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REVIEW

Opioid Use and Driving Performance

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Abstract

Introduction The USA is in an opioid epidemic, with an increased number of individuals taking psychoactive drugs while executing the tasks of everyday life, including operating a motor vehicle. The pharmacology of opioids has been widely studied, but the effects of opioids on psychomotor function, driving performance, and the risk of motor vehicle collision remain less clear. Clinicians are faced with the challenge of controlling patient pain while also reconciling conflicting messages from the literature about how safe it is for their patients taking opioids to engage in potentially dangerous routine tasks.

Discussion This review assesses the current literature regarding opioids as they relate to neurocognitive function, driving performance, and accident risk. Manuscripts are categorized by study context and subject matter: controlled experimental administration, illicit use, prescription use, retrospective forensic toxicology, and polydrug consumption.

Conclusion Illicit use, initiation of therapy, and opioid use in combination with other psychoactive medications are contexts most clearly associated with impairment of driving-related functions and/or operation of a motor vehicle. Clinicians should counsel patients on the risk of impairment when initiating therapy, when co-prescribing opioids and other psychoactive drugs, or when a patient is suspected of having an opioid use disorder.

Keywords Opioid · Driving · Impairment · Psychomotor · Vigilance

Introduction

Impaired driving occurs when a vehicle operator is unable to appropriately respond to environmental stimuli due to aberrations in psychomotor function. Impaired driving represents a serious public health issue with various causes, ranging from sleep deprivation to intoxication. The CDC estimates that 4.2 million US adults drive under the influence of alcohol over the course of an average month, which translates to approximately 121 million events per year with significant crash risk from alcohol alone [1]. The USA is currently in an opioid epidemic, resulting in an increased number of individuals taking psychoactive drugs while executing the tasks of everyday life, including operating a motor vehicle. Opioids are a widely prescribed class of drug of both natural and synthetic origin. They are primarily used clinically for their ability to produce analgesia by acting as agonists on opioid receptors located throughout the body, though are recognized to produce sedation as well [2].

A number of opioid receptor subtypes exist, all of which play important roles in normal physiology and are stimulated by endogenous compounds called "endorphins," named for their chemical similarity to morphine. Three opioid receptor subtypes, mu, delta, and kappa, have been best studied and are considered to be responsible for the majority of clinically relevant effects of opioid drugs. Mu opioid receptors are primarily located in the brainstem and medial thalamus and are responsible for modulating the analgesic effects of opioids. Mu receptor agonism produces supraspinal analgesia, respiratory depression, euphoria, sedation, decreased GI motility, and physical dependence [3, 4]. Delta receptors are thought to play an important role in the analgesic function of opioids as well, though to a lesser degree than mu receptors, and have been suggested to have psychotomimetic, anxiolytic, and anti-depressant effects as well [3, 4]. Kappa receptor primary agonism leads to spinal analgesia, sedation, dyspnea, dependence, dysphoria, and respiratory depression. [3, 4]. Generally, opioids produce their effects through a hyperpolarization mechanism. As a result of

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receptor binding, voltage-dependent calcium inflow into the cell is impaired, which in turn prevents neurotransmitter release into the synapse. Opioids are mainly metabolized in the liver via the CYP enzymes, and some opioids have metabolites active at opioid receptors, complicating the relationship between opioid pharmacology and the ease of defining the time point at which an individual may be considered to no longer be experiencing the effects of opioid drugs. For example, heroin is metabolized into 6-monoacetylmorphine (6-MAM), 3-monoacetylmorphine (3-MAM), and morphine, all of which have agonist activity at the mu receptor and variable half-lives [5]. The specific mechanisms and areas of the nervous system that may be involved in changes in psychomotor function secondary to opioid consumption have yet to be well categorized, though the major risks in operating a motor vehicle while consuming opioid drugs are considered to stem from their ability to produce sedation and cognitive impairment.

This review of the experimental, epidemiological, and forensic literature suggests a complicated picture in which the ability to operate a motor vehicle safely while taking opioid drugs may depend on the context of consumption, for example: if opioid consumption is illicit, if opioid drug therapy has been recently initiated, or if individuals take other psychoactive drugs in addition to opioids, among other variables.

Methods

A search of the literature was conducted using the following search terms: psychomotor impairment OR neurocognitive impairment OR psychomotor function OR neurocognitive function OR crash OR accident AND opioid OR opiate AND driving. Similar terms have been used in other reviews examining impaired driving and the included terms are believed to represent the various components that make up the driving-related processes, related opioid drug physiology, and public health risks. Articles were deemed eligible if published between October 1, 1992 through August 31, 2018. Databases included in the literature search include: PUBMED, which returned 157 hits and GOOGLE SCHOLAR which returned 9230 hits. The first 500 hits ordered by "most relevant" were evaluated after which the number of relevant manuscripts approached zero. Book chapters, non-peer reviewed publications, and expert opinions were excluded along with papers focusing on unique clinical contexts (e.g., hospice, end of life cancer care, medication assisted treatment for opioid use disorder), and those with concerning conflicts of interest. Studies examining dextromethorphan, a compound defined as an opioid agonist, though lacking clinically relevant action at the Mu receptor, were excluded from the review. A total of 84 papers were selected for inclusion based on their relevance to the question, "Does opioid drug use cause impairment relevant to the operation of a motor vehicle?" The publications included in this review include a sampling of experimental studies, forensic toxicology reports, and others. The review is divided into sections: (1) Experimental Administration, (2) Illicit Use, (3) Prescription use, (4) Forensic Toxicology, and (5) Polydrug Use. Each section compares studies of similar focus and synthesizes conclusions about what the data from that set of manuscripts suggests about the impact of opioid drugs on driving performance. The review closes with a summative interpretation and contextualization of the implications of the trends observed. The data presented in each paper is best understood as an individual puzzle piece which contributes to a holistic and contextual understanding of the psychomotor effects and risks associated with the use of opioid drugs.

Results

A total of 84 papers published between 1992 and 2018 met our eligiblity criteria for inclusion.

Experimental Administration

The 29 manuscripts included in this section (Table 1) generally examine the effects of opioid drugs as they are administered in a controlled experimental setting to volunteers. Manuscripts that support the conclusion that opioid drugs cause psychomotor impairment are indicated in red. Studies that fail to draw clear conclusions are noted in yellow, and studies that show no significant impact of opioid drugs on driving or driving-related neurocognitive function are noted in green. Twenty studies were determined to support the conclusion that opioid drugs cause psychomotor impairment, two studies failed to draw clear conclusions, and seven studies showed no significant impact of opioids on driving or driving-related neurocognitive function. The aims, findings, and notable strengths and weaknesses are noted for each citation.

Illicit Use

The six manuscripts included in this section (Table 2) relate to the illicit use of opioid drugs as opposed to the prescription use of opioid drugs. Manuscripts that support the conclusion that opioid drugs cause psychomotor impairment are indicated in red. Studies that fail to draw clear conclusions are noted in yellow, and studies that show no significant impact of opioid drugs on driving or driving-related neurocognitive function are noted in green. Six studies were determined to support the conclusion that opioid drugs cause psychomotor impairment, 0 studies failed to draw clear conclusions, and 0 studies showed no significant impact of opioids on driving or driving-

Table 1 Studies considering the effects of opioid drugs in controlled, experimental settings

#	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations	Opioid exposure history
[6]	Black ML, Hill JL, Zacny JP. Behavioral and physiological effects of remifentanil and alfentanil in healthy volunteers. Anesthesiology. 1999;90(3):718–26.	What are the neurocognitive effects of remifentanil and alfentanil?	$n = 10$	Remifentanil and alfentanil impaired psychomotor performance.	Randomized, double-blind, placebo--controlled, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[7]	Cherrier MM, Amory JK, Ersek M, Risler L, Shen DD. Comparative cognitive and subjective side effects of immediate-release oxycodone in healthy middle-aged and older adults. J Pain. 2009;10(10):1038–50.	What are the neurocognitive effects of oxycodone?	$n = 71$	Attention, working memory, and verbal memory were impaired 1 h post-dose.	Blinded, placebo--controlled, crossover design.	Not double blinded, age range (35–65) of participants limits ability to generalize.	No opioids in the last 30 days.
[8]	Jensen ML, Sjogren P, Upton RN, Foster DJ, Bonde P, Graae C, et al. Pharmacokinetic-pharmacodynamic relationships of cognitive and psychomotor effects of intravenous buprenorphine infusion in human volunteers. Basic Clin Pharmacol Toxicol. 2008;103(1):94–101.	What are the neurocognitive effects of buprenorphine?	$n = 23$	Buprenorphine caused significant deficits in cognitive and psychomotor function.	Crossover design.	Not blinded, no placebo infusion, relies on pharmacodynamic and kinetic predictive modeling.	Healthy, non-drug--abusing volunteers.
[9]	Schneider U, Bevilacqua C, Jacobs R, Karst M, Dietrich DE, Becker H, et al. Effects of fentanyl and low doses of alcohol on neuropsychological performance in healthy subjects. Neuropsychobiology. 1999;39(1):38–43.	What are the neurocognitive effects of fentanyl?	$n = 24$	Fentanyl produces pronounced cognitive impairment.	Two randomized placebo--controlled, crossover trials.	Very small n, translates to about 6 subjects per study group.	Healthy, non-drug--abusing volunteers.
[10]	Thapar P, Zacny JP, Choi M, Apfelbaum JL. Objective and subjective impairment from often-used sedative/analgesic combinations in ambulatory surgery, using alcohol as a benchmark. Anesth Analg. 1995;80(6):1092–8.	What are the neurocognitive effects of fentanyl?	$n = 12$	Fentanyl impaired psychomotor function.	Prospective, double-blind, randomized, crossover design.	Small n, participant age range 21–34 limits ability to generalize.	Healthy, non-drug--abusing volunteers.
[11]	Walker DJ, Zacny JP. Subjective, psychomotor, and physiological effects of cumulative doses of opioid mu agonists in healthy volunteers. J Pharmacol Exp Ther. 1999;289(3):1454–64.	What are the neurocognitive effects of morphine, hydromorphone, and meperidine?	$n = 16$	Morphine, hydromorphone, and meperidine all caused psychomotor impairment.	Randomized, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[12]	Walker DJ, Zacny JP, Galva KE, Lichtor JL. Subjective, psychomotor, and physiological effects of cumulative doses of mixed-action opioids in healthy volunteers. Psychopharmacology (Berl). 2001;155(4):362–71.	What are the neurocognitive effects of butorphanol, nalbuphine, pentazocine, and morphine?	$n = 15$	Butorphanol impaired function more than morphine and nalbuphine, dose-effect relationship observed. No impairment with pentazocine.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[13]	Zacny JP. Characterizing the subjective, psychomotor, and physiological effects of a hydrocodone combination product (Hycodan) in non-drug-abusing volunteers.	What are the neurocognitive effects of hydrocodone-homotropine (Hycodan) and morphine?	$n = 18$	Both opioids caused impairment on tests of psychomotor function.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.

