehended drivers in Sweden who also had a BAC above the legal limit for driving. Compare/contrast demographics of these traffic offenders, the types of drugs used, and blood concentrations **Study design; data sources**: Cross sectional; TOXBASE **Exposure**: Exposure to drugs and/or alcohol (opiates, amphetamines, cocaine metabolite, cannabis, and benzodiazepines) **Outcome:** Motorist pulled over by police for traffic offence, involvement in a crash, or as part of a routine stop **Covariates:** demographics of the traffic offenders **Sample Size; location**: N = 116,324; Sweden **Year(s) of data:** 2000–2009	• Both the median BAC (0.97 mg/g) and the mean age were lowest (36 ± 11 years, 92% male) in drivers who had consumed alcohol and used illicit drugs before driving. The opiate tramadol was identified in blood samples (median 0.4 mg/L) with alcohol. 81 (2.6%) cases were found to have tramadol present in addition to being above the BAC limit for driving Morphine was found in 115 (3.7%) cases where individuals were also above the legal BAC limit for driving Many traffic offenders are poly-drug users who use recreational illicit drugs, prescription medication as well as alcohol, making them a bigger danger in traffic compared with use of alcohol alone	• Poly-drug use was common among DUID offenders. However, DUI offenders had a higher median BAC and tended to be several years older than DUID offenders Zero-tolerance legislation did not deter hard-core offenders; recommend focus on treatment for substance disorder rather than conventional punishments
Lenné et al. (2003) (Lenné et al., 2003)	**Aim:** Study the effects of maintenance pharmacotherapies for heroin dependence (methadone, buprenorphine, LAAM) upon simulated driving) **Study design; data sources**: Randomized; trial data **Exposure**: opioid pharmacotherapies alone and in combination with alcohol **Outcome**: simulated driving ability **Covariates**: standard deviations of lateral position, speed, and steering wheel angle **Sample Size; location**: N = 55 total (N = 10 methadone; N = 13 LAAM; N = 11 buprenorphine; N = 21 controls); Australia **Year(s) of data:** circa 2002	• Significant main effects of drug group ($F(3, 58) = 10.66$, $p < 0.01$) and testing time ($F(2, 116) = 8.73$, $p < 0.01$), but no interaction effect Standard deviation of speed: significant main effect of alcohol compared to no-alcohol condition ($F(1, 52) = 4.28$, $p < 0.05$); Standard deviation of steering wheel angle: significant main effect of alcohol compared to no-alcohol condition ($F(1, 52) = 6.71$, $p < 0.05$)	• There should be community standards of driving safety for methadone, LAAM, and buprenorphine patients Findings are important due to widespread use of pharmacotherapy among drivers
Li and Chihuri (2019) (Li and Chihuri, 2019)	**Aim:** Assess the associations of PO use and alcohol use with the risk of fatal crash involvement in US drivers **Study design; data sources**: Case control; FARS, NRS **Exposure**: DUI of POs with or without alcohol **Outcome**: fatal crash involvement associated with prescription opioid use with and without alcohol **Covariates**: age, sex, geographic region **Sample Size; location**: *N* = 3,606 fatally injured drivers (cases); *N* = 15,600 drivers participating in the NRS (controls); U.S. **Year(s) of data:** 2007 and 2013 (NRS)	• Cases (from FARS data) were more likely than controls (from NRS data) to