Systematic Review of the Quality and Generalizability of Studies on the Effects of Opioids on Driving and Cognitive/Psychomotor Performance

Angela Mailis-Gagnon, MD, MSc, FRCPC (PhysMed),†‡ Shehnaz Fatima Lakha, MSc,*† Andrea Furlan, MD, PhD,†§‖ Keith Nicholson, PhD,*† Balaji Yegneswaran, MD,* and Rainer Sabatowski, MD¶*

Introduction: The effect of opioids on driving performance has been much debated. Driving is a complex task requiring integration of psychomotor, cognitive, motor and decision-making skills, visual-spatial abilities, divided attention, and behavioral and emotional control. The objective of this systematic review was to assess the quality of studies and to revisit the concept that patients on stable opioids are safe to drive as it applies to everyday practice.

Methods: We searched MEDLINE, EMBASE, PSYCinfo, CENTRAL, TRANSPORT, CINAHL, reference lists of retrieved articles and narrative reviews, for studies on chronic cancer and noncancer pain patients on opioids, tested by driving, driving simulator, or cognitive/psychomotor tests. Methodological quality was assessed with Methodological Index for Nonrandomized Studies, cognitive/psychomotor tests were appraised regarding their sensitivity and validation, and whether confounding variables potentially affecting the study conclusions were recorded. The results were analyzed both quantitatively and qualitatively.

Results: We included 35 studies (2044 patients, 1994 controls), 9% of the studies were of poor, 54% of fair, and 37% of high quality; 3 quarters of the studies used high sensitivity cognitive tests. Amount and dose of opioids varied largely in many studies. Mean number of possible but unreported confounders was 2.2 (range, 0 to 4), relating to failure of the studies to mention coprescriptions with psychotropic effects, pain severity, sleep disorder or daytime somnolence, and/or significant depressive or anxiety-related problems.

Interpretation: The commonly held concept that "chronic pain patients on stable opioids are safe to drive" cannot be generalized to all such patients in everyday practice, but may be applicable only to a subset who meet certain criteria.

Key Words: opioids, driving, chronic pain

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Chronic pain is one of the most significant issues in healthcare. Between 10% and 55% of people in western societies experience chronic noncancer pain.[1] Chronic pain may impair numerous aspects of one's existence resulting in unemployment, disability, disruption of social roles, and impaired quality of life.[2]

Driving is a complex task as individuals are required to integrate psychomotor and cognitive skills, visual-spatial abilities, decision making, divided attention, motor skills, and behavioral and emotional control[3] The role of opioids on driving performance has been much debated. Opioid treatment studies have demonstrated inconsistent influence on driving ability. A systematic review conducted in 2003[4] looked at 48 studies with specific attention to tests measuring visual processing, attention, psychomotor abilities, postural imbalance, and cognitive function. The investigators stated that they studied individuals on "stable opioids," though they provided no specific definition as to what stable opioids mean, and concluded that "opioids appear not to impair driving skills in opioid dependent patients" (pp 574). Nevertheless, they reported inconclusive evidence from multiple studies on the cognitive function of opioid maintained patients (pp 559), and remarked on the need for further studies to conclusively answer whether patients on long-term opioids have impaired driving skills. This review included studies on healthy volunteers or opioid-addicted patients without pain in addition to pain patients. Therefore, the results cannot be generalized to the patients who are prescribed opioids for chronic cancer or noncancer pain.

The most recent published review[5] looked specifically at chronic noncancer pain patients treated with opioids for at least 1 month. Altogether, 13 studies were found (3 randomized controlled trials, 2 nonrandomized comparative trials, and 8 observational studies classified as outcomes research). The authors concluded that "…. current evidence for benefit, harm or lack of appreciable effect of a long term stable opioid treatment on cognitive functioning in chronic non cancer pain patients is still limited" (pp 229), a result similar to that of the previous review.[4] They suggested the creation of "international collaboratives to propose and organize focused research activities in the field" (pp 230).

The variable results in the current literature with regard to opioids and driving may be due to a multiplicity of factors including pain severity, combinations of medications, sleep disturbance and fatigue, comorbid psychiatric and psychological disorders, or other factors. Although some studies have found that opioids do not impair psychomotor performance,[6–9] other studies have concluded that chronic pain patients may have impaired cognitive function.[10–15] It has been suggested that untreated pain by itself may pose a greater risk to cognitive function than opioids[16] and driving ability improves once the pain is treated with opioids.[17]

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From the *Comprehensive Pain Program; ‡Krembil Neuroscience Center, Toronto Western Hospital; §Institute for Work and Health; †Department of Medicine, Division of Physiatry, University of Toronto; ‖Toronto Rehabilitation Institute, Toronto, ON, Canada; and ¶Comprehensive Pain Center, University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany.

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Reprints: Angela Mailis-Gagnon, MD, MSc, FRCPC (PhysMed), Medical Director, Comprehensive Pain Program, Toronto Western Hospital, Senior Investigator, Krembil Neuroscience Center and, 4F811, 399 Bathurst Str., Toronto, ON, M5T 2S8 Canada. (e-mail: angela.mailis@uhn.on.ca).

Chronic pain is commonly associated with sleep disturbance and fatigue[18–20] and depressive, anxiety, or other psychological and psychiatric comorbidities.[21–29] Sleep disturbance, daytime sleepiness or fatigue,[30–35] and psychological and psychiatric comorbidities[36–39] are known to potentially interfere with cognitive functioning including driving ability. As well, several classes of pharmacologic agents used in the treatment of chronic pain and associated disorders may have adverse effects on driving ability. Drugs such as benzodiazepines,[40,41] antidepressants,[36,42,43] anticonvulsants,[44] and opioids[45] have been shown to impair driving and increase the risk of traffic accidents.[46]

The question "Can patients on opioids drive"? remains without a clear answer. There are increasing concerns about patients on long-term opioids and prescribers' liability in case such patients are involved in traffic accidents.[47] Therefore, we perceived the need to revisit the literature and attempt to outline which patients on opioids are safe to drive. The specific objectives of our systematic review were to scrutinize the existing literature on opioids, cognitive function, and driving ability relating to (1) methodological quality of existing studies specifically on chronic cancer and noncancer pain patients, (2) sensitivity and validity of cognitive and psychomotor tests used to assess the effects of opioids on cognition (often used as surrogate measures for driving ability), and (3) the reporting of other variables that may alter interpretation of study results and generalizability of the conclusions (such as other psychotropic drugs, sleep disorder, and daytime somnolence, mood or anxiety disorder, and level of pain), factors very prevalent and significant in patients with chronic pain.

METHODOLOGY

Search Strategy

A comprehensive search of the following sources (Fig. 1) was performed: MEDLINE (1966 to 2008), EMBASE (1988 to 2008), PsycINFO (1872 to 2008), CENTRAL, Transport, CINAHL, reference lists of retrieved articles, and narrative reviews. MeSH terms were used for MEDLINE, EMBASE, PyscINFO, Transport, and CINAHL. We also contacted experts in the field. An independent reviewer (A.F.) performed the electronic searches and entered the data into Reference Manager 10.0, removing all duplicates electronically and manually.

