Review Article

Are Opioid-Dependent/Tolerant Patients Impaired in Driving-Related Skills? A Structured Evidence-Based Review

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Abstract
Previous reviewers have concluded that opioids cause dose-related impairment in opioid-naive volunteers on psychomotor skills related to driving. Data relating to opioid-dependent/tolerant patients have not yet been reviewed. To determine what evidence, if any, exists for or against opioid-related driving skill impairment in opioid-dependent/tolerant patients, we performed a structured evidence-based review of all available studies addressing the issue of whether opioid-dependent/tolerant patients are impaired in driving-related skills. A computer and manual literature search for studies relating to opioid-dependent/tolerant patients and driving-related skills produced 48 relevant reports. These references were reviewed in detail, sorted, and placed into tabular form according to the following subject areas: (1) psychomotor abilities studies; (2) cognitive function studies; (3) effect of opioid dosing on psychomotor abilities studies; (4) motor vehicle driving violations and motor vehicle accident studies; and (5) driving impairment as measured in driving simulators and off/on road driving studies. For each topic area, each study was categorized for the type of study it represented according to guidelines developed by the Agency for Health Care Policy Research (AHCPR). The strength and consistency of the evidence in each subject area also then was categorized according to AHCPR guidelines and a quantitative method. This evidence-based review indicated the following: (1) There was moderate, generally consistent evidence for no impairment of psychomotor abilities of opioid-maintained patients; (2) There was inconclusive evidence on multiple studies for no impairment on cognitive function of opioid- maintained patients; (3) There was strong consistent evidence on multiple studies for no impairment of psychomotor abilities immediately after being given doses of opioids; (4) There was strong, consistent evidence for no greater incidence in motor vehicle violations/motor vehicle accidents versus comparable controls of opioid-maintained patients; and (5) There was consistent evidence for no impairment as measured in driving simulators off/on road driving of opioid-maintained patients. Based on the above results, it can be concluded that the majority of the reviewed

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studies appeared to indicate that opioids do not impair driving-related skills in opioid-dependent/tolerant patients. This evidence was consistent in four out of five research areas investigated, but inconclusive in one. As such, additional controlled studies are required. Until more data are available, however, physicians may wish to consider the approach to this problem recommended in this review. J Pain Symptom Manage 2003;25:559–577.

Key Words
Opioids, opiates, driving, cognitive impairment, psychomotor performance, opioid tolerance, structured review, evidence-based review, motor vehicle accidents, reaction times

Introduction

Driving performance is a complex multi-aspect task requiring mental alertness, visual, auditory and kinesthetic information processing, eye-hand coordination, and manual dexterity.[1] As such, most drugs that affect the central nervous system have the potential to impair driving.[2] Because opioid drugs are central nervous system depressants, some physicians have held the belief, mainly based on research with opioid-naive volunteers, that patients taking opioids should not drive.[3] This opinion, however, has been challenged by a number of researchers who cite evidence that patients taking stable opioid doses may drive safely and work.[4–8] This controversy has been growing in importance with the wide acceptance of chronic opioid treatment utilizing controlled-release opioids for cancer pain and chronic nonmalignant pain.[9] As potential instructions to stop driving to a patient utilizing opioids essentially dooms the patient to a life of disability, the answer to this controversy has widespread implications both for the patient and the medical practitioner.

The literature on the effect of opioids on driving performance has been reviewed by a number of researchers.[4,8,10–15] In the first early review, Gordon[15] concluded that the use of opioids in and of itself did not present a hazard or existed as a significant factor in automobile driving. In the second early review, Seppela et al.[10] reviewed the effects of all drugs on driving performance. Opioids received a cursory review. Seppela et al.[10] indicated that in laboratory studies with volunteers, opioids appeared to impair skills related to driving, while in clinical tests, opioids did not necessarily do so. In the third cursory review, Joo[4] reviewed some of the literature on methadone maintenance patients and driving ability and solicited the opinions of an expert panel on the subject. She reported that her panel of experts had concluded that methadone maintenance patients were fit to drive, but that driver fitness should be checked in every case.[4] In the fourth report, Payne[12] reviewed a limited number of studies on the effects of opioids on cognitive function and the impact of this problem on work. He concluded that the studies regarding neuropsychological functioning were contradictory,[12] but that the majority of studies indicated that chronic exposure to opioid analgesics had few deleterious effects on cognitive and motor function. No specific conclusions in reference to driving were drawn.[12]

Chesher[8] was the first to specifically review the literature relating to analgesic drugs and driving. He concluded that the number of opioid users was relatively small and that their involvement in road crashes should not be a source of significant concern.[8] However, he also concluded that there was an abundance of pharmacological evidence to suggest that the interaction between the opioid drugs and alcohol is of significance.[8] In the next recent report, Roth et al.[13] reviewed issues on drug related performance impairment. They listed drug groups that impair performance; opioids were not listed as a group that impair performance.[13] In another recent review, O'Neill[14] concluded that opioids do have an effect on cognitive and psychomotor function. O'Neill[14] also concluded that many of these effects diminish once the patient is on a stable dose, but that the evidence suggested that baseline pretreatment levels were not achieved. In another recent and complete review, Zacny,[11] reviewed the lines of evidence relating to two questions: Do opioids

cause a dose-related impairment in opioid-naive volunteers on psychomotor tests thought to be important to driving and is the degree of impairment related to concentrations of the opioid? He concluded that opioids do impair performance depending on the particular opioid, dose involved, the population studied, and the length of opioid use.[11] He also concluded that opioids that are most likely to be taken for pain relief or heroin pharmacotherapy do not cause marked cognitive or psychomotor impairment.[5,11] The most recent review was by Fishbain et al.[16] Here, Fishbain et al.[16] reviewed the evidence for a possible association between opioid use and intoxicated driving, motor vehicle accidents (MVA), and MVA fatalities. Little evidence for an association was found.[16]

There have been no reviews specifically aimed at answering the following questions: Do opioids affect driving abilities of patients who are on stable doses of opioids or who would be presumed to have developed some tolerance to the sedative effects of opioids? This question is important to chronic opioid pain treatment in cancer pain and chronic nonmalignant pain. The purposes of the present structured, evidence-based review (which is not a meta-analysis) was then the following: To review the scientific evidence relating to the above question and to evaluate the strength of that evidence through an evidence-based structured review process utilizing the Agency for Health Care Policy and Research (AHCPR) categories[17] for review of research evidence.