test positive for PO (5.0% vs. 3.7%; $p < 0.001$), alcohol (56.2% vs. 7.1%; $p < 0.0001$), and both substances (2.2% vs. 0.2%; $p < 0.001$) Compared to drivers testing negative for PO and alcohol, AORs of fatal crash involvement were: 1.72 (95% CI: 1.37–2.17) for PO positive and alcohol negative; 17.92 (95% CI: 16.19–19.84) for alcohol positive and PO negative; 21.89 (95% CI: 14.38–33.32) for both substances positive No statistically significant interaction effect on fatal crash risk of PO use and alcohol use	• Drivers' PO use is associated with significantly heightened risk of fatal crash involvement, independent of alcohol use Public awareness of DUI of rx opioids must be increased through enhanced education programs for rx opioid patients and prescribing clinicians
Li and Chihuri (2020) (Li and Chihuri, 2020)	**Aim:** Assess whether marijuana use is associated with decreased odds of PO use in US drivers. **Study design; data sources**: Cross-Sectional; FARS and NRS **Exposure**: Exposure to alcohol, marijuana, and other drugs (alcohol, prescription opioids, marijuana) **Outcome:** FARS - fatal car crash, NRS - Police surveillance action **Covariates:** Age, sex, geographic region, race/ethnicity, positive test results **Sample Size; location**: N = 55,483; U.S. **Year(s) of data:** 2011–2016 (FARS), 2013–2014 (NRS)	• Among the 47,602 drivers from the FARS, 7% positive for POs. Compared with drivers testing negative for marijuana, those testing positive for marijuana were 28% more likely to test positive for POs (adjusted OR = 1.28, 95% CI = 1.15–1.42). Among the 7881 drivers from the NRS, 4.5% positive for POs. Relative to drivers testing negative for marijuana, those testing positive for marijuana were twice as likely to test positive for POs (adjusted OR = 2.03, 95% CI = 1.29–3.20). In both study samples, marijuana use was associated with significantly increased odds of alcohol positivity. In the FARS study 34% of drivers tested positive for both Rx opioids and alcohol; only 3% drivers tested positive in the NRS study	• Drivers who test positive for marijuana are significantly more likely to test positive for prescription opioids. Results revealed that marijuana use is not associated with decreased odds of PO use among fatally injured drivers and in a nationally representative sample of drivers Longitudinal studies with rigorous designs and toxicological testing data are needed to further address the substitution hypothesis between marijuana and POs.
Linnoila and Hakkinen (1974) (Linnoila and Häkkinen, 1974)	**Aim:** Examine the effects of diazepam and codeine, with and without alcohol, on simulated driving in emergency and monotonous situations **Study design; data sources**: Randomized; trial data **Exposure**: drug positive and/or alcohol positive	• Zero group (i.e., no placebo; no drug, no drink): 60% of zero group felt impaired performance, increased inaccuracy of speed estimations Placebo (placebo capsule, placebo drink): group had more steering wheel reversals ($p < 0.05$) than zero group, switched on turning signals later ($p < 0.05$) than zero group Alcohol (placebo capsule, alcohol 0.5 gm/	• 0.5 gm/kg of alcohol, 10 mg of diazepam, and 50 mg of codeine, alone and in combination, can increase driving risks in emergency and monotonous situations Diazepam may have additive or potentiating effects in combination with alcohol When investigating the effects of drugged