Table 1 (continued)

#	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations	Opioid exposure history
	Psychopharmacology (Berl). 2003;165(2):146–56.						
[14]	Zacny JP, Conley K, Galinkin J. Comparing the subjective, psychomotor and physiological effects of intravenous buprenorphine and morphine in healthy volunteers. J Pharmacol Exp Ther. 1997;282(3):1187–97.	What are the neurocognitive effects of buprenorphine and morphine?	$n = 16$	Both opioids impaired psychomotor performance, buprenorphine more than morphine at equianalgesic dose.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[15]	Zacny JP, Gutierrez S, Bolbolan SA. Profiling the subjective, psychomotor, and physiological effects of a hydrocodone/acetaminophen product in recreational drug users. Drug Alcohol Depend. 2005;78(3):243–52.	What are the neurocognitive effects of hydrocodone--acetaminophen and morphine?	$n = 18$	Both opioids caused impairment on tests of psychomotor function.	Randomized, double-blind, crossover design.	Small sample size.	Recreational drug users.
[16]	Zacny JP, Gutierrez S. Characterizing the subjective, psychomotor, and physiological effects of oral oxycodone in non-drug-abusing volunteers. Psychopharmacology (Berl). 2003;170(3):242–54.	What are the neurocognitive effects of oxycodone and morphine?	$n = 18$	Both opioids caused impairment on tests of psychomotor function.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[17]	Zacny JP, Gutierrez S. Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers. Drug Alcohol Depend. 2009;101(1–2):107–14.	What are the neurocognitive effects of hydrocodone and oxycodone?	$n = 20$	Both opioids caused impairment on tests of psychomotor function.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[18]	Zacny JP, Hill JL, Black ML, Sadeghi P. Comparing the subjective, psychomotor and physiological effects of intravenous pentazocine and morphine in normal volunteers. J Pharmacol Exp Ther. 1998;286(3):1197–207.	What are the neurocognitive effects of pentazocine and morphine?	$n = 16$	Both opioids caused impairment on tests of psychomotor function, pentazocine more so than morphine.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[19]	Zacny JP, Lichtor SA. Within-subject comparison of the psychopharmacological profiles of oral oxycodone and oral morphine in non-drug-abusing volunteers. Psychopharmacology (Berl). 2008;196(1):105–16.	What are the neurocognitive effects of oxycodone and morphine?	$n = 20$	Both opioids caused impairment on tests of psychomotor function.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[20]	Zacny JP, Lichtor JL, Binstock W, Coalson DW, Cutter T, Flemming DC, et al. Subjective, behavioral and physiological responses to intravenous meperidine in healthy volunteers. Psychopharmacology (Berl). 1993;111(3):306–14.	What are the neurocognitive effects of meperidine?	$n = 10$	Eye-hand coordination was affected slightly by meperidine but other functions were unaffected.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.

Table 1 (continued)

#	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations	Opioid exposure history
[21]	Zacny JP, Lichtor JL, Flemming D, Coalson DW, Thompson WK. A dose-response analysis of the subjective, psychomotor and physiological effects of intravenous morphine in healthy volunteers. J Pharmacol Exp Ther. 1994;268(1):1–9.	What are the neurocognitive effects of morphine?	$n = 10$	Morphine produced impairment on tests psychomotor function, most effects were dose related.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[22]	Zacny JP, Lichtor JL, Klafta JM, Alessi R, Apfelbaum JL. The effects of transnasal butorphanol on mood and psychomotor functioning in healthy volunteers. Anesth Analg. 1996;82(5):931–5.	What are the neurocognitive effects of butorphanol?	$n = 10$	Psychomotor function impairment observed with increasing dose.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[23]	Zacny JP, Lichtor JL, Thapar P, Coalson DW, Flemming D, Thompson WK. Comparing the subjective, psychomotor and physiological effects of intravenous butorphanol and morphine in healthy volunteers. J Pharmacol Exp Ther. 1994;270(2):579–88.	What are the neurocognitive effects of butorphanol and morphine?	$n = 12$	Butorphanol IV produced impairment on tests of psychomotor function dose-dependently. Morphine had no effect on psychomotor functioning.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[24]	Zacny JP, Lichtor JL, Zaragoza JG, de Wit H. Subjective and behavioral responses to intravenous fentanyl in healthy volunteers. Psychopharmacology (Berl). 1992;107(2–3):319–26.	What are the neurocognitive effects of fentanyl?	$n = 13$	Fentanyl produced impairment on tests of psychomotor function.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[25]	Zacny JP, Paice JA, Coalson DW. Separate and combined psychopharmacological effects of alprazolam and oxycodone in healthy volunteers. Drug Alcohol Depend. 2012;124(3):274–82.	What are the neurocognitive effects of oxycodone and oxycodone/lorazepam?	$n = 20$	Oxycodone impaired psychomotor function, combining drugs potentiated psychomotor impacts.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[26]	O'Neill WM, Hanks GW, Simpson P, Fallon MT, Jenkins E, Wesnes K. The cognitive and psychomotor effects of morphine in healthy subjects: a randomized controlled trial of repeated (four) oral doses of dextropropoxyphene, morphine, lorazepam and placebo. Pain. 2000;85(1–2):209–15.	What are the neurocognitive effects of dextropropoxyphene and morphine?	$n = 10$	Morphine increased the accuracy on the choice reaction time task. Dextropropoxyphene impaired performance on choice reaction time and picture recognition.	Randomized, double-blind, four-way crossover study.	Small sample size.	Healthy, non-drug--abusing volunteers.
[27]	Verster JC, Veldhuijzen DS, Volkerts ER. Effects of an opioid (oxycodone/paracetamol) and an NSAID (bromfenac) on driving ability, memory functioning, psychomotor performance, pupil size, and mood. Clin J Pain. 2006;22(5):499–504.	What are the effects of oxycodone on driving ability?	$n = 18$	No difference in driving performance, more effort required after receiving oxycodone.	Randomized, double-blind, crossover design, real road conditions.	Small sample size.	Healthy, non-drug--abusing volunteers.
[28]	Amato JN, Marie S, Lelong-Boulouard V, Paillet-Loilier M, Berthelon C, Coquerel A,	What are the effects of codeine-acetaminophen on	$n = 16$	Driving and psychomotor performance were not affected.		Small sample size.	Healthy,

Table 1 (continued)

#	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations	Opioid exposure history
	et al. Effects of three therapeutic doses of codeine/paracetamol on driving performance, a psychomotor vigilance test, and subjective feelings. Psychopharmacology (Berl). 2013;228(2):309–20.	driving and task performance?			Randomized, double-blind, crossover design.		non-drug--abusing volunteers.
[29]	Brown TL, Milavetz G, Gaffney G, Spurgin A. Evaluating drugged driving: Effects of exemplar pain and anxiety medications. Traffic Inj Prev. 2018;19(sup1):S97-S103.	What are the effects of hydrocodone on simulated driving?	$n = 8$	No difference in performance compared to placebo controls.	Double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[30]	Pickworth WB, Rohrer MS, Fant RV. Effects of abused drugs on psychomotor performance. Exp Clin Psychopharmacol. 1997;5(3):235–41.	What are the effects of hydromorphone on psychomotor function?	$n = 8$	No impact of hydromorphone observed.	Repeated measures design.	Small sample size, study not blinded.	Healthy, non-drug--abusing volunteers.
[31]	Walker DJ, Zacny JP. Subjective, psychomotor, and analgesic effects of oral codeine and morphine in healthy volunteers. Psychopharmacology (Berl). 1998;140(2):191–201.	What are the effects of codeine and morphine?	$n = 12$	No effect of either codeine or morphine.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[32]	Zacny JP. Profiling the subjective, psychomotor, and physiological effects of tramadol in recreational drug users. Drug Alcohol Depend. 2005;80(2):273–8.	What are the effects of tramadol and morphine?	$n = 22$	Neither tramadol nor morphine impaired psychomotor performance.	Randomized, double-blind, crossover design.	Small sample size.	Recreational drug users.
[33]	Zacny JP, Goldman RE. Characterizing the subjective, psychomotor, and physiological effects of oral propoxyphene in non-drug-abusing volunteers. Drug Alcohol Depend. 2004;73(2):133–40.	What are the effects of propoxyphene?	$n = 18$	No impairment compared to controls.	Randomized, double-blind, crossover design.	Small sample size.	Healthy, non-drug--abusing volunteers.
[34]	Zacny JP, Gutierrez S. Subjective, psychomotor, and physiological effects of oxycodone alone and in combination with ethanol in healthy volunteers. Psychopharmacology (Berl). 2011;218(3):471–81.	What are the effects of oxycodone, ethanol, and oxycodone/ethanol?	$n = 14$	Psychomotor and cognitive performance not affected by either drug or their co-administration.	Randomized, double-blind, crossover design.	Small sample size, authors suggest impairment occurs at higher doses than studied here (10 mg).	Healthy, non-drug--abusing volunteers.