Methods

Relevant references were located by the following procedure. Medline, Psychological Abstracts, Science Citation Index, and the National Library of Medicine Physician Data Query (PDQ) databases were reviewed utilizing the following seven subject headings: cognitive impairment, driving, reaction times, drunk driving, neuropsychological performance, motor vehicle accidents, and psychomotor performance. Each of these was exploded with the following Medical Subject Headings (MeSH): Analgesics, narcotics, opioids, opiates. Each term was exploded for all subheadings in MeSH. All retrieved references were reviewed. The searches were not restricted to the English language. Any non-English language reports if necessary were reviewed with the help of interpreters. Searches were conducted back to 1966, except for Science Citation Index, which was conducted to back to 1974. All searches were conducted through 2001 if possible. A manual search was also done on cited references in the retrieved articles, key journals, pain meeting abstracts, and textbooks. For the following journals, the following years were reviewed: *Pain*, 1975–2001; *Spine*, 1976–2001; *Journal of Pain and Symptom Management*, 1986–2001; *The Pain Clinic*, 1986–2001; and *The Clinical Journal of Pain*, 1985–2001. Abstract books of the following meetings were reviewed for the following years: *International Association for the Study of Pain*, 1981, 1984, 1987, 1990, 1993, 1996, and 1999; and *American Pain Society Meetings*, 1982–2001. Three pain textbooks were reviewed for possible references. These were *Evaluation and Treatment of Chronic Pain, Third Edition*, G. Aronoff, ed., 1999; *Handbook of Pain Management, Second Edition*, C.D. Tollison, J.R. Satterthwaite, J.W. Tollison, eds., 1994; and *Textbook of Pain, Third Edition*, P. Wall, R. Melzack, eds., 1993. In addition, a chapter entitled "A review of the effects of analgesics on driving performance" (G.A. Starmer, pages 251–269), from a book entitled *Drugs and Driving* (J.F. O'Hanlon, J.J. de Grer, eds., Taylor and Francis, London and Philadelphia, 1986) was reviewed.

Two hundred and nine references were isolated in this manner and were subject to a cursory review. In addition, studies were obtained through the review process. Of all these studies, studies that could be construed to address driving abilities of patients who were on stable doses of opioids were isolated. These were 48 studies,[18–65] which were reviewed in detail.

Generally tests utilized to measure drug-related driving performance impairment break down into five areas:[66] visual processing, attention, psychomotor abilities, postural balance, and cognitive function. As such, these 48 references broke down naturally into the following topic areas: psychomotor abilities studies on opioid maintained patients; cognitive function studies on opioid-maintained patients; studies on effects of new opioid dosing on psychomotor abilities of opioid-maintained patients, motor vehicle violations and motor vehicle accident studies of opioid-maintained

patients; and driving impairments as measured in driving simulators and off-road driving studies on opioid-maintained patients. Thus, these 48 studies were grouped into tables organized according to these topic areas. Some of the above studies addressed a number of topic areas or addressed the topic area in more than one way. As such, some of these studies[21,23,25,26,33,45,47,48,56,65] were utilized more than once. These studies are highlighted with asterisks in the tables. Data for each table, in each topic area, were abstracted from each study according to the following format: Reference numbers, research question, study design, sample size, statistical analysis, results, categorization of type of evidence the study represented (according to Appendix A), and reviewer's comments. The categorization for the type of evidence each study represented was based on guidelines developed by the Agency for Health Care Policy and Research (AHCPR) for categorizing the levels of evidence represented by the reviewed studies.[17] These categories are presented in the Appendix A. Studies were categorized as 1 through 5 according to these categories. Here, "I" represents a meta-analysis of well-designed controlled studies and "V" represents a case report or clinical example. Category B (Appendix B), also developed by the AHCPR,[17] were then used to categorize the strength and consistency of the research evidence in each group of studies in each table, utilizing all the scale A categorizations for that grouping. It is to be noted that, as this study is not a meta-analysis, the data were abstracted into tabular form by the senior author only. No coding techniques were utilized and study quality was not rated. Only data pertaining to the problem area were abstracted. As the AHCPR categories are objective in nature, requiring no interpretation, the senior author was the only researcher to identify the type of study each study represented according to categories A, and to identify the strength/consistency of the evidence represented by each group of studies according to Categories B. In addition, because the AHCPR categories B are not quantitative as to whether findings are consistent, it was decided to also utilize a quantitative method previously utilized by Linton[67] and others.[68,69] This method is as follows:

(a) >>75% of the studies support hypothesis: strong evidence, consistent findings;
(b) >>50% of the studies support hypothesis: moderate evidence, generally consistent findings;
(c) >>50% of the studies support hypothesis: inconclusive evidence.

