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Rates of Opioid Misuse, Abuse, and Addiction in Chronic Pain:

A Systematic Review and Data Synthesis

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Abstract

Opioid use in chronic pain treatment is complex, as patients may derive both benefit *and* harm. The identification of individuals currently using opioids in a problematic way is important given the substantial recent increases in prescription rates and consequent increases in morbidity and mortality. The present review provides updated and expanded information with regard to rates of problematic opioid use in chronic. Because previous reviews have indicated substantial variability in this literature, several steps were taken to enhance precision and utility. First, problematic use was coded using explicitly defined terms, referring to different patterns of use (i.e., misuse, abuse, and addiction). Second, average prevalence rates were calculated and weighted by sample size and study quality. Third, the influence of differences in study methodology was examined. In total, data from 38 studies were included. Rates of problematic use were quite broad, ranging from < 1% to 81% across studies. Across most calculations, rates of misuse averaged between 21% and 29% (range 95% CI's: 13% - 38%). Rates of addiction averaged between 8% and 12% (range 95% CI: 3% - 17%). Abuse was reported in only a single study. Only one difference emerged when study methods were examined, where rates of addiction were lower in studies that identified prevalence assessment as a primary, rather than secondary, objective. While significant variability remains in this literature, this review provides guidance with regard to possible average rates of opioid misuse and addiction and also highlights areas in need of further clarification.

Keywords: Opioids; Chronic Pain; Problematic Use; Abuse; Addiction; Misuse

1. **Introduction**

In the treatment of chronic pain, there may be no area of greater controversy than that which surrounds the use of opioids. Changes in attitudes with respect to opioid use toward the end of the 20th century, and subsequent exponential increases in use, have been well documented [2,31,56,58]. More recently, the burgeoning public health issue with regard to opioid-related adverse events has perhaps been equally well documented, as the use of opioids in chronic pain brings with it marked potential for adverse events for the patient, including overdose, experience of physiological dependence and subsequent withdrawal, addiction, and negative impacts on functioning [2,6,38,56]. The attention paid to the so-called “opioid epidemic” (e.g., [19,32]) has highlighted the need to clearly differentiate and identify the types of problematic prescription opioid use (e.g., misuse, abuse, addiction) and discern their frequency in treated chronic pain patients.

Attempts to calculate rates of problematic opioid use behavior have suffered from imprecise and poorly defined terminology. Two recent sets of expert consensus statements, one suggesting a framework for measuring abuse liability for use in trials of analgesics for those with chronic pain [53] and the other a set of definitions for opioid-related adverse events [44], identified eight loose and overlapping categories of problematic use, including misuse, abuse, addiction, aberrant use, dependence, nonmedical or nontherapeutic use, physical dependence, and psychological dependence (also see the review of Webster & Fine [60], who further define “pseudoaddiction”). The vagueness inherent in these definitions, areas of overlap amongst them, and their sometimes interchangeable use have made it difficult to determine exact rates and types of problematic opioid use. For example, the narrative review of Højsted and Sjøgren [24] detailed the findings of 25 studies involving chronic pain patients prescribed opioids, concluding that the prevalence of problematic opioid use behavior ranged from 0% to 50%. Although this span was representative of the literature at the time, it was of questionable value for delineating the scope, impact, and prevalence of the problem or in facilitating informed

clinical and policy decisions with regard to the allocation of screening and treatment resources. Martell and colleagues [38], in their review of opioid use for low back pain, reported a similar range of current problematic opioid use (3% to 43%).

The purpose of the present study was to perform an updated review of problematic opioid use in chronic pain using explicitly defined terms [44,53] for rates of problematic use in the literature. We synthesized the data to clarify and calculate prevalence estimates to increase precision and utility. As a secondary set of analyses, we investigated whether variation in the rates of problematic opioid use were related to differences in study characteristics (i.e., primary study purpose, study design, method of assessment, clinical setting).

2. Methods

2.1 Literature Search Strategy

We searched the clinical and scientific literature using Science Direct, Google Scholar, PubMed, and PsychINFO/PsycArticles databases for articles published between January 2000 and January 2013. We repeated the search in November 2013 to include articles published or accepted since January 2013. We used broad search terms to increase the probability of accurate identification of target articles (Table 1). We also reviewed reference lists to identify any articles that the initial search had missed.

2.2 Abstract Screening

The abstracts of all studies identified in the literature search were read by two reviewers to assess eligibility for full text data extraction. To be eligible for data extraction, studies met the following criteria: (1) only adult participants (i.e., 18+ years of age), (2) sample composed of individuals with chronic non-cancer pain (persistent pain lasting longer than 3 months), (3) participants were using opioids orally (to exclude studies of opioids delivered transdermally or via injection/intrathecal pump), (4) the abstract listed one or more of the following terms in reference to opioid use: abuse, misuse, dependence, addiction, or aberrant/problematic

behavior, and (6) quantitative information was provided (as opposed to a commentary or qualitative review) with regard to rates of problematic opioid use.

2.3 Full Text Data Extraction

Each study fitting inclusion criteria was read in full by two members of the study team to extract and record data on a standardized data extraction form. The extracted information included participant demographics and pain details (i.e., sample size, gender, age, pain duration, ethnicity, pain location), primary objective (e.g., assessment of prevalence, medication safety/efficacy) study design (i.e., cross-sectional/prospective/ retrospective, study setting details, country of data collection), and method used to identify problematic opioid use [i.e., structured/unstructured clinical interview, urine drug screen (UDS), chart review, clinical judgment, questionnaire].

2.3.1 Coding of Current Opioid Misuse, Abuse, and Addiction

The problematic use of opioids was categorized according to recent consensus statements published by the *Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials* (IMMPACT) [44] and *Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks* (ACTTION) [53] panels, an overlapping group of experts with representation from private, public, and governmental domains. Based on these consensus statements, and the associated commentaries of Butler [9] and Sullivan [54], the following definitions were used to categorize problematic use as either misuse, abuse, or addiction.

- *Misuse:* Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects.
- *Abuse:* Intentional use of the opioid for a non-medical purpose, such as euphoria or altering one's state of consciousness.

- *Addiction:* Pattern of continued use with experience of, or demonstrated potential for, harm (e.g., “impaired control over drug use, compulsive use, continued use despite harm, and craving” [9], p. 2243).

Only these three terms were coded. Additional categorization of terms was not deemed appropriate, because the terms defined in the consensus statements were either not relevant to the purposes of the present review (e.g., diversion, intoxication, suicide-related use) or were not specific enough in their delineation of problematic use patterns (e.g., aberrant opioid-related behaviors, non-medical opioid use).