Inclusion Criteria

Two reviewers (S.F.L., B.Y.) screened all titles and abstracts for potential studies meeting specific inclusion and exclusion criteria. When eligibility could not be determined from the abstract, the full article was retrieved and reviewed and disagreements regarding eligibility were resolved by consensus. When in doubt, a third reviewer (A.F. or A.M.G.) was consulted.

- *Study design*: Controlled studies with a concurrent or historical comparison group were included.
- *Comparison group*: The following comparison groups were included for individuals receiving placebo, no drug

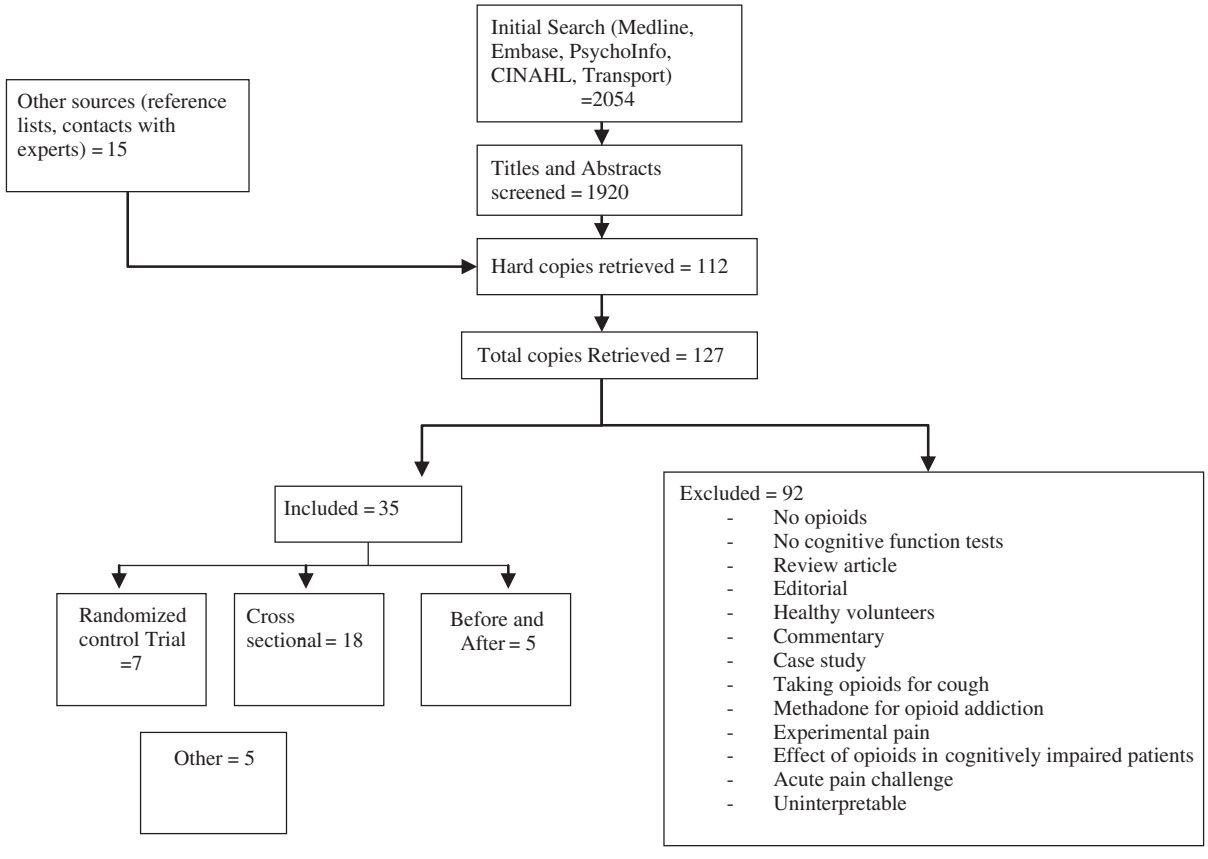

FIGURE 1. Flow chart of included and excluded studies.

for pain management, different dose, different route, different duration, different opioid, different combination of opioids with other drugs, other pain management drugs, or healthy volunteers.
- *Population*: Individuals receiving any type of opioids by any route for chronic cancer or noncancer pain. Only studies conducted with people of driving age were included.
- *Interventions*: Any opioid intervention, including methadone prescription for the management of chronic pain.
- *Language*: Articles in English, German, Dutch, Norwegian, and Danish were included.

Exclusion Criteria

We excluded studies conducted with patients on methadone maintenance treatment for addiction (unless methadone was specifically prescribed for chronic pain) and studies in which the pain was experimentally induced. Studies published only as abstracts were also excluded.

Data Extraction

The following data were extracted from all included studies: authors, publication year, country, study design, demographics of the population included, opioid intervention (type, dose, duration), control treatments, outcome measures, results (related to driving, cognitive function and psychomotor tests, pain relief, and sedation), and authors' main conclusion. Studies were considered to involve "unstable opioids" if measurements were performed after very short titration phase (< 3 d), only short-acting opioids were administered or dosing schedule was poorly described. We summarized the data using both quantitative and qualitative methods.

Assessment of Sensitivity and Validation of the Cognitive Tests

All cognitive and psychomotor tests that may be used as surrogate measures of ability to drive were recorded and appraised by the senior psychologist (K.N.): (1) as to the sensitivity of functions tested in representing the "complex act of driving," and (2) whether they had been well validated or not. Cognitive tests were given a sensitivity score of 3 if they tested more complex functions (attention and cognitive flexibility) and stressed a component of processing speed,[3] 2 for medium sensitivity functions and 1 for simpler functions that may not be very sensitive in capturing the complex act of driving. As most of the studies usually had more than 1 cognitive test, we calculated the mean of the sensitivity scores per study. For example, if a study had 3 cognitive tests with sensitivity scores of 3, 1, and 2, the mean of sensitivity scores for this study was 2. In addition, well-validated tests earned an A mark while poorly validated tests a score of B. Therefore, a cognitive test marked as 3(A) indicates a sensitive test of complex functions that has been well validated, whereas a test marked as 2(B) indicates a medium sensitivity or poorly validated test. We subsequently classified the neurocognitive tests in a dichotomous system, considering tests 2(A), 3(B), and 3(A) as better and more representative of driving abilities versus tests marked as 1(B), 1(A), or 2(B), which were considered poorer. The first group of tests will be referred to as high sensitivity and the second group as low sensitivity tests, respectively. Since most studies used batteries of tests, the number and proportion of high sensitivity versus low sensitivity tests was also calculated.

Assessment of Other Variables That May Affect Generalizability of Data

The clinician expert (A.M.G.) analyzed the retrieved studies for other confounding variables commonly present in everyday practice with chronic pain patients that may affect cognitive and psychomotor functions and driving ability. Given the nature and immense heterogeneity of the studies, "confounding variable points" were assigned to each of the studies to indicate the fact they did not take into account the presence of these factors that could alter driving ability by themselves. Such points were earned when:
(1) pain severity or related measures were not mentioned;
(2) other commonly prescribed drugs for chronic pain (antidepressants, antiepileptics, hypnotics and sedatives) were either not permitted or coprescriptions were not reported;
(3) daytime somnolence or sleep disorder was not mentioned; and
(4) significant mood, anxiety, or other psychiatric disorder was not assessed or reported.