Results

Table 1 presents the 22 studies,[18–33,46–48,56,59,64] one of which[25] was utilized more than once for a total of 23 reports on this topic area. Of the 22 studies in this group, one reference[21] represented Type IV evidence, and all the rest[18–20,22–33,46–48,56,59,64] Type III evidence. Of the 23 reports, seven or 30.4%, found that patients on stable opioid doses had some impairment of psychomotor abilities. The other 16 reports[18,19,21–23,25–28,32,33,48,56,59,64] or 69.6% did not. Based on these observations and according to the AHCPR Guidelines, the consistency of this evidence for no impairment in psychomotor abilities was categorized as B. By the quantitative method described above, as 69.6% of the studies supported no effect of psychomotor abilities, this indicated moderate, generally consistent evidence.

Table 2 presents 11 studies.[21,26,33–36,47,48,55–57] Of the 11 studies in this group, two,[21,36] represented Type IV evidence, and nine[26,33–35,47,48,55–57] represented Type III evidence. Of the 11 studies, five[21,33,34,48,55] or 45.4% found that patients on stable opioid doses had no impairment in cognitive abilities. Of these five reports, one[21] was a Type IV, the rest being Type III. Based on these observations, and according to the AHCPR Guidelines, the consistency of this evidence for no impairment on cognitive function was categorized at C. By quantitative method described above, as only 45.4% of the studies supported no effect on cognitive function, this indicated inconclusive evidence.

Table 3 presents 15 studies.[23,37–39,49–54,58,60–63] Four of these[23,37–39] represented Type III evidence. The rest (twelve) represented Type II evidence. Of these 15 studies, only one[62] indicated that acute administration of opioids to opioid-maintained patients would affect psychomotor abilities. The rest (14) indicated no effect. Based on these observations and according to the AHCPR guidelines, the consistency of this evidence for no impairment of psychomotor abilities on acute opioid administration was A. By the quantitative method

Table 1
Psychomotor Abilities of Opioid Maintenance Patients

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Appel, 1982[18]	Do high-dose methadone PTs have impaired RTs measured by CPT?	Methadone PTs, ex-heroin addicts, opioid-naïve individuals compared on CPT.	48 M 24 Ex 24 N	Chi-square.	Groups did not differ in accuracy, response, latency, or commission errors.	III	Methadone PTs do not have impaired CPT.
Gordon, 1970[19]	Do methadone maintenance PTs have impaired psychomotor abilities?	Volunteers, methadone maintenance PTs, and addicts who had recently withdrawn from opioids; RT measured.	27 M 29 V 29(W)	Chi-square.	Methadone maintenance PTs had shortest RT.	III	Methadone maintenance PTs do not have impaired psychomotor abilities.
Banning, 1990[20]	Are CRTs impaired in cancer PTs on stable opioid doses?	Cancer PTs on stable opioid doses compared to no opioid controls for CRTs.	34 PTs 32 C	Mann-Whitney Rank Sum. Test.	CRTs prolonged in opioid group.	III	Cancer PTs on opioid have impaired CRTs.
Sjøgren, 2000[46]	Are CRTs impaired in cancer PTs on stable opioids?	Cancer PTs on stable opioids compared for CRTs to cancer PTs without opioids.	90 PTs 40 C	Mann-Whitney Rank Sum. Test.	CRTs faster in control group.	III	Cancer PTs on opioids have impaired CRTs.
Rossler, 1993[21a]	Are RTs impaired in methadone PTs?	Methadone PTs tested for RTs.	34 M	None.	No PTs had RTs in abnormal range.	IV	Methadone PTs have normal RTs.
Sjøgren, 1989[22]	Are CRTs affected by chronic opioid therapy?	Cancer PTs CRTs measured before and after initiation of the chronic opioid therapy and compared?	14	Chi-square.	No statistically significant difference?	III	Chronic opioid therapy does not affect CRTs.
Rothenberg, 1977[23a]	Are visual RTs affected by chronic opioid therapy?	Methadone PTs compared to opioid-free controls.	16 M 12 C	ANOVA	Methadone PTs faster than controls.	III	Methadone PTs do not have impaired RTs and are even faster than controls.
Sjøgren, 1994[24]	Are auditory RTs affected by chronic opioid therapy in cancer PTs?	Cancer PTs on chronic opioid treatment compared to healthy individuals without opioids.	53 44 C	ANOVA	Healthy individuals faster than cancer PTs.	III	Cancer PTs on opioids have impaired auditory RTs.
Moskowitz, 1985[25a]	Is pursuit tracking impaired in methadone PTs?	Methadone PTs compared to drug-free ex-heroin addicts for pursuit tracking skills.	12 M 12 C	Chi-square.	No differences between the two groups.	III	Pursuit tracking not impaired in methadone PTs.
Moskowitz, 1985[25a]	Is critical tracking impaired in methadone PTs?	Methadone PTs compared to drug-free ex-heroin addicts for critical tracking.	15 M 15 C	ANOVA	No difference between groups found.	III	Critical tracking not impaired in methadone PTs.
Robinson, 1985[26a]	Does methadone maintenance affect central visual processing?	Methadone PTs compared to drug-free ex-heroin addicts.	15 M 16 C	ANOVA	No difference between groups.	III	Central visual processing not impaired in methadone PTs.