The following guidelines were used to code type of problematic use. First, the percentage of study participants meeting criteria for each type of problematic use was extracted and recorded, where possible, to the tenths decimal place. A single percentage was recorded from studies that met criteria for only a single type of problematic use, while studies that reported separately on more than one type of problematic use provided more than one estimate (e.g., one percentage for participants meeting criteria for misuse and one for participants meeting criteria for addiction). Second, when studies reported a range of values with regard to the percentage of patients meeting criteria for one type of problematic use, a minimum and maximum value was recorded. Third, only current problematic opioid use was recorded; data were not used if a study reported only on historical or lifetime problematic opioid use. When insufficient or ambiguous information was provided in the published articles or available supplemental data, we contacted study authors for additional details.

When possible, rates of opioid misuse, abuse, and addiction were recorded directly from study text (e.g., [5,36]). When no specific rate was reported, a calculation was performed based on the number of patients meeting criteria for misuse, abuse, or addiction divided by the sample size (e.g., [57,65]). When multiple forms of behavior indicating the same type of problematic use were collapsed and reported in the study as a single value, the single value was recorded (e.g., [17], where a percentage of 3.2% was presented as a combined value for various forms of

opioid misuse). Finally, when the original study included a psychometric evaluation of a questionnaire and used non-questionnaire data to evaluate issues of sensitivity and specificity (e.g., in the identification of questionnaire cut-scores), then rates of problematic use from the non-questionnaire data were recorded (e.g., [21]).

Each included study had at least one codeable percentage (with an upper limit of six if minimum and maximum values for misuse, abuse, and addiction were all reported). The categorization of problematic opioid use was performed independently by two reviewers (KEV & MLM) and, in the case of disagreement with regard to categorization, a consensus was reached following discussion.

2.3.2 Rating of Study Quality

The quality of each study was rated using eight of the nine criteria employed by Chou and colleagues ([13]; p. 146.e3) in their review of measures to predict and identify problematic drug-related behaviors. The first of Chou et al.'s criteria, which determines if the study evaluated test performance in a population other than the one used to derive the instrument (i.e., derivation vs validation study), was coded but eventually discarded as it was deemed less useful in discriminating between high and low quality.

The remaining eight criteria evaluate study sampling issues (e.g., consecutive sample or random subset; proportion of missing data), adequate description of study methods (e.g., sample and patterns of opioid prescription, criteria to identify problematic behavior), and potential influence of raters on the identification of problematic behavior (e.g., rater blinding with regard to the identification of problematic use). Consistent with Chou and colleagues, studies that met the majority of the criteria (five or more) were regarded as higher quality.

2.4 Analytic Plan

Extracted data were entered into SPSS (version 21; IBM Corporation). The primary variables of interest were average rates of misuse, abuse, and addiction across studies. Because a small number of studies reported these rates as a range of values, two sets of

calculations were performed for each type of problematic use, a minimum and a maximum. When only a single value was recorded, that value was entered as both the minimum and maximum value as that ensured that both the minimum and maximum calculations included the complete set data. While we expected minimum and maximum values to be close to one another, this method of calculation was deemed to make best use of all available data and allow equal weightings for each study's data.

The first analytic step involved the calculation of unweighted raw means and SDs for rates of misuse, abuse, and addiction across all included studies. In addition, we calculated a number of weighted means, including weighting for raw sample size and log transformed sample size. The log transformation was performed to address the large variability in sample size and apparent exponentiation of the sample size distribution within the largest studies. In addition, a Winsorizing procedure was performed for studies with sample sizes of greater than 1334 participants, which was the point at which outliers were identified within stem-and-leaf plots; there was also evidence of a bi-modal distribution at this cut-point. For the analyses using the Winsorized sample size data, samples size for all studies with greater than 1334 participants were set to 1334, the value of the next largest sample size.

In addition to the analyses involving weightings by sample size, weighted means were calculated for study quality. Further, means for studies of high and low quality were evaluated separately. Finally, a weighted interaction term of log-transformed sample size and quality rating was calculated using standardized scores (z-scores).

As a secondary set of analyses, differences in rates of problematic use were assessed in relation to primary study purpose (i.e., Was the assessment of prevalence of misuse, abuse, and addiction the primary aim?), study design (i.e., retrospective, cross-sectional, prospective), method of identification (e.g., questionnaire, structured/semi-structured interview, chart review, UDS), and clinical setting (e.g., primary care, pain clinic). A series of Analyses of Variance

(ANOVAs) was utilized to analyze for differences in rates of problematic use based on these study characteristics.

3. Results

3.1 Search Results

Figure 1 displays the flow of information throughout the different phases of the search in a manner consistent with the PRISMA statement [41]. The search yielded a total of 311 records for screening after the exclusion of 46 non-empirical papers, such as reviews, letters, and commentaries. An additional nine records were identified in the updated, November 2013, search, yielding a total of 320 records for screening.

Kappa values indicated an acceptable level of agreement among raters, range $\kappa = 0.79 – 0.91$. All articles that had a discrepant rating following this stage of evaluation were retained for full text data review.

A total of 78 articles were retained for full-text review. Of these, 40 were excluded for the reasons outlined in Figure 1. Therefore, 38 articles were used in data synthesis.

3.2 Characteristics of Selected Studies

Individual study characteristics are located in Table 2. The majority of studies, 35 (92%), reported on either misuse or addiction, while the remaining three studies reported on both. In total, 29 studies (76%) reported on rates of misuse and 12 (32%) on rates of addiction. Abuse was reported in only a single study, that of Banta-Green and colleagues [5], as this was the only study that reported specifically on participant intention. Therefore, no further calculations of abuse prevalence were performed.

Generally, considerable variability with regard to study characteristics was apparent. Sample size, for example, ranged from 63 to 938,586 participants. Quality ratings ranged from zero to eight. Sample size and quality ratings were significantly and negatively correlated with one another, $r = -.36$, $p < .05$. There was also variability in reporting of basic demographic and pain-related information. Specifically, 77.5% of studies reported on participant sex, 70.0%

provided some information on age (with 15.0% providing non-numeric information that could not be extracted – e.g., “most patients fell into the 35-50 year old range”), 47.5% provided information of any kind on participant ethnicity, and only 22.5% provided information on education. With regard to pain-related information, a minority of studies provided information on pain location (42.5%), or information on pain duration (37.5%).

