Is Smoking Associated with Alcohol-Drug Dependence in Patients with Pain and Chronic Pain Patients? An Evidence-Based Structured Review

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Abstract

Objective. The objective of this study was to determine if there is consistent evidence for smoking to be considered a red flag for development of opioid dependence during opioid exposure in patients with pain and chronic pain patients (CPPs).

Methods. Six hundred and twenty-three references were found that addressed the areas of smoking, pain, and drug-alcohol dependence. Fifteen studies remained after exclusion criteria were applied and sorted into four groupings addressing four hypotheses: patients with pain and CPPs who smoke are more likely than their nonsmoking counterparts to use opioids, require higher opioid doses, be drug-alcohol dependent, and demonstrate aberrant drug-taking behaviors (ADTBs). Each study was characterized by the type of study it represented according to the Agency for Health Care Policy and Research (AHCPR) guidelines and independently rated by two raters according to 13 quality criteria to generate a quality score. The percentage of studies in each grouping supporting/not supporting each hypothesis was calculated. The strength and consistency of the evidence in each grouping was rated by the AHCPR guidelines.

Results. In each grouping, 100% of the studies supported the hypothesis for that grouping. The strength and consistency of the evidence was rated as A (consistent multiple studies) for the first hypothesis and as B (generally consistent) for the other.

Conclusions. There is limited consistent indirect evidence that smoking status in patients with pain and CPPs is associated with alcohol-drug and opioid dependence. Smoking status could be a red flag for opioid-dependence development on opioid exposure.

Key Words. Chronic Pain; Smoking; Drug Dependence; Alcohol Dependence; Opioid Dependence; Review

Introduction

The Tobacco Supplement to the National Comorbidity Survey has determined that the lifetime prevalence for nicotine dependence in the United States is 24% [1], while 15% are thought to be currently nicotine dependent [2]. These figures, however, do not apply to alcoholics and drug-dependent individuals. Over 90% of alcoholic inpatients are smokers [3] and alcoholism is estimated to be 10 times more common in smokers vs nonsmokers [4]. When formal criteria are applied to these groups, it has been reported that 34% of individuals with alcohol disorders [5] and 52% with substance use disorders [6] meet the full Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4) criteria for nicotine dependence. As such, the association between alcoholism and
other substance use disorders and smoking is well-documented and accepted [7–10]. Early research [8,11] also indicated that there was a very high prevalence of smoking within opioid-dependent individuals who were on methadone maintenance treatment [12–14]. More than 80% of these opioid-dependent patients smoke [9]. Among these individuals, cigarette smoking is associated with illicit substance use, particularly cocaine use. More interestingly, methadone-maintained patients who reduce their tobacco use reduce cocaine use [15]. Also, methadone-maintained patients who successfully quit smoking are three times more likely not to use cocaine vs smoking peers [16]. Finally, illicit substance use measured through urine toxicology increases in a stepwise fashion from methadone-maintained nonsmoking individuals to smoking chippers (smokers without objective signs of dependence) to heavy smokers [17]. As such, associations among alcoholism and other substance use disorders and smoking are well-documented. For example, analysis of the 1989 National Alcohol and Drug Use Survey from a Canadian database has demonstrated that a positive response to the question “Have you ever smoked cigarettes?” correctly classified 76% of substance abusers [18]. At issue then is whether these smoking research findings apply to patients with pain and chronic pain patients (CPPs) and whether within these groups smoking should be considered a potential red flag for development of opioid dependence on opioid exposure.

In 2007, Fishbain et al. [19] reported that current smoking status in CPPs was predicted by current alcohol-abuse dependence and that smoking up to one pack per day was also predicted by current alcohol-abuse dependence. Additionally, current smokers were more likely to have a current Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III-R) diagnosis of substance use for alcohol, cannabis, amphetamines, or cocaine, but not opioid-abuse dependence [19]. These findings, except for opioid-abuse dependence, fit in well with the findings from the above dependence literature on the association between smoking and alcoholism and illicit drugs. In the same year, Dhingra and Passik [20] in a narrative review raised the issue of whether smoking in CPPs is associated with aberrant drug-taking behaviors (ADTBs). Here, they reviewed five studies [13,18,21–23], of which one [23] addressed ADTBs. They concluded that smokers are at higher risk for ADTBs on opioid therapy compared with nonsmokers. Since that narrative review, there have been a significant number of studies that have been added to the literature, which have addressed the association of smoking in patients with pain or CPPs and opioid use through a number of different questions. These are the following: 1) Are patients with pain or CPPs who smoke significantly more likely to use opioids vs nonsmoking comparators? 2) Are patients with pain or CPPs who smoke more likely to require more opioids for pain than nonsmoking comparators? 3) Are CPPs who smoke more likely to be drug-alcohol dependent than nonsmoking comparators? and 4) Are patients with pain or CPPs who smoke more likely to demonstrate ADTBs on opioids vs nonsmoking comparators? It is the objective of this evidence-based structured review (described below) to review these four lines of evidence utilizing the type of evidence, strength, and consistency of evidence guidelines [24]. These guidelines are presented in Table 1. It is hoped that this approach can add to the information available as to whether smoking should be considered a red flag for potential opioid-dependence development on opioid exposure.

