Accident Analysis and Prevention 109 (2017) 123–131

Contents lists available at ScienceDirect

Accident Analysis and Prevention

journal homepage: www.elsevier.com/locate/aap

Use of prescription opioids and motor vehicle crashes: A *meta* analysis

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ARTICLE INFO

Keywords:
Driving safety
Drugged driving
Opioids
Motor vehicle crashes
Traffic injury

ABSTRACT

Objectives: Opioid analgesics are a major driver of the ongoing opioid epidemic in the United Sates, accounting for about two thirds of drug overdose fatalities. There are conflicting reports regarding the effects of prescription opioids on driving safety. A *meta*-analysis was performed to assess the epidemiologic evidence for the association between use of prescription opioids and the risk of motor vehicle crashes.

Methods: Studies examining the association between driver prescription opioid use and motor vehicle crash involvement or crash culpability and published in English were identified through a comprehensive search of 15 bibliographic databases. Eligible articles were fully reviewed and summarized. Study quality was assessed using the Newcastle-Ottawa Scale. Overall summary odds ratios (ORs) and 95% confidence intervals (CIs) were estimated through random effects models.

Results: Overall, 15 studies were included in the *meta*-analysis; of them, 10 assessed the association of prescription opioid use with the risk of crash involvement and 5 assessed the association of prescription opioid use with the risk of crash culpability. Reported crude ORs associated with prescription opioid use ranged from 1.15 to 8.19 for the risk of crash involvement and from 0.75 to 2.78 for the risk of crash culpability. Summary ORs based on pooled data were 2.29 (95% CI: 1.51, 3.48) for crash risk and 1.47 (95% CI: 1.01, 2.13) for crash culpability.

Conclusions: The existent epidemiologic evidence indicates that use of prescription opioids by drivers is associated with significantly increased risks of crash involvement and crash culpability. Further research is needed to understand the epidemiologic patterns of prescription opioid use in the driver population and the interaction effects between opioids and alcohol on driving safety.

1. Introduction

In the United States and many other industrialized countries, driving is an essential activity of daily living and is correlated with independence and access to employment and social activities (Borgeat, 2010; Fricke and Unsworth, 2001). Operating a motor vehicle is a complex task that requires a variety of skills such as eye-hand coordination, manual dexterity, and sensory-perceptual, cognitive and physical abilities (Walter et al., 2001; Weiler et al., 2000). Driving under the influence of drugs (DUID) has become a serious safety concern because of the marked increase in per capita consumption of prescription drugs, particularly opioid analgesics (Brady et al., 2014; Wilson et al., 2014), and the aging of the driver population (Colby and Ortman, 2014). Motor vehicle crashes (MVCs) are the second leading cause of unintentional injury mortality in the United States, surpassed only by drug overdose (National Center for Health Statistics, 2016; Sise et al., 2014). From 2014–2015, there was a 3.6% increase in fatality rate per 100 million vehicle miles traveled in the US (National Highway Traffic Safety Administration, 2016).

Prescription opioids (e.g., oxycodone and hydrocodone) are widely used for pain management and can cause sedation, drowsiness, nausea, impaired cognition and can interfere with psychomotor functioning (Altilio et al., 2007, Monárrez-Espino et al., 2013). Opioids may also impair reaction time, alertness, attention and concentration during driving (Manchikanti and Singh, 2008; Menefee et al., 2004; Ramaekers, 2003; Verster et al., 2006). The prevalence of prescription opioids detected in fatally injured drivers in the United States has increased from 1.0% in 1995 to 7.2% in 2015 (Chihuri and Li, 2017). Annual numbers of prescriptions for opioid analgesics have quadrupled from 76 million in 1991 to nearly 300 million in 2014, with an estimated 3900 people initiating nonmedical use of prescription opioids daily (Brady et al., 2014; Center for Behavioral Health Statistics and Quality, 2015).

The effects of prescription opioids on driving ability have been

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http://dx.doi.org/10.1016/j.aap.2017.10.004
Received 24 April 2017; Received in revised form 17 August 2017; Accepted 7 October 2017

studied using both experiment and observational studies but the results are inconsistent. Previous reviews of experimental studies reported conflicting evidence (Borgeat, 2010; Fishbain et al., 2002, 2003; Kress and Kraft, 2005; Tan, 2007; Leung, 2011; Orriols et al., 2009; Soyka, 2014; Strand et al., 2013). There is inadequate epidemiological evidence for the association between opioid use and MVC risk. A recent systematic review of observational studies suggests that exposure to some prescription opioids might be significantly associated with an increased risk of MVCs (Rudisill et al., 2016), whereas an earlier *meta*-analysis found inconclusive evidence for the association between opioid use and MVC risk (Monárrez-Espino et al., 2013).

The inconsistent results may be due to differences in study designs, time periods, and study samples (e.g., opioid-naïve subjects, chronic opioid users on stable doses, chronic opioid users on changing dosages or combined). Given the increasing prevalence of prescription opioid use and abuse, it is important to better understand the role of opioids in motor vehicle crashes. The objective of this study was to synthesize the epidemiologic evidence for the association between use of prescription opioids and the risk of MVCs.