3.3 Rates of Opioid Misuse and Addiction

Overall, sizeable variability in rates of both misuse and addiction was indicated across reviewed studies. Rates of abuse ranged from 0.08% to 81.0% and addiction rates ranged from 0.7% to 34.1% across all studies. For high quality studies (*n* = 13 for misuse and 10 for addiction), misuse rates ranged from 2.0% to 56.3% and addiction rates from 0.7% to 23.0%. For low quality studies (*n* = 16 for misuse and 2 for addiction), misuse rates ranged from 0.08% to 81.0% and for addiction from 8.4% to 34.1%.

Table 3a and 3b display means, SDs and 95% CI calculations for misuse and addiction, respectively. With regard to the calculation methods used to evaluate average rates of misuse and addiction, most means (excluding means calculated by raw sample size weighting and low quality studies) were within 8% of one another for misuse and within 3% of one another for addiction. Specifically, rates of misuse ranged from a minimum of 21.7% for the mean weighted by the Winsorized sample size to a maximum of 29.3% for the unweighted mean. Rates of addiction ranged from a minimum of 7.8% for the mean weighted by Winsorized sample size to a maximum of 11.7% for the unweighted mean. Calculation of 95% CIs indicated an overall range across all methods of mean calculation of 12.9% to 37.5% for misuse and 3.2% to 17.3% for addiction.

Two mean calculation methods yielded means that were markedly different from the rest including means weighted by raw sample size and means of low quality studies. Means weighted by raw sample size were approximately 69% for misuse and approximately 4% for addiction. For low quality studies, means were approximately 32% for misuse and 23% for

addiction. The 95% CIs calculated for these two methods were also noticeably more broad than those calculated using the other methods, overall range of 16.5% to 76.5% for misuse and 0.8% to 39.2% for addiction.

3.4 Comparisons of Study Design, Diagnostic Method, and Clinical Setting

As noted, because the studies identified for data extraction were quite varied with regard to their characteristics, we examined rates of misuse and addiction across studies with regard to primary study purpose, study design, assessment method used to identify problematic behavior, and clinical setting. For each of these four variables, four ANOVAs were conducted (minimum/maximum; misuse/addiction). A Bonferroni-correction was used for all pairwise comparisons to help control against the commission of a Type I error.

Across all analyses, results indicated only one significant difference in relation to study characteristics. Specifically, mean unweighted rates of opioid addiction were lower in the seven studies that identified the assessment of prevalence as the primary study objective, minimum/maximum mean = 5.5%/6.2% (*SD* = 4.6%/6.2%; 95% CI = 2.1% - 10.8%), in comparison to five studies for which prevalence assessment was a secondary objective, minimum/maximum mean = 18.4%/19.4% (*SD* = 10.7%/9.4%; 95% CI = 9.0% - 27.6%), all $Fs > 8.3$, all $ps < .02$.

For opioid misuse, 11 studies (37.9%) identified the assessment of prevalence as the primary study aim and 18 studies (62.1%) as a secondary aim. No significant differences were indicated in average rate of misuse across studies, *all* $Fs \leq 2.7$, all $ps \geq .11$.

All other comparisons did not indicate any significant differences in relation to the additional study characteristics evaluated. Specific findings are detailed in the following paragraphs and descriptive information is provided in Table 4.

With regard to study design, of the 38 studies reviewed, 39.5% were prospective, 34.2% were cross-sectional, and 26.3% were retrospective. No significant differences were indicated

by any of the analyses comparing rates of misuse and addiction with design, all *F*s $\leq$ 1.0, all *p*s $\geq$ .37.

The assessment method used also varied substantially across studies with the majority, 64.9%, using only a single assessment method (questionnaire: 21.6%, clinical judgment/chart review: 21.6%; structured/semi-structured interview: 13.5%; UDS: 8.1%). The remaining 35.1% of studies used a UDS plus at least one other method, which were coded as a single assessment category (i.e., UDS plus at least one other method). The misuse comparisons were non-significant, all *F*s $\leq$ .71, all *p*s $\geq$ .59. For addiction, while the comparisons of questionnaire and structured/semi-structured interviews with multiple assessment methods reached a traditional level of significance, $p < .05$, the follow-up Bonferroni-controlled pairwise comparisons were not significant.

Finally, for the evaluations involving clinical setting, 52.6% of studies involved data collected within a specialty chronic pain clinic with an additional 26.3% of data collected in primary care. Of the remaining studies, the clinical setting from which the data were collected was not clearly identified (e.g., clinical trials registry; toxicology laboratory). Given the diversity in clinical setting, comparisons used only data from pain clinics and primary care. Consistent with the other analyses of study characteristics, no significant differences were indicated, all *F*s $\leq$ .52, all *p*s $\geq$ .49.

4.0 Discussion

Accurate identification and enumeration of problematic opioid use in those with chronic pain is important. Our review evaluated the current state of the literature with regard to rates of opioid misuse, abuse, and addiction in chronic pain. The results are concordant with previous work in many ways. Chiefly, the substantial variability in studies evaluating problematic opioid use remains apparent as there were many designs employed, methods of identification utilized, and study settings examined. The range of rates of problematic use was even broader than has been reported in previous work [24,38] with rates ranging from 0.08% [52] to 81% [62].

We took several steps within the review to address this expected variability. First, we coded for specific types of problematic use by adopting the definitions offered by the IMMPACT and ACTTION groups [44,53]. In order of severity, these types were: Misuse (use not in accordance with prescribed directions, regardless of the presence or absence of harm resulting from use), abuse (intentional use for a non-medical purpose), and addiction (use demonstrated harm or high potential for harm). In total, 38 articles were included in the full review, with 76% providing information on misuse and 32% providing information on addiction. Only a single study reported on abuse. While the rates of misuse encompassed the entire range documented (i.e., 0.08% to 81%), the range for rates of addiction was somewhat more constrained, 0.7% to 34.1%.

Second, we calculated several weighted means and also separate means for high and low quality studies, with the overall goal of determining if a subset of these scores would provide a degree of confidence with the rates identified. With the exception of means weighted by sample size and means for low quality studies, which were particularly different than other means calculated, there appeared a level of concordance across the majority of mean calculations. On average, misuse was documented in approximately 1 out of 4 or 5 patients (actual mean percentage range: 21.7% to 29.3%) and addiction in approximately 1 out of 10 or 11 patients (actual mean percentage range: 7.8% to 11.7%). Perhaps the two most robust calculation methods were the sample size by study quality interaction term and the mean of the high quality studies only. For these two methods, rates of misuse ranged from 23.6% to 24.9% and rates of addiction from 8.8% to 10.7%. Furthermore, the observed standard deviation for the high quality studies was approximately half of that observed for the low quality studies and two-thirds of that observed across all other calculations, suggesting a lesser degree of variability amongst these studies, and therefore perhaps bolstering confidence to at some degree in the accuracy of these values.