Table 2 Studies considering the effects of opioid drugs in the context of illicit consumption

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
[35]	Asbridge M, Cartwright J, Langille D. Driving under the influence of opioids among high school students in Atlantic Canada: prevalence, correlates, and the role of medical versus recreational consumption. Accid Anal Prev. 2015;75:184–91.	What risk factors are associated with driving under the influence of opioids?	$n = 3655$	Increased incidence of driving under the influence among those consuming opioids both recreationally and medically (25.1%) compared to those with exclusive medical use (9.6%).	Anonymous data collection, large sample size, age matched controls.	Limited generalizability as only considered high school students, survey methodology subject to reporting bias.
[36]	Bachs L, Hoiseth G, Skurtveit S, Morland J. Heroin-using drivers: importance of morphine and morphine-6--glucuronide on late clinical impairment. Eur J Clin Pharmacol. 2006;62(11):905–12.	What is the relationship between major heroin metabolites and psychomotor function?	$n = 70$, control $n = 79$	Heroin metabolites have a concentration--dependent effect on the CNS that may lead to impairment.	Population wide database, excludes cases involving polypharmacy.	High proportion of men in sample, younger people overrepresented.
[37]	Bassiony MM, Youssef UM, Hassan MS, Salah El-Deen GM, El-Gohari H, Abdelghani M, et al. Cognitive Impairment and Tramadol Dependence. J Clin Psychopharmacol. 2017;37(1):61–6.	What is the prevalence of cognitive impairment among tramadol-abuse patients?	$n = 100$, control n = 100	Tramadol-abuse patients were more than twice as likely to show cognitive impairment as control subjects.	Attempts to control for polysubstance abuse in the tramadol-abuse group, uses Montreal Cognitive Assessment which is a well-studied cognitive test.	Data shows negative cognitive effect may be limited to memory without comparable affects detected in other cognitive domains, limited sample size.
[38]	Ceder G, Jones AW. Concentration ratios of morphine to codeine in blood of impaired drivers as evidence of heroin use and not medication with codeine. Clin Chem. 2001;47(11):1980–4.	Which opioids and/or opioid metabolites are observed in blood samples of drivers suspected of impairment?	$n = 979$	85% of opiate-positive blood samples were from heroin use rather than prescription opioids.	Quantitative data, large sample size.	Possibility of prescription morphine use cannot be completed excluded due to reliance on morphine/codeine unity ratios.
[39]	Jones AW, Holmgren A, Kugelberg FC. Driving under the influence of opiates: concentration relationships between morphine, codeine, 6-acetyl morphine, and ethyl morphine in blood. J Anal Toxicol. 2008;32(4):265–72.	Are opioids identified in body fluid samples of impaired drivers from prescription opioid use or illicit heroin use?	$n = 2573$	Approximately 90% of apprehended drivers in Sweden with morphine and codeine in their blood had used heroin.	Large population, longitudinal design.	Inconsistency in fluid sampling protocol, possibility of prescription morphine use cannot be completed excluded due to reliance on morphine/codeine unity ratios.
[40]	Wang GY, Wouldes TA, Kydd R, Jensen M, Russell BR. Neuropsychological performance of methadone--maintained opiate users. J	Are there differences in neurocognitive performance between individuals taking methadone, illicit opioid users, and	Methadone $n = 32$, illicit opioids $n = 17$, controls n = 25	Controls preformed slightly better than methadone patients on 3 psychomotor tasks, illicit opioid users preformed significantly worse than controls on tests	Quantitative data, design allows isolation of opioid agonist effect vs. impact of substance abuse.	Small sample size.

Table 2 (continued)

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
	Psychopharmacol. 2014;28(8):789–99.	non-opioid controls?		of attention and executive function.		

related neurocognitive function. The aims, findings, and notable strengths and weaknesses are noted for each citation.

Prescription Use

The 29 manuscripts included in this section (Table 3) focus on prescription use of opioid drugs as opposed to recreational use of opioid drugs. Manuscripts that support the conclusion that opioid drugs cause psychomotor impairment are indicated in red. Studies that fail to draw clear conclusions are noted in yellow, and studies that show no significant impact of opioid drugs on driving or driving-related neurocognitive function are noted in green. Fifteen studies were determined to support the conclusion that opioid drugs cause psychomotor impairment, 4 studies failed to draw clear conclusions, and 10 studies showed no significant impact of opioids on driving or driving-related neurocognitive function. The aims, findings, and notable strengths and weaknesses are noted for each citation.

Forensic Toxicology

The 13 manuscripts included in this section (Table 4) include studies that explore the relationship between opioid drug use and the risk of unsafe driving action, obtaining an injury, or being in a fatal accident. Manuscripts that support the conclusion that opioid drugs cause psychomotor impairment are indicated in red. Studies that fail to draw clear conclusions are noted in yellow, and studies that show no significant impact of opioid drugs on driving or driving-related neurocognitive function are noted in green. Nine studies were determined to support the conclusion that opioid drugs cause psychomotor impairment, two studies failed to draw clear conclusions, and two studies showed no significant impact of opioids on driving or driving-related neurocognitive function. The aims, findings, and notable strengths and weaknesses are noted for each citation.

Polydrug Use

The seven manuscripts included in this section (Table 5) generally relate to studies that explore the important role of polydrug use in populations who consume opioid drugs. These manuscripts generally fail to draw conclusions about the impact of opioid drugs and psychomotor performance due to high rates of polydrug use in the populations considered. These manuscripts are noted by a neutral color, blue. The aims, findings, and notable strengths and weaknesses are noted for each citation.

Discussion

The majority of articles in the *Experimental Administration* section indicate opioids generally impair psychomotor function in volunteers without a history of opioid use. Sixty-nine percent of studies support the conclusion that opioids impair driving or driving-related neurocognitive performance. While many studies were inconclusive or showed no effect, the majority of studies support the conclusion that opioids cause neurocognitive impairment. This suggests a baseline risk associated with the use of opioids and complex psychomotor activities, such as driving. There is evidence to suggest a dose-response relationship between opioid drug therapy and impairment as well. This conclusion is in accord with what is known about the hyperpolarization mechanism of action of opioid drugs on neurons in the central nervous system producing impairment in memory, decision making, and coordination. However, not all data supports the conclusion that opioids impair performance, which conflicts with what is known about the hyperpolarization mechanism of action of opioids. There are a number of possibilities which may explain the variation in the data including selection bias (e.g., administration in a population of drug users vs. naive volunteers), small sample size increasing vulnerability to Type II error, and the experimental administration of opioids at doses insufficient to produce impairment. The majority of studies in this section have a small sample size and are vulnerable to the influence of outlying data points and confounding variables.

All of the studies considered in the "Illicit Use" section generally favor the conclusion that the consumption of opioid drugs in the settings and populations considered is associated with unsafe driving, neurocognitive impairment, and/or arrest. When considering which populations and individuals may be considered to be at higher risk for poor outcome when using opioids and driving, those doing so illicitly merit particular concern. However, young people and men were often overrepresented in the populations included in the studies in this

