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The impact of therapeutic opioid agonists on driving-related psychomotor skills assessed by a driving simulator or an on-road driving task: a systematic review

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Running head: Opioid agonists and driving - A systematic review

Abstract

Background: Driving cessation is associated with poor health-related outcomes. People with chronic diseases are often prescribed long-term opioid agonists that have the potential to impair driving. Studies evaluating the impact of opioids on driving-related psychomotor skills report contradictory results likely due to heterogeneous designs, assessment tools and study populations. A better understanding of the effects of regular therapeutic opioid agonists on driving can help to inform the balance between individuals' independence and community safety.

Aim: To identify the literature assessing the impact of regular therapeutic opioid agonists on driving-related psychomotor skills for people with chronic pain or chronic breathlessness.

Design: Systematic review reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement; PROSPERO Registration CRD42017055909.

Data sources: Six electronic databases and grey literature were systematically searched up to January, 2017. Inclusion criteria: (i) empirical studies reporting data on driving simulation, on-the-road driving tasks or driving outcomes; (ii) people with chronic pain or chronic breathlessness; and (iii) taking regular therapeutic opioid agonists. Critical appraisal used the National Institutes of Health's quality assessment tools.

Results: From 3809 records screened, three studies matched the inclusion criteria. All reported data on people with chronic non-malignant pain. No significant impact of regular therapeutic opioid agonists on people's driving-related psychomotor skills was reported. One study reported more intense pain significantly worsened driving performance.

Conclusions: This systematic review does not identify impaired simulated driving performance when people take regular therapeutic opioid agonists for symptom control, although more prospective studies are needed.

Key Statements

What is already known about the topic?

- Being able to drive is important for most adults
- Not being able to drive is associated with worse health-related outcomes
- Different studies, from different participant groups, using differing assessment tools, show conflicting results on the impact of opioids on driving-related psychomotor skills

What this paper adds?

- There is a paucity of studies evaluating the impact of opioid agonists on driving-related psychomotor skills in participants with chronic pain or chronic breathlessness
- Stable doses of opioid agonists may pose no increased driving risk to people using them for long term symptom control
- Pain may have a negative impact on people's performance, itself more significant than regular therapeutic opioid agonists

Implications for practice, theory or policy

- There is a need to further investigate what is the impact of therapeutic opioid agonists for long term symptom control on people's driving skills
- Prospectively collected data need to focus on specific populations, opioid formulations and driving outcomes as regular therapeutic opioid agonists are initiated, titrated and maintained
- Defining which specific groups of patients may be able to drive or not drive safely will contribute to informed decision making by clinicians faced with providing advice to patients and their families, with the potential to improve health-related outcomes

Introduction

For many adults, driving is a key daily activity, strongly associated with personal freedom and independence.[1] Not being able to drive impacts on one's self-image, limits the ability to work, impairs independence for many basic activities and reduces overall quality of life. [1,2] Driving cessation is associated with social isolation [3] which has been associated with decrements in several health-related domains, higher risk of being admitted into long-term care facilities and higher mortality.[4-6] Being unable to drive is associated with doubling of depressive symptoms.[6-8]

For patients with chronic conditions requiring palliative care, being able to drive is still important. From a cohort of 173 people with life-limiting illnesses, 23% were current drivers and 16% still considered it an option.[9] Almost all patients mentioned that keeping their driving licences was important stating reasons such as identification, hope and emergencies.[9]

Concurrently, many people with chronic conditions live with a significant symptom burden requiring a range of management strategies including the use of regular therapeutic opioid agonists.[10,11] Regular therapeutic opioid agonists are currently recommended as the first line treatment for moderate to severe cancer pain,[12] moderate to severe chronic non-malignant pain when other medications fail to provide relief [13] and for reducing chronic breathlessness when symptom relief is unattainable with optimal treatment of underlying causes.[14,15] When initiated, titrated and managed using the best available evidence, regular therapeutic opioid agonists have been shown to be safe, have minimal potential for addiction and improve quality of life.[15,16]

Despite their benefits, some studies evaluating the efficacy and safety of therapeutic opioids report high incidences of dizziness, sedation [17] and cognitive and psychomotor impairment,[18-20] while others report no significant problems [21-23] A systematic review on this topic identified that most studies are heterogeneous and fail to report confounders, limiting the generalizability of results.[24]

To address this gap, this systematic review is based on the best available evidence in relevant populations, covering pure opioid agonists. Outcomes were selected to minimise heterogeneity of study design or populations where possible. This study therefore investigates the effect of regular therapeutic opioid agonists for chronic pain or chronic breathlessness on driving safety.