Third and finally, we examined whether differences in study results could be at least partially explained by variability in the study methods that were employed. Almost all comparisons based on study characteristics indicated a lack of significant differences with regard to rates of abuse and addiction across different study designs, methods of assessment, and clinical settings (specialty pain clinic vs. primary care). As these analyses were likely underpowered due to small cell sizes and the ranges analyzed were broad, these results ought to be interpreted cautiously and we include them here to primarily provide information of potential use to future studies in this area.

Only a single statistically significant difference was indicated between studies with a primary purpose of assessing addiction prevalence and those that assessed it as a secondary purpose such that lower rates of addiction were indicated in studies specifically designed to assess prevalence. Bearing in mind the exploratory nature of these analyses and the caveats identified in the preceding paragraph, a key implication of this finding is that, assuming that studies designed to specifically address the issue of prevalence provide more accurate estimates, then these studies may provide more conservative estimates, perhaps because they utilize pre-defined or more specific methods for defining these outcomes.

We can make several recommendations for future studies of problematic opioid use in chronic pain. First, studies must specify the relevant demographic and pain-related details. At a minimum, we suggest that these include gender, age, and ethnicity, as well as pain location and duration. These details were included in a surprisingly small number of studies in spite of their demonstrated relevance in treatment response and role in potential for problematic opioid use [24]. The inclusion of measures of pain intensity and interference would likely provide valuable additional information. Second, there is likely benefit to be found in specifying type of problematic use that is being assessed and specifically designing studies to evaluate prevalence as a primary objective. Such specification may aid in decreasing variability across studies with regard to rates of problematic use and perhaps also have the added benefit of

allowing for greater precision in the language used in relation to patterns of opioid use in chronic pain. Third, at the present time, there is no clear gold standard for use in the identification of misuse, abuse, and addiction [48]. Perhaps the most thorough method is Butler and colleagues' [10] "Aberrant Drug Behavior Index" (ADBI). The ADBI involves a triangulation approach consisting of self-reported patterns of opioid use evaluated via a structured interview, physician-reported patterns of use, and a UDS. A positive ADBI, indicating the presence of problematic opioid use, consisted of either a positive rating on the structured clinical interview or positive ratings on both the physician report and UDS. In the present review, this triangulation method was coded as indicating misuse, but it seems feasible to modify it so that it also provides information regarding abuse and addiction.

The results of this review have two key implications. First, misuse and addiction do appear to be distinct patterns of problematic opioid use, at least based on the definitions utilized here and the differences in observed mean rates between them. Second, misuse appears more common than addiction. Several types of misuse were identified within studies and included underuse, erratic or disorganized use, inappropriate use (for example, to manage symptoms of anxiety or other sorts of distress), use in conjunction with alcohol or illegal substances (e.g., marijuana), and, of course, overuse. If it is accurate that approximately 1 in 4 patients on opioids display patterns of opioid misuse, but not addiction, then perhaps more efficient targeting of treatment resources would be of benefit. Some forms of misuse, for example, may be readily addressed through relatively low intensity methods such as education or frequent follow-up visits. One prominent example of a fairly low intensity intervention is that of Jamison et al. [28], who held monthly meetings with patients deemed to be at "high risk" of opioid misuse. These meetings were a combination of motivational approaches, opioid education, and opioid use monitoring, including a UDS, held monthly over the course of six months. At the conclusion of the study period, the documented rates of aberrant behavior was low and comparable to rates documented for another group of patients, who were deemed to be of "low risk" of opioid misuse

at the onset of the study. These findings suggest that there are alternatives available to providers who treat high risk patients beyond simply not prescribing the medications at all. A more recent study from the same group [37] further highlights a potential key role of cravings in opioid misuse, which presents another option for intervention given that the substance abuse literature already provides effective interventions directed at altering the impact of drug cravings more generally and these could perhaps be readily adapted to problematic opioid use [7,63,64].

The results of this review have several limitations. The most obvious is the degree of variability within this literature. In spite of our attempts to minimize the impact of this variability, the range of misuse and addiction were incredibly broad, as were measures of dispersion. Further, there are other potential sources of variability in findings that were not possible to code and extract in a uniform manner. These include duration of opioid use, previous history of non-opioid substance misuse, abuse, or addiction, dosage levels and frequency of use, as well as healthcare system variables, such as frequency of prescription reviews, drug testing, or use of opioid “contracts”. These sources of variability will likely continue to cloud our ability to make precise estimates. There is clearly room here for a series of carefully controlled studies where sources of variability are held constant, or as constant as possible, to more clearly illuminate prevalence rates of problematic opioid use in individuals with chronic pain.

There was one curious finding that we have not yet emphasized. The overwhelming majority of studies within this review took place in the United States (US). Only 3 of the 38 studies took place in other countries, which suggests that this issue is of both high interest and is perhaps a problem that is somehow uniquely relevant to the US. The latter interpretation is supported by the finding of Manchikanti and colleagues indicating that the US population, which represents approximately 5% of the Earth’s population, consumed approximately 80% of the global supply of prescribed opioids in the first decade of this century [31]. This is an intriguing issue and while there are likely many factors involved, neither the abundance of opioids prescribed for the treatment of chronic pain nor the large proportion of studies of problematic

opioid use appear to have helpfully diminished the prevalence, impact, or cost of chronic pain in the US since the explosion in opioid use for chronic pain [22].

One final, related, comment on the use of opioids in chronic pain seems appropriate. In short, it is not clear that the risks of opioid use outweigh the potential for benefit. The efficacy of opioids and their suitability for the long-term management of chronic pain still remains very much in question [3,4,13,51,54,55] and while this uncertainty in effectiveness is well established, it stands in somewhat stark contrast to the clinical reality of chronic pain treatment, where rates of prescriptions have skyrocketed such that opioids are now amongst the most frequently prescribed medications. What does seem clear, however, is that the rapid increase in opioid use has had what Sullivan [54] referred to as “unintended” consequences that, for at least some patients, requires an additional form of intervention to curtail patterns of problematic use and potential for harm. We are not certain that the benefits derived from opioids, which are rather unclear based on the extant literature, compensate for this additional burden to patients and healthcare systems.

References

[1] Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi J a, Schnoll SH, Senay EC, Woody GE. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage 2006;31:465–476.

[2] Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioids analgesics from 2004 to 2011. Pain Physician 2014;17:E119–E128.

[3] Ballantyne JC. Is lack of evidence the problem? J Pain 2010;11:830–832.