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Table 1 (*continued*)

	Characteristics	Results	Conclusions and implications
	Outcome: simulated driving performance **Sample Size; location**: N = 70 professional drivers from the Finnish Army; Finland **Year(s) of data:** circa 1973	kg): 50% felt performance impairment, increased number of steering wheel reversals < p < 0.01), brake used more often (p < 0.05), neglected more instructions (p < 0.01), and more collisions (p < 0.01) than zero group Codeine (codeine phosphate 50 mg, placebo drink): slightly overestimated speed, smaller pulse reactions during emergencies, greatest increase in collisions Codeine + alcohol (codeine phosphate 50 mg, alcohol 0.5 gm/kg): felt impaired performance, overestimated speed, smaller pulse reactions (p < 0.05), neglected instructions, drove off the road, caused more collisions (p < 0.001) than controls	driving with a simulator, monotonous and emergency situations should be included
Palmentier et al. (2009) (Palmentier et al., 2009)	**Aim:** Retrospectively examine blood samples from drivers suspected of driving under the influence of alcohol in Ontario from 2001 to 2005 **Study design; data sources**: Cross-Sectional; cases considered for this study were submitted to the Toxicology sections of the Centre of Forensic Sciences (CFS) in Toronto and the Northern Regional Laboratory (NRL) in Sault Ste. Marie **Exposure**: Individuals suspected of driving under the influence of alcohol **Outcome:** Motor vehicle crashes **Covariates:** sex, age, type of motor vehicle crash (e.g., single vehicle vs. multi-vehicle crash), time of day, day of week **Sample Size; location:** N = 733; Canada **Year(s) of data:** 2001 – 2005	• N = 691 cases (94%) were only analyzed for alcohol. In 16 cases (2%) samples were analyzed for alcohol and one other specified drugs, and in 26 cases (4%) more extensive analyses were performed, including general screening for pharmaceuticals and drugs of abuse The BACs for the 17 cases that were drug positive and alcohol positive ranged from 10 to 161 mg/100 mL (mean 88 mg/100 mL; median 95 mg/100 mL), while the number of drug positive cases that had quantified BACs below 80 mg/100 mL was 7	• More investigation is needed to determine the frequency and type of drug use by Ontario drivers. Ability of the investigating officers to form grounds to arrest suspected impaired drivers using the tools they have available such as observable signs of intoxication, indicators of impairment during observation of driving, and/or a "Fail" message on an approved screening device correlates well with the high number of alcohol positive drivers
Pelletti et al. (2019) (Pelletti et al., 2019)	**Aim:** Assess the prevalence of a large set of psychoactive substances (n = 53) in Italian drivers involved in a road traffic crash and in predefined population subgroups (gender, age, crash time) **Study design; data sources**: Cross-Sectional; Toxicological analyses were performed on drivers involved in road traffic crashes **Exposure**: Use of therapeutic drugs and/or alcohol while driving (benzodiazepines and Z-drugs, antipsychotics, medical opioids, alcohol) **Outcome:** Road traffic crash **Covariates:** Age, gender, crash time **Sample Size; location**: N = 1,026; Italy **Year(s) of data:** January 2017 – March 2018	• The highest prevalence was found for alcohol (17%), followed by medicinal drugs (14%) and illicit drugs (6%). No significant association was found between alcohol and age groups (p > 0.05), while there was a significant increasing trend in the combination of alcohol and medicinal drugs with increasing age. The combination of alcohol and illicit drugs was highest in the age group 26–35 Alcohol alone was found in 12.6% of cases; in 1.5% of cases it was associated with illicit drugs and in 3.6% of cases with medicinal drugs (in 0.3% of cases it was associated with both). In less than a half of cases medicinal drugs were detected as a "unique finding", as they are often found in combination with alcohol, illicit drugs, or other medicinal drugs The presence of illicit drugs was significantly higher in nighttime crashes (p < 0.01) but not in the weekend crashes (p > 0.05)	• The high frequency of polypharmacy/ polydrug use may lead to important considerations on per se cut-off- legislation, which is based on the impairing effect of a single illicit drug. Authors recommend a comprehensive information system for physicians, pharmacists and patients; potential legal procedures could be considered that focus on combined consumption of medicines and alcohol (i.e., zero-tolerance approach for combined use) Future study design should account for blood concentration of drugs to study risk of MVC due to medicinal drugs
Romano and Pollini (2013) (Romano and Pollini, 2013)	**Aim:** Characterize drug prevalence among fatally injured drivers, identify significant associations (day of week, time of day, age, gender), and compare findings with those for alcohol **Study design; data sources**: Cross-Sectional; FARS **Exposure**: Exposure to drugs and alcohol (narcotics, depressants, stimulants, hallucinogens, cannabinols, Phencyclidine/ PCP, anabolic steroids, inhalants, alcohol) **Outcome:** RTCs (only included fatal crashes) **Covariates:** Time **Sample Size; location**: N = 16,942; U.S. **Year(s) of data:** 1998 – 2010	• 45% of fatally injured drivers tested positive for alcohol (40% BAC >/=legal limit) and 26% for drugs Most common drugs present were stimulants (7%) and cannabinols (7%), followed by 'other' drugs (4%), multiple drugs (4%), narcotics (2%) and depressants (2%). Drug classes found most commonly among multi-drug users were stimulants (57%), cannabinols (54%), narcotics (48%), and depressants (46%). Adjusted OR of positive opioid test among fatally injured drivers, controlling for time and demographic variables: Weekday versus weekend (time of crash): 1.003; Night versus daytime: 1.03*; Age 16–20 vs. 21–34: 0.97*; Age 35–64 vs. 21–34: 1.07*; Age greater than/equal to 65 vs. 21–34: 1.04*; Female vs. Male: 1.05*; 0 < BAC < 0.08 vs, BAC = 0.00: 0.99; BAC>/ =0.08 vs. BAC = 0.00: 1.02; *indicates statistical significance at 95% level	• Fatal single-vehicle crashes involving drugs are less common than those involving alcohol and the characteristics of drug-involved crashes differ, depending upon drug class and whether alcohol is present. Concerns about drug-impaired driving should not detract from the current law enforcement focus on alcohol-impaired driving. More research on the key components of the DUID problem is needed to characterize the actual contribution of drugs to impairment and crashes, both alone and combined with alcohol is needed before targeted drug testing can become a feasible policy.

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Table 1 (*continued*)