Opioids

i) Type of Opioids

Opioids have heterogeneous pharmacokinetic and pharmacodynamic profiles which influence clinical responses.[25,26] For example, opioids bind with different affinities to the opioid receptors.[27] Full agonists have high affinity to opioid receptors, producing maximum clinical effect. These opioids do not have a ceiling effect for analgesia and the dose selected is the one that produces maximum clinical effect with manageable adverse events.[27] Other classes of opioids (e.g. partial agonists; mixed agonists-antagonists) have a sub-optimal action on the opioid receptors. These classes have a celling effect which limits the dose escalation.[27]

Even within opioid agonists, there are substantial differences. For example, methadone is an opioid agonist that also has action as an antagonist of N-methyl-D aspartate (NMDA) receptors.[28] NMDA receptors play an important role in memory dysfunction and cognition,[29] meaning any effect observed on driving performance may be caused by this mechanism of action rather the its effect on opioid receptors. As such, within opioid class differences must be considered when evaluating driving performance.

ii) Routes of administration and Formulations

Oral opioids are available in two formulation types: immediate release and extended release.[30] Long-acting opioid formulations are now recommended as first-line options for prolonged therapy.[31,32] Their pharmacokinetic profiles show less fluctuations in plasma concentration, higher minimum plasma concentration (C_{min}) and longer time with maximum concentrations (T_{max}).[33] This is important because a lower C_{max} can potentially be associated with fewer adverse events [34] including sedation, cognitive impairment and psychomotor performance. Transdermal formulations are similar to oral extended release formulations because they allow a slow diffusion of the drug to the bloodstream which also enables steady plasma concentrations over a prolonged period.[35] Other formulations (e.g. intravenous, intranasal, buccal, sublingual, rectal) exhibit variable pharmacokinetic characteristics [36] and are not recommended as first line, regular therapy.

iii) Opioid Agonist Dose

Sedation is a common side effect of opioids that may impact on cognition, psychomotor performance and driving ability. Some longitudinal studies have suggested that high doses of opioids may cause cognitive impairment while low opioid doses may not.[37] There is a wide therapeutic window for opioids in healthy individuals [38] due to genetic and acquired influences.[39] While pharmacokinetic characteristics contribute to inter-individual differences in opioid response, pharmacodynamic adaptations play a crucial role in changes in opioid response longitudinally.[39] For example, the μ-opioid receptor, the most important mediator for analgesia and sedation [27] has a highly dynamic pattern of expression. This receptor is over-expressed in peripheral inflammatory states [40] frequently associated with pain and breathlessness but under-expressed in other situations like chronic opioid exposure.[41]

As such, some specific situations, rather than the opioid dose *per se*, need to be considered in the clinical setting:

a) Dose initiation: Single-dose studies show that side-effects of opioids are accentuated when therapy is initiated. [42,43] Most people rapidly develop tolerance to opioid-induced sedation,[44] allowing safe driving.[45]
b) Upward dose titration: Patients taking therapeutic doses of opioids may experience increased sedation and cognitive and psychomotor impairment following an increase in their regular opioid dose.[18]
c) High steady state: Opioid agonists bind to the opioid receptors in a log-linear fashion.[25] As opioid-agonist doses increase, symptom relief improves or side effects emerge.[25] After this point, sedation, cognitive and psychomotor impairment may persist even with stable doses.

Patients taking opioids for chronic breathlessness constitute a particular case because the doses required to relieve this symptom are particularly low (up to 30mg/day oral morphine equivalent dose).[46] As such and for the purpose of this work, this cut-off was used to differentiate high and low-doses. This is important because it is currently not fully understood the effects of such small doses in patients-related psychomotor skills, particularly in steady state.

Population who stop driving

Amongst the elderly population, the most common reason to stop driving is impairment as a result of medical problems.[47] This population has a higher incidence of chronic conditions [48] that reduce mobility and require treatment with multiple medications.[49]. Additionally, chronic pain or chronic breathlessness are often present and require symptomatic treatment and palliative approaches.[50-52] For the purpose of this work, chronic pain is defined as "ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury or more than 3 to 6 months, ad which adversely affects the individual's well-being".[53] Chronic breathlessness is defined as "breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability".[54] Understanding

the real effects of long-term opioids in patients' driving-related skills is therefore challenging because many factors (e.g. age, chronic diseases, chronic symptoms and other medications) may interact to produce cognitive and psychomotor impairment.[55,56] These factors need to be taken into account when considering any driving outcomes in this population.

Measures of Driving Performance

The current best way to evaluate driving skills is an on-the-road driving test [57] which consists of a 100-km drive on a public highway, under regular traffic conditions. Because it is time consuming, this test is difficult to apply in clinical or research settings. As such, researchers have been looking for alternative outcome measures that could accurately predict on-road outcome.[58] Driving is a task requiring numerous skills, including concentration over long periods of time, being able to receive multiple sensory stimuli, process them, make decisions and respond appropriately.[59] This requires preserved cognitive abilities like concentration, attention, perceptual skills, insight and memory.[60] Based on this, batteries of cognitive and psychomotor tests are frequently used as quick and easy predictors of on-road driving performance.[61]. However, research indicates these tests or combination of tests are poor predictors of driving performance.[58,62,63] In fact, a battery of five psychometric tests has been shown to have a total predictive value of only 33.4% to the on-the-road driving test.[58] A good alternative to these tests is driving in a simulator because they have higher external validity to detect drugs' (alcohol or illicit drugs) or sleep disorders' detrimental effects on driving.[64-67] There is increasing evidence driving simulators are able to predict driving outcomes on the road.[68,69]

Research Questions

Given the methodological research issues when considering the use of regular therapeutic opioid agonists and driving, a broad research question was developed with progressively narrower sub-questions:

Research question: *Does treatment with regular therapeutic opioid agonists for long-term symptom control (chronic pain, chronic breathlessness) impact on driving-related psychomotor skills as assessed by a driving simulator or an on-road driving task?*

Sub-questions:

1. Are people taking therapeutic regular opioid agonists for long-term symptom control (chronic pain, chronic breathlessness) able to drive safely?
2. Do any data specifically relate to either:
    a. Prescribed extended-release or transdermal formulations?
    b. Prescribed low doses (≤30mg/day oral morphine equivalent dose) or is there a dose-response relationship?
    c. Both a and b?