### Methods

Relevant references were located by the following procedure. MEDLINE, Embase, AMED, Psychological Abstracts, Science Citation Index, and the National Library of Medicine Physician Data Query databases were reviewed utilizing the following subject headings: pain, chronic pain, CPPs, alcohol abuse, alcohol dependence, alcoholism, cannabis abuse, cannabis dependence, cocaine abuse, cocaine dependence, illicit drug abuse, illicit drug dependence, addiction, aberrant drug-related behaviors, ADTBs, opioid abuse, opioid dependence, heroin dependence, methamphetamine abuse, methamphetamine dependence, and addiction. Each of these was sequentially exploded with the medical subject headings smoking and nicotine. Each term was exploded for

### Table 1  Levels of evidence as developed by the agency for health care policy and research for guideline development [24]

<table>
<thead>
<tr>
<th>Type of Evidence and Strength/Consistency of the Evidence Guidelines According to the AHCPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. There is evidence of type I or consistent findings from multiple studies of type II, III, or IV.</td>
</tr>
<tr>
<td>B. There is evidence of type II, III, or IV, and findings are generally consistent.</td>
</tr>
<tr>
<td>C. There is evidence of type II, III, or IV, but findings are inconsistent.</td>
</tr>
<tr>
<td>D. There is little or no evidence, or there is type V evidence only.</td>
</tr>
<tr>
<td>E. Panel consensus: Practice recommended on the basis of opinion of experts.</td>
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</tbody>
</table>

Downloaded from https://academic.oup.com/painmedicine/article-abstract/13/9/1212/1865224 by guest on 28 January 2019
subheading in MESH and all retrieved references were reviewed. The searches were not restricted to the English language and conducted back to 1966, except for Science Citation index, which was conducted back to 1974. The upper limit of each search was 2011. A manual search was also performed using key pain journals, pain meeting abstracts, and textbooks. For the following journals, the following years were reviewed: Pain, 1975–2011; Spine, 1986–2011; The Pain Clinic, 1986–2011; Clinical Journal of Pain, 1985–2011; and Pain Medicine, 2000–2011. Abstracts of the following meetings were reviewed for the following years: International Association for the Study of Pain 1981, 1984, 1987, 1990, 1993, 1996, 1999, 2002, 2005, 2008, 2011 and the American Pain Society Meetings, 1982–2011. Three pain textbooks were reviewed for possible references. These were Evaluation and Treatment of Chronic Pain, 3rd Edition, G. Aronoff (ed.), 1999; Handbook of Pain Management, 2nd Edition, C.D. Tollison, J.R., J.R. Satterthwaite, J.W. Tollison (eds.), 1999; and Textbook of Pain, 3rd Edition, P. Wall, R. Melzak (eds.), 1999. Six hundred and twenty-three references were found and subjected to a cursory review. As it is well-accepted that smoking is associated with populations dependent on opioids, cocaine, and alcohol (Introduction), studies dealing with these populations and not relating to pain were excluded. Studies were included for database review if they were not excluded by these exclusion criteria and addressed one of the following four major lines of evidence: 1) opioid use/opioid nonuse in patients or CPPs who smoke; 2) levels of opioid use in patients with pain or CPPs who smoke; 3) alcohol-drug dependence in CPPs who smoke; and 4) ADTBs in patients with pain or CPPs who smoke. Of the original 623 references, 608 were excluded by this process, leaving 15 studies that fulfilled these inclusion/exclusion criteria. The remaining 15 studies [19,23,25–37] were reviewed in detail and sorted into the four lines of evidence described earlier. Research information from these studies was then abstracted into tabular form and is presented according to the lines of evidence (above) in Tables A1–A4. Tables A1–A4 are arranged to present the author, year publication, study question, design and type of study, sample size, type of pain measures used, definition of smoking status, how dependence diagnosis was derived, type of statistical analysis, study findings, type of evidence the study represents according to Table 1 subsection I, quality score (assigned according to the procedure below), and comments. The quality of studies was categorized according to the systems developed and reported by Hoogendoorn et al. [38] and De Vet et al. [39]. These researchers developed and tested a list of 23 criteria to be used to assess methodological quality of prospective, historical cohort, and case–control studies. For details of how these criteria were developed, the reader is referred to the original studies [38,39]. Ten criteria were selected from their list, which were appropriate to the studies utilized (Table A5). The other 13 criteria addressed randomized trials and were therefore not appropriate to the reviewed studies. In addition to the selected criteria, three criteria (positive if the data were collected by means of a standardized method of acceptable quality to measure smoking, dependence, and ADTBs) were added for the quality analysis of each study. This resulted in a total of 13 criteria. For each included study, each criterion was rated either present/fulfilled (+), not present/unfulfilled (−), or not applicable (NA). NA was used as follows. There were basically four types of studies analyzed for quality: case–control, cohort, correlational, and case series. Thus, some criteria in Appendix Table A5 pertained only to case–control studies, while others applied only to cohort studies, etc. As such, NA was used if the criterion in question pertained to another type of study other than the one being reviewed. In addition, NA was used when that criterion did not pertain to the study in question. NA was not used when information was not available or not described [40]. Under those circumstances, a negative was assigned [40]. A negative was also assigned if the item did not meet the preselected criteria [40]. Each study was rated independently for each criterion by the senior author (DAF) and another author (BC). Both raters chose either a positive, negative, or NA for each criterion for each study selected for detailed review. The assigned categorizations by DAF and BC for each study were then compared in a meeting. Any discrepancies in the categorizations were resolved by mutual agreement. This resulted in a final decision as to whether each criterion received a negative, positive, or NA categorization. Categorizations were then summarized and placed into tabular format (Table A5). A quality score was obtained by counting the number of positives obtained. This score was divided by 13 (the total number of criteria) minus the number of NAs and multiplied by 100, which gave the percentage quality score.