	Characteristics	Results	Conclusions and implications
Schwilke et al. (2006) (Schwilke et al., 2006)	**Aim:** Examine how drug use patterns have changed over 9 years in fatally injured drivers in Washington State **Study design; data sources**: Cross-Sectional; Washington State Toxicology Laboratory (WSTL) **Exposure**: Driving under the influence of drugs and alcohol (alcohol, cocaine, cannabinoids, benzodiazepines, barbiturates, amphetamines, phencyclidine, propoxyphene, methadone, tricyclic antidepressants, opiates, morphine) **Outcome:** Fatal car crash **Sample Size; location**: N = 370; U.S. **Year(s) of data:** February 1, 2001 – January 31, 2002	• Of 370 cases tested, 41% were positive for ethanol. The mean ethanol in 2002 was not significantly different from the mean in 1992. The data reveal that over the past decade, while alcohol use has declined, some drug use, notably methamphetamine, has increased significantly (from 2% to 5% of fatally injured drivers) between 1992 and 2002. Of the 150 cases positive for alcohol, 42% were positive for one or more impairing drugs. Combined drug and alcohol use was common. Methadone was found in 13% of drivers with BAC < 0.08, 0.8% of drivers with BAC>/=0.08, and 3% of drivers with BAC > 0.00	• Alcohol use declined among fatally injured drivers between 1992 and 2002, but drug use increased from 2% to 5% Combined drug and alcohol use is significant and likely overlooked in DUI enforcement programs Laws relating to driving after consuming illicit drugs could promote behavioral change
Valen et al. (2019) (Valen et al., 2019)	**Aim:** Examine associations between driving under the influence of drugs and/or alcohol and driver-related risk factors that have been reported as significantly contributing to fatal road traffic crashes **Study design; data sources**: Cross-Sectional; Road Traffic Accident Registry of Statistics Norway **Exposure**: alcohol and/or drugs: benzodiazepines, Z-hypnotics, stimulants, cannabis, opioids, other drugs (e.g., LSD) **Outcome:** Fatal car, van, or motorcycle crash **Covariates:** Age group, sex, time of crash, age of vehicle, single-vehicle crash, type of impairment, valid driver license, speeding, use of a seatbelt/motorcycle helmet, incorrect, position on the road, incorrect driving decisions, technical driving errors, lack of driving or vehicle experience, inattention while driving, and drowsy driving **Sample Size; location**: N = 772; Norway **Year(s) of data:** 2005–2015	• Drug/alcohol-impaired drivers compared to sober drivers were more often speeding (68% v. 32%), without seatbelt (69% v. 30%), and without a valid license (26% v. 1%) Among drivers investigated for both drugs and alcohol, the prevalence of alcohol impairment: 20%; drug impairment: 16% Drivers exclusively impaired by alcohol or by substances within the drug groups of medicinal drugs, stimulants, or cannabis constituted respectively 15% (n = 86), 4% (n = 23), 2% (n = 11), and 1% (n = 7) of the drivers. Prevalence of impairment from only alcohol (15%) was significantly higher than prevalence of impairment from only one drug group (7%), ($\chi 2 = 15{,}945$, $p < 0.0005$)	• Drug/alcohol impairment among drivers was significantly associated with not having a valid license, speeding, and non-use of a seatbelt Seatbelt alarms and speeding enforcement may reduce fatalities related to alcohol or drug impairment

AOR = adjusted odds ratio; BAC = blood alcohol concentration; CI = confidence interval; DUI = driving under the influence; DUID = driving under the influence of drugs; FARS = Fatality Analysis Reporting System; LAAM = levo-alpha-acetyl-methodol; LAC = Los Angeles County; MVC = motor vehicle crash; NRS = National Roadside Study of Alcohol and Drug Use by Drivers; PDMP = prescription drug monitoring program; PO = prescription opioid; RTC = road traffic crash; Rx = prescription. For a more complete list of acronyms and abbreviations often used in this literature, please see Table S1.

et al., 2006; Jones and Holmgren, 2012; Jones et al., 2012) focused on drivers suspected of using drugs or alcohol even if a crash did not take place. Three studies (Chihuri and Li, 2017; Duren et al., 2019; Schwilke et al., 2006) describe trends over time in substance involvement in road safety-related outcomes. Seven studies estimated an association between alcohol and opioids and driving-related outcomes (Conner et al., 2017; Valen et al., 2019; Fitzpatrick et al., 2006; Li and Chihuri, 2020; Chihuri and Li, 2019; Lenné et al., 2003; Linnoila and Häkkinen, 1974).

4. Prevalence of polysubstance involvement

4.1. Fatal crashes

In cases of fatally injured drivers, studies analyzed toxicology results to indicate the presence of drugs or alcohol. The percent of fatally injured drivers in the U.S. between 1985 and 2015 who had a positive alcohol result ranged from 39% (Chihuri and Li, 2017) to 52% (n = 102) (Budd et al., 1989). The percent of drivers who tested positive for opioids, when opioid positivity was reported independent of alcohol, ranged from 1% in 1995 to 7.2% in 2015 (Chihuri and Li, 2017) in the U.S. Other studies have identified prevalence point estimates within the same range (2.1% (Romano and Pollini, 2013), 3.2% (n = 370) (Schwilke et al., 2006); 4.5% (Li and Chihuri, 2020), and 6.9% (Li and Chihuri, 2020)) in the U.S. between 1998 and 2016. Some studies indicate the presence of polysubstance use by reporting the percent positive result for opioids or alcohol, given a positive result for the other. For example, a U.S. based study of alcohol-positive fatally injured drivers in 1998–2010 indicated that 2.1% (Romano and Pollini, 2013) were also positive for opioids; and of opioid-positive fatally injured drivers (n = 346), 50% (Conner et al., 2017) were positive for alcohol (though the latter conditional percentage is based on a small sample of just 2 drivers). Overall rates of detected opioid and alcohol co-presence in the U.S. were reported at 1.0% (Chihuri and Li, 2019) positive for culpable drivers from 1993 to 2016 and 2.2% (Li and Chihuri, 2019) positive for all drivers in fatal crashes from 2006 to 2008 and from 2012 to 2014.