Table 3 Studies considering the effects of prescribed opioid drugs

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
[41]	Buckeridge D, Huang A, Hanley J, Kelome A, Reidel K, Verma A, et al. Risk of injury associated with opioid use in older adults. J Am Geriatr Soc. 2010;58(9):1664–70.	Is there a dose-response relationship between opioid dose and injury?	$n = 403,339$	Opioids found to increase risk of injury, codeine combinations showed highest risk, no dose relationship observed.	Large sample size.	Only considered those aged 65 and older, limits generalizability.
[42]	Engeland A, Skurtveit S, Morland J. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. Ann Epidemiol. 2007;17(8):597–602.	What is the crash risk in the time period after filling a prescription for a psychoactive drug?	Accidents $n = 13,000$	2x more likely to be in accident if taking a natural opium alkaloid.	Large sample size, good generalizability.	Only considers accident risk in first 7 days after prescription dispensed.
[43]	French DD, Campbell R, Spehar A, Cunningham F, Bulat T, Luther SL. Drugs and falls in community-dwelling older people: a national veterans study. Clin Ther. 2006;28(4):619–30.	What psychoactive medications are associated with increased fall risk in the year after prescription?	$n = 20,551$, control $n = 20,551$	Increased fall incidence in groups taking prescribed opioid drugs.	Retrospective, cross-sectional national sample, age and sex-matched controls.	Limited to veterans care network and elderly population which limits generalizability.
[44]	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. Am J Epidemiol. 2009;169(6):761–8.	What is the relationship between having a certain drug prescription and crash risk?	accidents $n = 49,821$	1.7x increased crash risk with opioid prescription, 2x crash risk with opioid/-acetaminophen combination.	Large sample size, good generalizability.	Methods cannot distinguish between effect of event triggering opioid Rx (frequently MVC) and intrinsic opioid drug effect.
[45]	Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. JAMA Intern Med. 2013;173(3):196–201.	Is there a relationship between prescription opioid dose and the likelihood of involvement in road trauma?	$n = 5300$, control $n = 5300$	Significant relationship between drug dose and risk of road trauma to driver.	Controls matched for age, sex, prior trauma, and disease risk index.	Case population visited the ED more frequently, notably for alcohol related complaints, on average than control population.
[46]	Karjalainen K, Haukka J, Lintonen T, Joukamaa M, Lillsunde P. The use of psychoactive prescription drugs among DUI suspects. Drug Alcohol Depend. 2015;155:215–21.	What psychoactive medications are associated with increased risk of driving under the influence (DUI)?	DUI suspect $n = 29,470$, control $n = 30,043$	DUI suspects had increased odds of having purchased an opioid prescription than controls.	Large sample size, age and sex-matched controls.	Population level differences in prescribing of opioid drugs by gender.
[47]	Leveille SG, Buchner DM, Koepsell TD, McCloskey LW, Wolf ME, Wagner EH. Psychoactive medications and injurious motor vehicle collisions involving	Are psychoactive medications associated with increased injurious crash risk?	$n = 234$, control $n = 447$	88% increased risk of crash in older drivers taking opioids.	Age and sex-matched controls.	Limited to age 65 or above who sought care after a motor vehicle collision. Socioeconomics, medical comorbidities risk factors for crash.

Table 3 (continued)

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
	older drivers. Epidemiology. 1994;5(6):591–8.					
[48]	Marco CA, Mann D, Rasp J, Ballester M, Perkins O, Holbrook MB, et al. Effects of opioid medications on cognitive skills among Emergency Department patients. Am J Emerg Med. 2018;36(6):1009–13.	What are the neurocognitive effects of opioids given for acute pain?	Emergency department pain patients $n = 65$	Mean mini-mental status exam scores decreased 1 point after taking opioids, a greater proportion of tests administered were abnormal after opioids.	Uses well-studied tests of neurocogniti-ve function, crossover design.	Small effect size, 35% were considered cognitively impaired at baseline.
[49]	Meuleners LB, Duke J, Lee AH, Palamara P, Hildebrand J, Ng JQ. Psychoactive medications and crash involvement requiring hospitalization for older drivers: a population-based study. J Am Geriatr Soc. 2011;59(9):1575–80.	Is there an association between psychoactive medication prescription and crash risk?	$n = 1616$	50% greater risk of being in a crash requiring hospitalization was found for people prescribed opioids.	Retrospective, crossover study	Only considers drivers over 60, limiting generalizability.
[50]	Monarrez-Espino J, Laflamme L, Rausch C, Elling B, Moller J. New opioid analgesic use and the risk of injurious single-vehicle crashes in drivers aged 50–80 years: A population-based matched case-control study. Age Aging. 2016;45(5):628–34.	Is there a relationship between opioid prescription and injurious crash risk?	crash $n = 4445$, control $n = 17{,}780$	Increased odds of crash involvement in both new users and those with an established prescription history.	Large sample size, well-matched controls.	Only considers drivers aged 50–80, limits generalizability.
[51]	Rudisill TM, Zhu M, Davidov D, Leann Long D, Sambamoorthi U, Abate M, et al. Medication use and the risk of motor vehicle collision in West Virginia drivers 65 years of age and older: a case-crossover study. BMC Res Notes. 2016;9:166.	Which prescription drugs are associated with increased risk of injurious crash?	crash $n = 611$	Tramadol was associated with increased odds of injurious crash.	Large sample size, crossover design.	Only considers drivers over the age of 65, limiting generalizability.
[52]	Schiltenwolf M, Akbar M, Hug A, Pfuller U, Gantz S, Neubauer E, et al. Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids. Pain Physician. 2014; 17(1):9–20.	How does the neurocognitive performance of chronic pain patients receiving chronic opioid therapy compare to controls?	Chronic back pain/chronic opioids $n = 37$, chronic back pain without opioids $n = 33$, control $n = 25$	Both pain subgroups preformed worse than controls, opioid patients preformed worse than non-opioid patients and pain-free controls.	Explores influence of pain and depression on neurocogniti-ve performance.	Small sample size, non-randomized, observational study.
[53]	Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and	Is the risk of hip fracture associated with codeine or	patient $n = 4500$,	Increased relative risk (1.6) of hip fracture with opioid	Large sample size,	Only considers those age 65 or greater,

Table 3 (continued)

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
	the risk of hip fracture in the elderly: codeine and propoxyphene. J Gerontol. 1992;47(4):M111–5.	propoxyphene prescription?	control $n = 24{,}041$	prescription. In new users, significantly increased relative risk of fracture (2.2) compared to users with prescription history (1.3).	well-matched controls.	limiting generalizability.
[54]	Sjogren P, Thomsen AB, Olsen AK. Impaired neuropsychological performance in chronic nonmalignant pain patients receiving long-term oral opioid therapy. J Pain Symptom Manage. 2000;19(2):100–8.	How does the neurocognitive performance of chronic pain patients receiving chronic opioid therapy compare to controls?	Patient $n = 40$, control $n = 40$	Pain patients receiving chronic opioid therapy performed significantly poorer than controls.	Controlled, experimental setting.	Comparison group did not have pain at baseline, unable to separate effect of opioids and effect of pain.
[55]	Soderberg KC, Laflamme L, Moller J. Newly initiated opioid treatment and the risk of fall-related injuries. A nationwide, register-based, case-crossover study in Sweden. CNS Drugs. 2013;27(2):155–61.	Is there an increased risk of injurious fall after receiving an opioid prescription?	Injurious fall $n = 167{,}257$	Increased risk on injurious fall with new opioid prescription, increased odds of injury in the days after filling prescription compared to 4 weeks later.	Large sample size, crossover design	Increased odds ratio of injury if between the ages of 18 and 29 (7.17), age is a possible confounding variable.
[56]	Jamison RN, Schein JR, Vallow S, Ascher S, Vorsanger GJ, Katz NP. Neuropsychological effects of long-term opioid use in chronic pain patients. J Pain Symptom Manage. 2003;26(4):913–21.	How do chronic opioids in chronic non-cancer pain patients affect neurocognitive performance over time?	$n = 44$	Test scores significantly improved while subjects were taking opioids for pain compared to when they were not.	Crossover design, decent sample size	No control group, results demonstrate psychomotor impact of untreated pain more than effect of opioids, only two psychomotor tests were administered
[57]	Sabatowski R, Scharnagel R, Gyllensvard A, Steigerwald I. Driving Ability in Patients with Severe Chronic Low Back or Osteoarthritis Knee Pain on Stable Treatment with Tapentadol Prolonged Release: A Multicenter, Open-label, Phase 3b Trial. Pain Ther. 2014;3(1):17–29.	What effect does tapentadol have on driving performance after 6 weeks of stable dosing in chronic non-cancer pain patients?	$n = 35$	66% of patients were classified as fit to drive at doses > 200 mg/day, doses < 200 mg/day did not impair performance.		Small sample size, potentially non-generalizable cut-off dose for analysis, pain possible confounding variable.
[58]	Schumacher MB, Jongen S, Knoche A, Petzke F, Vuurman EF, Vollrath M, et al. Effect of chronic opioid therapy on actual driving performance in non-cancer pain patients. Psychopharmacology (Berl). 2017;234(6):989–99.	What impact does chronic opioid therapy have on driving task performance in chronic non-cancer pain patients?	$n = 20$, control $n = 19$	Driving performance did not significantly differ from that of controls due to inter-individual variations.	Standardized, on-the-road driving tests in normal traffic.	Small sample size.