Studies scoring less than 50% historically have been rated as “low quality” [40]. These studies are usually not utilized to arrive at conclusions about a review topic. For the purposes of this review, we arbitrarily set the acceptable quality score at 60% in order to avoid marginal studies. Studies scoring less than 60% were then not utilized at arriving at our conclusions.

The senior author was the one who independently abstracted the data into Tables A1–A4. However, data abstraction was checked independently by BC. Any discrepancies in this classification were also resolved by mutual agreement. In addition, BC checked the classifications of the reviewed studies, that is, whether the reviewed study was a cohort, case–control, etc. Any discrepancies in this classification were also resolved by mutual agreement.

The categorization of the type of evidence the study represented was based on the guidelines developed by the Agency for Health Care Policy and Research (AHCPR) for categorizing the levels of evidence represented by reviewed studies (Table 1, Evidence Guidelines subsection I) [24]. Studies were categorized I through V according to this scheme. This categorization was also independently arrived at by the senior author and BC. Any discrepancies were again resolved by mutual agreement in a meeting format.
The strength and consistency of the research evidence for each study grouping (Tables A1–A4) was then rated according to the AHCPR consistency of evidence guidelines [24] developed for this purpose (Table 1, subsection II). These guidelines allow the researcher to categorize the reviewed evidence as being consistent, generally consistent, inconsistent, or demonstrating little or no evidence for supporting the hypothesis under study. The hypotheses from the four lines of evidence in this review were the following: 1) patients with pain or CPPs who smoke will be more likely to be on opioids vs their nonsmoking counterparts; 2) patients with pain or CPPs who smoke will be more likely to use larger quantities of opioids vs their nonsmoking counterparts; 3) CPPs who smoke will be more likely to be diagnosed with substance dependence/addiction vs their nonsmoking counterparts; and 4) patients with pain or CPPs who smoke will be more likely to demonstrate ADTBs vs their nonsmoking counterparts. In using the consistency rating guidelines, only studies attaining a score of 60% or greater were used. Ratings according to these guidelines (Table 1) were performed independently by the senior author and BC. Any discrepancies were later resolved by mutual agreement.