According to one U.S. study that reported types of driving errors, the most common type of driving error that contributed to fatal MVCs from 1993 to 2016 – occurring in 41% of fatal crashes – was inability to stay in lane; this error was even more frequently reported (55%) in drivers positive for opioids (Chihuri and Li, 2019).

4.2. Non-fatal crashes

Studies also reported toxicology results in the event of non-fatal MVCs. In a study that analyzed a set of blood samples taken from drivers involved in MVCs who were admitted to a Padova, Italy hospital from 2014 to 2017, 24% tested positive for alcohol (n = 378) (Favretto et al., 2018). Alcohol was present in 17% of fatal or non-fatal MVCs in Bologna, Italy from 2017 to 2018, whereas licit and illicit drugs were present in 14% and 5.5% of cases, respectively (Pelletti et al., 2019). Finally, in a set of records of living drivers suspected of driving under the influence of drugs including alcohol in Canton de Vaud, Switzerland who were involved in MVCs (40% of records), stopped by routine police

controls, or pulled over due erratic driving between 1982 and 1994, 36% of cases were positive for opioids; 36% tested positive for alcohol; and the combined use of opioids and alcohol was identified in 7% of cases (Augsburger and Rivier, 1997).

4.3. Suspected driving under influence

Studies also included cases where suspected driving under the influence of drugs and/or alcohol occurred without necessarily resulting in a crash. In a set of blood samples from drivers suspected of driving under the influence of alcohol in Canada between 2001 and 2005, 97% tested positive for alcohol (Palmentier et al., 2009). In a set of Swiss records collected between 1982 and 1994 of living drivers suspected of driving under the influence of a drug, one or more psychoactive drugs were found in 93% of the records: opiates in 36%, ethanol in 36%, and methadone in 10%. Drivers were identified as suspected of driving under the influence most commonly via judgement of police or through investigation following an MVC (Augsburger and Rivier, 1997). In a study (Christophersen et al., 1999) of drivers apprehended by police in Nordic countries who were suspected to be under the influence of alcohol or drugs, opioids were detected in < 1% to 6% of samples depending on the country. A study (Fitzpatrick et al., 2006) of drivers suspected by police of aberrant driving in Ireland showed that 1.4% of those drivers who were over the legal limit for alcohol were also positive for opioids; of drivers with minimal or no alcohol detected, 13.7% were positive for opioids. Finally, in another study (Jones and Holmgren, 2012) of drivers pulled over by police in Sweden between 2000 and 2009, morphine (a metabolite of heroin) was the fifth most frequently detected drug used in combination with alcohol in drivers above the legal limit for alcohol. Morphine was detected with alcohol 115 times in this study, representing 3.6% of cases in which both alcohol and an illicit drug was present (Jones and Holmgren, 2012).

4.4. Time trends

Three of the studies inform not only a snapshot in time for the phenomena of interest, but also how indicators have changed over time. Using FARS data, researchers found that the prevalence of opioids in fatally injured drivers increased from 1% in 1995 to 7% in 2015 (Chihuri and Li, 2017) and from 8% in 2006 to 14% in 2017 (Duren et al., 2019). From 2006 to 2017, overall MVC rates decreased, while the number of opioid-related crashes increased (Duren et al., 2019). Between 1992 and 2002, based on a sample size of 370, alcohol use in fatally injured drivers declined (Schwilke et al., 2006). The presence of the opioids hydrocodone and morphine increased from 0.3% to 1.9% and from 1.3% to 1.6%, respectively, in fatally injured drivers (Schwilke et al., 2006).

4.5. Estimates of association

Seven studies (Conner et al., 2017; Valen et al., 2019; Fitzpatrick et al., 2006; Li and Chihuri, 2020; Chihuri and Li, 2019; Lenné et al., 2003; Linnoila and Häkkinen, 1974) quantified associations between opioid and alcohol use and road safety-related outcomes, derived from both experimental and observational research. According to a simulation-based study of 55 participants, alcohol impaired all types of driving performance measured (i.e., lateral position, speed and steering wheel angle, and reaction time to a subsidiary task) (Lenné et al., 2003). In another study using simulated driving scenarios of 70 participants, subjects that consumed a combined opioid and alcohol dose neglected instructions, drove off the road, and caused collisions more frequently than subjects who consumed no substances (Linnoila and Häkkinen, 1974).