Of note, this system makes no provisions to score for confounding variables that were mentioned but not controlled for in the conclusions of the studies. A maximum score of 4 in our system indicates, therefore, that none of the confounding variables listed above were mentioned in a given study. As very few if any studies actually mentioned AND controlled for these variables, "controlling for" was not part of our system scoring, which makes it extremely generous, underestimating the magnitude of confounders. Additional confounding variables if possible were recorded (eg, high variability in reported pain ratings, high level of placebo responses, poor reporting of patients or results, high dropout rate), though no score was given for these.

Methodological Quality Assessment

Two independent reviewers (B.Y., S.F.L.) assessed the methodological quality of each study and met to reach consensus and, in cases of disagreement, a third reviewer was consulted. For quality assessment, we used the Methodological Index for Nonrandomized Studies (MINORS) instrument to evaluate all studies, as it can also be applicable in randomized studies.[48] The MINORS methodological checklist contains 12 items. Each item is scored from 0 to 2 as follows: 0 = not reported, 1 = inadequately reported, or 2 = reported adequately in the evaluated article. Studies were classified as high (score 15 to 24), fair (score 11 to 14), or poor (score 10 or less) quality.

Statistical Analysis

Data analyses pertaining to sensitivity of tests assessing cognitive and psychomotor performance and MINORS scores were carried out using the SAS program version 9.2 (SAS Institute Inc., Cary, NC). Data were analyzed using the 2-sided Wilcoxon Mann-Whitney *U* test. The means of the sensitivity scores from all the studies were compared within the MINORS (poor, fair, and high) groups.

RESULTS

The initial search yielded 2054 studies; of these, 1920 titles and abstracts and another 15 studies generated through different sources, resulted in 127 hard copies retrieved. Altogether, 92 studies were excluded and 35 studies formed the basis for this review.[6–9,16,45,49–77] Although we attempted to determine whether the studies used "stable" versus "unstable" opioid regimes, in none of

the studies the term "stable opioids" was defined. We considered 11 of the 35 studies[52,53,57–59,61,62,69–71,74] as clearly using "unstable opioid doses" based on our definition (see Methods), whereas the rest of the studies were deemed to be using "stable doses" though at times information about the exact combination of long-acting and short-acting opioids was lacking. Ultimately, for the results of the study, stable or unstable opioid doses as defined here, did not really matter.

Ten of the studies were conducted in USA,[49,53,58,60,61,63,66,68–70] 9 studies conducted in Germany,[7,54,56,57,62,65,72,75,76] 7 studies conducted in Denmark,[8,9,16,50,51,73,74] 2 studies conducted in Canada,[52,67] 2 studies conducted in Finland,[45,71] and 1 study conducted in each of the following countries: Australia,[59] Brazil,[64] France,[77] Norway,[55] and UK.[6] The average dose of morphine or equivalent per day in milligrams was 119.68. However, there was a high-dose variability as the range of average doses was 16.3 to 210 mg, the range of minimum doses 6.6 to 130 mg, and the range of maximum doses 20.3 to 1110 mg. A total of 3724 individuals were included in the 35 studies (2044 patients on opioids, 523 of which were cancer patients, and 1994 controls). As for the methodological quality based on their MINORS score, 9% of the studies were of poor quality (3 of 35; mean score, 7.3 ± 2.08; MINORS range, 5 to 9), 54% of the studies were of fair quality (19 of 35; mean score, 13.6 ± 1.11; range, 11 to 14), and 37% of the studies were of high quality (13 of 35; mean score, 18.07 ± 1.93; range, 15 to 23).

Relating to the use of cognitive and psychomotor tests, 75% of the tests used in high-quality studies, 84% of the tests in fair quality studies, and 71% of the these in low-quality studies, were of higher sensitivity [2(A), 3(B), 3(A)]. Total mean sensitivity score for all included studies was 1.91 ± 0.47 (range, 0 to 2.4). When the mean sensitivity scores of the studies were compared based on the MINORS subgroups (low, fair, and high quality), no statistical differences were detected.

Analysis of "confounding variables" revealed that the majority of the studies were possibly affected by factors that could significantly alter the interpretation of the data. This is indicated by the fact that only 2 studies (6%) had no confounders based on our system; 29% of the studies (10 of 35) had 1 confounding variable, 29% of the studies (10 of 35) had 2 confounding variables, 31% of the studies (11 of 35) had 3 confounding variables, and 6% of the studies (2 of 35) had 4 confounding variables. The mean number of confounding variables was 2.2 with a range of 0 to 4. The methodological quality of the studies proved to be irrelevant to the number of confounding variables: high-quality studies had a mean of 2.2 such variables, fair quality studies had a mean of 2.1, and low-quality studies had a mean of 2 confounding variables. The results are presented cumulatively in Table 1.

Separate analysis was conducted in the 4 studies that tested driving on the road[53] or through a driving simulator,[58,66,75] which were considered superior to studies using only psychomotor and cognitive tests. Except 1 study[66] that demonstrated that patients on fentanyl not only had no problem driving but also had improved in several performance measures on opioids, the investigators of the remaining 3 studies suggested at minimum caution when patients on opioids are allowed to drive. Careful consideration of these 4 studies demonstrated significant limitations in the applicability of their conclusions (Table 2).

DISCUSSION

This systematic review concluded that although most of the included studies were of fair or high methodological quality and largely used high sensitivity and well-validated cognitive and psychomotor tests, they suffered primarily from significant lack of clinically relevant information that limits the interpretation of the results, therefore their generalizability to everyday practice. The vast majority of studies paid little attention, if any, to variables that can affect cognition and psychomotor function or driving ability, commonly found in chronic pain populations.

This review differs substantially from previous reviews because it (1) included studies both on chronic cancer or noncancer pain patients on opioids that tested cognitive/psychomotor functions by psychological tests, driving simulator, or on road driving; (2) rated all studies for quality; (3) assessed the validity and sensitivity of psychomotor/cognitive tests; and (4) scrutinized the studies for possible confounders, which could affect the generalizability of conclusions in our everyday practice.

Sleep deprivation, fatigue, or daytime somnolence may markedly interfere with aspects of human performance.[30,32,34] Furthermore, several studies have concluded that depression or anxiety may have a significant effects on cognitive or psychomotor performance[36–39] although there is considerable variability and certain subsets of such patients may be more vulnerable. Although we did not find studies that had specifically examined the effect of such psychoemotional disturbance on driving performance, there have been multiple studies on the effects of medications used to treat psychoemotional problems. Ramaekers,[42] in a review of published studies from 1983 to 2000, found that the adverse effect of acute doses of sedating antidepressants on vehicular "weaving" were comparable to those seen in drivers with a blood alcohol concentration of 0.8 mg/mL or more. Thomas,[40] in a systematic review of studies from 1980 to 1997, concluded that the use of benzodiazepines approximately doubles the risk of motor vehicle accidents. We must stress that chronic pain patients are more likely to be on more than 1 kind of medications[47] with several of these drugs (ie, tricyclic antidepressants, sedatives, etc.) shown to impair cognitive functions, particularly in the elderly.[43,78] Of note, the current review did not assess such psychoemotional factors as irritability, euphoria, and risk-taking behaviors that may also be associated with chronic pain, opioids, and traffic accidents.