(continued)

Table 1
Continued

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Specka, 2000[27]	Do methadone PTs have slower RTs?	Methadone PTs compared to drug-free age/sex/educational status matched controls for RTs?	54 M 54 C	ANOVA	Methadone PTs slower.	III	Methadone PTs slower; however, majority variance better explained by sociodemographic features.
Appel, 1976[28]	Do methadone PTs have slower RTs?	Methadone PTs compared to former opiate (FOC) consumers and healthy controls for multiple choice RTs (age controlled for).	48 M 24 FOC 24 C	Regression analysis.	Methadone PTs faster.	III	Methadone PTs have normal RTs.
Gerhard, 1989[29]	Do methadone PTs have slower RTs?	Methadone PTs compared to healthy controls (policemen and firemen- not age matched).	23 M 29 C	Regression analysis.	Controls faster.	III	Methadone PTs have lower RTs.
Stack, 1993[30]	Do methadone PTs have slower RTs?	Methadone PTs compared to age/sex/educational status matched controls.	13 M 13 C	Regression analysis.	Controls faster.	III	Methadone PTs have lower RTs.
Hornung, 1996[31]	Do methadone PTs have slower RTs?	Methadone PTs. Utilizing other drugs compared to age/sex/educational status matched controls.	20 M 20 C	Regression analysis.	Controls faster.	III	Methadone PTs have lower RTs.
Kubitzki, 1997[32]	Do methadone PTs have slower RTs?	Methadone PTs. Utilizing other drugs compared to age/gender/educational status matched controls.	20 M 20 C	Regression analysis.	Equal speed.	III	Methadone PTs have normal RTs.
Sjøgren, 2000[47a]	Are RTs impaired in CNP PTs maintained on opioids?	CNP PTs maintained on opioids compared to healthy controls on test of RT.	40 40 C	Chi-square.	RT tests impaired in CNP PTs on opioids.	III	RT impaired in CNP PTs on opioids.
Haythornthwaite, 1988[48a]	Are CNP PTs psychomotor abilities impaired by being put on opioids?	CPPs placed on chronic opioid treatment; subjected to psychomotor tests pre- and post; non-treatment CNP PTs used as controls.	19 10 C	ANOVA	Measures of psychomotor speed and attention improved.	III	Psychomotor speed improved.
Vainio, 1995[33a]	Do cancer PTs on stable opioid doses show psychomotor impairment versus cancer PTs not on opioids?	Cancer PTs on stable doses of opioids compared to cancer PTs not on opioids on psychomotor tests.	24 25 C	Chi-square.	No difference between groups on vigilance, concentration, motor reaction, or attention or RTs.	III	No impairment psychomotor abilities.

(continued)

Table 1
Continued

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Gritz, 1975[56a]	Do methadone PTs show psychomotor impairment versus former addicts?	Methadone PTs compared to former addicts on Digit Symbol Substitution test and Cross-out test.	10 M 10 FA	ANOVA	No difference between groups.	III	No impairment psychomotor abilities.
Lodemann, 1995[59]	Do methadone PTs show psychomotor impairment versus controls?	Methadone PTs compared to controls on 3 psychomotor tests.	34 M	Chi-square.	No difference between groups.	III	Methadone PTs not different.
Staak, 1993[64]	Do methadone PTs show psychomotor impairment versus age, sex, and education matched controls?	Methadone PTs compared to controls on 7 psychomotor tests.	6 M 13 C	Chi-square.	No difference between groups.	III	Methadone PTs not different, however, only 17.6% of PTs were fit to drive because of concomitant drug use.

RT = Reaction Times; CPT = Continuous Performance Tests; PTs = Patients; CRTs = Continuous Reaction Times; CNP = Chronic Nonmalignan Pain; M = Methadone; FA = Former Addicts; ANOVA = Analysis of Variance.
[a] = Studies utilized more than once.

described above, as 93.3% of the studies supported no effect on psychomotor function, this indicated strong evidence, consistent findings.

Table 4 presents four studies,[40–42,65] which were all Type III. Of the seven reports, six or 85.7% found that patients on stable opioids had no more motor vehicle violations, convictions, and motor vehicle accidents than the comparable general population. Based on these observations and according to the AHCPR Guidelines, the consistency of this evidence for no more motor vehicle violations and convictions than the comparable population was categorized as B. By the quantitative method described above, as 85.7% of the studies supported no effect on motor vehicle convictions/motor vehicle violations/motor vehicle accidents, this indicated strong evidence, consisted findings.

Table 5 presents three studies.[43–45] All studies in this group represented Type II evidence. Of the four reports, three,[44,45,45] or 75%, found that patients on stable opioids did not demonstrate impairments on driving measures in driving simulators or off-on road driving as compared to controls. Based on these observations and according to the AHCPR Guidelines, the consistency of this evidence for no impairment was categorized as B. By the quantitative method described above, as 75% of the reports supported no effect for driving simulators or off/on road driving, this indicated strong evidence, consistent findings.

Discussion

This structured review has attempted to critically examine the available study evidence on the question of whether opioids affect driving abilities of patients who are on stable doses of opioids and who would be presumed to have developed some tolerance to the sedative effects of opioids. Different lines of evidence (Tables 1 through 5) relating to this question were reviewed with the following results. The majority of the reviewed studies (69.6%) indicated that opioids do not impair psychomotor abilities (Table 1) in opioid-dependent patients. According to the AHCPR guidelines, this evidence was generally consistent (B). By the quantitative method, this was considered moderate evidence, generally consistent. The evidence