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[70]

Design: Systematic Review

Protocol and Registration

This systematic review protocol was registered in PROSPERO – international prospective register of systematic reviews (Registration Number CRD42017055909; available in https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017055909).

Eligibility Criteria

English language, peer-reivewed studies were included if they reported empirical data on: driving-simulation, 'real-world' driving or driving outcomes in adults taking therapeutic opioid agonists for long term symptom control. Studies using opioid-agonists with a strong action on NMDA receptors (e.g. methadone) were excluded. By acting both on the opioid receptors and NMDA receptors, they have the potential to cause cognitive side effects by different mechanisms. As such it would be difficult to generalise results to other opioid agonists. Anaesthesia and surgical settings were excluded because of single dose or short term exposure, and the likelihood of exposure to other centrally acting medications, surgical interventions, and invasive procedures that all could influence driving ability.[71] Studies conducted with populations with severe renal or hepatic impairment were also excluded because opioid agonists are, to different extents, metabolised/excreted by these organs.[72]

The participant / intervention / control / outcome (PICOS) for this systematic review is in Table 1.

Table 1- PICO

P (Population)	Adults (≥ 18 years) requiring opioid agonists for pain or breathlessness control
I (Intervention)	Therapeutic regular opioid agonists for chronic pain or chronic breathlessness Sub-group examination of: I. Extended-release or transdermal formulations II. Low doses (≤30mg/day oral morphine equivalent dose) or dose-response relationship III. Both a and b
C (Comparison)	Placebo / No intervention / Control group
O (Outcome)	Impairment on driving-related psychomotor skills as assessed by: - Driving simulator - On-the road driving tasks - Driving outcomes (e.g. accidents)
S (Setting)	Hospital, community, ambulatory

Information Sources and Search Strategy

The following databases were systematically searched up until 15 January 2017: Medline (Ovid, 1946-2016), PubMed (Non-Medline subset only which includes citations not yet or never-to-be indexed for Medline), Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effect), EMBASE (Ovid, 1974-2016), Scopus and the Cumulated Index to Nursing and Allied Health Literature: CINAHL (ESBCOhost).

The final search strategy included two sets of terms. Set 1 was designed to include all literature relating to opioids, particularly the most common opioid agonists used in clinical practice. Set 2 was created to capture all terms related to driving-related psychomotor skills which included driving-simulation, driving tasks and driving outcomes (e.g. accidents). Within each set, terms were combined using the Boolean Operator 'OR'. Both sets were then combined using the Boolean

Operator 'AND' (Table 2). Pain and breathlessness were not included as a separate set of terms but they were hand searched at a later stage from the list of retrieved articles.

Before running the final search strategy, a preliminary search of Medline was conducted to identify suitable Medical Subject Headings (MeSH terms) and useful textwords included in titles and abstracts. A detailed search was then constructed in Medline (Ovid; Table 2) and translated for each database of interest (Appendix 1). Consultation with a specialist research librarian was undertaken to ensure that the search strategy was appropriate.

Grey literature was searched using Google, Google Scholar, the Australian New Zealand Clinical Trials Registry (ANZCTR), the ClinicalTrials.gov database and the ProQuest Dissertations & Theses Database (PQDT). Additionally, the reference lists of relevant articles were hand searched.

#	Searches	
1	analgesics, opioid/ or codeine/ or fentanyl/ or hydromorphone/ or morphine/ or oxycodone/	Set 1
2	(opioid* or codeine or fentanyl or hydromorphone or morphine or oxycodone).tw.	
3	or/1-2	
4	automobile driving/ or driving under the influence/ or Accidents, Traffic/	Set 2
5	((abilit* or competen* or skill* or task* or simulation* or aptitude* or perform* or capacit* or capab* or function* or risk* or safe* or unsafe or impair* or danger* or influence or fit* or unfit or impact or advice or cessation or restrict*) adj4 driv*).tw.	
6	(automobile* or car or cars or road or traffic or accident* or crash*).tw.	
7	reaction time/	
8	(react* adj2 time*).tw.	
9	or/4-8	
10	3 and 9	
11	Animals/ not (Human/ and Animals/)	
12	(Letter or comment or editorial or news or case reports).pt.	
13	10 not (11 or 12)	
14	limit 13 to English language	

Table 2 - Medline search strategy: conducted in December 2016

Study Selection

Relevant articles were managed using Endnote X7 (Thomson Reuters, Philadelphia, PA). First, duplicates were removed. Subsequently, articles that did not match the eligibility criteria were excluded. Two authors (DF, JP) independently reviewed all titles and abstracts in order to assess their relevance for inclusion. Full-text papers were retrieved for all those fulfilling the inclusion criteria or anywhere there was equivocation using title and abstract alone. Full texts of all remaining relevant studies were then assessed. Specific reasons were provided for any articles excluded at this stage. Disagreement at all stages was resolved by discussion or recourse to a third author (DC).