Table 3 (continued)

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
[59]	Strumpf M, Willweber-Strumpf A, Herberg KW, Zenz M. [Safety-relevant performance of patients on chronic opioid therapy]. Schmerz. 2005;19(5):426–33.	Is there a difference in psychomotor performance between patients on chronic opioid therapy and controls?	$n = 80$, control $n = 243$	Significant variability in data, effects of opioid drugs may be mediated by variable such as age, status as a current driver, etc.	Computer-based tests provide quantitative data for analysis.	Relatively small sample, significant impact of confounding variables.
[60]	Byas-Smith MG, Chapman SL, Reed B, Cotsonis G. The effect of opioids on driving and psychomotor performance in patients with chronic pain. Clin J Pain. 2005;21(4):345–52.	What differences in psychomotor task performance and driving performance between patients with chronic pain on opioids and controls?	$n = 21$, control $n = 11$	No significant differences were found on driving performance or neuro/psychomotor function.	Driving evaluated directly by in-car task performance including turning and parallel parking.	Small sample size, only considers patients on stable drug regimen.
[61]	Dagtekin O, Gerbershagen HJ, Wagner W, Petzke F, Radbruch L, Sabatowski R. Assessing cognitive and psychomotor performance under long-term treatment with transdermal buprenorphine in chronic non-cancer pain patients. Anesth Analg. 2007;105(5):1442–8, table of contents.	What is the effect of chronic transdermal buprenorphine on driving performance in patients with chronic nonmalignant pain?	$n = 30$, control $n = 90$	Patients receiving transdermal buprenorphine did not perform inferiorly to controls.	Quantitative data, matched pairs.	Definition of "non-inferior to control" defined as scoring above the 16th percentile on the standardized psychomotor tests lack rigor.
[62]	Gaertner J, Radbruch L, Giesecke T, Gerbershagen H, Petzke F, Ostgathe C, et al. Assessing cognition and psychomotor function under long-term treatment with controlled release oxycodone in non-cancer pain patients. Acta Anaesthesiol Scand. 2006;50(6):664–72.	What are the effects of long-term treatment with oxycodone on driving performance?	$n = 30$, control $n = 90$	No difference in performance observed between patients treated with oxycodone and controls.	Multiple tests of performance, well-matched controls.	Definition of "non-inferior to control" defined as scoring above the 16th percentile on the standardized psychomotor tests lack rigor.
[63]	Hooper TI, DeBakey SF, Pearse L, Pratt S, Hoffman KJ. The use of electronic pharmacy data to investigate prescribed medications and fatal motor vehicle crashes in a military population, 2002–2006. Accid Anal Prev. 2010;42(1):261–8.	What psychoactive medications are associated with increased risk of fatal crash?	$n = 962$, control $n = 2886$	No associated increased crash risk with opioid prescription.	Well-matched controls.	Population is 93% male, all active duty military, limiting generalizability. Presence of medical comorbidity likely confounding variable affecting crash risk.
[64]	Krebs EE, Paudel M, Taylor BC, Bauer DC, Fink HA, Lane NE, et al. Association of Opioids with Falls, Fractures, and Physical Performance among Older Men with Persistent	Do chronic opioids affect fall risk, injury risk, or physical performance?	Population $n = 5994$, chronic opioid $n = 309$	No difference in fall risk, fractures, or physical performance in those taking opioids.	Large sample size, prospective longitudinal cohort design.	Only considers those aged 65 or greater, limiting generalizability.

Table 3 (continued)

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
	Musculoskeletal Pain. J Gen Intern Med. 2016;31(5):463–9.					
[65]	Menefee LA, Frank ED, Crerand C, Jalali S, Park J, Sanschagrin K, et al. The effects of transdermal fentanyl on driving, cognitive performance, and balance in patients with chronic nonmalignant pain conditions. Pain Med. 2004;5(1):42–9.	Does adding transdermal fentanyl to the regimen of chronic non-cancer pain patients already on opioids impact driving performance, cognition, and/or balance?	$n = 23$	No negative impact of adding transdermal fentanyl.	Prospective crossover design.	Participants on opioids at baseline, patients were given a month to stabilize on the fentanyl before performance retesting.
[66]	Nilsen HK, Landro NI, Kaasa S, Jenssen GD, Fayers P, Borchgrevink PC. Driving functions in a video simulator in chronic nonmalignant pain patients using and not using codeine. Eur J Pain. 2011;15(4):409–15.	Do pain and/or codeine influence performance on a driving simulator?	Chronic pain on long-term codeine $n = 20$, chronic pain patients not using codeine $n = 20$, control $n = 20$.	Patients using codeine did not differ in driving performance from controls.	Controlled experimental environment.	Not able to distinguish effect of drug and effect of pain.
[67]	Ray WA, Fought RL, Decker MD. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. Am J Epidemiol. 1992;136(7):873–83.	Is psychoactive drug prescription associated with risk of injurious crash in an elderly population?	Population $n = 16{,}262$, crash $n = 495$.	No significant difference in relative risk of injurious crash in patients taking opioid drugs.	Retrospective cohort design, age and health status matched controls.	Only considers those aged 65 or greater, socioeconomic confounding variable as study only considered Medicaid recipients.
[68]	Sabatowski R, Schwalen S, Rettig K, Herberg KW, Kasper SM, Radbruch L. Driving ability under long-term treatment with transdermal fentanyl. J Pain Symptom Manage. 2003;25(1):38–47.	What are the effects of long-term treatment with transdermal fentanyl on complex activities, such as driving?	$n = 30$, control n = 90	Patients receiving fentanyl did not perform inferiorly to controls.	Well-matched controls, prospective study design.	Small sample size, 9 patients excluded due to contaminant drug abuse, so patient $n = 21$.
[69]	Tassain V, Attal N, Fletcher D, Brasseur L, Degieux P, Chauvin M, et al. Long-term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. Pain. 2003;104(1–2):389–400.	What are the neurocognitive effects of chronic morphine in chronic non-cancer pain patients?	Morphine $n = 18$, control $n = 10$	Patients receiving morphine did not perform inferiorly to controls.	Long-term prospective study, 12 months.	Small sample size, control group consists of patients who started morphine and discontinued due to side effects.

section. The overrepresentation of young people, for example, may bias the data as you people are more prone to risk-taking behavior. This suggests that factors intrinsic to the populations considered (e.g., age, sex) may modulate driving risk as it relates to opioid drugs to a significant degree. Further, this population is difficult to study due to the illegal status of opioid consumption, limiting the amount of studies present on the subject in the literature as well as their sample size and power.

Prescription use was not as clearly associated with increased or decreased risk, though more studies support the

Table 4 Studies that use forensic toxicological methodology to draw conclusions

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
[70]	Dubois S, Bedard M, Weaver B. The association between opioid analgesics and unsafe driving actions preceding fatal crashes. Accid Anal Prev. 2010;42(1):30–7.	Is positive opioid toxicology associated with committing an unsafe driving action?	$n = 2541$	Positive opioid toxicology is associated with increased risk of unsafe driving action.	Large sample size.	Effect only seen in certain demographic groups, specifically females aged 25–55 and males aged 25–65, suggests possibility of confounding variables.
[71]	Hamnett HJ, Ilett M, Izzati F, Smith SS, Watson KH. Toxicological findings in driver and motorcyclist fatalities in Scotland 2012–2015. Forensic Sci Int. 2017;274:22–6.	What toxicological profiles are observed in fatally injured drivers and motorcyclists?	$n = 118$	Opioids were the third most common class of drug detected	Quantitative analysis.	Mixed vehicle classes included, cases were 63% car drivers, 27% motorcyclists, 10% other vehicles. Majority of fatally injured drivers were men.
[72]	Kumar S, Bansal YS, Singh D, Medhi B. Alcohol and Drug Use in Injured Drivers - An Emergency Room Study in a Regional Tertiary Care Centre of North West India. J Clin Diagn Res. 2015;9(7):HC01–4.	What is the toxicological profile of drivers involved in injurious crash?	$n = 200$	Alcohol (40.5%) was the most prevalent substance consumed followed by opiates (13%).	Adequate sample size.	Lacks control comparisons.
[73]	Movig KL, Mathijssen MP, Nagel PH, van Egmond T, de Gier JJ, Leufkens HG, et al. Psychoactive substance use and the risk of motor vehicle accidents. Accid Anal Prev. 2004;36(4):631–6.	Is there an association between psychoactive drug use and risk of crash requiring hospitalization?	$n = 110$, control $n = 816$	Increased risks were found for drivers positive for opioids (2.35 OR).	Prospective case-control design, large population considered.	Young people overrepresented in crash group. Poor case-control matching, cases were ED patients and controls were drivers randomly sampled on the roadside.
[74]	Mura P, Kintz P, Ludes B, Gaulier JM, Marquet P, Martin-Dupont S, 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 Sci Int. 2003;133(1–2):79–85.	How do the toxicological profiles of injured drivers compare to those in patients visiting the emergency department for non-trauma complaints?	$n = 900$, controls = 900	Injured drivers had an increased odds ratio of 8.2 for positive morphine toxicology.	Large sample size, age matched controls.	Drivers only considered "opioid positive" if morphine levels exceeded 20 ng/mL. Authors do not report on other opioid toxicology or compounds.
[75]	Price JW. A comparison of random and post-accident urine opiate and opioid tests. J Addict Dis. 2015;34(1):36–42.	Is there an association between opioid use and work-related accidents?	Accident $n = 2070$, control $n = 2506$	Accident group was 4.45 times more likely to be taking an opioid than the control group.	Large sample size.	Small number of positive urine samples, analysis does not include heroin, 6-MAM, or fentanyl, or fentanyl analogues.
[76]	Reguly P, Dubois S, Bedard M. Examining the impact of opioid analgesics on crash responsibility in truck drivers involved in fatal crashes. Forensic Sci Int. 2014;234:154–61.	What is the relationship between opioid use and crash responsibility in truck drivers?	Population $n = 8325$, opioid positive $n = 102$	Odds of committing an unsafe driving action significantly increased in individuals taking opioids.	Age, polysubstance use, and driving history matched controls.	Small proportion of sample tested positive, men overrepresented in study sample.
[77]	Wilson FA, Stimpson JP, Pagan JA. Fatal crashes		$n = 2363$	Hydrocodone and oxycodone are	Large sample size.	Study design only reveals prevalence of drug

Table 4 (continued)