Table 2
Cognitive Function of Opioid Maintenance Patients

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Robinson, 1985[26a]	Does methadone maintenance affect information processing (immediate memory to short-term memory)?	Methadone PTs compared to controls on cognitive function tests.	12 M 12 C	ANOVA	Difference between groups.	III	Methadone affects information processing.
Lombardo, 1976[34]	Is cognitive function affected by stable methadone doses?	Methadone PTs on 80 mg and 50 mg/day compared on the Wechsler Adult Intelligence Scale (WAIS).	18 M 20 M	ANOVA	No difference on subset scales of WAIS between two groups.	III	Methadone does not affect cognitive function.
Haythornthwaite 1998[48a]	Are CPPs' cognitive abilities impaired by being put on opioid maintenance treatment?	CPPs placed on opioid maintenance treatment; subjected to cognitive test pre- and post; results compared; non-treatment CPPs used as control group.	19 PTs 10 C	ANOVA	Cognitive abilities remained stable pre to post opioids with few differences in treatment group and controls.	III	CPP placement on chronic opioid treatment does not appear to negatively affect measured cognitive abilities pre- and post-testing.
Clemons, 1996[35]	Are there changes in alertness and cognition in cancer PTs placed on chronic opioid treatment?	Cancer PTs on opioids, opioid-free cancer PTs and healthy volunteers compared on various neuropsychological measures including RTs.	7(O) 6(NO-O) 16 C	ANOVA	No differences between two cancer groups but differences between cancer groups and controls.	III	Alertness in cancer PTs most affected by the disease itself.
Rossler, 1993[21a]	Are methadone PTs' cognitive function affected to preclude them from driving?	Methadone PTs tested for verbal memory, visual memory and attention concentration.	34 M	None.	No PTs assessed as being unable to drive.	IV	Methadone does not affect cognitive function.
Sjøgren, 2000[47a]	Does chronic opioid treatment affect neuropsychological status?	CPPs on long-term opioid therapy compared to healthy volunteers on PASAT.	40 40 L	Chi-square.	PASAT impaired in CPPs.	III	Opioids affect cognitive function.

(continued)

Table 2
Continued

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Wood, 1998[36]	Is cognitive function of opioid maintenance PTs affected?	Opioid maintenance hospice PTs completed various cognitive function tests.	18	None.	Current intellectual function, delayed recall, trail making below normal values.	IV	Subtle cognitive functions affected.
Vainio, 1995[33]	Do cancer PTs on stable maintenance doses of opioids show cognitive impairment versus PTs not on opioids?	Cancer PTs on stable doses of opioids compared to cancer PTs not on opioids on cognitive performance tests.	24 25 C	Chi-square.	All cognitive tests similar between groups.	III	Cancer PTs on stable opioid doses show no cognitive impairment.
Moulin, 1996[55]	Is cognitive function of CPPs affected by being placed on opioids?	CPPs completed a high sensitivity cognitive screen pre- and post placement on chronic opioid treatment, control group also utilized.	46 PTs 46 Placebo	ANOVA	No difference cognitive function pre- to post- and to control group.	III	Cognitive abilities not affected pre and post testing.
Gritz, 1975[56a]	Is cognitive function of methadone PTs impaired versus FA?	Methadone PTs and FA compared on cognitive function tests.	10 M 10 FA	ANOVA	Cognitive function affected on a small number of tests.	III	Cognitive abilities subtly affected.
Darke, 2000[57]	Is cognitive function of methadone PTs impaired versus controls?	Methadone PTs and age, gender, and education matched controls compared on cognitive function tests.	30 M 30 C	T-Tests.	All cognitive tests lower in methadone PTs.	III	Cognitive abilities affected. However, methadone PTs had greater frequency alcohol history, overdose history and psychiatric comorbidity.

PTs = Patients; WAIS = Wechsler Adult Intelligence Scale; CPPs = Chronic Pain Patients; PASAT = Paced Auditory Addition Tasks; FA = Former Addicts; M = Methadone.
[a] = Studies utilized more than once.

Table 3
Do New Opioid Doses Affect Psychomotor Abilities in Opioid-Maintained Patients?

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Kelley, 1978[37]	Are perceptual motor capabilities in methadone maintenance PTs affected by methadone doses?	Perceptual motor capabilities measured at 24 hours after methadone ingestion.	30	Multi-variable Analysis.	No treatment effect for auditory threshold, simple RT, time perception, and digit span.	III	No effect opioids in opioid dependent PTs on perceptual motor capabilities.
Rothenberg, 1977[23a]	Are visual RTs in methadone PTs affected by additional methadone doses?	Visual RTs measured pre and post additional doses methadone.	16	ANOVA	No significant decrease in visual RT.	III	No effect opioids in opioid dependent PTs on visual RTs.
Strain, 1997[38]	Are psychomotor/ cognitive performance measures of buprenorphine PTs affected by additional doses of buprenorphine or hydromorphone?	PTs on buprenorphine completed recall memory and digit symbol substitution tasks pre- and post-addition IM opioid.	8	ANOVA	None of the drug conditions produced significant effects on psycho/motor/ cognitive performance tasks.	III	No effect opioids in opioid dependent PTs on cognitive performance measures.
Bruera, 1989[39]	Are psychomotor/cognitive performance measures of cancer PTs on stable doses of opioids affected by their usual doses?	PTs on stable doses of opioids completed tests of psycho/motor/ cognitive function once before usual dosage and once 45 minutes after.	20	Paired T-test.	No difference except for drowsiness.	III	No effect opioids in opioid dependent PTs on cognitive/ psychomotor performance.
Preston, 1987[49]	Is psychomotor performance impaired in methadone PTs on exposure to additional opioid (hydromorphone)?	Psychomotor abilities via digit symbol substitution tests on IM opioid compared to IM placebo.	5	Repeated measures ANOVA.	No difference for psychomotor abilities.	II	Placebo controlled.
Preston, 1988[50]	Is psychomotor performance impaired in methadone PTs on exposure to additional opioid (hydromorphone and butorphanol)?	Psychomotor abilities on IM opioids compared to placebo.	5	ANOVA	No difference for psychomotor abilities.	II	Placebo controlled.
Preston, 1989[51]	Is psychomotor performance impaired in methadone PTs on exposure to additional opioid (hydromorphone, nalbuphine)?	Psychomotor abilities on IM opioids compared to placebo.	5	Repeated measures ANOVA.	No difference on psychomotor abilities.	II	Placebo controlled.