[4] Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: A review of the evidence. Clin J Pain 2008;24:469–478.

[5] Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain - development of a typology of chronic pain patients. Drug Alcohol Depend 2009;104:34–42.

[6] Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med 2011;12:657–667.

[7] Bowen S, Chawla N, Marlatt GA. Mindfulness-based relapse prevention for addictive behaviors: A clinician's guide. New York, NY: Guilford Press, 2010 179 p.

[8] Brown J, Setnik B, Lee K, Wase L, Roland CL, Cleveland JM, Siegel S, Katz N. Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. J Opioid Manag 2011;7:467–483.

[9] Butler S. The IMMPACT factor or IMMPACT strikes again! Pain 2013;154:2243–2244.

[10] Butler SF, Budman SH, Fanciullo GJ, Jamison RN. Cross validation of the Current Opioid Misuse Measure (COMM) to monitor chronic pain patients on opioid therapy. Clin J Pain 2010;26:770–776.

[11] Butler SF, Budman SH, Fernandez K, Jamison RN. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain 2004;112:65–75.

[12] Chelminski PR, Ives TJ, Felix KM, Prakken SD, Miller TM, Perhac JS, Malone RM, Bryant ME, DeWalt D a, Pignone MP. A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. BMC Health Serv Res 2005;5:3.

[13] Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: A review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. J Pain 2009;10:131–146.

[14] Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement non-compliance. J Pain Symptom Manage 2008;36:383–395.

[15] Couto JE, Romney MC, Leider HL, Sharma S, Goldfarb NI. High rates of inappropriate drug use in the chronic pain population. Popul Health Manag 2009;12:185–190.

[16] Cowan DT, Wilson-Barnett J. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med 2003;4:340–351.

[17] Edlund MJ, Martin BC, Fan M, Devries A, Braden JB, Sullivan MD. Risks of opioid abuse and dependence among recipients of chronic opioid therapy: Results from the TROUP study. Drug Alcohol Depend 2010;112:90–98.

[18] Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? Pain Med 2007;8:647–656.

[19] Federal Drug Administration. Attention prescribers: FDA seeks your help in curtailing the US opioid epidemic. 2013 1–5 pp. Available: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm330614.htm. Accessed 13 May 2014.

[20] Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain 2007;8:573–582.

[21] Fleming MF, Davis J, Passik SD. Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. Pain Med 2008;9:1098–1106.

[22] Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain 2012;13:715–724.

[23] Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. Eur J Pain 2010;14:1014–1020.

[24] Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: A literature review. Eur Jounal Pain 2007;11:490–518.

[25] Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, Shilliday BB, DeWalt DA, Pignone MP. Predictors of opioid misuse in patients with chronic pain: A prospective cohort study. BMC Health Serv Res 2006;6:46.

[26] Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender differences in risk factors for aberrant prescription opioid use. J Pain 2010;11:312–320.

[27] Jamison RN, Link CL, Marceau LD. Do pain patients at high risk for substance misuse experience more pain? A longitudinal outcomes study. Pain Med 2009;10:1084–1094.

[28] Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: A randomized trial. Pain 2010;150:390–400.

[29] Katz NP, Sherburne S, Beach M, Rose RJ, Vielguth J, Bradley J, Fanciullo GJ. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg 2003:1097–1102.

[30] Manchikanti L, Cash KA, Damron KS, Manchukonda R, Pampati V, McManus CD. Controlled substance abuse and illicit drug use in chronic pain patients: An evaluation of multiple variables. Pain Physician 2006;9:215–226.

[31] Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: A ten-year perspective. Pain Physician 2010;13:401–435.

[32] Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, Grider JS, Boswell M V. Opioid epidemic in the United States. Pain Physician 2012;15:ES9–E38.

[33] Manchikanti L, Manchukonda R, Damron KS, Brandon D, McManus CD, Cash K. Does adherence monitoring reduce controlled substance abuse in chronic pain patients? Pain Physician 2006;9:57–60.

[34] Manchikanti L, Manchukonda R, Pampati V, Damron KS. Evaluation of abuse of prescription and illicit drugs in chronic pain patients receiving short-acting (hydrocodone) or long-acting (methadone) opioids. Pain Physician 2005;8:257–261.

[35] Manchikanti L, Pampati V, Damron KS, Beyer CD, Barnhill RC, Fellows B. Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. J Ky Med Assoc. 2003;101:511–517.

[36] Manchikanti L, Pampati V, Damron KS, Fellows BM, Barnhill RC, Beyer C. Prevalence of opioid abuse in interventional pain medicine practice settings: A randomized clinical evaluation. Pain Physician 2001;4:358–365.

[37] Martel MO, Dolman AJ, Edwards RR, Jamison RN, Wasan AD. The association between negative affect and prescription opioid misuse in patients with chronic pain: The mediating role of opioid craving. J Pain 2014;15:90–100.

[38] Martell B, O'Connor P, Kerns R, Becker W, Morales K, Kosten T, Fiellin D. Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann Intern Med 2007;146:187–192.

[39] Meltzer EC, Rybin D, Meshesha LZ, Saitz R, Samet JH, Rubens SL, Liebschutz JM. Aberrant drug-related behaviors: Unsystematic documentation does not identify prescription drug use disorder. Pain Med 2012;13:1436–1443.

[40] Meltzer EC, Rybin D, Saitz R, Jeffrey H, Schwartz SL, Butler SF, Jane M. Identifying prescription opioid use disorder in primary care: Diagnostic characteristics of the Current Opioid Misuse Measure (COMM). Pain 2011;152:397–402.

[41] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Br. Med J 2009;339:332–336.

[42] Morasco BJ, Dobscha SK. Prescription medication misuse and substance use disorder in VA primary care patients with chronic pain. Gen Hosp Psychiatry 2008;30:93–99.

[43] Naliboff BD, Wu SM, Schieffer B, Bolus R, Pham Q, Baria A, Aragaki D, Van Vort W, Davis F, Shekelle P. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain 2011;12:288–296.

[44] O'Connor AB, Turk DC, Dworkin RH, Katz NP, Colucci R, Haythornthwaite J a, Klein M, O'Brien C, Posner K, Rappaport BA, Reisfield G, Adams EH, Balster RL, Bigelow GE, Burke LB, Comer SD, Cone E, Cowan P, Denisco R a, Farrar JT, Foltin RW, Haddox JD, Hertz S, Jay GW, Junor R, Kopecky EA, Leiderman DB, McDermott MP, Palmer PP, Raja SN, Rauschkolb C, Rowbotham MC, Sampaio C, Setnik B, Smith SM, Sokolowska M, Stauffer JW, Walsh SL, Zacny JP. Abuse liability measures for use in analgesic clinical trials in patients with pain: IMMPACT recommendations. Pain 2013;154:2324–2334.