Data Extraction Process

Data from potentially relevant studies were extracted by two authors (DF, JB). A Data Extraction Form was developed to collect information from potentially relevant studies. Fields included year of publication, journal, title, first author, country, settings, study design, time period, number of subjects, % men, mean age, diagnose, type of opioid agonist, dose, acute or chronic administration (≥7 days), route, formulation, type of test performed and outcomes. The data collection forms were complied with randomised controlled trials, observational studies, systematic reviews and meta-analyses.

Quality and risk of bias appraisal

Critical appraisal of the included studies was conducted using the quality assessment tools from the National Institutes of Health (NIH).[64] The NIH tools can accommodate a range of study designs. All included studies were independently rated by two researchers (DF, JB) for quality and risk of bias. Incongruences in rating were discussed in order to achieve a consensus.

Synthesis of results

Given the variety of study designs, a narrative synthesis was conducted based on the methods described by Popay *et al.*[73]

Results

Study Selection

The initial systematic search retrieved a total of 6553 articles: MEDLINE (n=1179), PubMed (non-Medline content only) (n=221), Embase (n=2197), CINAHL (n=64), Cochrane Database of Systematic Reviews (n=3), Cochrane Central Register of Controlled Trials (n=234), Database of Abstracts of Reviews of Effect (n=5), and Scopus (n=2650). Three more articles were found by hand search. A total of 3809 articles remained after removal of duplicates. After screening title and abstract, 29 papers had full text assessed, 26 excluded, leaving three articles meeting inclusion criteria (Figure 1).

Study Characteristics, Quality and Bias

Of the three included studies, one was a cross-sectional study,[74] one had a pre- and post-test design[75] and one was a case-control study [76] (Table 3). All were published between 2000 and 2011. Two studies were conducted in the USA [75,76] and one in Norway.[74] The quality of studies was 'good' or 'fair' according to the NIH quality assessment tools (Tables 4). The heterogeneity in methodology and reporting made a meta-analysis impossible.