In addition, high level of pain may also affect aspects of cognition and psychomotor function, as poorly controlled pain is known to compete with attentional resources or to impact on other aspects of cognitive functioning.[10–16] Only 1 study has specifically examined the role of poorly controlled chronic pain on driving performance in patients taking acetaminophen, nonsteroidal anti-inflammatory drugs, or no medications. That study measured the standard deviation of lateral position, which is a validated measure of the amount of weaving the car on the road, as a primary variable in the on-the-road driving test. The standard deviation of lateral position performance of chronic pain patients even in the absence of any medications was abnormal and similar to that of volunteers who

TABLE 1. Characteristics of All Included Studies

	Study	Opioid Reporting (Range in Brackets)	Confounding Variables (A) Pain Control [Range, (Mean)] (B) Other Drugs Affecting CNS (C) Sleep Disorder and/or Somnolence (D) Mood/Anxiety Disorder	Cognitive Tests Used	(A) Minors Score (M) and Summary of Quality Assessment (B) No. High Sensitivity Tests Used (C) No. Confounders	Additional Comments
1	Strumpf et al[75]	Noncancer patients Unclear as to type of opioid used Mean WHO III 199 mg M/d (40-600) Mean WHO II 48 mg M/d (20-70)	(A) NRS 3.1 (0-10) (B) Not mentioned* (C) Not mentioned* (D) Not mentioned*	Driving simulator Letter cancellation test 2(A)	(A) MINORS = 13/24 Fair quality Driving Simulator (B) 1/1 HS test (C) C = 3	Huge pain range, large variability in dosing, not controlling for high levels of pain
2	Clemons et al[6]	Cancer patients on M 70-200 mg/d controlled release or M sulphate solution	(A) Low pain ratings in cancer patients on M (30/100); cancer patients on no opioids (only 7/100) (B) Allowed (C) Not mentioned* (D) Mentioned/present	NART 1(A) Logical Memory test 1(A) GRT 2(B) CRT 2(A) Stroop test 2(A)	(A) MINORS = 9/24 Low quality, (B) 2/5 HS tests (C) C = 1	
3.	Banning et al[51]	Cancer patients sustained release M + other opioids Median 150 mg (30-400 mg)	(A) Median VAS cancer patients on M: 26 (0-93); cancer patients on no opioids 25 (0-88) (B) Excluded* (C) Mentioned (D) Mentioned, absent	CRT 2(A)	(A) MINORS = 12/24 Fair Quality (B) Single HS test (C) C = 1	Huge pain range
4	Jamison et al[63]	Noncancer patients on oxycodone + acetaminophen or fentanyl patch Proper level/range, multiple dose levels	(A) VAS mean 5.7 ± 2.2 (1-10) (B) Excluded* (C) Not mentioned* (D) Mentioned, absent	DSST 2(A) TMT 2(A)	(A) MINORS = 13/24 Fair quality (B) 2/2 HS tests (C) C = 2	VAS wide range BDI mean 8.4 ± 6.9 (0-31), some patients had mild-to-moderate depression with BDI score > 13 and at least one severe depression > 30
5	Tassain et al[77]	Noncancer patients Mean 62 mg M at 3 mo and 65 mg M at 6 mo with narrow range	(A) Proper (B) Allowed (C) Not mentioned* (D) Mentioned, same patients—controls	SRT 2(A) TMT 2(A) DS 1(A) DSST 2(A) Stroop test 2(A) FCSRT 1(A)	(A) MINORS = 11/24 Fair quality (B) 4/6 HS tests (C) C = 1	Cointerventions in patient and control group dissimilar
6	Sabatowski et al[72]	Noncancer patients for final analysis Only 3/30 patients > 100 mcg/h fentanyl	(A) Proper (B) Benzos > 3 times/wk, barbs, amitriptyline > 75 mg, antihistamines, excluded* (C) Not mentioned* (D) Not mentioned*	COG 2(A) DT 3(A) TAVT 2(A) Two Hand 3(A) VIG 2(A)	(A) MINORS = 14/24 Fair quality (B) 5/5 HS tests (C) C = 3	Due to exclusions not generalizable
7	Raja et al[68]	Noncancer patients MS Contin, mean 92 mg (15-225) Nortriptyline mean 89 mg (40-140)	(A) Proper (B) Excluded* (C) Mentioned (D) Mentioned, not present	DSST 2(A) HVLT 1(A) GPT 2(A)	(A) MINORS = 19/24 High quality (B) 2/3 HS tests (C) C = 1	High dropout rates and learning effect
8	Sjogren et al[8]	Cancer patients Median group 4a (pain + opioids): 120 mg M (25-420) Median group 4b (opioids + no pain): 40 mg M (20-180)	(A) VAS group 3 (pain + no opioids): median 24 (10-93) Group 4a (pain + opioids): 35 (2-88) (B) Excluded* (C) Not mentioned* (D) Not mentioned*	CRT 2(A) FTP 2(A) PASAT 3(A)	(A) MINORS = 17/24 High Quality (B) 3/3 HS tests (C) C = 3	Huge pain variation, 4a group had worse pain despite higher opioids and poorer performance
9	Sjogren et al[16]	Noncancer pain patients, median 60 mg long acting M preparations (15-300 mg)	(A) VAS Median 39 (0-80) (B) Excluded* (C) Not mentioned* (D) Mentioned, existed: anxiety 50%, depression 38%	CRT 2(A) FTP 2(A) PASAT 3(A)	(A) MINORS = 12/24 Fair Quality (B) 3/3 HS tests (C) C = 2	Significant pain variability but median low
10	Larsen et al[65]	Cancer pain patients Mean 67 mg M (10-430 mg)	(A) Well controlled, VAS low (B) Allowed (C) Daytime tiredness mentioned, did not affect results (D) Anxiety mentioned, did not affect results	(Brickenkamp's) d2 2(A) RT 2(A)	(A) MINORS = 14/24 Fair Quality (B) 2/2 HS test (C) C = 0	Huge dose variability

(continued)

TABLE 1. (*continued*)