(continued)

Table 3
Continued

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Strain, 1992[52]	Is psychomotor performance impaired in methadone PTs on exposure to additional opioid (hydromorphone, buprenorphine)?	Psychomotor abilities on IM opioids compared to placebo.	6	Repeated measures ANOVA.	No difference on psychomotor abilities.	II	Placebo controlled.
Strain, 1995[53]	Is psychomotor performance impaired in methadone PTs on exposure to additional opioid (hydromorphone, buprenorphine)?	Psychomotor abilities on IM opioids compared to placebo.	7	Repeated measures ANOVA.	No difference on psychomotor abilities.	II	Placebo controlled.
Strain, 2002[54]	Is psychomotor performance impaired in buprenorphine PTs on exposure to additional opioid (hydromorphone)?	Psychomotor abilities on IM opioids compared to placebo.	6	Repeated measures ANOVA.	No difference on psychomotor abilities.	II	Placebo controlled.
Comer, 1997[58]	Is psychomotor performance impaired in morphine PTs on exposure to additional opioid (IN heroin)?	Psychomotor performance on IN opioids compared to placebo.	5	Repeated measures ANOVA.	Psychomotor abilities on 2 out of 4 tests affected, but only on highest dose heroin (100 mg).	II	Placebo controlled.
Preston, 1988[60]	Is psychomotor performance impaired in PTs on exposure to additional opioid (SC) hydromorphone, and buprenorphene?	Psychomotor performance on SC opioids compared to placebo on 2 psychomotor/ cognitive tests.	6	Repeated measures ANOVA.	None of drug conditions had significant effects.	II	Placebo controlled.
Preston, 1989[61]	Is psychomotor performance impaired by exposure to hydromorphone in PTs who are post addicts?	Psychomotor performance on IM opioids compared to placebo on one psychomotor test.	6	Repeated measures ANOVA.	Drug did not impair psychomotor performance.	II	Placebo controlled.
Pickworth, 1993[62]	Is psychomotor performance impaired by exposure to buprenorphine in PTs who are post addicts?	Psychomotor performance on IV opioids compared to placebo on one psychomotor test.	6	Repeated measures ANOVA.	Drug caused a slight decrease in response rate.	II	Placebo controlled.
Preston, 1992[63]	Is psychomotor performance impaired by exposure to hydromorphone in PTs who are post addicts?	Psychomotor performance on IM opioids compared to placebo on one psychomotor test.	4	Repeated measures ANOVA.	Drug did not impair psychomotor performance.	II	Placebo controlled.

PTs = Patients; RTs = Reaction times; IM = Intramuscular; IN = Intranasal; SC = Subcutaneous.
[a] = Studies utilized more than once.

Table 4

Are Individuals on Stable Opioid Doses More Likely to Have More Convictions for Motor Vehicle Violations and/or Motor Vehicle Accidents?

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Blomberg, 1974[40]	Do methadone maintenance PTs have more convictions for motor vehicle violations (speeding, reckless driving, disobeying traffic signals, etc.) versus controls?	Methadone maintenance PTs' driver's abstracts compared to controls for serious motor vehicle violations.	718 579 C	Chi-square.	No statistically significant differences.	III	Motor vehicle convictions do not differ between methadone maintenance PTs and controls.
Blomberg, 1974[40a]	Are MVA more frequent in methadone maintenance group than for comparable controls?	PTs from methadone treatment programs (at least 6 months) compared to a comparable control group for MVA in New York.	718 579 C	Chi-square.	No statistically significant difference in % MVA.	III	MVA rates similar in methadone maintenance PTs and controls.
Blomberg, 1974[40a]	Is the MVA rate (mile driven per year for drivers involved in MVA) for New York State different from that of methadone maintenance PTs?	PTs from methadone treatment programs (at least six months); their MVA rate was calculated and compared to the MVA rate for New York State drivers.	718 PTs	Chi-square.	MVA rate no different from New York State drivers.	III	MVA rates similar in methadone maintenance PTs and controls.
Maddux, 1977[41]	Is methadone maintenance associated with MVA in Texas?	Driving records of methadone maintenance PTs examined for MVA after entrance into methadone program; compared to all Texas drivers.	104	Compared statistically to expected frequency.	Did not differ statistically from expected frequency.	III	Opioid use (methadone maintenance) not associated greater frequency MVA.
Babst, 1973[42]	Are MVA and driving infractions conviction rates greater for methadone maintenance PTs than for a comparable control group?	PTs in a methadone treatment program (at least six months) matched to their driving records (1/65–9/69); compared to randomly selected New York drivers for accidents and driving conviction rates.	448 182 drivers	Chi-square.	Rates similar for 30+ and ≪24 year olds; marginally greater for 25–29-year-old methadone PTs.	III	Accident and driving conviction rates similar in methadone maintenance PTs to controls.

(continued)

Table 4
Continued

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Smart, 1976[65]	Are MVA greater for high school students who use opioids vs. a comparable control group?	High school students who admitted to using opioids (questionnaire) compared for MVA to a comparison group who had not used opioids.	1558 students, 685 non-users 25 users.	Chi-square.	Significant difference users vs. non-users.	III	Accident rate greater users.
Smart, 1976[65]	Are driving offenses greater for high school students who use opioids vs. a comparable control group?	High school students who admitted to using opioids (by questionnaire) compared to a comparison group who had not used opioids for driving offenses.	1558 students, 685 non-users 25 users.	Chi-square.	No significant difference.	III	No difference driving offenses.