Finally, the data from Tables A1–A4 were placed into a summary table (Table 2). This table was designed to summarize the overall findings of the structured review for each hypothesis. It has the following headings: hypothesis, number of studies, % of studies by type of evidence, average quality score for the group, % of all studies supporting the hypothesis, and strength/consistency of the findings for the hypothesis (according to the AHCPR guidelines in Table 1 [24]).

Results

Six studies addressed the hypothesis that pain patients/CPPs who smoke are significantly more likely to use opioids vs nonsmoking comparators (Table 2). Of these studies, 50% were type 3 and 50% were type 4. Average quality score was 85.4%. Here, 100% of the studies found that patients with pain or CPPs who smoke are significantly more likely to use opioids. The strength/consistency of this evidence was rated as A (Table 1).

Three studies addressed the hypothesis that patients with pain or CPPs who smoke are significantly more likely to require more opioids for pain than nonsmoking comparators (Table 2). Of these studies, 100% were type 4. Average quality score was 87.8%. Here, 100% of the studies found that patients with pain or CPPs who smoke are significantly more likely to use more opioids for pain than nonsmoking comparators. The strength/consistency of this evidence was rated as B (Table 1).

Three studies addressed the hypothesis that CPPs who smoke are more likely to be diagnosed with drug dependence vs their nonsmoking counterparts (Table 2). Of these studies, 66.6% were type 3 and 33.3% were type 4.
Average quality score was 86.9%. Here, 100% of the studies found that CPPs who smoke are more likely to be diagnosed with drug dependence vs their nonsmoking counterparts. The strength and consistency of this evidence was rated as B (Table 1) as there were only three studies.

Three studies addressed the hypothesis that patients with pain or CPPs who smoke are more likely to demonstrate ADTBs vs their nonsmoking counterparts (Table 2). Of these studies, 66.6% were type 3 and 33.3% were type 4. Average quality score was 80.6%. Here, 100% of the studies found that patients with pain or CPPs who smoke were more likely to demonstrate ADTBs vs nonsmoking counterparts. The strength/consistency of this evidence was rated as B (Table 1) as there were only three studies.

Overall, 46.6% of the 15 studies utilized in this evidence-based structured review (Table 2) were type 3 and 53.4% were type 4 (Table 1). Of the 15 studies, none had quality scores below 60% and therefore all studies were all in the strength/consistency ratings. The overall average quality score for the 15 studies was 85.3%. A total of 100% of the studies in each grouping supported the hypothesis for that grouping. Overall, this led to one A (consistent multiple studies) and three B (generally consistent) consistency ratings (Table 2).

Discussion

This evidenced-based structured review has attempted to answer the question of whether there is evidence in patients with pain or CPPs that smoking should be considered a potential red flag for development of dependence on opioids on opioid exposure. To that end, this review has examined four lines of evidence: Are patients with pain or CPPs who smoke more likely to use opioids vs nonsmoking counterparts? Are patients with pain or CPPs who smoke more likely to require more opioids vs nonsmoking counterparts? Are CPPs who smoke more likely to be drug-alcohol dependent vs nonsmoking counterparts? And are patients with pain or CPPs who smoke more likely to demonstrate ADTBs vs nonsmoking counterparts? In each line of evidence, 100% of the studies indicated that smokers differ from nonsmokers for the hypothesis derived from that line of evidence (Table 2). This generated high consistency scores (A’s and B’s) for each hypothesis. Overall, therefore, there is limited indirect evidence that smoking may be a red flag for potential opioid-dependence development on opioid exposure.

However, although these lines of evidence are extremely consistent, at issue is whether they can be utilized as proof for potential opioid-dependence development on opioid exposure or whether they represent other processes? The first line of evidence was smokers are more likely to use opioids. Here, there is some evidence in the literature that CPPs who smoke report more pain [28,41–43]. As such, they may be on opioids precisely for that reason and may require more opioids for pain control because they have more pain (second line of evidence). However, there is significant evidence that nicotine has an antinociceptive/analgesic effect [44,45] and that smoking increases pain thresholds and pain tolerances in men and women [45,46]. As such, according to these physiological studies, pain patients who smoke should report less pain as they are able to control their pain by using nicotine [47]. In addition, there are six studies [21,22,48–51] in non-CPPs from the general populations, which indicate that smokers are more likely to be on opioids vs nonsmokers. These were very large cross-sectional population studies and, as such, it is not clear why the respondents in these studies were on opioids and these studies were therefore excluded from this review. However, these studies indirectly support the results of the studies in Table A1 and are consistent with those studies. Therefore, the above literature indirectly supports the results in Table A1.