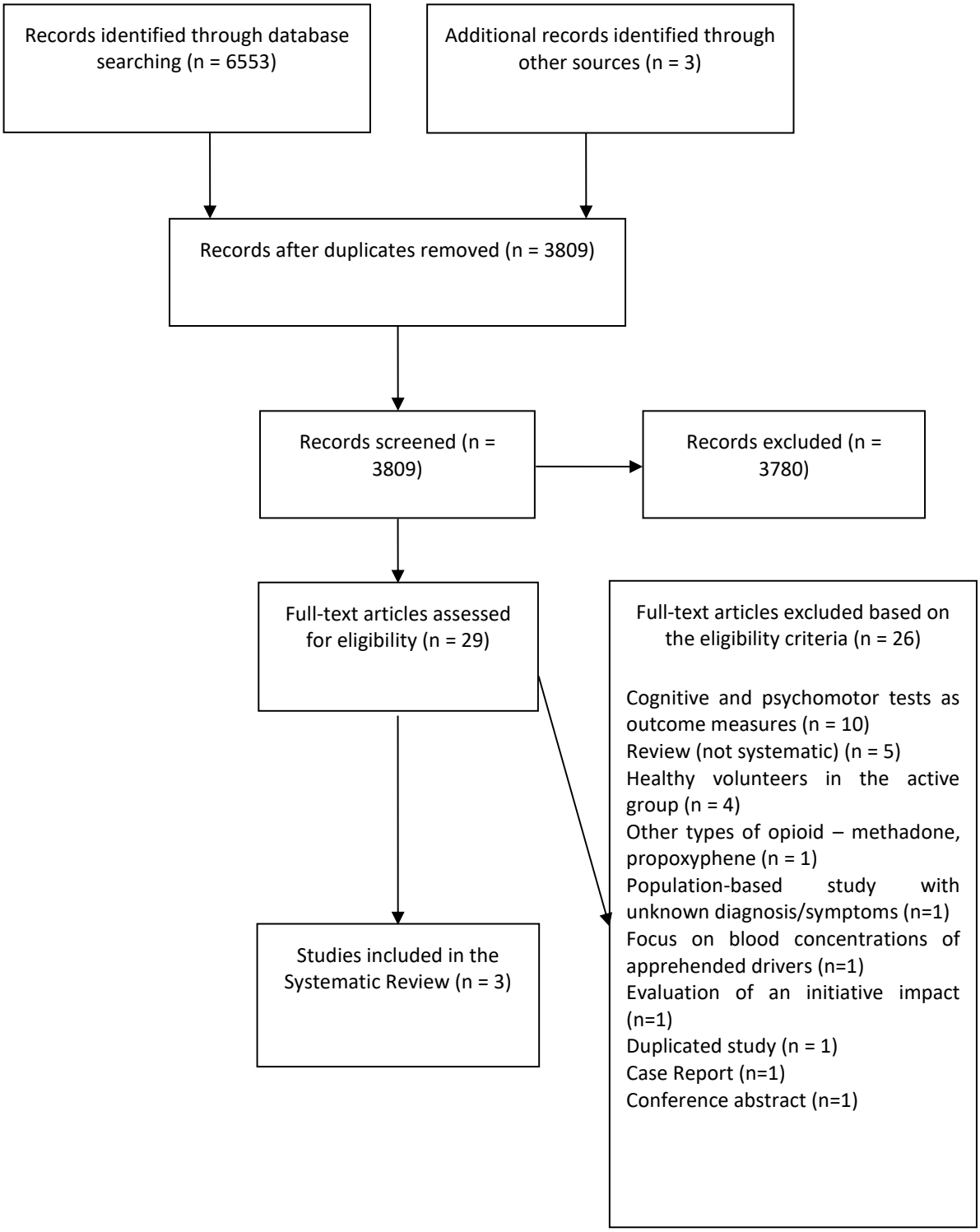
Identification

Screening

Eligibility

Included

Figure 1 – PRISMA Diagram



Population and Setting

All studies included participants with chronic non-malignant pain followed in outpatient pain clinics. Mean age in the opioid group (N=59) was 43-48 years old.[74-76] For two of the studies, diagnosis in the opioid group (N=43) included musculoskeletal conditions (62.8%), neuropathic pain (32.6%), abdominal pain (2.3%) and chronic headache (2.3%). The third study [76] reported additional diagnoses of fibromyalgia and reflex sympathetic dystrophy but distribution of participants in each diagnostic group was not reported. Mean pain intensity was reported in all studies using Numerical Rating or Visual Analogue Scales (NRS; VAS). Menefee *et al* [75] reported a statistically and clinically significant reduction in mean pain scores between the baseline visit and the stabilization visit (mean VAS score at baseline = 67; mean VAS score at the stabilization visit = 53; p=0.02).[75] Nilsen *et al* [74] reported no significant differences between the chronic pain group taking opioids (mean NRS score = 5.8) and the first control group of participants with chronic pain not taking opioids (mean NRS score = 5.5; p NS) over the week prior to the assessment. Additionally, pain scores did not differ significantly between groups at the time of the first (NRS scores = 4.8 and 4.6 respectively; p NS) and second driving assessments (NRS scores = 5.1 and 5.7 respectively; p NS). However, a significant difference in the average pain score over the preceding week was reported between the chronic pain group and the second control group (healthy volunteers; NRS scores = 5.6 and 0.4 respectively; $p<0.05$).[74] Galski *et al* [76] reported no significant differences in pain scores between the active (mean NRS score = 3.48 ± 2.4) and the control group (mean NRS score = 3.66 ± 2.5) at the time of the driving assessments.[76]

Type of opioids, dose, formulations and routes reported

All studies included only participants on regular therapeutic opioid agonists. One study included only short-acting opioids and two studies included only extended-release formulations as regular therapy.[76] Nilsen *et al* included participants taking regular oral codeine. Menefee *et al* [75] included participants taking transdermal fentanyl only with a maximum of 3 *pro re nata* (PRN) tablets of acetaminophen 325mg/oxycodone 5mg per day during the titration period (75). Galski *et al* [76] included participants taking long-acting opioids which comprised controlled-release oral morphine and transdermal fentanyl. PRN opioids including hydromorphone and oxycodone were allowed. Doses utilised in this study were not reported. Fentanyl doses ranged from 25 to 75µg/hour in the Menefee *et al* study [75] with a median dose of 50ug/hour (oral morphine daily equivalent doses: 60-180mg, median 120mg).[77] Codeine doses ranged from 120- 270mg/day in the study from Nilsen *et al* [74] with a median dose of 180mg (oral morphine daily equivalent doses: 12-27mg, median 18mg).[77]

Driving Outcomes

Overall, studies found no significant changes in driving-related outcomes with opioid-agonists (Table 5).

Nilsen *et al* [74] tested the participants twice on the same day coinciding with peak and trough codeine blood concentrations respectively. Reaction times, steering precision and missed signs were analysed in rural and urban driving settings. No significant differences were found between participants with chronic pain taking codeine (n=20) and participants with chronic pain free of opioids (n=20) in any of the study measures ($p>0.5$; CI 95%). However, the chronic pain group (n=40) performed significantly worse compared with healthy controls in all study parameters ($p<0.036$).

Menefee *et al* subjected participants to four different driving tasks where simple braking reaction time, cue reaction time, destination driving and evasive action were evaluated. For the first three tasks, the average of errors in breaking, steering, speed and signalling were calculated to achieve a final score. Evasive action was measured using the average time spent to take appropriate action in

three different driving situations. This study found no significant differences in driving-simulator performance parameters before and after fentanyl therapy ($p \geq 0.2$).[75]