PTs = Patients; MVA = Motor Vehicle Accidents.
[a] = Studies utilized more than once.

for no effect of opioids on cognitive function was less persuasive. Here only 45.4% of the studies indicated no effect. According to the AHCPR guidelines, this evidence was inconsistent (C). By the quantitative method, this was considered inconclusive evidence. The evidence in Table 3, however, on the effects of usual or additional opioid doses on psychomotor abilities in opioid-dependent patients was extremely consistent. Because there were multiple studies, of which 93.3% indicated no opioid effect, this evidence was categorized as A according to the AHCPR guidelines. By the quantitative method, this evidence was categorized as strong and consistent. Similarly, data from Table 4 was also extremely consistent, categorized as (B) according to the AHCPR guidelines, and as strong and consistent by the quantitative method. These data indicated that opioid-dependent patients did not appear to have a greater incidence of motor vehicle violations and/or motor vehicle accidents than the general population. Table 5 summarizes the study evidence from driving simulators and actual off/on road driving. Here, 75% of the studies indicated that opioids did not impair driving performance. This evidence was categorized as (B) by the AHCPR guidelines and as strong and consistent by the quantitative method. Overall, the majority of the studies in these five different lines of evidence appear to indicate that opioid-dependent patients are not impaired by opioids in reference to driving skills. This evidence was not consistent in only one line of evidence. Conversely, there appear to be no consistent evidence that opioid-dependent patients are impaired by opioids in reference to driving skills.

Why is the evidence in the cognitive impairment studies inconsistent (Table 2)? The literature provides some clues. It is to be noted that the studies in these tables relate to three groups of patients: methadone maintained patients who were former heroin addicts,[21,26,34,56,57] chronic pain cancer patients,[33,35,36] and chronic nonmalignant pain patients.[47,48,55] The first possible reason for this problem relates to the issue of unrelieved pain. There is strong study evidence[46–48,70] that unrelieved pain may decrease psychomotor cognitive performance. It is interesting that contrary to the above data, some researchers have considered pain to be a "natural antagonist" to opioid-related psychomotor/cognitive impairment.[11,71,72] Perhaps there is a

Table 5
Do Patients on Stable Opioid Doses Demonstrate Driving Impairments, as Measured in a Driving Simulator, Once Off/On Road Driving?

Author(s), Year	Research Question	Study Design	Sample Size	Statistical Analysis	Results	Type of Evidence	Reviewer's Comments
Bergnaus, 1993[43]	Do methadone PTs demonstrate driving impairments as measured in a driving simulator?	Methadone maintenance PTs compared to opioid free controls for driving performance in a driving simulation situation.	13 13 C	Chi-square.	Methadone PTs yielded poorer results on all performance tests.	II	Performance poorer than control group.
Galsky, 2000[44]	Do COAT PTs demonstrate driving impairments as measured in a driving simulator?	COAT PTs performance in a driving simulator compared to cerebrally compromised PTs who had undergone the driving simulation and had gone on to pass ($n = 162$) or fail ($n = 165$) in on-road behind-the-wheel evaluation.	16 327 C	ANOVA	COAT PTs as a group outperformed the control group.	II	Performance better than control group.
Chapman, 2001[45a]	Do COAT PTs demonstrate driving impairments as measured in a driving simulator?	COAT PTs' performance in a driving simulator compared to CPPs (not on opioids) and PTs without pain (pain PTs matched for age).	17 13 CPPs 49 C	?	No difference groups.	II	Performance same as controls.
Chapman, 2001[45a]	Do COAT PTs demonstrate driving impairments as measured in actual road driving?	Coat PTs' performance on actual road driving compared to CPPs (not on opioids) and PTs without pain (PTs matched for age.)	17 13 CPPs 49 C	?	No difference groups.	II	Performance same as controls.

PTs = Patients; COAT = Chronic Opioid Analgesic Therapy.
[a] = Studies utilized more than once.

bell-shaped curve here with lower levels of pain being a "natural antagonist" to sedation with higher levels of pain interfering with psychomotor/cognitive function. In any case, because only two of the studies[47,48] in Table 2 controlled for pain, the results emanating from some of the cancer studies in this table could be suspect. Another confounder to the studies in Table 2 and some studies in Table 3 could have been that of educational level. Educational level has been shown to better correlate with measures of neuropsychological function than current or past levels of opioid use.[27,73] None of the studies in Tables 2 or 3 controlled for educational level. As such, this problem could have confounded the results of these studies. Another confounder in the studies utilizing cancer patients in Tables 1, 2, and 3 was that of the disease state. Recent evidence indicates that in cancer patients utilizing opioids, the disease itself has the greatest impact on alertness.[35] None of the cancer patient studies in Tables 1 through 3 controlled for disease-associated symptoms, such as fatigue. As such, this could have been a significant confounder. Another potential confounder to the studies where drug addicts were utilized (Tables 1 through 4) was that of associated non-opioid drug abuse history. It has been demonstrated[74] that drug abusers with a history of alcohol dependence/abuse and/or polysubstance dependence/abuse have greater neuropsychological impairment than cocaine dependence/abuse addicts, who in turn will have greater impairment than controls. Thus, the type of previous drug abuse/dependence is potentially important to the severity of the neuropsychological impairment. This could have impacted on the studies in Table 2. Other types of drug abuse/dependence are usually comorbidly associated with opioid drug abuse/dependence.[74] As such, in neuropsychological studies where opioid abuse/dependence subjects are utilized, it is important to control for an associated history of nonopioid drug abuse/dependence. This was not done in studies in Tables 1, 2, 3, and 4. As such, this could have confounded the results of these studies. The above issues could, therefore, be a potential explanation for the inconsistent data presented by the studies in Table 2. At the same time, these issues could have confounded the results of some of the studies in Tables 1, 3 and 4.