The second line of evidence (pain patients or CPPs who smoke require more opioids than their counterparts) could also be related to other factors besides opioid dependence. Here, recent evidence indicates that people differ in their ability to metabolize opioids [52,53]. Smokers probably because of enzyme induction by nicotine have been reported to have less pain efficacy from proopiophene [54], demonstrate increased metabolic clearance of pentazocine [55], require high doses of pentazocine [56], and have significantly lower levels of hydrocodone [31] vs nonsmokers. Thus, the requirement for more opioids in smokers and actual demonstration of ADTBs (the fourth line of evidence) could be a result of differences in the metabolism of opioids between smokers and nonsmokers [20]. As such, the strongest line of evidence for smoking being a red flag for potential opioid dependence development on opioid exposure rests with the third line of evidence where there are currently only three studies.

Additional evidence that speaks to the question raised by this review and not presented in Tables A1–A4 as it did not come from pain studies relates to genetic and neurophysiological studies in humans. Here, the evidence is as follows. Alcohol dependence and habitual smoking co-occur and this co-occurrence is transmitted within families, which has been well-established through adoption, twin, and family studies [57]. Several DNA regions have been identified, which may contain genes that confer susceptibility to alcoholism and risk for habitual smoking [58–60]. Recent neurophysiological studies have found a direct overlap between nicotine, alcohol, and cocaine cue-reactivity in the ventral striatum for self-reported craving for these drugs [61]. Finally, there is a significant evidence that nicotine is involved in the development of other drug dependencies and that development of dependence to nicotine generally precedes development of dependence on alcohol and illicit drugs [10]. Nicotine has thus been identified as a “gateway drug” to other dependencies [10]. It also appears that people who never smoked rarely
abuse alcohol or illicit drugs [10]. Overall, these nonpain studies indicate that patients with pain or CPPs who smoke should be at higher risk than nonsmoking counterparts for development of dependence on opioids if so exposed.

What are the possible confounders to the results of this review? The first major confounder is how smoking is defined. A review of the studies included in Tables A1–A4 indicated that studies generally differ on how they define smoking/nonsmoking. Here, smoking has been defined as heavy, light [62], intermittent [62], greater than one pack per day, some day smokers, less than one pack per day, etc. In addition, some studies looked at and included former smokers [63]. These different categories make it difficult to compare studies and could serve as sources of confounding in the actual studies. Another issue here is how to treat the concept of nicotine dependence [64]. None of the reviewed studies utilized this concept. It is also unclear as to which of the terms utilized for smokers (above) translates into actual nicotine dependence, which is highly heritable [7]. The closest probably would be smoking one pack or greater per day. This translation is important because it is likely that it is the heavy smoker who actually fulfills the diagnostic criteria for nicotine dependence [64]. This is the smoker who would be at greatest risk for opioid dependence on opioid exposure.

The second major potential confounder to the results of this review is depression. It appears that persons with depression are more likely to be smokers, to be dependent smokers, and to have difficulty stopping smoking [65]. None of the studies in Tables A1–A4 controlled for depression, except for Fishbain et al. [19]. As such, this omission could have served as a potential confounder in these studies and thus could have impacted on the results of this review.

What are the implications for the pain clinician from the findings of this evidence-based structured review (there is limited indirect evidence that smoking may be a red flag for potential opioid dependence development on opioid exposure)? The major implication is that pain clinicians when evaluating CPPs for possible chronic opioid maintenance should begin to pay attention to and document the CPP’s past and present smoking status. Presently, as demonstrated in this review, there are few prospective studies that address the problem studied in this review. As such, it is the opinion of this research group that a finding of past or current smoking should not necessarily preclude that CPP from chronic opioid maintenance. However, these patients should be perceived as potentially being at greater risk than nonsmoking CPPs for development of opioid dependence on opioid exposure, and if placed on opioids, they should be monitored closely for ADTBs. CPPs who are smoking one pack or greater should be monitored even more closely as these smoking levels are likely to indicate significant nicotine dependence, which, as pointed out, is highly heritable and, in turn, may be associated with alcoholism predisposition.

Recently, a number of inventories [66–68] have been developed in order to try to predict ADTBs in CPPs who are candidates for chronic opioid analgesic therapy. One of these tools [67,68] includes smoking as an item. If further studies continue to link smoking status with drug-alcohol dependence in patients with pain or CPPs, it may be advantageous to test smoking status by itself as a potential ABTB predictor.