[45] Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. J Pain Symptom Manage 2011;41:116–125.

[46] Portenoy RK, Farrar JT, Backonja M-M, Cleeland CS, Yang K, Friedman M, Colucci S V, Richards P. Long-term use of controlled-release oxycodone for noncancer pain: Results of a 3-year registry study. Clin J Pain 2007;23:287–299.

[47] Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 2002;17:173–179.

[48] Savage SR. Assessment for addiction in pain-treatment settings. Clin J Pain 2002;18:S28–S38.

[49] Schneider, JP, Kirsh, KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. J Opioid Manag 2010;6:385–395.

[50] Sekhon R, Aminjavahery N, Davis CN, Roswarski MJ, Robinette C. Compliance with opioid treatment guidelines for chronic non-cancer pain (CNCP) in primary care at a Veterans Affairs Medical Center (VAMC). Pain Med 2013;14:1458–1556.

[51] Sites BD, Beach ML, Davis MA. Increases in the use of prescription opioid analgesics and the lack of improvement in disability metrics among users. Reg Anesth Pain Med 2014;39:6–12.

[52] Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? Pain 2011;152:1555–1561.

[53] Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, Degroot A, Edwards RR, Haddox JD, Jaffe JH, Jones CM, Kleber HD, Kopecky E a, Markman JD, Montoya ID, O'Brien C, Roland CL, Stanton M, Strain EC, Vorsanger G, Wasan AD, Weiss RD, Turk DC, Dworkin RH. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain 2013;154:2287–2796.

[54] Sullivan M. Clarifying opioid misuse and abuse. Pain 2013;154:2239–2240.

[55] Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, Patel S, Manchikanti L. Opioids in the management of chronic non-cancer pain: An update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. Pain Physician 2008;11:S5–S62.

[56] United Nations Office on Drugs and Crime. Ensuring availability of controlled medications for the relief of pain and preventing diversion and abuse: Striking the right balance to achieve the optimal health outcome. 2011 Available: www.unodc.org/docs/treatment/Pain/Ensuring_availability_of_controlled_medications_FINAL-15_March_CND_version.pdf.

[57] Vaglienti RM, Huber SJ, Noel KR, Johnstone R E. Misuse of prescribed controlled substances defined by urinalysis. WV Med J 2003;99:67–70.

[58] Volkow ND, McLellan TA, Cotto JH, Marithanom M, Weiss RRB. Characteristics of opioid prescriptions in 2009. J Am Med Assoc. 2011;305:1299–1300.

[59] Wasan AD, Butler SF, Budman SH, Fernandez K, Weiss RD, Greenfield SF, Jamison RN. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients ? Clin J Pain 2009;25:193–198.

[60] Webster LR, Fine PG. Approaches to improve pain relief while minimizing opioid abuse liability. J Pain 2010;11:602–611.

[61] Webster LR, Webster RM. Predicting aberrant behaviors opioid-treated patients : Preliminary validation of the Opioid Risk Tool. Pain Med 2005;6:432–443.

[62] Wilsey BL, Fishman SM, Tsodikov A, Ogden C, Symreng I, Ernst A. Psychological comorbidities predicting prescription opioid abuse among patients in chronic pain presenting to the emergency department. Pain Med 2008;9:1107–1117.

[63] Witkiewitz K, Bowen S. Depression, craving, and substance use following a randomized trial of mindfulness-based relapse prevention. J Consult Clin Psychol. 2010;78:362–374.

[64] Witkiewitz K, Bowen S, Donovan DM. Moderating effects of a craving intervention on the relation between negative mood and heavy drinking following treatment for alcohol dependence. J Consult Clin Psychol 2011;79:54–63.

[65] Wu SM, Compton P, Bolus R, Schieffer B, Pham Q, Baria A, Van Vort W, Davis F, Shekelle P, Naliboff BD. The Addiction Behaviors Checklist: Validation of a new clinician-based measure of inappropriate opioid use in chronic pain. J Pain Symptom Manage 2006;32:342–351.

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Figure Caption

Figure 1: Flow of information thought the different phases of the review, as specified by the PRISMA statement.