	Study	Opioid Reporting (Range in Brackets)	Confounding Variables (A) Pain Control [Range, (Mean)] (B) Other Drugs Affecting CNS (C) Sleep Disorder and/or Somnolence (D) Mood/Anxiety Disorder	Cognitive Tests Used	(A) Minors Score (M) and Summary of Quality Assessment (B) No. High Sensitivity Tests Used (C) No. Confounders	Additional Comments
11	Hay-thornthwaite et al[60]	Noncancer pain patients Long-acting opioid mean at baseline 22.8 ± 21 mg M; at follow-up 111.1 ± 69.6; usual care mean at baseline 16.9 ± 18.5 mg M, at follow-up 19 ± 18.5	(A) Detailed multidimensional pain inventory report (B) Allowed except Benzos* (C) Mentioned (D) Mentioned. Some patients depressed at start in both groups equally improved at follow up (no explanation why)	TMT 2(A) HVLT 1(A) GPT 2(A) DS 1(A) DSST 2(A)	(A) MINORS = 17/24 High Quality (B) 3/5 HS tests (C) C = 1	Pain decreased in both groups (?effect of time or repeat measures). Long-acting opioid group had higher baseline pain (confounder)
12	Moulin et al[67]	Noncancer pain patients Sustained release M mean 83.5 mg (SD ± 33)	(A) Pain effect only in graphs, reported as p values* (B) Tricyclics tried and failed. Nil else reported (C) Not mentioned* (D) Mentioned, tested	High sensitivity cognitive screen 2(A)	(A) MINORS = 19/24 High quality (B) 1/1 HS test (C) C = 2	Statistically significant reduction in memory in M group not mentioned nor commented in results
13	Vainio et al[45]	Cancer patients, slow release M, median 209 mg (60-1100 mg)	(A) Not specified, "pain under control"* (B) Excluded* (C) Not mentioned* (D) Not mentioned*	FTT or FTS 2(A) SRT 2(A) Posture control—2(A) ART-90: M30 1(A) Q1 2(A) LL5 2(A) Set3 2(A) PVT 3(A)	(A) MINORS = 12/24 Fair quality (B) 7/8 HS tests (C) C = 4	Huge-dose variation may explain tendency for more errors and slower reaction time in some
14	Banning and Sjogren[50]	Cancer patients Slow release M and/or other immediate or controlled release opioids, median 168 mg M (30-920 mg)	(A) VAS 0-93, low median 29 VAS 0-93, low median 29 (B) Excluded* (C) Not mentioned* (D) Not mentioned*	CRT 2(A)	(A) M = 8/24 Low quality (B) 1/1 HS test (C) C = 3	Huge pain variation and opioid dose Different Karnofsky stages
15	Sjogren and Banning[73]	Cancer patients Slow release M and/or other immediate or controlled release opioids, median 210 mg oral (130-400); median 80 mg epidural (32-240)	(A) VAS median 27 (0-48) on failed oral; 16 (0-77) on epidural (B) Excluded* (C) Not mentioned* (D) Not mentioned*	CRT 2(A)	(A) MINORS = 12/24 Fair Quality (B) 1/1 HS test (C) C = 3	No good reason why changed from oral to epidural if Pain VAS and Sedation VAS did not change from one treatment to the other. Epidural treatment emphasized by investigators
16	Grellner et al[7]	Cancer and non cancer patients Dose not reported, multiple opioids WHO II and III	(A) No pain measurements at all* (B) Allowed (C) Mentioned (D) Not mentioned*	Vienna test: DT 3(A) CORSI 1(A) LVT 1(A) TAVT 2(A) COG 2(A) Two hand 3(A) RT1 2(A) RT5 2(A) RT6 2(A)	(A) MINORS = 5/24 Low quality (B) 7/8 HS tests (C) C = 2	
17	Strumpf et al[76]	Noncancer patients WHO II and III opioids nonspecified, mean 151 mg M (6.6-1000)	(A) VAS scores not reported* (B) Allowed (C) Not mentioned* (D) Not mentioned*	DT 3(A) VIG 2(A) TAVT 2(A) COG 2(A) Two hand 3(A)	(A) MINORS = 13/24 Fair quality (B) 5/5 HS tests (C) C = 3	Huge dose variation Uninterpretable conclusions

(*continued*)

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	Study	Opioid Reporting (Range in Brackets)	Confounding Variables (A) Pain Control [Range, (Mean)] (B) Other Drugs Affecting CNS (C) Sleep Disorder and/or Somnolence (D) Mood/Anxiety Disorder	Cognitive Tests Used	(A) Minors Score (M) and Summary of Quality Assessment (B) No. High Sensitivity Tests Used (C) No. Confounders	Additional Comments
18	Gaertner et al[56]	Noncancer patients, mean 76 mg controlled release oxycodone (20-280)	(A) NRS mean 5 ± 2 (B) Benzos > 3 times/week, barbs, amitriptyline > 75 mg, antihistamines, excluded* (C) Not mentioned* (D) Not mentioned*	DT 3(A) VIG 2(A) TAVT 2(A) COG 2(A) Two hand 3(A)	(A) MINORS = 23/24 High Quality (B) 5/5 HS tests (C) C = 3	This is one of the best studies regarding methodology with the highest MINORS, though it had several confounders
19	Dagtekin et al[54]	Noncancer patients Transdermal buprenorphine mean 45 ± 20 mcg/hr (17.5-105)	(A) NRS mean 4.2 ± 2.9 (B) Benzos > 3 times/week, barbiturates, amitriptyline > 75 mg, antihistamines, excluded* (C) Not mentioned* (D) Not mentioned*	DT 3(A) VIG 2(A) TAVT 2(A) COG 2(A) Two hand 3(A)	(A) MINORS = 17/24 High Quality (B) 5/5 HS tests (C) C = 3	Noninferiority shown in buprenorphine group regarding ability to drive However, due to variability of results individual assessment recommended Age a factor
20	Agarwal et al[49]	Noncancer patients Mean maintenance transdermal fentanyl 106 mcg/hr (25-150)	(A) Reported in detail as average % pain reduction (B) Allowed (C) Not mentioned* (D) Cannot interpret stats as no explanation given*	GPT 2(A) DSST 2(A)	(A) MINORS = 17/24 High quality (B) 2/2 HS tests (C) C = 2	Very poor reporting as stats not explained
21	Fredheim et al[55]	Noncancer patients mean 202 mg slow release M (50-800) switched to methadone via formula and stable for at least 1 week before testing	(A) NRS 5.8 (3-9) baseline decrease by 3/10 points after first week; 2.4 after 3 mo and 2.9 at 9 mo compared with baseline pain (B) Not mentioned* (C) Mentioned, reported (D) Not mentioned*	Stroop 2(A) PASAT 3(A) Number Letter Span 2(A)	(A) MINORS = 15/24 High quality (B) 3/3 HS tests (C) C = 2	Double switching before methadone; mentioned no worsening of cognition but did not indicate whether baseline values were normal in this opioid titrated group
22	Sjogren et al[9]	Noncancer patients Group 2 (opioid treated 60 mg M (8-360); group 4 (opioids and other) 90 mg M (4-440)	(A) Group 1 VAS 56 (0-92) Group 2 71 (10-90); Group 3 56 (14-95); Group 4 58 (0-99) (B) Allowed (C) Not mentioned* (D) Not mentioned*	CRT 2(A) FTT 2(A) PASAT 3(A)	(A) MINORS = 12/24 Fair quality (B) 3/3 HS tests (C) C = 2	Huge pain and dose variation; patients did poorer but attributed to combined effect of pain, sedation and meds
23	Menefee et al[66]	Noncancer patients 25-75 mcg/hr fentanyl	(A) VAS mean pre: 67 ± 21post: 53 ± 29 (B) Benzos, lioresal excluded* (C) Mentioned (D) Mentioned, absent	Driving Simulator Cognition: TMT 2(A) Attention: Rey O 1(A) Copy) 2(A) WMS III 1(A) Memory: d2 2(A) CPT II 2(A)	(A) MINORS = 14/24 Fair quality (B) 4/6 HS tests (C) C = 1	
24	Kurita et al[64]	Cancer patients Different opioids 69.9 ± 53.1 mg to 112.8 ± 62.3 mg M/day narrow range, dose unchanged in 3 assessments	(A) Details provided (pain scale) for all 3 assessments (B) Allowed (C) Not mentioned* (D) Mentioned, tested	Brief Cognitive Screening Battery 1(A) TMT 2(A) DS 1(A) MMSE 1(A)	(A) MINORS = 18/24 High quality (B) 1/4 HS tests (C) C = 1	
25	Bruera et al[52]	Cancer patients dose converted to mean equivalent parenteral M: "stable" 16.3 ± 4;	(A) "Stable" dose group (unchanged for 7 days): VAS 38 ± 15 before,12 ± 10 after dose; "Increased" dose group	FTS or FTT 2(A) Arithmetic test 2((B) Memory for	(A) MINORS = 18/24 (B) High quality (C) 2/4 HS tests (D) C = 3	Sedation worse in those recently increased. Never tested 1 week