As pointed out in the Introduction, driving a motor vehicle is a complex task requiring mental alertness, visual, auditory, and kinesthetic information processing, eye-hand coordination, and manual dexterity.[1] Blanke et al.[2] have claimed that tests of combined cognitive and motor function presumed to be pertinent to skills associated with driving are usually novel to the subject and, as such, do not represent driving well, which is usually an over-learned behavior. This critique may be unwarranted, however, as there is an absence of data that within the same study there is no correlation between these. Laboratory studies may in turn be compromised by poor subject selection, poor trial design and limited validity of the chosen tests.[10] Some of these last problems were discussed above. Thus, the most relevant evidence as to whether opioid tolerant patients should or should not be allowed to drive may be that found in Table 5. Here there is relatively consistent data that opioid tolerant patients appear to perform driving skills as well as controls.

Another issue relates to how the research in Tables 1 through 5 can be improved. Recommendations for improvement relate to the possible cofounders presented above. Thus, future psychomotor and cognitive studies should control for pain, educational status, and history of drug/alcohol abuse/dependence, besides controlling for sex and age. In addition, these studies probably can be improved by utilizing different types of control groups. Typically, in the reviewed studies, a treatment group (patients placed on opioids) is compared to controls (patients not on opioids). However, this often leads to a situation where the effects of the patient's disease state, e.g., cancer (fatigue, etc.), pain, etc. are not controlled for. Thus, a better control group could be to utilize the patient as his/her own control. As such, psychomotor and cognitive studies should be performed pre-opioid placement and post-opioid placement and compared. Of all the reviewed studies, there were only three[22,23,39] that utilized this type of control. Interestingly, all three found no opioid effect on cognition or psychomotor abilities. Another possible improvement to this type of research is to include a patient control group. For example, an additional control group when comparing cancer patients placed on opioids to nonpatient opioid-free controls would be to add a cancer patient opioid-free control group. A number of

studies[18,19,28,35,45] have utilized this approach, with some success. The use of this type of control group has demonstrated that the disease state of the patient can affect cognitive and psychomotor performance.[35] A final improvement to these studies has been suggested by Zacny.[11] He has advocated the use of positive controls as a benchmark. Here patients would be given drugs, such as diazepam, that are known to affect cognitive and psychomotor performance. Opioid effects then would not only be compared to opioid-free controls, but to this positive control group. Such a design has the advantage of comparing opioid impairment, if any, to a benchmark.

The majority of the reviewed studies indicated that opioids appear not to impair driving-related skills in opioid-dependent patients. However, some of this evidence is inconsistent (Table 2). As such, additional well-controlled studies are required in order to definitively answer the question of whether opioid-dependent patients are impaired in their driving skills. Unfortunately, well-controlled studies usually accumulate slowly over the years. At issue, then, is what should be the position presently, in reference to driving, of the physician maintaining patients on chronic opioid treatment. First, that physician should be aware that the preponderance of the evidence (as demonstrated in this review) indicates that under certain conditions, patients stabilized on long-term opioid therapy can drive. Thus, the physician should not necessarily take the position that being on opioids precludes driving. Instead, the following approach is recommended. The patients placed on long-term opioid treatment should be advised of the current status of this research. Second, they should then be advised that whether they do/do not drive should be based on this information, but that it is their own personal decision. Third, they should then be advised that if they choose to drive, they should follow the following rules:

(a) After beginning opioid treatment or after a dose increase they should not drive for 4–5 days.
(b) They should not drive if they ever feel sedated.
(c) They should report sedation/unsteadiness/cognitive decline immediately to the physician so that reduction in dosage can be initiated.
(d) Under no circumstances should they utilize alcohol or other illicit drugs such as cannabinoids and drive.
(e) They should avoid taking any over-the-counter antihistamines.
(f) They should not make any changes in their medication regimens without consulting with the physician.

A final issue relates to what should the physician do if he/she is requested to complete paperwork where questions are asked about the patient's driving ability. For this problem, the same type of approach is recommended. The physician should report the current status of this research in the paperwork. In addition, the physician should also report whether he/she has noted any opioid side effects, which may interfere with driving, or absence of these. However, if a specific question relating to whether the patient can/cannot drive is encountered, that question should be marked unknown. As an explanation, the physician should state that he/she does not have knowledge of the patient's ability to drive, as that can only be determined in a driving simulator and/or on-road/off-road driving tests.

Conclusions

The majority of the reviewed studies indicated that opioids appear not to impair driving-related skills in opioid-dependent patients. The evidence for this observation was consistent in four of the five research areas investigated, but inconsistent in one. As such, additional well-controlled studies are required in order to definitely answer the question of whether opioid-dependent patients are impaired in these driving skills. Until such data are available, however, physicians may wish to utilize the approach to this problem recommended in this review.

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Appendices A and B

Guidelines for Levels of Evidence as Applied by the Agency for Health Care Policy and Research.[17]

A. Type of Evidence Guidelines

a.) Meta-analysis of multiple well-designed controlled studies.

b.) At least one well-designed experimental study.

c.) Well-designed, quasi-experimental studies such as nonrandomized controlled, single group pre-post, cohorts, time series, or matched case-controlled studies.

d.) Well-designed nonexperimental studies, e.g., comparative, correlational, descriptive, case control.

e.) Case reports and clinical examples.

B. Strength and Consistency of Evidence Guidelines

a.) There is evidence of Type I or consistent findings from multiple studies of Type II, III, or IV.

b.) There is evidence of Type II, III, or IV, and findings are generally consistent.

c.) There is evidence of Type II, III, or IV, but findings are inconsistent.

d.) There is little or no evidence, or there is Type V evidence only.

e.) Panel consensus: practice recommended on the basis of opinion of experts in pain management.