Table 3 – Summary of studies characteristics

Study	N Subjects	N (% men)	Population	Mean Age (years)	Design	Comparison	Time Period	Formulation	Type of Assessment	Outcome	Statistical Power
Nilsen, 2011	60 (20 per group)	50%	Participants with chronic non-malignant pain	43.2 codeine group; no significant differences between groups	Cross-sectional	Oral Codeine (12mg-27mg OME/day (mean 18mg OME/day) vs Matching Chronic pain participants not using codeine vs Matching Healthy Volunteers	NA	Rapid Release	Driving-Simulator	**Primary outcome:** Reaction time (seconds) to traffic-sign symbols and missed reactions. **Secondary outcome:** steering precision (pixels).	Twenty subjects per group provide over 80% power for detecting a difference with $p < 0.05$
Menefee, 2004	23	26%	Participants with non-malignant pain	47	Pre- and Post-test design	Fentanyl TD (60-180 mg OME/day, median 120mg OME/day); Participants tested before and after exposure	before initiating drug; vs after 1 month of stable dose	Extended-release	Driving-simulator	Average of errors in the following tasks: Simple braking reaction time; Cue reaction time; Destination Driving. Average of time spent to take appropriate action in 3 different driving scenarios (evasive action).	No reference
Galsky, 2000	16 opioid group; 327 historical control group	NI	Participants with non-malignant pain	48.38	Case-control study	Opioid agonist in stable doses; vs Cerebral compromised participants previously cleared to drive	NA	Slow or extended-release	Driving-simulator	Number of errors in braking, steering, accelerating, speed and signalling.	No reference

*OME: Oral morphine equivalent

Table 4 - NIH Quality Assessment Tools (Critical appraisal)

	Study		
Questions	**Nilsen, 2011**	**Menefee, 2004**	**Galsky, 2000**
	NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group	NIH Quality Assessment of Case-Control Studies
1. Research question / objectives clearly stated	Yes	Yes	Yes
2. Study population clearly identified	Yes	Yes	Yes
3. Similarity between sample and population of interest	Yes	Yes	No
4. Application of the eligibility criteria	Yes	Yes	Yes
5. High % of eligible participants enrolled or randomly selection of eligible participants	No	Yes	Yes
5. Sample size calculation	Yes	No	No
6. Exposure preceded outcome	Yes	Yes	Yes
7. Definition and consistent measures of exposure	Yes	Yes	Yes
8. Definition and consistent measures of outcomes	Yes	Yes	Yes
9. For exposures that vary in amount or level, measurement of different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)	Yes	NA	NA
10. Blinding of outcome assessors	NR	NR	No
11. Loss to follow up ≤ 20% (included in the analysis)	Yes	Yes	NA
12. Timeframe adequacy	Yes	NA	NA
13. Measurement of confounding variables	Yes	NA	No
14. Measurement of effects at a group level	NA	NA	NA
Classification (Good, Fair, Poor)	**Good**	**Good**	**Fair**

NR: Not Reported
NA: Not Applicable

Table 5 - Driving Simulator Performance: Specific Outcomes

	Simulator Measures					
Nilsen, 2011		**CP* taking Codeine Group 1 Mean (SD)**	**CP* no opioids Group 2 Mean (SD)**	**Healthy Volunteers Group 3 Mean (SD)**	**P values (Group 1 *vs* 2; Groups 1+2 *vs* 3)**	**Statistical Test**
	Reaction Time Rural Test (choice reaction) [b]	0.96 (0.14)	0.93 (0.11)	0.84 (0.13)	P=0.53 ; P=0.026[c]	Multiple Regression
	Reaction Time Urban Test (simple reaction) [b]	0.87 (0.21)	0.88 (0.13)	0.76 (0.13)	P=0.98 ; P=0.035[c]	
	Missed Reactions Rural Test	Because missed reactions in the rural condition were <1% only the results for the urban condition were reported				
	Missed Reactions Urban Test [a,b]	10.20 [CI 95% (8.85-11.69)]	10.85 [CI 95% (9.45-12.39)]	6.10 [CI 95% (5.07-7.28)]	P=0.19 ; P=0.001	
	Steering Precision Rural Test	The steering precision results were equal				Poisson Regression
	Steering Precision Urban Test	The steering precision results were equal				
Menefee, 2004		**Before fentanyl Mean (SD)**	**On fentanyl Mean (SD)**	**P value**		
	Simple breaking reaction time, seconds	0.90 (0.17)	0.91 (0.18)	0.74		Wilcoxon Signed Rank Test
	Cue recognition reaction time, seconds	0.88 (0.17)	0.91 (0.23)	0.72		
	In-town driving, errors made	13.2 (4.4)	13.0 (3.6)	0.20		
	Highway destination driving, errors made	5.3 (2.4)	5.3 (2.8)	0.24		
	Evasive action reaction time, seconds	0.90 (0.03)	0.76 (0.36)	0.29		
Galsky, 2000		**CP* taking opioids**	**CCompromised** Participants**	**P value**		Analysis of Variance (ANOVA); Tukey's honest significant differences (HSD) test: differences between CPP taking Opioids and CCompromised** Participants who passed the behind-the-wheel driving test (*post hoc* comparisons)
	Basic Acceleration % Errors	3.50 ± 6.26	7.15 ± 11.47	No significant difference		
	Basic Signalling % Errors	14.63 ± 15.01	23.30 ± 20.27	No significant difference		
	Basic Breaking % Errors	31.25 ± 26.22	37.66 ± 23.12	No significant difference		
	Basic Steering Distance	56.19 ± 24.74	70.74 ± 20.47	No significant difference		
	Evasive Action Braking Distance	39.83 ± 19.33	48.95 ± 25.95	No significant difference		
	Evasive Action Braking % Valid	73.44 ± 24.95	65.17 ± 31.55	No significant difference		
	Evasive Action Steering Distance	75.79 ± 39.36	69.46 ± 37.44	No significant difference		
	Evasive Action Steering % Valid	43.79 ± 32.09	40.86 ± 29.67	No significant difference		
	Threat Recognition Braking Distance	113.74 ± 22.13	125.95 ± 34.22	No significant difference		
	Threat Recognition Braking % Valid	82.50 ± 29.10	60.47 ± 33.63	P<0.05		
	Threat Recognition Steering Distance	102.88 ± 32.72	117.99 ± 25.10	No significant difference		
	Threat Recognition Steering % Valid	75.00 ± 28.75	78.59 ± 27.51	No significant difference		