In observational studies of crash records, prescription opioid use was associated with increased risk of fatal crash involvement. MVC initiation was more likely when opioids were present compared to when they were absent, and the likelihood increased in combination and with increasing levels of alcohol (Li and Chihuri, 2019). Drivers culpable of initiating crashes were more likely than their nonculpable counterparts to test positive for prescription opioids, alcohol, and both substances combined. The odds of crash initiation was greater for drivers testing positive for prescription opioids compared with drivers testing negative for them (adjusted odds ratio (AOR): 2.18 [95% CI: 1.91–2.48]), and the odds increased with higher BAC levels (using a reference group of BAC < 0.01 g/dL, for BAC between 0.01 and 0.07 g/dL: AOR was 1.97; for BAC>=0.08 g/dL: AOR was 8.20) (Chihuri and Li, 2019).

One study (Li and Chihuri, 2020) identified an inverse association between opioid and alcohol positivity among fatally injured drivers: positivity for one substance was associated with negative result for the other. More specifically, using FARS data, the researchers found that among those testing positive for alcohol, the odds of opioid presence were 0.68 times that of those testing negative for alcohol (AOR: 0.68 [0.63–0.74]). A point estimate of similar magnitude was found when the same researchers used data from the National Roadside Surveys of Alcohol and Drug Use by Drivers (NRS) (AOR: 0.56[0.24–1.31]) (Li and Chihuri, 2020).

Among a sample of 161 fatally injured drivers and 185 suicide decedents, researchers using New Mexico medical examiner system data in 2012 found that combined alcohol and drug use was more likely in suicide decedents than fatally injured drivers (AOR: 4.3[1.7–11.0]), while presence of drugs without alcohol and alcohol without drugs did not differ between the groups (Conner et al., 2017). Based on a separate study, impairment from medicinal drugs (a category defined by the study as including benzodiazepines, z-hypnotics, and opioids) was associated with lack of a valid driver's license (AOR: 9.5[1.9–46.5]) and no seatbelt use (AOR: 3.7[1.6–8.8]), but not with speeding (AOR: 1.3 [0.5–3.5]) (Valen et al., 2019). Odds ratios for smaller drug subgroups that isolated estimated associations of opioids were not reported due to small subgroup sizes in both aforementioned studies (Conner et al., 2017; Valen et al., 2019).

Prescription opioid prevalence in fatally injured drivers was higher in females than in males (4% vs 3%; p <.001), according to a U.S. study from 1995 to 2015 (Chihuri and Li, 2017). Being female (AOR = 1.05) and belonging to older age groups (35–64: AOR = 1.07; 65+: AOR = 1.04) relative to the 21–34 years of age range was associated with elevated risk of opioid positivity for fatally injured drivers (Romano and Pollini, 2013). These AOR were statistically significant at the 95% level. Randomized control trials of simulated driving performance (n = 55 (Lenné et al., 2003) and 70 (Linnoila and Häkkinen, 1974) did not investigate heterogeneity of effects across subgroups (Lenné et al., 2003; Linnoila and Häkkinen, 1974).

4.6. Study implications

Authors often communicated how their research findings might apply to the greater context of policy interventions and indicated areas of future research. From a primary prevention perspective, discussion centered around recommendations for clinicians, calling for clinicians to consider the adverse effects of opioids in their prescribing decisions (Chihuri and Li, 2019) and to warn patients about the risk of potential MVCs prior to prescribing opioids (Christophersen et al., 1999; Schwilke et al., 2006; Li and Chihuri, 2019). Authors also frequently highlighted the importance of increasing public awareness about the risks associated with driving while taking prescription opioids (Li and Chihuri, 2019) and the need for educational programs about these potential risks for people with substance use disorders (Augsburger and Rivier, 1997; Li and Chihuri, 2019). An example of another proposed countermeasure to combat impaired driving was the creation of a comprehensive information system for physicians, pharmacists, and patients about the side effects from medicinal drugs which can impair driving abilities (Pelletti et al., 2019).

Researchers emphasized the need for police action in cases of suspected drug or alcohol-impaired driving (Schwilke et al., 2006) and

suggested increased training for police on this subject (Christophersen et al., 1999). Some studies identified a need for stricter drug laws (Schwilke et al., 2006) and regulations surrounding increased road monitoring for speed violations and seatbelt enforcement (Valen et al., 2019). Studies also indicated that routine testing for drugs in fatally injured drivers could improve data availability and quality of research (Budd et al., 1989). In contrast to a punitive approach, some researchers also noted the importance of treatment for people with substance use disorders who are involved in MVCs instead of conventional punishments (Conner et al., 2017; Duren et al., 2019; Jones and Holmgren, 2012).

Several authors discussed areas for future research, including the need for research tools for simulating real-world driving and for testing effects of substance use on driving in both monotonous and emergency situations (Linnoila and Häkkinen, 1974). Researchers pointed out a need for longitudinal study designs paired with toxicological data to inform the substitution hypothesis between marijuana and opioids (Li and Chihuri, 2020). Researchers also suggested examining: potential impairment of people receiving methadone maintenance therapy for their OUD; methadone's interactions with other drugs (Augsburger and Rivier, 1997); the role of prescription opioids in MVCs; how PDMPs and intervention programs might decrease risks (Chihuri and Li, 2017); and the development of targeted drug testing for impaired drivers (Augsburger and Rivier, 1997; Palmentier et al., 2009; Romano and Pollini, 2013; Christophersen et al., 1999; Fitzpatrick et al., 2006).