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
	from drivers testing positive for drugs in the U.S., 1993–2010. Public Health Rep. 2014;129(4):342–50.	What toxicological profiles are observed in fatally injured drivers?		the second and third most frequently observed drugs in fatally injured drivers.		consumption, limiting conclusions.
[78]	Wong OF, Tsui KL, Lam TS, Sze NN, Wong SC, Lau FL, et al. Prevalence of drugged drivers among non-fatal driver casualties presenting to a trauma centre in Hong Kong. Hong Kong Med J. 2010;16(4):246–51.	What are the toxicological profiles of injured drivers?	$n = 395$	38 drivers (9.6%) tested positive for drugs. Of opioid positive drivers, morphine most common (31%).	Adequate sample size.	Cross-sectional design. Young people overrepresented. Participation was voluntary, subject to reporting bias.
[79]	Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid Anal Prev. 2004;36(2):239–48.	Is there a relationship between drug use and crash culpability in fatally injured drivers?	$n = 3398$	Non-significant, weakly positive associations between positive opioid toxicology and crash culpability.	Multicenter case-control study design.	Drivers showing the highest culpability rates were in the under 25 and over 65 age groups, indicating that age may be a confounding variable.
[80]	Marquet P, Delpla PA, Kerguelen S, Bremond J, Facy F, Garnier M, et al. Prevalence of drugs of abuse in urine of drivers involved in road accidents in France: a collaborative study. J Forensic Sci. 1998;43(4):806–11.	How do the toxicological profiles of injured drivers compare to those in patients visiting the emergency department for non-trauma complaints?	$n = 296$, control $n = 278$	Opiates were present in 10.5% of drivers and 10.4% of patients (non-trauma).	Adequate sample size.	Groups not well matched by demographic variables, females represented 28.4% of "drivers" and 44.2% of controls, age range restricted to 18–35, limiting generalizability.
[81]	Drummer OH, Yap S. The involvement of prescribed drugs in road trauma. Forensic Sci Int. 2016;265:17–21.	What is the relationship between opioid blood toxicology and fatal crash risk?	$n = 2638$	Crash risk of drivers taking opioids was not increased compared to drug-free controls.	Large sample size.	Difficult to control for presence of confounding variables at time of crash.
[82]	Van der Linden T, Isalberti C, Silverans P, Legrand SA, Verstraete AG. Comparison of drug concentrations measured in roadside surveys and in seriously injured drivers in Belgium. Drug Test Anal. 2013;5(7):541–8.	How do the toxicological profiles of injured drivers compare to the profiles of drivers randomly selected on the roadside?	$n = 377$, control = 2750	Most of the injured drivers who were positive for opioids had sub-therapeutic concentrations in their systems.	Multicenter case-control study design.	Limited sample size, results potentially implicate uncontrolled pain as a risk factor for serious crash.

conclusion that there is an increased risk of impairment and/or crash involvement associated with prescription opioid use. Fifty-two percent of studies considered favor the conclusion that opioids impair driving or driving-related neurocognitive performance. Some data note an increased risk specifically with the initiation of treatment or first-time prescribing and other studies note that no increased risk is observed when comparing the performance of patients on stable, chronic

Table 5 Studies that demonstrate the role of polydrug use on driving and driving-related neurocognitive performance in individuals consuming opioids

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
[83]	Bachs LC, Engeland A, Morland JG, Skurtveit S. The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol. Clin Pharmacol Ther. 2009;85(6):596–9.	Are drivers who have filled a prescription for codeine or tramadol at increased crash risk involving serious injury compared with age matched controls?	Crash $n = 201$, (181 codeine+, 20 tramadol+)	Risk of being involved in an accident was increased for drivers using codeine but not tramadol. Codeine result becomes non-significant when you control for co-prescription of other psychoactive substances.	Large longitudinal data set analyzed, age matched controls.	Confounder: of 83 codeine exposed subjects, 65 had been prescribed other psychoactive drugs near filling their codeine prescription.
[84]	Bernard JP, Morland J, Krogh M, Khiabani HZ. Methadone and impairment in apprehended drivers. Addiction. 2009;104(3):457–64.	What rates of co-intoxication exist in moving violation cases in which methadone was detected in the blood of drivers?	$n = 635$	Extremely high rates of polypharmacy present, methadone was the only psychoactive drug detected in blood in 1.5% of cases.	Large population studied	Majority of drivers were men with history of heroin abuse aged between 30 and 40 years, limits generalizability.
[85]	Chihuri S, Li G. Trends in Prescription Opioids Detected in Fatally Injured Drivers in 6 US States: 1995–2015. Am J Public Health. 2017;107(9):1487–92.	What opioid toxicological profiles are seen in fatally injured drivers?	$n = 36{,}729$	Of the deceased drivers who were positive for prescription opioids, 30% had elevated blood alcohol and 67% tested positive for other drugs.	Very large population studied	There is concern that this sample is not representative as some evidence (90) shows most states do not follow testing protocols.
[86]	Jonasson U, Jonasson B, Saldeen T, Thuen F. The prevalence of analgesics containing dextropropoxyphene or codeine in individuals suspected of driving under the influence of drugs. Forensic Sci Int. 2000;112(2–3):163–9.	What is the prevalence of dextropropoxyphene and codeine in body fluid samples taken from individuals suspected of driving under the influence?	$n = 4896$	486 cases where dextropropoxyphene and/or codeine were found, polydrug use in all but 28 cases. In 71% of the 486 cases, benzodiazepines were also present and in 38% of the cases amphetamine and/or cannabis were present.	Longitudinal study, large sample size.	Only considered 2 opioid drugs.
[87]	Jones AW, Kugelberg FC, Holmgren A, Ahlner J. Five-year update on the occurrence of alcohol and other drugs in blood samples from drivers killed in road traffic crashes in Sweden. Forensic Sci Int. 2009;186(1–3):56–62.	What opioid toxicological profiles are seen in fatally injured drivers?	$n = 1403$	Mean 2.4 drugs/person in cases with positive opioid toxicology, most frequently detected classes of drug were sedative-hypnotics, followed by opioids.	Large sample size.	83% of individuals involved in fatal crashes were men, limits generalizability.
[88]	Li G, Brady JE, Chen Q. Drug use and fatal motor vehicle crashes: a case-control study. Accid Anal Prev. 2013;60:205–10.	What is the association between psychoactive drug use and fatal crash risk?	$n = 737$, control $n = 771$-9	Increased odds ratio (4.83) of being involved in a fatal crash for drivers using "non-alcohol depressants", which includes opioids as well as other classes of drugs such as benzodiazepines.	Large population studied.	Authors grouped opioids and benzodiazepines together when analyzing the data, unable to distinguish drug effects.
[89]	Musshoff F, Lachenmeier DW, Madea B. Methadone substitution: medicolegal problems in Germany. Forensic Sci	What rates of co-intoxication exist in moving violation cases in which methadone	$n = 153$	Methadone was the only drug detected in just 4.5% of cases, high rates of use of	Large population studied.	87% of those who drove while taking methadone were men, limits generalizability.

Table 5 (continued)

Number	Citation	Research question of interest	Participants	Key findings	Strengths	Limitations
	Int. 2003;133(1–2):118–24.	was detected in the blood of drivers?		benzodiazepines, alcohol, and morphine.		

regimens compared to healthy controls. This suggests that individuals on stable, chronic regimens without additional risk factors, such as substance abuse disorder, may be considered a group of opioid users at lower risk for impairment. Answers about who is safe to operate a motor vehicle while using prescription opioids must be given individual consideration with examination of baseline risks and comorbidities which may influence neurocognitive function and/or driving performance (e.g., age, medical comorbidity). Significant variability in study design, sample size, and methodology exists in the studies considered in this section, and selection bias and confounding variables are present. The presence of these biases suggest that factors intrinsic to the populations considered (e.g., age, sex) may modulate driving risk as it relates to opioid drugs to a significant degree.

Positive opioid toxicology was shown to be associated with increased risk of injury, unsafe driving, or crash in the majority of studies considered. 69% of studies considered favor the conclusion that opioids impair driving or driving-related neurocognitive performance. This generally supports the conclusion that there is some population level risk associated with the consumption of opioid drugs. However, some studies suggest no impact of opioid drugs. It is possible that other variables including population characteristics, methodology, baseline pain, substance abuse, and/or sample size may act as confounding variables and/or mediate crash risk to a greater degree than the presence or absence of opioids. A common limitation among many studies which rely on toxicologic data is the inability and/or failure to differentiate between prescription and illicit use. As such, the data in these studies may only reflect the prevalence of drug consumption and not the circumstances of consumption, limiting the conclusions which may be drawn.

Polydrug use is observed to be frequent in populations consuming opioid drugs. The presence of polydrug use in these studies precludes our ability to draw conclusions about the impact of opioid drugs. However, they highlight the prevalence of polydrug use as a confounding variable that is difficult to avoid when studying populations consuming opioids. These studies demonstrate the safety risks associated with polydrug use as well as highlight the importance of discussing the impact of polydrug use on psychomotor function and complex tasks with all patients who consume multiple psychoactive drugs, including opioids.

Limitations

It is important to acknowledge the limitations of this review. Most importantly, the heterogeneity of studies included in this review precludes the use of validated assessments of study quality (e.g., GRADE). In general, due to the difficult nature of studying opioid drug use and driving, a majority of studies included are considered to be of low quality due to small sample size, selection bias, and the presence of confounding variables. Although some literature on the topic of impairment associated with opioid use might have been published prior to 1992, we limited our search to those studies published after 1992 to meet the aims of our current review.