References
5 Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the USA. Results from the National Epidemiological Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004;61:1107–14.
Fishbain et al.


## Appendix

**Table A1** Summary of studies addressing the hypothesis that smoking patients with pain or CPPs are significantly more likely to use opioids vs nonsmoking counterparts

<table>
<thead>
<tr>
<th>Ref #, Author, Year</th>
<th>Study Question</th>
<th>Design and Type of Study</th>
<th>Sample Size</th>
<th>Type of Pain Measures</th>
<th>Definition of Smoking Status</th>
<th>How Dependence Diagnosis was Derived</th>
<th>Type of Statistical Analysis</th>
<th>Study Findings</th>
<th>Type of Evidence the Study Represents</th>
<th>Quality Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[26], Barton et al., 1989</td>
<td>Are smoking CPPs more likely to use opioids?</td>
<td>Cross-sectional</td>
<td>137 CPPs</td>
<td>NA</td>
<td>Smokers are those who smoke 1/2 pack or more</td>
<td>NA</td>
<td>Chi-square</td>
<td>Smokers significantly more likely to use opioids</td>
<td>4</td>
<td>87.5</td>
<td>Smoking quantity not controlled for</td>
</tr>
<tr>
<td>[27], Stover et al., 2006</td>
<td>Newly injured worker compensation low back pain patients who smoke more likely to be placed on opioids?</td>
<td>Prospective cohort</td>
<td>1,067 Controlled for</td>
<td>Daily tobacco use</td>
<td>NA</td>
<td>Bivariate logistic regression</td>
<td>Adjusting for demographics, pain intensity, and physical disability opiate prescription significantly associated with daily tobacco use</td>
<td>3</td>
<td>75.0%</td>
<td>Pain controlled for</td>
<td></td>
</tr>
<tr>
<td>[28], Hooten et al., 2009</td>
<td>Are smokers with chronic pain more likely to be using opioids at admission to a pain center?</td>
<td>Retrospective cross-sectional</td>
<td>1,241</td>
<td>NA</td>
<td>Smokers, former smokers, never smokers</td>
<td>NA</td>
<td>Chi-square</td>
<td>Smokers were more likely to be using opioids at admission ($P = 0.001$)</td>
<td>4</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>[29], Krebs et al., 2010</td>
<td>What predicts long-term opioid use in LBP Pts. at 24 months?</td>
<td>Prospective cohort</td>
<td>28% report continued opioid use at 24 months of 42% using opioid at baseline, 210</td>
<td>Current Smoking</td>
<td>NA</td>
<td>Generalized estimating equations</td>
<td>In adjusted models, smoking predicted opioid continuation</td>
<td>3</td>
<td>75.0%</td>
<td>Did not apply specific criteria to define smoking</td>
<td></td>
</tr>
<tr>
<td>[30], Cox et al., 1997</td>
<td>Is there a relationship between smoking and analgesic use in treated arthritis or LBP Pts.?</td>
<td>Prospective cohort</td>
<td>2,300 men, 3,052 women</td>
<td>Smoking history</td>
<td>NA</td>
<td>Multivariate logistic regression controlling for age and socioeconomic status</td>
<td>Positive association smoking history and current prescribed analgesics for both sexes</td>
<td>3</td>
<td>87.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[37], Ekholm et al., 2009</td>
<td>Are CPPs on opioids more likely to be smokers?</td>
<td>Cross-sectional</td>
<td>5,292</td>
<td>NA</td>
<td>Smokers vs nonsmokers vs heavy smokers</td>
<td>NA</td>
<td>Multivariable logistic regression</td>
<td>CPPs using opioids have 2.19 higher odds of being a daily smoker and 2.28 higher odds of being a heavy smoker</td>
<td>4</td>
<td>87.5%</td>
<td></td>
</tr>
</tbody>
</table>
Table A2  Summary of studies addressing the hypothesis that smoking patients with pain or CPPs are significantly more likely to require higher doses of opioids vs their nonsmoking counterparts