* CP: Chronic-pain participants ** CCompromised: Cerebral compromised

[a] Mean numbers of long reaction times(>3.95 s) for each subject (out of 104 possible reaction times for each subject).

b No significant differences were found between high (peak) and low (trough) blood concentration levels (p>0.05).[c] Age-adjusted P values and differences

Galski *et al* found no significant differences in driving parameters (number of errors in braking, steering, accelerating, speed and signalling) between participants with chronic pain taking opioid-agonists and cerebrally compromised participants accessed as fit to drive after an on-the-road driving test.[76]

Discussion

Summary of Evidence

This research highlights the paucity of studies evaluating the impact of regular opioid agonists in driving-related psychomotor skills of participants with chronic pain or breathlessness, the most common symptoms requiring the use of therapeutic opioids and other palliative interventions. All three studies included in this review report data on participants with chronic non-malignant pain which demonstrates the lack of evidence available for participants with chronic cancer pain or chronic breathlessness. Additionally, only one study provided a power calculation.[74] Nevertheless, all three studies showed no negative impact on participants' driving-related skills when compared to control groups which suggests that participants with chronic non-malignant pain on stable doses of regular therapeutic opioid agonists can drive safely.

Are participants on <u>therapeutic,</u> <u>regular</u> opioid agonists for chronic pain or chronic breathlessness able to drive safely?

All three studies filled the inclusion criteria for this question. All studies reported similar results: for participants with chronic non-malignant pain, <u>*regular*</u> <u>*therapeutic*</u> opioid-agonists did not significantly impair driving-related psychomotor skills.[74-76] This is line with results from a previous review that examined the effects of opioids on opioid-dependent/tolerant participants' driving-related skills that found no association between opioids and changes in driving-related outcomes.[45] These results are also similar to those published in a previous observational work showing no effect of opioids on the driving ability of participants with chronic pain.[23] Byas-Smith *et al* evaluated two groups of participants with chronic pain through a community-driving task and an obstacle-course task. The first group was not taking opioids and the second group was taking stable doses of opioids for chronic pain. No significant differences were found between groups in all specific measures of driving ability, even though different types of opioids were included.[23] Importantly, no studies reporting data on participants with chronic cancer pain or chronic breathlessness filled the inclusion criteria for this review which highlights an important research gap.

<u>Extended-release</u> or <u>transdermal</u> formulations

The inclusion criteria for this question encompassed participants taking regular, extended-release oral or transdermal opioid-agonists which are frequently prescribed for long-term therapy.[32] Two studies were included in this group: one using transdermal fentanyl;[75] and other several types of strong opioid agonists in controlled-release formulations.[76] Controlled-release opioid-agonists showed no significant impact on driving-simulator performance even with the addition of occasional PRN opioids for incidental pain. Based on the current available evidence, it is difficult to know if the use of extended-release opioids agonists represents any advantage compared with immediate-release preparations when considering participants driving performance. However, one study comparing the two types of formulations has found that participants reported statistically significant more tiredness after a titration period with the immediate-release formulation [78] which could potentially cause a detrimental impact on participants' driving-related skills.[76] Studies comparing these two types of formulations should then be developed to bring light into this issue.

<u>Low doses</u> (dose-response relationship)

Nilsen *et al* [74] was the only study using low doses of opioids (median dose 18mg oral morphine equivalent dose). This dose range is effective in reducing the sensation of breathlessness in most participants with chronic breathlessness [15] and its importance should be highlighted. Importantly, these findings are similar to the ones from Menefee *et al* [75] (median oral morphine equivalent dose 120mg) and Galski *et al* [76] (unknown doses). One theory is based on the fact that neuroadaptation quickly develops following exposure to an unchanged dose of an opioid agonist.[61] This corroborates findings from previous studies showing that stable doses of opioids fail to produce cognitive impairment while therapy initiation and up-titration produce significant cognitive and psychomotor impairment.[18,61] However, epidemiological data suggest that very low doses of opioids (defined as doses <20 mg of oral morphine equivalent a day) may be safer than higher doses when it comes to performance on the road [79] even when controlling for potential confounders like age, hospitalizations, other medication use and number of emergency department visits in the previous year. Further research should also take this factor into consideration.

Prescribed extended-release, low dose opioid agonists
No study was available evaluating the effects of therapeutic, regular, low-dose, extended release opioids for pain or breathlessness on driving-related psychomotor performance. As such, the answer to this question remains unknown. Further research should focus on examining the effects of low-dose, extended-release opioid formulations in participants' driving ability.