2. Methods

2.1. Study eligibility

Studies were included if they: 1) used an epidemiologic design ensuring that exposure (prescription opioids) preceded the outcome (MVC or culpability given a crash), such as cohort, case-control, nested case control and case-crossover studies; 2) included exposure to intravenous, oral or transdermal prescription opioids as defined under the Anatomical Therapeutic Chemical classification N02 group (World Health Organization Collaborating Centre for Drug Statistics Methodology, 2013) such as codeine, oxycodone, or morphine; 3) had an appropriate comparison group that was not exposed to opioids or other psychoactive substances; 4) presented quantitative data and at least one measure of association (OR, RR) between opioid use and MVCs that resulted in fatalities or injuries requiring medical attention such as emergency department visit or hospitalization; and 5) were published in English language. No date restrictions were applied. Excluded from the *meta*-analysis were cross-sectional studies, experimental studies, qualitative studies, commentaries, opinion pieces, reviews, and studies focusing on illicit opioids such as heroine or combined licit and illicit opioids.

2.2. Search strategy, data sources and extraction

Relevant literature was identified through a comprehensive search of 15 electronic databases with a final search conducted on April 5, 2017: Medline (Ovid) (1946-present), American Psychological Association PsycInfo (1967-present), EMBASE (Ovid) (1980-present), Health and Psychosocial Instruments (1985-present), Joanna Briggs Institute EBP Database (1996-present), Scopus (1960-present), Transport Research International Documentation (TRID) (1970-present), American College of Physicians Journal Club (1967-present), the Cumulative Index to Nursing and Allied Health (1982-present), Cochran Central Register of Controlled Trials (CENTRAL), Science Direct (1997-present), PubMed, Web of Science (1900 to present), MELVYL (the online catalog of the University of California library system) (1970-present). Two databases (SafetyLit and Web of Science) also capture grey literature such as doctoral theses, conference abstracts and agency reports. Databases were thoroughly searched using subject terms [(car or motor vehicle or traffic) and (crashes or accidents) and (opioids or opiates) and (injuries or fatalities or deaths)]. One author (SC) verified and screened titles and abstracts of identified studies using the inclusion criteria. Studies whose eligibility was less obvious were reviewed in full text. References of identified studies were manually screened. Data on primary author, publication year, country of origin of study, study population, exposure and outcome assessments, and results were abstracted from included studies. Two authors (SC and GL) independently extracted data from the studies included in the *meta*-analysis in order to calculate the summary OR. Any discrepancies with regards to data from included studies were resolved through discussion.

2.3. Quality assessment and data analysis

The quality of all included studies was evaluated using the Newcastle-Ottawa Scale (Wells et al., 2015) as recommended by the Cochrane Collaboration for bias assessment in nonrandomized studies (Higgins and Green, 2011). Higher scores indicate better quality and the highest possible score depends on the type of study design with a highest possible score of 10 for a case-control study. The Q and I^2 tests were used to assess heterogeneity; $P \leq 0.05$ and $I^2 > 0.5$ were considered heterogeneous (Borenstein et al., 2009). Individual odds ratios (ORs) and 95% confidence intervals (CIs) for each study were computed from the abstracted data and summary ORs were estimated based on the pooled data to measure the association of prescription opioid use and the risk of MVC involvement or culpability given a crash. Because of the presence of heterogeneity, summary estimates from random-effects models were used. A sensitivity analysis was conducted using data from studies in which exposure to opioids was based on toxicological tests. Funnel plots and Rosenthal's fail-safe N were used to assess publication bias (Borenstein et al., 2009). The *meta*-analysis component followed standard methodology and adhered to reporting and procedures outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2009) and Meta-analysis Of Observational Studies in Epidemiology guidelines (Stroup et al., 2000). The individual and summary ORs were computed using Comprehensive Meta-Analysis software (versions 3) that weights data from individual studies through the inverse variance (Borenstein et al., 2005).

3. Results

The comprehensive database search identified 2,388 records. After removing 472 duplicates, 1916 records were screened. The screening ruled out 1799 records because they did not meet the inclusion criteria. The full-text articles for the remaining 117 records were reviewed for eligibility; of them, 15 met the inclusion criteria and were included in the *meta*-analyses, including 10 studies assessing the association between prescription opioid use and MVC involvement and 5 studies assessing the association between prescription opioid use and crash culpability (Fig. 1).

3.1. Study characteristics

Studies included in this *meta*-analysis were published between 1992 and 2016. Four of the fifteen studies were conducted in the United States (Dubois et al., 2010; Leveille et al., 1994; Reguly et al., 2014; Romano et al., 2014), two in Canada (Dussault et al., 2002; Gomes et al., 2013), three in France (Corsenac et al., 2012; Gadegbeku et al., 2011; Mura et al., 2003), two in Australia (; Drummer et al., 2004; Meuleners et al., 2011), one in Norway (Gjerde et al., 2011), one in Sweden (Monárrez-Espino et al., 2016), one in the Netherlands (Movig et al., 2004) and one in six European countries (Bernhoft et al., 2012). Of the 15 studies, 8 used a case-control design, 1 used a nested case-control design, 1 used a case-crossover design, and 5 used a quasi-induced exposure design. Three studies were conducted in adults aged 50 years or older (Leveille et al., 1994; Meuleners et al., 2011; Monárrez-Espino et al., 2016). Sample sizes ranged from 926 to 72,685 (Table 1a and Table 1b).

Exposure to prescription opioid use was measured based on either medical records (n = 5) or toxicological testing (n = 10). Six studies were restricted to fatal crashes, 8 to injurious crashes requiring medical attention and 1 included both fatal and nonfatal crashes. All studies