<table>
<thead>
<tr>
<th>Ref #, Author, Year</th>
<th>Study Question</th>
<th>Design and Type of Study</th>
<th>Sample Size</th>
<th>Type of Pain Measures</th>
<th>Definition of Smoking Status</th>
<th>How Dependence Diagnosis was Derived</th>
<th>Type of Statistical Analysis</th>
<th>Study Findings</th>
<th>Type of Evidence the Study Represents</th>
<th>Quality Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[31], Ackerman et al., 2007</td>
<td>Do smokers with low back pain require more hydrocodone?</td>
<td>Prospective case-control not matched for amount (mg) hydrocodone used over 24 hours</td>
<td>50 smokers 50 nonsmokers</td>
<td>VAS</td>
<td>Current smokers</td>
<td>NA</td>
<td>Chi-square</td>
<td>Smokers required more hydrocodone, but had significantly lower serum levels</td>
<td>4</td>
<td>81.8%</td>
<td>Smokers had lower serum levels hydrocodone but used more</td>
</tr>
<tr>
<td>[32], Creekmore et al., 2004</td>
<td>Do smokers who quit smoking for surgery require more opioids post-op?</td>
<td>20 smokers compared to 69 nonsmokers, case-control</td>
<td>20 smokers 69 nonsmokers</td>
<td>NA</td>
<td>Current smokers</td>
<td>More opioid use first 2 days post-op</td>
<td>Chi-Square</td>
<td>When normalized for mass index, smokers required more opiate (P = 0.023)</td>
<td>4</td>
<td>81.8%</td>
<td>Smoking quantity not controlled for and smoking not defined</td>
</tr>
<tr>
<td>[33], Hooten et al., 2011</td>
<td>Do smokers use more opioids at baseline admission to a pain center?</td>
<td>Retrospective cross-sectional with measured daily morphine equivalent</td>
<td>1,241</td>
<td>NA</td>
<td>Current smokers, former smokers, never smokers</td>
<td>N/A</td>
<td>Multivariate regression analysis</td>
<td>Current smoking independently associated with greater opioid use</td>
<td>4</td>
<td>100%</td>
<td>Smoking quantity not controlled for</td>
</tr>
</tbody>
</table>
Table A3  Summary of studies addressing the hypothesis that smoking patients with pain or CPPs are significantly more likely to be diagnosed with alcohol/drug dependence vs nonsmoking counterparts

<table>
<thead>
<tr>
<th>Ref #, Author, Year</th>
<th>Study Question</th>
<th>Design and Type of Study</th>
<th>Sample Size</th>
<th>Type Pain Measures</th>
<th>Definition of Smoking Status</th>
<th>How Dependence Derived</th>
<th>Type of Statistical Analysis</th>
<th>Study Findings</th>
<th>Type of Evidence the Study Represents</th>
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</thead>
<tbody>
<tr>
<td>[19], Fishbain et al., 2007</td>
<td>Is smoking status in CPPs associated with any form of alcohol and/or drug dependence?</td>
<td>Retrospective, cohort model building.</td>
<td>140 nonsmokers 81 smokers</td>
<td>NA</td>
<td>Current smoker, current nonsmoker, and number of cigarettes smoked per day.</td>
<td>DSM III diagnoses</td>
<td>Logistic regression analysis</td>
<td>Current smokers were more likely to have a current substance use diagnosis for alcohol, cannabis, amphetamines, and cocaine. Smoking was predicted by current alcohol abuse/dependence. Smoking up to one pack per day was predicted by current alcohol abuse/dependence.</td>
<td>3</td>
<td>100%</td>
<td>Smokers in CPPs associated with other addictions but not opioid-abuse dependence</td>
</tr>
<tr>
<td>[34], Højsted et al., 2010</td>
<td>Do CPPs diagnosed as drug dependent smoke more?</td>
<td>Cross-sectional prospective CPPs diagnosed as drug dependent by two different criteria: ICD-10 and Portenoy’s criteria</td>
<td>253</td>
<td>NA</td>
<td>Number of cigarettes per day</td>
<td>Portenoy’s criteria* (reference #[69])</td>
<td>Chi-square</td>
<td>CPPs diagnosed with drug dependence smoked more statistically.</td>
<td>3</td>
<td>90.9%</td>
<td></td>
</tr>
<tr>
<td>[25], Friedman and Mehrotra, 2003</td>
<td>Do CPPs on opioids with dependence smoke more?</td>
<td>Case–control</td>
<td>48 CPPs</td>
<td>NA</td>
<td>Smoking vs nonsmoking</td>
<td>NA</td>
<td>Chi-square</td>
<td>Smoking more commonly found in CPPs currently using heroin or cocaine</td>
<td>4</td>
<td>70.0%</td>
<td></td>
</tr>
</tbody>
</table>

*Intense desire for drug, overwhelming concern about continued availability.
Table A4  Summary of studies addressing the hypothesis that patients with pain or CPPs are more likely to demonstrate aberrant drug-taking behaviors vs nonsmoking counterparts