(*continued*)

TABLE 1. (*continued*)

	Study	Opioid Reporting (Range in Brackets)	Confounding Variables (A) Pain Control [Range, (Mean)] (B) Other Drugs Affecting CNS (C) Sleep Disorder and/or Somnolence (D) Mood/Anxiety Disorder	Cognitive Tests Used	(A) Minors Score (M) and Summary of Quality Assessment (B) No. High Sensitivity Tests Used (C) No. Confounders	Additional Comments
		"increased/unstable" 15.8 ± 4 mg. Unclear what the oral dose is. Patients tested before and after their opioid dose	(dose increased less than 3 days before testing) 42 ± 16 before, 14 ± 9 after dose (B) Not mentioned* (C) Not mentioned* (D) Not mentioned*	digits (Digit span) 2(A) Visual memory 1(A)		after 30% dose increase, conclusion unsubstantiated that increased opioids are stable after 1 week
26	Rowbotham et al[70]	Noncancer patients Mean high dose (15.75 mg/(D) and mean Low dose (2.7 mg/(D) levorphanol in neuropathic patients	(A) VAS 65.4 ± 18.2 (high levorphanol group); 69.3 ± 17.0 (low levorphanol group) (B) Allowed (C) Not mentioned* (D) Mentioned, tested	SDMT 2(A)	(A) MINORS = 18/24 (B) High quality (C) 1/1 HS test (D) C = 1	Cognition test data not reported, learning effect not counted, high dropout rates
27	Huse et al[62]	Noncancer patients 70-300 mg M/d after titration with 7/12 patiens on 70-100 mg and only one at 300 mg	(A) Modified VAS baseline 4.65 ± 1.06; oral retarded morphine sulfate (MST) phase 3.26 ± 1.59; placebo 3.99 ± 1.23 (B) Not mentioned* (C) Not mentioned* (D) Mentioned, tested	d2 2(A)	(A) MINORS = 17/24 (B) H quality (C) 1/1 HS test (D) C = 2	Small study on 12 patients with long follow-up in 6 and 12 mo MST phase associated with poor performance on day 2 attention test
28	Galski et al[58]	Noncancer patients, Only report: dose > 30 mg M	(A) NRS 3.65 ± 1.94 (B) Excluded* (C) Not mentioned* (D) Not mentioned*	Driving Simulator DSST WAIS - R2(A) TMT A 2(A) Visual Form recognition test 1((B) Block design WAIS-R 2(A) Double letter	(A) MINORS = 11/24 (B) Fair quality (C) 5/8 HS tests (D) C = 3	Very poor description of chronic opioid therapy patients No explanation of opioid patients' high impulsivity and possible effect on driving
29	Sjogren et al[74]	Cancer patients IM M before procedure in opioid naive and opioid treated patients Oral opioid group 30-920 mg M/day, median 180 mg; Epidural opioid Group 12-600 mg M (median 79) in 3-4 doses/day	(A) VAS Oral opioid group 34 (0-93); Epidural opioid group 4.5 (0-73) (B) Excluded psychotropics* (C) Not mentioned* (D) Not mentioned*	CRT 2(A)	(A) MINORS = 14/24 (B) Fair quality (C) 1/1 HS test (D) C = 3	
30	Saarialho-Kere et al[71]	(1) Dextropropoxyphene (DXP) 130 mg/d 2) DXP 65 mg + amitriptyline 25 mg/d 3) placebo	(A) VAS mean 42.3 ± 6.1, median 43, high variability (B) Allowed for rheumatological diseases (C) Mentioned, tested (D) Mentioned, tested	DSST 2(A) SCT 2(B) FFT 1(A) DAT 3(B) TCRT (Tracking and Choice Reaction Test) 3(B)	(A) MINORS = 14/24 (B) Fair quality (C) 3/5 HS tests (D) C = 0	Conflicting results regarding opioids Highly unstable dose Short titration time Extremely weak opioid, doses 4-9 mg of morphine equivalent
31	Hendler et al[61]	Noncancer patients No dose, type, duration, route or stable/unstable dose	(A) No pain ratings* (B) Not mentioned* (C) Not mentioned* (D) Not mentioned*	WAIS 1(A) Memory Quotient 1(A) Bender Gestalt 1(A)	(A) MINORS = 11/24 (B) Fair quality (C) 3/3 LS tests (D) C = 4	
32	Byas Smith et al[53]	Noncancer patients Incredible variability, mix of short and long acting mean 118 mg M; stratified patients as low and high	(A) Opioid group 45.8, nonopioid group 40 (VAS 0-100) (B) Allowed (C) Mentioned, tested (D) Not mentioned*	Only On the Road study TOVA 2(A) DSST 2(A)	(A) MINORS = 14/24 (B) Fair quality (C) Road test, 2/2 HS tests (D) C = 1	Decreased power due to (a) participation of 15% of 215 patients asked and (b) less patients than

(*continued*)

TABLE 1. (*continued*)

Study	Opioid Reporting (Range in Brackets)	Confounding Variables (A) Pain Control [Range, (Mean)] (B) Other Drugs Affecting CNS (C) Sleep Disorder and/or Somnolence (D) Mood/Anxiety Disorder	Cognitive Tests Used	(A) Minors Score (M) and Summary of Quality Assessment (B) No. High Sensitivity Tests Used (C) No. Confounders	Additional Comments
	opioids based on 20 mg M/day cutoff point				stipulated by design (50 instead of 150); significant selection bias; short distance driving only; clement weather
33 Gourlay et al[59]	Cancer patients Escalation over the course of many days Bolus epidural versus continuous infusion epidural M with some patients changed to intrathecal M	(A) Bolus mean VAS 1.48 cm; infusion mean 1.23 cm (B) Not mentioned* (C) Not mentioned* (D) Mentioned, tested	Symbol digit test = 2(A) WRT 2((B) Williams delayed Recall 1(A)	(A) MINORS = 17/24 (B) High quality (C) 1/3 HS tests (D) C = 2	Mood and cognitive unchanged Unclear if baseline mood and cognition normal Learning effect not counted
34 Gaertner et al[57]	Noncancer patients At baseline 30 mg M median (20-180), after increase Group I 49 mg M mean, Group II 77 mg M median	(A) NRS Group I: 5.9 ± 1.7 before; 4.1 ± 2.2 after increase Group II: 4.8 ± 2.1 before; 4.4 ± 2.5 after (B) Allowed (C) Not mentioned* (D) Not mentioned*	TAVT 2(A) RT 2(A) DT 3(A) COG 2(A)	(A) MINORS = 12/24 (B) Fair quality (C) 4/4 HS tests (D) C = 2	
35 Brown et al[69]	Noncancer patients 95% daily users Daily M equivalent 92.3 mg (SD 136.5 mg M)	(A) Not reported in detail in text but tested* (B) Not mentioned but study "pragmatic" (C) Mentioned, recorded (D) Mentioned, not tested	MOS MHI	(A) MINORS = 12/24 (B) Fair quality (C) 1/1 LS tests (D) C = 1	Very large dose variation

Marking Confounders: Mark * if pain measure not mentioned; other drugs are not allowed, or not mentioned; sleep disorder/somnolence not mentioned and mood or anxiety is not mentioned or tested. MINORS score: Quality is defined as low 1 to 10, fair 11 to 14, high 15 to 24. Stable opioid studies 1 to 24, stable/unstable opioid studies: 25 to 35.