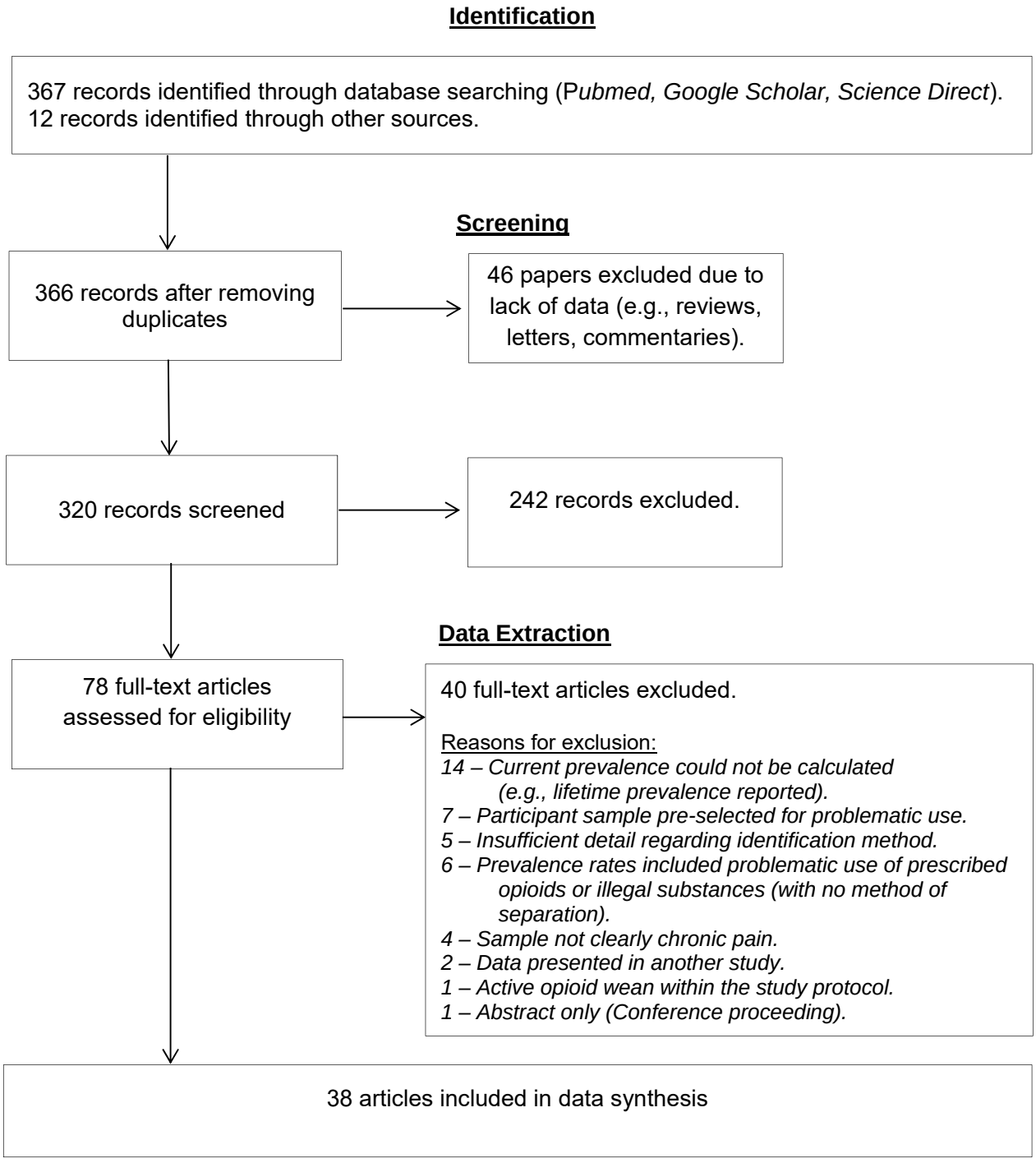
Identification
367 records identified through database searching (Pubmed, Google Scholar, Science Direct).
12 records identified through other sources.
Screening
366 records after removing duplicates
46 papers excluded due to lack of data (e.g., reviews, letters, commentaries).
320 records screened
242 records excluded.
Data Extraction
78 full-text articles assessed for eligibility
40 full-text articles excluded.
Reasons for exclusion:
14 – Current prevalence could not be calculated (e.g., lifetime prevalence reported).
7 – Participant sample pre-selected for problematic use.
5 – Insufficient detail regarding identification method.
6 – Prevalence rates included problematic use of prescribed opioids or illegal substances (with no method of separation).
4 – Sample not clearly chronic pain.
2 – Data presented in another study.
1 – Active opioid wean within the study protocol.
1 – Abstract only (Conference proceeding).
38 articles included in data synthesis

Table 1: Search terms

<*chronic pain*> AND
(<*opioid*> OR <*opiate*>) AND
(<*addiction*> OR <*dependence*> OR <*abuse*> OR <*misuse*> or <*aberrant behavior*>)

Table 2: Characteristics of included studies

First author (year)	Sample size (Country)	Design	Setting	Method of Assessment	Rate (%) of Problematic Use			Quality
					Misuse	Abuse	Addiction	
Adams (2006) [1]●	4,278 (USA)*	Prospect	Not Specified	Q	--	--	4.9%	7
Banta-Green (2009) [5]	704 (USA)	Retrospec	Primary Care	SI	--	8%	13%	8
Brown (2011) [8]●	561(USA/ Puerto Rico)	Prospect	Primary Care	CJ, Q, UDS	2-6%	--	--	6
Butler (2004) [11]	95 (USA)	Prospect	Pain Clinic	CJ, Q, UDS	46.3%	--	--	5
Butler (2010) [10]	226 (USA)	Prospect	Pain Clinic	CJ, Q, UDS	34.2%	--	--	3
Chelminski (2005) [12]	63 (USA)	Prospect	Primary Care	CJ, UDS	32%	--	--	2
Compton (2008) [14]	135 (USA)	Prospect	Pain Clinic	CJ, UDS	28%	--	--	5
Couto (2009) [15]●	938,586 (USA)	Cross-sect	Toxicology Lab Database	UDS	75%	--	--	0
Cowan (2003) [16]●	104 (UK)	Retrospec	Pain Clinic	SI	--	--	2.8%	7
Edlund (2007) [18]●	9,279 (USA)	Cross-sect	Community Database	Q	3.3%	--	0.7%	5
Edlund (2010) [17]●	46,256 (USA)	Cross-sect	Not Specified	INSUR CL	3.2%	--	--	5
Fleming (2007) [20]●	801 (USA)	Cross-sect	Primary Care	SI	--	--	3.8%	8

Table continues

Table 2 (con't)

First author (year)	Sample size (Country)	Design	Setting	Method of Assessment	Rate (%) of Problematic Use			Quality
					Misuse	Abuse	Addiction	
Fleming (2008) [21]●	904 (USA)	Cross-sect	Primary Care	SI	--	--	3.4%	6
Højsted (2010) [23]●	207 (Denmark)	Cross-sect	Pain Clinic	CJ	--	--	14.4%-19.3%	7
Ives (2006) [25]●	196 (USA)	Prospect	Pain Clinic	CJ, UDS	32%	--	--	4
Jamison (2010) [26]	455 (USA)	Prospect	Pain Clinic	CJ, SI, UDS	24.0%-37.1%	--	34.1%	4
Jamison (2009)** [27]	110 (USA)	Cross-sect	Pain Clinic	Q	46.4%	--	--	1
Katz (2003) [29]●	122 (USA)	Retrospec	Pain Clinic	CJ, UDS	43%	--	--	4
Manchikanti (2001) [36]	100 (USA)	Retrospec	Pain Clinic	CJ	24%	--	--	6
Manchikanti (2003) [35]●	500 (USA)	Retrospec	Pain Clinic	CJ	9.4%	--	8.4%	4
Manchikanti (2005) [34]●	200 (USA)	Cross-sect	Pain Clinic	UDS	3%-12%	--	--	1
Manchikanti (2006) [33]●	500 (USA)	Prospect	Pain Clinic	CJ	9%	--	--	5

Table continues

Table 2 (con't)