<table>
<thead>
<tr>
<th>Ref #, Author, Year</th>
<th>Study Question</th>
<th>Design and Type of Study</th>
<th>Sample Size</th>
<th>Type Pain Measures</th>
<th>Definition of Smoking Status</th>
<th>How Dependence Diagnosis Derived</th>
<th>Type of Statistical Analysis</th>
<th>Study Findings</th>
<th>Type of Evidence the Represents</th>
<th>Quality Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[35], Broekmans et al., 2010</td>
<td>Is medication overuse associated with ADTB and current smoking in CPPs?</td>
<td>Cross-sectional</td>
<td>359</td>
<td>NA</td>
<td>Smoker vs nonsmoker</td>
<td>NA</td>
<td>Multivariable logistic regression</td>
<td>54% of overusers were smokers vs 28% of the adherent; overuse was associated with smoking and opioid prescriptions</td>
<td>3</td>
<td>80.0%</td>
<td>Smoking not defined</td>
</tr>
<tr>
<td>[36], Barry et al., 2011</td>
<td>Is using an opioid not prescribed to the Pt. (an ADTB) associated with smoking status?</td>
<td>Cross-sectional</td>
<td>4,122</td>
<td>NA</td>
<td>Smoker vs nonsmoker</td>
<td>NA</td>
<td>Logistic regression</td>
<td>Using a nonprescribed opioid was predicted by past month cigarette use</td>
<td>3</td>
<td>80.0%</td>
<td>Smoking not defined</td>
</tr>
<tr>
<td>[23], Michna et al., 2004</td>
<td>Do CPPs on opioids considered to be at high risk for ADTBs smoke?</td>
<td>Case–control</td>
<td>145</td>
<td>NA</td>
<td>Smokers vs nonsmokers</td>
<td>NA</td>
<td>Stepwise regression</td>
<td>More high risk Pts. smoked and needed a cigarette within first hour of the day. Cigarette need in first hour of the day predicted high risk.</td>
<td>4</td>
<td>81.8%</td>
<td>Smoking not defined</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------------</td>
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<td>------------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>1. Positive if the study had a clearly defined objective</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2. Positive if the main features (description of the sampling frame, distribution of the population according to age and sex) of the study population were described</td>
<td>+</td>
<td>(−)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>3. Positive if the participation rate at baseline was at least 80%</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<td>(+)</td>
</tr>
<tr>
<td>4. Positive if cases and controls were drawn from the same population and clear definitions of cases and controls were given</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>5. Positive if the participation rates of cases and controls selected and invited to participate at baseline were at least 80%</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>6. Positive if data were collected by means of standardized methods of acceptable quality for smoking</td>
<td>+</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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</tbody>
</table>

**Table A5** Quality ratings for studies in Tables A1–A5

Chronic Pain, Smoking, Drug Dependence, Opioids, Review
## Table A5  Continued

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>7. Positive if data were collected by means of standardized methods of acceptable quality for drug dependence</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(+)</td>
<td>(+)</td>
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<tr>
<td>8. Positive if data were collected by means of standardized methods of acceptable quality for ADTBs</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>(+)</td>
</tr>
<tr>
<td>9. Positive if the exposure was measured in an identical manner among cases and controls</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
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<tr>
<td>10. Positive if the method used for the statistical analysis was appropriate for the study</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<td>(+)</td>
<td>(+)</td>
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<tr>
<td>11. Restriction to a homogeneous study population</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<tr>
<td>12. Allocation procedure not leading to bias</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<td>(+)</td>
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<td>(+)</td>
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<td>(+)</td>
</tr>
<tr>
<td>13. Smallest group bigger than 50 participants</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
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<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Overall quality score</td>
<td>87.5%</td>
<td>75.0%</td>
<td>100%</td>
<td>75.0%</td>
<td>87.5%</td>
<td>87.5%</td>
<td>81.8%</td>
<td>81.8%</td>
<td>81.8%</td>
<td>100%</td>
<td>100%</td>
<td>90.9%</td>
<td>70.0%</td>
<td>80.0%</td>
<td>80.0%</td>
</tr>
</tbody>
</table>

Key for appendix Tables A1--A5: NA = not applicable; VAS = visual analog scale; Pts. = patients; ADTBs = aberrant drug-taking behaviors; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; ICD-10 = International Classification of Diseases, Tenth Edition; HIV = human immunodeficiency virus.