Note that all ART measures are very rarely used in North American Neuropsychology. Note that we mention cancer or no cancer patients but all studies have comparator groups of cancer or noncancer pain patients or healthy volunteers. Doses are reported in morphine or equianalgesic doses unless otherwise specified.

BDI indicates Beck Depression Inventory; HS, high sensitivity; LS, less sensitivity; M, morphine or morphine equivalents; MINORS, Methodological Index for Nonrandomized Studies; NRS, Numeric Rating Scale; VAS, Visual Analogue Scale.

had consumed alcohol achieving a blood alcohol concentration of 0.08%,[15] indicating that the complex act of driving is affected by untreated or poorly treated pain. It is important to note that Kuhajda et al[79] demonstrated that cognitive difficulties occur in pain patients when pain intensity levels exceed a threshold that varied in the 4 studies they reviewed between 64 and 71 of 100 on a 0 to 100 Numerical Rating Scale. It should also be noted that those attending tertiary care pain clinics differ from pain patients in primary care settings[80,81] as they present with higher levels of psychosocial dysfunction and comorbidities and compensable issues. In addition, it is often the interaction and cooccurrence of confounding variables that may result in impairment.[82]

Most studies in our systematic review included patients with a wide range of pain scores. Although reporting of pain levels did not earn the studies a confounding variable point, most studies did not control for either level of pain or other factors even when they mentioned them. In addition, for most studies included in our review, the dose of opioids used was extremely variable. It is unclear how high doses of opioids (ie, well over 400 mg of morphine equivalent and up to thousands of mg daily) affect cognition (even when the daily opioid dose is considered "stable"), as no studies have been conducted on patients on stable long-acting moderate versus high doses of opioids. Determination of "stable" opioid level was very difficult due to lack of definition of "stable doses" and the poor reporting of opioid doses and timing in several studies. Finally, many studies included short-acting opioids, which by themselves could alter cognition (depending on the dose, route of administration, and schedule or lack of it), though "scheduled" short-acting preparations can effectively treat chronic pain. In a double-blind, placebo-controlled, crossover study of cancer patients on slow release opioid preparations, administration of immediate release morphine produced transient anterograde and retrograde memory impairment and decrement in 2-target tracking, despite the fact that it further reduced pain. The investigators suggested that these changes may impact negatively on patients' everyday functioning.[83]

TABLE 2. Driving and Driving Simulator Studies

Study	Testing Method	Tested Groups	Authors' Conclusions	Study Weaknesses
Byas Smith et al[53]	On road driving	Noncancer chronic pain patients on (1) opioids[21]; (2) nonopioids,[11] and (3) normal controls[51]	Many patients with chronic pain, even if treated with potent analgesics such as morphine and hydromorphine, show comparable driving ability as normal controls	Decreased power due to less patients than stipulated by design; significant selection bias; short distance driving only; clement weather; huge opioid variability with 11/21 patients on short-acting and long-acting opioids and 6/17 only on long-acting opioids, daily opioid dose ranging between few mg of morphine or equivalent to 160 mg hydromorphone/day = 800 mg of morphine/day; 1 confounding variable (mood/anxiety disorder not tested/taken in account)
Strumpf et al[75]	Driving simulator	Four groups: Cancer pain patients; noncancer pain patients; pain of unclear origin; and mixed etiology (cumulative number = 33) Controls: 4 groups, patients with preop sedation; volunteers under the influence of alcohol; volunteer MDs on call with less than 4 hours of sleep; healthy normals	Long-term therapy with opioids does not inevitably impair complex skills, but the decision to permit driving a car can only be made on an individual basis	Only 20/33 opioid patients completed all tests and analyzed; 3 confounders (drugs affecting CNS, somnolence, and mood/anxiety disorder not mentioned; 14/20 on strong opioids with significant variability of dose (40-600 mg of morphine or equivalent); significant pain variability (range, 0-10); patients on opioids had longer reaction time, slower speed of driving, as compared with some of the groups
Galski et al[58]	Driving simulator	Sixteen patients on COAT compared with 327 CComp historical controls who failed or passed a driving tests	Although there was general support for the notion that COAT did not significantly impair, perception, cognition, coordination and behavior measured in off-road tests …, methodological problems may limit the generalizability of results	Poor description of COAT patients; opioid dose unspecified except that at minimum it was 30 mg morphine; several confounders (other CNS-acting drugs not allowed, somnolence and depression/anxiety not mentioned/teste(D); COAT drivers made more errors on a number of cognitive tests than CComp, and demonstrated difficulty following instructions and some impulsivity
Menefee et al[66]	Driving simulator	Twenty-three patients on fentanyl patch 25-75 mcg/hr	Addition of transdermal fentanyl to a treatment regime containing no opiates or opiates in small amounts for patients with chronic nonmalignant pain did not negatively affect their driving performance, reaction time, cognition, or balance. Patients on stable doses had improvement in several measures	Limited power as the sample was small. Findings cannot be generalized to individuals of populations with higher opioid doses, older individuals. or patients on benzos

CComp indicates cerebrally compromised; CNS, central nervous system; COAT, chronic opioid analgesic therapy.

As for the risk of traffic accidents in the presence of medical diseases or medications, few studies have looked specifically at patients with pain. Although a structured evidence-based systematic review[4] had presented "strong consistent evidence" that opioid users had no greater incidence of motor vehicle violation or accidents versus comparable controls, several studies have been published since furnishing evidence to the contrary. A recent epidemiological study on middle-aged workers demonstrated that pain alone or in combination with pain medications was associated with increased traffic accident risk. However, the study was unable to differentiate the effects of high levels of pain and those of analgesic drugs.[84]

In 2010, a large registry-based study in the USA demonstrated increased risk of unsafe driving in female drivers aged 25 to 55 years and male drivers aged 25 to 65

years involved in fatal traffic accidents when receiving opioids.[85] However, due to the diversity of the opioid formulations detected in this study (eg, slow release vs. immediate release formulations) and missing information regarding the purpose of opioid use (eg, pain relief vs. recreational use), it is difficult to make a final judgment on the impact of opioids prescribed for pain management. The frequency of the use of immediate release opioids and the higher odds ratio for unsafe driving actions in younger drivers as compared with those aged 65 to 75 years, reduce the generalizability of the results. In addition, both the pharmacokinetics and the purpose of opioid use may impact greatly on traffic accident risk.[85]

Another registry-based study in Norway[86] showed that the risk of involvement in a traffic accident was markedly increased in users of natural opium alkaloids, benzodiazepine tranquillizers, and benzodiazepine hypnotics. Coprescription of benzodiazepines has been shown to be highly prevalent and increases in parallel with the amount of prescribed opioid drugs.[78] Therefore, it might be assumed that, in the case of chronic pain patients on opioids, the risk of causing a traffic accident further increases in the presence of coprescriptions of other psychoactive drugs, poor response to treatment of pain, and impaired sleep or comorbid psychiatric disorders.