First author (year)	Sample size (Country)	Design	Setting	Method of Assessment	Rate (%) of Problematic Use			Quality
					Misuse	Abuse	Addiction	
Manchikanti (2006) [30]●	500 (USA)	Prospect	Pain Clinic	UDS	9%	--	--	3
Meltzer (2011) [40]	238 (USA)	Cross-sect	Primary Care	SI	11%	--	--	4
Meltzer (2012) [39]	264 (USA)	Cross-sect	Primary Care	CR	--	--	23%	8
Morasco (2008) [42]	127 (USA)	Cross-sect	Primary Care	Q	78%	--	--	1
Naliboff (2011) [43]	135 (USA)	Prospect	Pain Clinic	CJ, UDS	27%	--	--	5
Passik (2011) [45]	1,160 (USA)	Retrospec	Clinical Database	CJ	--	--	6%-11%	7
Portenoy (2007) [46]	219 (USA)	Prospect	Clinical Trial Registry	Q	2.6%	--	--	3
Reid (2002) [47]	98 (USA)	Retrospec	Primary Care,	CJ	24%-31%	--	--	7
Schneider (2010) [49]	184 (USA)	Retrospec	Pain Clinic	CJ, UDS	--	--	15.7%	7
Sekhon (2013) [50]	797 (USA)	Retrospec	Primary Care,	CJ	22.9%	--	--	5
Skurtveit (2011) [52]●	17,252 (Norway)	Prospect	Prescription Database	CJ	0.08%-0.3%	--	--	3

Table continues

Table 2 (con't)

First authors (year)	Sample size (Country)	Design	Setting	Method of Assessment	Rate (%) of Problematic Use			Quality
					Misuse	Abuse	Addiction	
Vaglienti (2003) [57]●	184 (USA)	Retrospec	Pain Clinic	CJ, UDS	25.5%	--	--	5
Wasan (2009) [59]	455 (USA)	Cross-sect	Pain Clinic	CJ,Q, UDS	34.1%	--	--	7
Webster (2005) [61]	183 (USA)	Prospect	Pain Clinic	Q	56.3%	--	--	6
Wilsey (2008) [62]	113 (USA)	Cross-sect	Emergency Room	Q	81%	--	--	2
Wu (2006) [65]	136 (USA)	Prospect	Pain Clinic	CJ, UDS	27.9%	--	--	3

Notes:

● Primary study aim was assessment of prevalence of opioid misuse, abuse, or addiction.

* Adams et al. (2006) - only data from the group taking hydrocodone used.

**Jamison et al. (2009) – only baseline data used (i.e., patients who screened as "high risk" on questionnaire).

Method of Assessment: CJ: Clinical Judgment (including chart review), INSUR CL: Insurance Claims Database, Q: Questionnaire; SI: Structured Interview; USI: Unstructured Interview; UDS: Urine Drug Screen.

Quality: Possible range 0 to 8; higher scores indicate higher quality (quality Criteria adopted from Chou et al. [13]).

Table 3a

Opioid Misuse - Unweighted and Weighted Means, SD's and 95% CI's

	Minimum		Maximum	
	Mean (SD)	*95% CI*	Mean (SD)	*95% CI*
Unweighted	28.1% (22.9%)	*19.8% - 36.4%*	29.3% (22.5%)	*21.1% - 37.5%*
Weighted means:				
Sample Size	69.4% (19.1%)	*62.4% - 76.4%*	69.5% (19.1%)	*62.5% - 76.5%*
Log Sample Size	27.4% (24.5%)	*18.5% - 36.3%*	28.4% (24.1%)	*19.6% - 37.2%*
Winsorized	21.7% (24.2%)	*12.9% - 30.5%*	22.6% (24.1%)	*13.8% - 31.4%*
Quality Rating	25.2% (18.9%)	*18.3% - 32.1%*	26.4% (18.7%)	*19.6% - 33.2%*
Sample Size x Quality*	23.8% (20.6%)	*16.3% - 31.3%*	24.9% (20.4%)	*17.5% - 32.3%*
Quality:				
High Quality Studies	23.6% (16.4%)	*14.7% - 32.5%*	24.5% (16.2%)	*15.7% - 33.3%*
Low Quality Studies	31.8% (31.2%)	*16.5% - 47.1%*	33.2% (30.3%)	*18.4% - 48.0%*

* Interaction term the product of standardized scores for the log transformed sample size and quality rating.

Table 3b

Opioid Addiction - Unweighted and Weighted Means, SD's and 95% CI's

	Minimum		Maximum	
	Min (SD)	*95% CI*	Max (SD)	*95% CI*
Unweighted	10.9% (9.8%)	*5.3% - 16.5%*	11.7% (9.9%)	*6.1% - 17.3%*
Weighted means:				
Sample Size	4.3% (6.2%)	*0.8% - 7.8%*	4.7% (6.5%)	*1.0% - 8.4%*
Log Sample Size	10.1% (9.5%)	*4.7% - 15.5%*	10.8% (9.6%)	*5.4% - 16.2%*
Winsorized	7.8% (8.2%)	*3.2% - 12.4%*	8.6% (8.3%)	*3.9% - 13.3%*
Quality Rating	10.5% (8.8%)	*5.5% - 15.5%*	10.4% (8.9%)	*5.4% - 15.4%*
Sample Size x Quality*	9.9% (8.7%)	*5.0% - 14.8%*	10.7% (8.9%)	*5.7% - 15.7%*
Quality:				
High Quality Studies	8.8% (7.3%)	*4.3% - 13.3%*	9.8% (7.8%)	*5.0% - 14.6%*
Low Quality Studies	23.1% (12.9%)	*3.4% - 39.2%*	23.1% (12.9%)	*3.4% - 39.2%*

* Interaction term the product of standardized scores for the log transformed sample size and quality rating.

Table 4

Descriptive information regarding Comparisons of Study Design, Diagnostic Method, and Clinical Setting

	Misuse		Addiction	
	Min (SD)	Max (SD)	Min (SD)	Max (SD)
Study Design				
Prospective	23.6% (17.0%)	24.8% (17.0%)	19.5% (20.6%)	19.5 % (20.6%)
Cross-Sectional	37.2% (34.0%)	38.2% (33.0%)	9.1% (9.4%)	10.0% (10.3%)
Retrospective	25.0% (10.7%)	26.2% (11.0%)	9.1% (5.2%)	10.2% (4.9%)
Method of Assessment				
Questionnaire	38.2% (35.9%)	38.3% (35.9%)	2.8% (3.0%)	2.8% (3.0%)
Clinical Judgment	17.9% (7.9%)	19.3% (9.7%)	13.0% (7.6%)	15.4% (6.9%)
(Semi) Structured Interview	11.0% (--)	11.0% (--)	5.8% (4.9%)	5.8% (4.9%)
Urine Drug Screen (UDS)	29.0% (39.9%)	32.0% (37.3%)	--	--
Multiple Methods (incl UDS)	29.0% (22.8%)	30.2% (22.3%)	10.9% (9.8%)	11.7% (10.0%)
Setting				
Primary Care	28.3% (26.5%)	30.2% (25.7%)	10.8% (9.3%)	10.8% (9.3%)
Pain Clinic	28.3% (14.8%)	29.6% (14.1%)	15.1% (11.8%)	16.1% (11.9%)