Conclusion

Illicit use, the use of opioid drugs in combination with other psychoactive medications, and the initiation of opioid therapy are contexts most clearly associated with impairment of neurocognitive and psychomotor functions as they pertain to complex tasks including the operation of a motor vehicle. Variables besides drug consumption may significantly mediate crash risk in populations consuming opioid drugs including gender, age, and comorbid medical conditions. Clinicians should counsel patients on the risk of driving impairment when initiating opioid therapy, when adding psychoactive drugs to an existing opioid regimen, or when the clinician suspects a patient uses opioids illicitly.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Jewett A, Shults RA, Banerjee T, Bergen G. Alcohol-impaired driving among adults—United States, 2012. MMWR Morb Mortal Wkly Rep. 2015;64(30):814–7.
2. Hemmings HC, Egan TD. Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application. Second ed. Elsevier; October 19, 2018. 994 p
3. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11(2 Suppl):S133–53.

4. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. Anesthesiology. 2011;115(6):1363–81.
5. Gottas A, Oiestad EL, Boix F, Vindenes V, Ripel A, Thaulow CH, et al. Levels of heroin and its metabolites in blood and brain extracellular fluid after i.v. heroin administration to freely moving rats. Br J Pharmacol. 2013;170(3):546–56.
6. Black ML, Hill JL, Zacny JP. Behavioral and physiological effects of remifentanil and alfentanil in healthy volunteers. Anesthesiology. 1999;90(3):718–26.
7. Cherrier MM, Amory JK, Ersek M, Risler L, Shen DD. Comparative cognitive and subjective side effects of immediate-release oxycodone in healthy middle-aged and older adults. J Pain. 2009;10(10):1038–50.
8. Jensen ML, Sjogren P, Upton RN, Foster DJ, Bonde P, Graae C, et al. Pharmacokinetic-pharmacodynamic relationships of cognitive and psychomotor effects of intravenous buprenorphine infusion in human volunteers. Basic Clin Pharmacol Toxicol. 2008;103(1):94–101.
9. Schneider U, Bevilacqua C, Jacobs R, Karst M, Dietrich DE, Becker H, et al. Effects of fentanyl and low doses of alcohol on neuropsychological performance in healthy subjects. Neuropsychobiology. 1999;39(1):38–43.
10. Thapar P, Zacny JP, Choi M, Apfelbaum JL. Objective and subjective impairment from often-used sedative/analgesic combinations in ambulatory surgery, using alcohol as a benchmark. Anesth Analg. 1995;80(6):1092–8.
11. Walker DJ, Zacny JP. Subjective, psychomotor, and physiological effects of cumulative doses of opioid mu agonists in healthy volunteers. J Pharmacol Exp Ther. 1999;289(3):1454–64.
12. Walker DJ, Zacny JP, Galva KE, Lichtor JL. Subjective, psychomotor, and physiological effects of cumulative doses of mixed-action opioids in healthy volunteers. Psychopharmacology. 2001;155(4):362–71.
13. Zacny JP. Characterizing the subjective, psychomotor, and physiological effects of a hydrocodone combination product (Hycodan) in non-drug-abusing volunteers. Psychopharmacology. 2003;165(2):146–56.
14. Zacny JP, Conley K, Galinkin J. Comparing the subjective, psychomotor and physiological effects of intravenous buprenorphine and morphine in healthy volunteers. J Pharmacol Exp Ther. 1997;282(3):1187–97.
15. Zacny JP, Gutierrez S, Bolbolan SA. Profiling the subjective, psychomotor, and physiological effects of a hydrocodone/acetaminophen product in recreational drug users. Drug Alcohol Depend. 2005;78(3):243–52.
16. Zacny JP, Gutierrez S. Characterizing the subjective, psychomotor, and physiological effects of oral oxycodone in non-drug-abusing volunteers. Psychopharmacology. 2003;170(3):242–54.
17. Zacny JP, Gutierrez S. Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers. Drug Alcohol Depend. 2009;101(1–2):107–14.
18. Zacny JP, Hill JL, Black ML, Sadeghi P. Comparing the subjective, psychomotor and physiological effects of intravenous pentazocine and morphine in normal volunteers. J Pharmacol Exp Ther. 1998;286(3):1197–207.
19. Zacny JP, Lichtor SA. Within-subject comparison of the psychopharmacological profiles of oral oxycodone and oral morphine in non-drug-abusing volunteers. Psychopharmacology. 2008;196(1):105–16.
20. Zacny JP, Lichtor JL, Binstock W, Coalson DW, Cutter T, Flemming DC, et al. Subjective, behavioral and physiological responses to intravenous meperidine in healthy volunteers. Psychopharmacology. 1993;111(3):306–14.
21. Zacny JP, Lichtor JL, Flemming D, Coalson DW, Thompson WK. A dose-response analysis of the subjective, psychomotor and physiological effects of intravenous morphine in healthy volunteers. J Pharmacol Exp Ther. 1994;268(1):1–9.
22. Zacny JP, Lichtor JL, Klafta JM, Alessi R, Apfelbaum JL. The effects of transnasal butorphanol on mood and psychomotor functioning in healthy volunteers. Anesth Analg. 1996;82(5):931–5.
23. Zacny JP, Lichtor JL, Thapar P, Coalson DW, Flemming D, Thompson WK. Comparing the subjective, psychomotor and physiological effects of intravenous butorphanol and morphine in healthy volunteers. J Pharmacol Exp Ther. 1994;270(2):579–88.
24. Zacny JP, Lichtor JL, Zaragoza JG, de Wit H. Subjective and behavioral responses to intravenous fentanyl in healthy volunteers. Psychopharmacology. 1992;107(2–3):319–26.
25. Zacny JP, Paice JA, Coalson DW. Separate and combined psychopharmacological effects of alprazolam and oxycodone in healthy volunteers. Drug Alcohol Depend. 2012;124(3):274–82.
26. O'Neill WM, Hanks GW, Simpson P, Fallon MT, Jenkins E, Wesnes K. The cognitive and psychomotor effects of morphine in healthy subjects: a randomized controlled trial of repeated (four) oral doses of dextropropoxyphene, morphine, lorazepam and placebo. Pain. 2000;85(1–2):209–15.
27. Verster JC, Veldhuijzen DS, Volkerts ER. Effects of an opioid (oxycodone/paracetamol) and an NSAID (bromfenac) on driving ability, memory functioning, psychomotor performance, pupil size, and mood. Clin J Pain. 2006;22(5):499–504.
28. Amato JN, Marie S, Lelong-Boulouard V, Paillet-Loilier M, Berthelon C, Coquerel A, et al. Effects of three therapeutic doses of codeine/paracetamol on driving performance, a psychomotor vigilance test, and subjective feelings. Psychopharmacology. 2013;228(2):309–20.
29. Brown TL, Milavetz G, Gaffney G, Spurgin A. Evaluating drugged driving: Effects of exemplar pain and anxiety medications. Traffic Inj Prev. 2018;19(sup1):S97–S103.
30. Pickworth WB, Rohrer MS, Fant RV. Effects of abused drugs on psychomotor performance. Exp Clin Psychopharmacol. 1997;5(3):235–41.
31. Walker DJ, Zacny JP. Subjective, psychomotor, and analgesic effects of oral codeine and morphine in healthy volunteers. Psychopharmacology. 1998;140(2):191–201.
32. Zacny JP. Profiling the subjective, psychomotor, and physiological effects of tramadol in recreational drug users. Drug Alcohol Depend. 2005;80(2):273–8.
33. Zacny JP, Goldman RE. Characterizing the subjective, psychomotor, and physiological effects of oral propoxyphene in non-drug-abusing volunteers. Drug Alcohol Depend. 2004;73(2):133–40.
34. Zacny JP, Gutierrez S. Subjective, psychomotor, and physiological effects of oxycodone alone and in combination with ethanol in healthy volunteers. Psychopharmacology. 2011;218(3):471–81.
35. Asbridge M, Cartwright J, Langille D. Driving under the influence of opioids among high school students in Atlantic Canada: prevalence, correlates, and the role of medical versus recreational consumption. Accid Anal Prev. 2015;75:184–91.
36. Bachs L, Hoiseth G, Skurtveit S, Morland J. Heroin-using drivers: importance of morphine and morphine-6-glucuronide on late clinical impairment. Eur J Clin Pharmacol. 2006;62(11):905–12.
37. Bassiony MM, Youssef UM, Hassan MS, Salah El-Deen GM, El-Gohari H, Abdelghani M, et al. Cognitive impairment and tramadol dependence. J Clin Psychopharmacol. 2017;37(1):61–6.
38. Ceder G, Jones AW. Concentration ratios of morphine to codeine in blood of impaired drivers as evidence of heroin use and not medication with codeine. Clin Chem. 2001;47(11):1980–4.
39. Jones AW, Holmgren A, Kugelberg FC. Driving under the influence of opiates: concentration relationships between morphine, codeine, 6-acetyl morphine, and ethyl morphine in blood. J Anal Toxicol. 2008;32(4):265–72.