Impact of pain and breathlessness
Pain and breathlessness are often reported by participants suffering from chronic diseases like cancer, degenerative joint disease, and chronic cardiorespiratory diseases amongst others.[50,51] In fact, participants that are suffering from pain are more likely to report breathlessness and participants with breathlessness have also a higher prevalence of pain.[80] Additionally, pain and breathlessness commonly emerge and subside together which highlights the association between the two symptoms.[80] One explanation is that both symptoms share common neural pathways especially in the limbic region.[81] Another important idea is that both pain and breathlessness may be a reflection of the same underlying disease process. Whatever the extent of influence of these factors, these symptoms commonly occur in similar populations which motivated its inclusion together in this review.

An interesting finding from the only *a priori* adequately powered study in this review [74] is that participants with chronic pain (taking and not taking opioids) performed significantly worse than healthy volunteers after adjusting for age, gender, education, driving experience, personality traits, emotional stability and extraversion. This corroborates previous findings suggesting that uncontrolled pain is a stronger influence on cognitive and psychomotor performance than prescribed opioids.[82,83] Importantly, the difference in mean pain scores reported between the chronic non-malignant pain group and the healthy volunteer group was not only statistically significant but also clinically significant (pain NRS mean score 5.6 and 0.4 respectively).[84] Although no studies were found for participants with breathlessness, there is evidence suggesting that an increase in the intensity of breathlessness correlates with worsening driving-related neuropsychological performance skills.[85] These studies highlight that symptom intensity may influence driving performance and should be taken into account as potential confounders when analysing the impact of opioids in populations with chronic pain or chronic breathlessness.

Strengths
This systematic review was conducted in line with the methodology proposed by the PRISMA Statement.[70] This is the first systematic review assessing opioids and driving-related psychomotor skills with a focus on population, intervention and outcomes. The selection criteria were carefully

thought to include: (i) a representative population of people with chronic conditions, (ii) the most common types of prescribed opioids selected based on current pharmacologic knowledge (iii) the most robust outcome measures. It is also important to highlight that the simulators used in the studies included in this systematic review have been previously validated for on-road driving.[68,69] This approach prevented the inclusion of a heterogeneous group of studies whose results would not be generalisable.

Limitations

Only three studies were included in this review as a result of the selection criteria applied. This is regarded by the authors as both a strength and a limitation. On the one hand, the population, opioids and outcomes selected are relatively homogeneous which would allow the generalisability of results to this group of participants. On the other hand, the scarcity of studies available means the conclusions cannot be definitive. This systematic review only included articles published in English which may have increased the risk of selection bias. Also, given the heterogeneity of study designs, a meta-analysis could not be performed.

Recommendations for future research

Currently there is a lack of studies assessing the impact of therapeutic opioid-agonists in people's driving-related skills. All the studies included in this systematic review selected a population of participants with chronic non-malignant pain and the results obtained may not be generalizable for participants with chronic malignant pain or chronic breathlessness. However, it is important to note that chronic pain is a common feature of non-malignant life-limiting diseases and the results of this work are important for this population.[86] Nonetheless, future research should also focus on populations with chronic malignant pain and chronic breathlessness.

The impact of oral extended-release and TD formulations during the titration phase on cognitive and psychomotor skills is unknown, although studies in other populations suggest they may have fewer adverse events.[34,78] Another important issue to explore in future research is the true impact of different intensities of pain/breathlessness in driving outcomes as they might be important predictors of poorer driving performances.

Clinical implications

Although opioids are currently recommended as the first line treatment for moderate to severe pain, many clinicians remain reluctant to use them.[87] Fear of side effects is one of the top concerns identified by clinicians.[87,88] One problem is that clinicians may withhold or withdraw opioid therapy from people who could potentially benefit from this therapy. Additionally, clinicians' beliefs and a poor clinician-patient relationship have been shown to decrease adherence to taking analgesics as prescribed.[89,90]

The studies included in this review suggest that participants with chronic non-malignant pain are able to drive safely while taking regular, stable doses of a therapeutic opioid agonist. One important factor to take into consideration is that uncontrolled symptoms like pain and breathlessness may contribute to worsen driving-related psychomotor skills and performance on the road, to a greater extent than opioids.[74,82]

Conclusions

This systematic review examined the literature about driving-related psychomotor performance of people with chronic pain or chronic breathlessness taking opioid agonists. Despite the evidence supporting the use of opioids for symptom reduction in these populations, their effects on driving need further exploration. From the limited available studies, for people with chronic non-malignant pain, stable doses of therapeutic opioid agonists do not seem to cause any significant changes in

driving-related psychomotor performance. More intense chronic pain may have a significant effect on driving skills and should be carefully monitored and controlled. Clinicians are recommended to use their best clinical judgement to advise patients to drive or not to drive based not only on the regular therapeutic opioid agonist prescribed but also on their comorbidities, symptoms and pre-morbid driving abilities.

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Declaration of conflict of interests

DC is an unpaid advisory board member for Helsinn Pharmaceuticals. He is a paid consultant and receives payment for intellectual property with Mayne Pharma and is a consultant with Specialist Therapeutics Australia Pty. Ltd.

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