4.7. Quality assessment

The quality assessment showed that studies were of moderate to high methodological quality, with at least 80% of quality appraisal items satisfied in 16 of the 20 studies. Table S4 reports details of the quality assessment for each study.

5. Discussion

5.1. Descriptive findings and measures of association

Descriptive study results indicated that alcohol presence increases with road crash severity. Of reviewed studies, alcohol was present in 17% (Pelletti et al., 2019) to 24% (Favretto et al., 2018) of non-fatal crashes and in 39% (Chihuri and Li, 2017) to 52% (Budd et al., 1989) of fatal crashes. The prevalence of opioid use among fatally injured drivers has increased over time, as has the occurrence of opioid-involved crashes. Meanwhile, alcohol use in fatally injured drivers decreased over time, although the published data was less recent (spanning 1992–2002). Studies (Chihuri and Li, 2017; Duren et al., 2019; Schwilke et al., 2006) informing time trends are based on data from a subset of U. S. states rather than a nationally representative sample, so generalizability to the national level is limited. Further, the increasing frequency of testing for opioids would account at least partially for the time trends reflected in these studies.

The high variability in which drugs and combinations of drugs were the focus of study poses a challenge in the interpretation of research findings. Studies confirmed that the presence of general "drugs" is often high in crashes, but several studies did not specifically isolate opioid use in results as they did with alcohol. The studies which did report this metric showed that 7% (Chihuri and Li, 2017; Li and Chihuri, 2020) to 14% (Duren et al., 2019) of fatally injured drivers were positive for opioids.

Across studies, drivers were more frequently positive for one substance alone (i.e., opioids or alcohol) rather than both; simultaneous presence was identified in 1% (Chihuri and Li, 2019) to 2.2% (Li and Chihuri, 2019) of fatally injured drivers. The conditional probabilities of alcohol given opioid presence, however, were high: people involved in a crash who were positive for opioids were often (28% (Duren et al., 2019) to 30% (Chihuri and Li, 2017)) also positive for alcohol.

Only two studies (Chihuri and Li, 2019; Li and Chihuri, 2019) quantified the risk of a crash caused by opioid and alcohol polysubstance use relative to the risk associated with the use of just one or neither of the substances. Studies which produced estimates of association between substance use and adverse driving outcomes give better insight on substance-related impacts on road safety than purely descriptive statistics. Evidence points to a highly elevated risk for fatal MVC involvement for people positive for both opioids and alcohol (AOR = 21.9 [14.4–33.3]). Comparatively in the same study, the AOR for those positive for opioids and negative for alcohol was 1.7 [1.4–2.2]; and the AOR for those negative for opioids and positive for alcohol was 17.9 [16.2–19.8] (Li and Chihuri, 2019). Studies (Chihuri and Li, 2019; Li and Chihuri, 2019) did not find statistically significant evidence for an interaction effect between the two substances, yet speculated this could be due to the relatively low prevalence of polysubstance use in the data sets. More research is needed to determine the potential synergistic magnitude of the simultaneous opioid and alcohol use effect on road safety outcomes, with study designs centering around an opioid-specific research objective rather than a more general "drug" group. Beyond this, research could also be extended to explore interactions between alcohol and other specific drug groups, such as stimulants or marijuana, given their high prevalence of use.

6. Limitations and considerations for future research

Data is a central limitation in attempts to study the effects of opioids on driving outcomes. Unlike alcohol which is testable with relative ease using the behavioral Standardized Field Sobriety Testing (SFST) at roadside, and which has standard procedures already built into the law enforcement infrastructure, opioids are not as easily detectable and opioids testing is not standardized. Testing protocol may vary in other ways in addition to threshold levels, such as whether blood, urine, or breath are the subject of testing and the typical delay between occurrences of a driving event and the test administration. The proportion of fatally injured drivers that are tested for opioids by medical examiners is also variable (Slater et al., 2016). Analyses of 2019 U.S. FARS data indicated that drug testing of fatally injured drivers ranged from nearly 0% in North Carolina to over 95% in Alaska, resulting from considerable variation in state drug testing laws and policies (Berning et al., 2022). Furthermore, opioid testing can be costly, which limits how often it is performed and the resulting data availability. Data sources for research on this topic restrict the current scope of measurable outcomes and type of appropriate analyses. Methods of data collection vary in their ability to capture the presence of opioids and alcohol, affecting the generalizability of findings and comparisons between studies. Additionally, inconsistencies in collection and non-uniformity exist in databases such as FARS (U.S. Department of Transportation National Highway Traffic Safety Administration, 2014). While FARS is one of the largest available data sources and as demonstrated by its frequency in this review, often used to study substance use as related to fatal crashes, it has important limitations. The National Highway Traffic Safety Administration (NHTSA) has stated (U.S. Department of Transportation National Highway Traffic Safety Administration, 2014) its opinion that FARS is currently insufficient to compare drugs across years or across states, and that one should not make inferences about impairment, crash causation, or comparisons to alcohol using the data source. We observed a dearth of studies that apply statistical inference estimation methods to quantify association between polysubstance use and adverse driving outcomes.