40. Wang GY, Wouldes TA, Kydd R, Jensen M, Russell BR. Neuropsychological performance of methadone-maintained opiate users. J Psychopharmacol. 2014;28(8):789–99.
41. Buckeridge D, Huang A, Hanley J, Kelome A, Reidel K, Verma A, et al. Risk of injury associated with opioid use in older adults. J Am Geriatr Soc. 2010;58(9):1664–70.
42. Engeland A, Skurtveit S, Morland J. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. Ann Epidemiol. 2007;17(8):597–602.
43. French DD, Campbell R, Spehar A, Cunningham F, Bulat T, Luther SL. Drugs and falls in community-dwelling older people: a national veterans study. Clin Ther. 2006;28(4):619–30.
44. 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. Am J Epidemiol. 2009;169(6):761–8.
45. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. JAMA Intern Med. 2013;173(3):196–201.
46. Karjalainen K, Haukka J, Lintonen T, Joukamaa M, Lillsunde P. The use of psychoactive prescription drugs among DUI suspects. Drug Alcohol Depend. 2015;155:215–21.
47. Leveille SG, Buchner DM, Koepsell TD, McCloskey LW, Wolf ME, Wagner EH. Psychoactive medications and injurious motor vehicle collisions involving older drivers. Epidemiology. 1994;5(6):591–8.
48. Marco CA, Mann D, Rasp J, Ballester M, Perkins O, Holbrook MB, et al. Effects of opioid medications on cognitive skills among emergency department patients. Am J Emerg Med. 2018;36(6):1009–13.
49. Meuleners LB, Duke J, Lee AH, Palamara P, Hildebrand J, Ng JQ. Psychoactive medications and crash involvement requiring hospitalization for older drivers: a population-based study. J Am Geriatr Soc. 2011;59(9):1575–80.
50. Monarrez-Espino J, Laflamme L, Rausch C, Elling B, Moller J. New opioid analgesic use and the risk of injurious single-vehicle crashes in drivers aged 50-80 years: a population-based matched case-control study. Age Ageing. 2016;45(5):628–34.
51. Rudisill TM, Zhu M, Davidov D, Leann Long D, Sambamoorthi U, Abate M, et al. Medication use and the risk of motor vehicle collision in West Virginia drivers 65 years of age and older: a case-crossover study. BMC Res Notes. 2016;9:166.
52. Schiltenwolf M, Akbar M, Hug A, Pfuller U, Gantz S, Neubauer E, et al. Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids. Pain Physician. 2014;17(1):9–20.
53. Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. J Gerontol. 1992;47(4):M111–5.
54. Sjogren P, Thomsen AB, Olsen AK. Impaired neuropsychological performance in chronic nonmalignant pain patients receiving long-term oral opioid therapy. J Pain Symptom Manag. 2000;19(2):100–8.
55. Soderberg KC, Laflamme L, Moller J. Newly initiated opioid treatment and the risk of fall-related injuries. A nationwide, register-based, case-crossover study in Sweden. CNS Drugs. 2013;27(2):155–61.
56. Jamison RN, Schein JR, Vallow S, Ascher S, Vorsanger GJ, Katz NP. Neuropsychological effects of long-term opioid use in chronic pain patients. J Pain Symptom Manag. 2003;26(4):913–21.
57. Sabatowski R, Scharnagel R, Gyllensvard A, Steigerwald I. Driving ability in patients with severe chronic low back or osteoarthritis knee pain on stable treatment with tapentadol prolonged release: a multicenter, open-label, phase 3b trial. Pain Ther. 2014;3(1):17–29.
58. Schumacher MB, Jongen S, Knoche A, Petzke F, Vuurman EF, Vollrath M, et al. Effect of chronic opioid therapy on actual driving performance in non-cancer pain patients. Psychopharmacology. 2017;234(6):989–99.
59. Strumpf M, Willweber-Strumpf A, Herberg KW, Zenz M. Safety-relevant performance of patients on chronic opioid therapy. Schmerz. 2005;19(5):426–33.
60. Byas-Smith MG, Chapman SL, Reed B, Cotsonis G. The effect of opioids on driving and psychomotor performance in patients with chronic pain. Clin J Pain. 2005;21(4):345–52.
61. Dagtekin O, Gerbershagen HJ, Wagner W, Petzke F, Radbruch L, Sabatowski R. Assessing cognitive and psychomotor performance under long-term treatment with transdermal buprenorphine in chronic noncancer pain patients. Anesth Analg. 2007;105(5):1442–8 table of contents.
62. Gaertner J, Radbruch L, Giesecke T, Gerbershagen H, Petzke F, Ostgathe C, et al. Assessing cognition and psychomotor function under long-term treatment with controlled release oxycodone in non-cancer pain patients. Acta Anaesthesiol Scand. 2006;50(6):664–72.
63. Hooper TI, DeBakey SF, Pearse L, Pratt S, Hoffman KJ. The use of electronic pharmacy data to investigate prescribed medications and fatal motor vehicle crashes in a military population, 2002-2006. Accid Anal Prev. 2010;42(1):261–8.
64. Krebs EE, Paudel M, Taylor BC, Bauer DC, Fink HA, Lane NE, et al. Association of opioids with falls, fractures, and physical performance among older men with persistent musculoskeletal pain. J Gen Intern Med. 2016;31(5):463–9.
65. Menefee LA, Frank ED, Crerand C, Jalali S, Park J, Sanschagrin K, et al. The effects of transdermal fentanyl on driving, cognitive performance, and balance in patients with chronic nonmalignant pain conditions. Pain Med. 2004;5(1):42–9.
66. Nilsen HK, Landro NI, Kaasa S, Jenssen GD, Fayers P, Borchgrevink PC. Driving functions in a video simulator in chronic non-malignant pain patients using and not using codeine. Eur J Pain. 2011;15(4):409–15.
67. Ray WA, Fought RL, Decker MD. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. Am J Epidemiol. 1992;136(7):873–83.
68. Sabatowski R, Schwalen S, Rettig K, Herberg KW, Kasper SM, Radbruch L. Driving ability under long-term treatment with transdermal fentanyl. J Pain Symptom Manag. 2003;25(1):38–47.
69. Tassain V, Attal N, Fletcher D, Brasseur L, Degieux P, Chauvin M, et al. Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. Pain. 2003;104(1–2):389–400.
70. Dubois S, Bedard M, Weaver B. The association between opioid analgesics and unsafe driving actions preceding fatal crashes. Accid Anal Prev. 2010;42(1):30–7.
71. Hamnett HJ, Ilett M, Izzati F, Smith SS, Watson KH. Toxicological findings in driver and motorcyclist fatalities in Scotland 2012-2015. Forensic Sci Int. 2017;274:22–6.
72. Kumar S, Bansal YS, Singh D, Medhi B. Alcohol and drug use in injured drivers - an emergency room study in a regional tertiary care centre of North West India. J Clin Diagn Res. 2015;9(7):HC01–4.
73. Movig KL, Mathijssen MP, Nagel PH, van Egmond T, de Gier JJ, Leufkens HG, et al. Psychoactive substance use and the risk of motor vehicle accidents. Accid Anal Prev. 2004;36(4):631–6.
74. Mura P, Kintz P, Ludes B, Gaulier JM, Marquet P, Martin-Dupont S, 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 Sci Int. 2003;133(1–2):79–85.
75. Price JW. A comparison of random and post-accident urine opiate and opioid tests. J Addict Dis. 2015;34(1):36–42.
76. Reguly P, Dubois S, Bedard M. Examining the impact of opioid analgesics on crash responsibility in truck drivers involved in fatal crashes. Forensic Sci Int. 2014;234:154–61.

77. Wilson FA, Stimpson JP, Pagan JA. Fatal crashes from drivers testing positive for drugs in the U.S., 1993-2010. Public Health Rep. 2014;129(4):342–50.
78. Wong OF, Tsui KL, Lam TS, Sze NN, Wong SC, Lau FL, et al. Prevalence of drugged drivers among non-fatal driver casualties presenting to a trauma centre in Hong Kong. Hong Kong Med J. 2010;16(4):246–51.
79. Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid Anal Prev. 2004;36(2):239–48.
80. Marquet P, Delpla PA, Kerguelen S, Bremond J, Facy F, Garnier M, et al. Prevalence of drugs of abuse in urine of drivers involved in road accidents in France: a collaborative study. J Forensic Sci. 1998;43(4):806–11.
81. Drummer OH, Yap S. The involvement of prescribed drugs in road trauma. Forensic Sci Int. 2016;265:17–21.
82. Van der Linden T, Isalberti C, Silverans P, Legrand SA, Verstraete AG. Comparison of drug concentrations measured in roadside surveys and in seriously injured drivers in Belgium. Drug Test Anal. 2013;5(7):541–8.
83. Bachs LC, Engeland A, Morland JG, Skurtveit S. The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol. Clin Pharmacol Ther. 2009;85(6):596–9.
84. Bernard JP, Morland J, Krogh M, Khiabani HZ. Methadone and impairment in apprehended drivers. Addiction. 2009;104(3):457–64.
85. Chihuri S, Li G. Trends in prescription opioids detected in fatally injured drivers in 6 US states: 1995-2015. Am J Public Health. 2017;107(9):1487–92.
86. Jonasson U, Jonasson B, Saldeen T, Thuen F. The prevalence of analgesics containing dextropropoxyphene or codeine in individuals suspected of driving under the influence of drugs. Forensic Sci Int. 2000;112(2–3):163–9.
87. Jones AW, Kugelberg FC, Holmgren A, Ahlner J. Five-year update on the occurrence of alcohol and other drugs in blood samples from drivers killed in road-traffic crashes in Sweden. Forensic Sci Int. 2009;186(1–3):56–62.
88. Li G, Brady JE, Chen Q. Drug use and fatal motor vehicle crashes: a case-control study. Accid Anal Prev. 2013;60:205–10.
89. Musshoff F, Lachenmeier DW, Madea B. Methadone substitution: medicolegal problems in Germany. Forensic Sci Int. 2003;133(1–2):118–24.