In summary, we believe that we are underreporting factors that affect the generalizability of the results on the reviewed studies. We should stress, however, that opioids alone should not be singled out. The presence of other factors that can by themselves or in conjunction with opioids results in altered cognition or driving performance, should be considered carefully in chronic pain patients.

The difficulty to create an easily applicable system regarding opioids and driving is apparent by the fact that regulations vary significantly between different countries, and even within different jurisdictions in the same country. For example, in Ontario, Canada (but not necessarily in all Canadian provinces and Canadian Territories), it is mandatory for the physician to report to the Ministry of Transportation a patient who has a condition that "may make him/her unsafe to drive."[87] Unfortunately, there are no specific guidelines advising the physicians what to do except telling the patients "not to drive" during titration of opioid dose and/or use of short-acting analgesic medications, or when they have side effects from the medications, whereas they are also told to avoid using alcohol. Warning or advising the patients not to drive, however, seems insufficient to prevent unsafe drivers from being on the road, as a recent study showed that, despite warnings regarding driving, the majority of patients who use psychotropic drugs reported they drive regularly.[88]

In the United Kingdom, although there are no specific regulations concerning chronic pain and treatment with opioids, it is forbidden in general to drive under the influence of opioids and any other substance, which might impair driving. The law, however, does not distinguish between illicit drugs and prescribed medicines. On notification of a physician of possible risk, every driving license holder has the duty to notify the Driver and Vehicle Licensing Agency (DVLA), about any medical condition … which may affect safe driving, including "prospective disability" (driving safety in the future). Although such conditions might be treated with analgesics such as opioids, they are not specifically mentioned by the DVLA. If such a patient surrenders his/her license, the DVLA will not make formal medical enquiries into driving fitness. If the patient is incapable of understanding the physician's advice to surrender his driving license to DVLA, physicians may also inform the agency.[89] Of note, if a patient is involved in an accident and it is found that his/her health condition was a contributing factor, the patient may be prosecuted and the insurance may not be valid.

In Germany, driving under the influence of "recreational or street" narcotics is a legal offence, whereas patients on opioids and other centrally acting drugs for medical reasons are excluded. However, physicians must inform every patient about potential risks when prescribing psychoactive drugs. When there are major concerns about driving fitness and a patient is not willing to refrain from driving, the physician may inform the public authority, which then will be in charge of further enquiries.[90] Much higher demands concerning medical conditions, use of psychoactive substances, and psychomotor and cognitive performance tests are required for professional car drivers such as truck and bus drivers in Germany and in the United Kingdom.

Given the substantial differences in regulations pertaining to driving and psychoactive drugs, a very recent project of 19 European countries (Driving under the Influence of Drugs, Alcohol and Medicines, 2010)[91] attempts to develop an empirically based classification and categorization system that allows consistent labeling of medicines with respect to their impact on driving. One major goal of the project is to harmonize the existing differences of national conditions and health care practices and to develop prescribing and dispensing guidelines for health care professionals.

In answering the question "Can patients on opioids drive"? our study suggests that indeed certain patients on pharmacologically stable doses of opioids are able to drive provided they (1) lack coprescriptions or other substance use (alcohol and illicit drugs) that may exert significant central nervous system effects, (2) do not experience high levels of pain, (3) lack a substantial sleep disorder or daytime somnolence, and (4) do not have significant depression or anxiety disorder or other diagnosable psychiatric condition. Unfortunately, it still remains unclear what level of "stable" opioids may be considered safe to drive (as studies comparing cognitive function or driving performance of chronic pain patients on moderate doses of opioids vs. high doses of opioids do not exist). We do acknowledge that many medications for medical conditions such as diabetes, high blood pressure, coronary artery disease, chronic sinusitis, or psychological or psychiatric conditions may affect driving safety but reporting on these individually is beyond the scope of this study.

A word of caution: systematic reviews such as this study, attempt to guide evidence-based medical practice. However, evidence-based medicine is "about tools, not about rules" and is not meant to take away expertise and judgment on behalf of the physician. We stress, therefore, that the prescribing physician ultimately should retain and exercise his/her judgment as each patient should be considered individually.

The results of our study resonate with the recent excellent review by Chapman et al.[92] These authors pointed out the need to show "effectiveness" of long-term opioid therapy in actual everyday practice, reiterated that opioid therapy is "usually embedded" in combination therapy and pointed out the great need for future studies relating to the

interaction of opioids with other medications, dietary supplements, alcohol, and licit or illicit drugs used recreationally as there is limited information to guide physicians concerned regarding chronic non cancer pain polypharmacy and nonopioid drug administration that may interfere with the assessment of opioid effectiveness and drug-drug interactions.

To assess the effects of opioids on driving in a population with chronic pain, future studies need to strive for balance between internal validity (risk of bias) and external validity (generalizability). Studies conducted with healthy volunteers, in experimental settings where pain is artificially induced have very little generalizability to the population where the results will be applied. Studies conducted in administrative databases are useful to raise hypothesis about association of opioids and traffic accidents, but they usually have very little information with regard to type of opioids, dose, route of administration, comorbidities, and co-interventions. Neuropsychological or related cognitive/psychomotor tests may provide useful surrogate measures of driving performance, but they need to be validated further, especially in "borderline" cases in which it is not a clear-cut decision about whether a person should or should not be driving. Driving simulators can vary in terms of visual and auditory input and sophistication, but a major problem is the high drop-out due to motion sickness. On-road driving tests are generally considered the gold standard for driving evaluation, but they may not simulate all situations faced in real driving and may not take into account various individual variables. We consider that the gold standard for the evaluation of driving risk is the incidence of actual traffic accidents involving opioid use. We have included a couple of such studies in the study and we have pointed out to some problems, as such studies may suffer from a decision about the risk versus benefits of allowing persons who are taking opioids to drive.

Future studies should look at the effects of opioids on driving as the primary research question, and use a study design that offers low risk of bias, such as a randomized, controlled trial with blinded outcome assessors, and analyses that take into consideration the most relevant confounders in this area. In addition, such studies should provide evidence that (1) the prescribed drug(s) are present and (2) there is absence of other nonprescribed legal or illegal substances, through confirmatory drug testing. Finally, studies with only short-acting opioids should also be considered, as in real life there are many patients who take 3 to 4 short-acting opioid preparations daily and can be very productive and manage their pain well. However, and until such studies can be conducted, the present systematic review offers some guidance to the practicing physicians at least in relationship to those patients on long-term opioid therapy who are fairly safe to drive.

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