While the overall methodological quality of the studies was moderate to high, quality assessments indicated areas of weakness. Selection of individuals included in analysis is a critical component that is often limited by available data and determines possible inferences from the analysis. When drivers are included in analysis based on an objective selection procedure, such as decedents from fatal crashes, inferences may be made through analysis that would not be appropriate in a study where individuals were selected in a biased manner such as suspected

driving under the influence of drugs or alcohol. For example, among cross-sectional studies, the selection of people included in the analyses was often limited by the subjective judgement of police prior to any drug testing. Two out of the three case control studies had weak comparability of cases and controls. The largest methodology challenge in RCTs surrounded treatment allocation concealment and blinding. Another inherent limitation to the RCTs, which were simulation studies, is that the concentration levels tend to be lower than the analogous measured in the real world.

Most of the study designs identified in the review depend on measurements of concentrations of drugs in one's system as an indicator for the degree of impairment from the given drug. However, a limitation of this assumption is that tolerance to substances can vary considerably across individuals. A given concentration of morphine in one person, for example, does not necessarily indicate the same degree of impairment as it would for another individual. Variability in tolerance levels is difficult to account for in data that does not include details of proximate tolerance indicators such as individual drug use history.

The diversity represented in geographies and time periods is also an important consideration for appropriate interpretation. Findings in one location or time period may not easily generalize to others. Impaired driving policies, behaviors, and cultures vary by country. For example, while the U.S. maintains a 0.08 BAC limit for drivers aged 21 or older, several other high-income nations have a 0.05 BAC limit (World Health Organization, 2018). Public transit infrastructure and utilization is another area of potentially important variability across countries, where observed higher rates of substance-impaired driving could be a function of the scarcity of public transit alternatives. Further, generalizability of findings may be limited not only across countries but within countries – for example, within the U.S., given policy changes implemented in light of the opioid crisis. Several opioid-related policies (e.g., PDMP policies, prescribing limits) have been enacted in response to the opioid crisis in the U.S. over the last several years that may have substance use and road safety implications (Lovecchio et al., 2019; Kominek, 2018). Research indicates that cultural and social acceptability of driving after consuming substances varies within and between countries, which also influences road safety outcomes (Cestac et al., 2016; Stringer, 2018). Therefore, researchers and policymakers should carefully consider the political and legal contexts that shape findings around the prevalence of polysubstance impaired driving and associated outcomes when interpreting results.

Historically, both general deterrence methods, such as education campaigns, applied to the population and specific deterrence methods, such as legal penalties, applied to individuals who committed a road safety offense have each played a role to reduce substance-involved driving. While many studies included recommendations focused on education and enforcement, many of these strategies have not proven effective for sustained change in road safety outcomes. With some exceptions (Conner et al., 2017; Duren et al., 2019; Jones and Holmgren, 2012), studies in the review generally lacked attention to the importance of treatment for people post-crash. As with other substance-use-related outcomes, research shows a focus on treatment and system structures around substance misuse and development of use disorders have better long-term outcomes than purely punitive approaches (Chandler et al., 2009; Department of Health and Human Services, 2016).

This review is limited to studies published in English, therefore preventing the inclusion of all literature on our topic of interest published in other languages. However, our inclusion of international studies allowed us to widen the breadth of inclusion geographically beyond the U.S. and other English-speaking countries. Also, our analyses of study findings included in this review are limited by the underlying epidemiological data systems used to study road safety outcomes, and by the existing studies' research objectives. While available data enable some study designs evident in this review, existing studies were not designed to optimally collect data for the purpose of this specific polysubstance research question. Further, while the studies included analyzed opioids and alcohol as exposures and one or more road safety outcome, many studies did not define a central research objective specifically about the connection between simultaneous opioids and alcohol use and the road safety outcomes, which positions this focused research question as an opportunity for further research. Future studies that isolate opioid and alcohol use, with estimates of association and causal effect on road safety outcomes, can provide the research community and general public with a better understanding of the risks involved when these substances are combined.

Despite these limitations, this review synthesized knowledge contained in existing literature on the overall landscape of opioid and alcohol-related road safety research, including studies that have sought to quantify associations, along with how this research pertains to recommendations for practice and future study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aap.2022.106713.

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