Title: An Informal Review of Opioid Dependence (Addiction) Associated with Chronic Opioid Assisted Therapy (COAT) for Chronic Pain.

Author: James K. Rotchford, M.D., M.P.H.

Medical Director of Olympas Pain & Addiction Services, P.C.

Contact information:

James K. Rotchford, M.D.

c/o OPAS P.C.

1136 Water Street, Suite 107

Port Townsend, WA 98368

Tel: 360.382.54843

Fax: 360.379.]1441

E-mail: [JKRotchford@gmail.com](mailto:JKRotchford@gmail.com)

[www.opas.us](http://www.opas.us) / [www.drrotchford.com](http://www.drrotchford.com)

**ABSTRACT:**

The diagnosis of opioid dependence (addiction) in pain patients on chronic opioid assisted therapy (COAT) is reviewed. Some of the clinical implications of managing pain in opioid dependent patients, or those pain patients who are at high risk for opioid dependence are discussed.

Clinical observations and an informal review of the pertinent literature support a common failure to make an appropriate opioid addiction diagnosis in pain patients on COAT.

The paper aims to help opioid addiction be better recognized, prevented, and treated when pain is managed with COAT. The paper provides an important foundation for justifying and designing studies which establish the prevalence and incidence of opioid addiction in pain patients who receive COAT.

**Key words:**  Opioid, Opioid Dependence, Substance Abuse, Substance Dependence, Substance Use Disorder, Addiction, Pain management, Chronic Pain, Opioid Therapy, Epidemiology, Sensitivity, False Negative.

Title: An Informal Review of Opioid Dependence (Addiction) Associated with Chronic Opioid Therapy (COAT) for Chronic Pain.

**Introduction:**

Established and validated criteria for the diagnosis of opioid dependence are available. Opioid addiction is synonymous with opioid dependence based on DSM-IV TR criteria. (See Table 1) Some clinicians confuse physical dependence with drug dependence. Drug dependence is the label for addiction under DSM-IV terminology. To avoid confusion with physical dependence, the term opioid addiction, rather than the DSM-IV TR term of opioid dependence, will be used in this paper.

Inadequate treatment of pain has significant morbidity and mortality (1) The failure to make an opioid addiction diagnosis in pain patients on chronic opioid therapy (COAT) likely adds further to this significant morbidity and mortality.(2-5) Multiple studies report patients addicted to opioids have high levels of mortality and morbidity regardless of pain status. Examples include:

In a 2003 yearlong Swedish study, 4 out of 20 opioid addicted controls died compared to none in the group being treated for opioid addiction with buprenorphine. (6)

A 2009 Norwegian study confirmed the importance of ready access to Opioid Maintenance Therapy (OMT) to prevent high mortality rates from untreated opioid addiction.(7)

The above studies involve heroin addicted patients. Hence, it could be argued these patients represent a more severe spectrum of opioid addiction.(8) Regardless of opioid used unrecognized and untreated opioid addiction can be expected to have serious health consequences. The recent public health crisis of prescription drug overdoses confirms significant mortality risks.(3) According to the Centers for Disease Control and Prevention, multiple drugs were listed in 72.]3% of “opioid-related fatality” death certificates.(9) While opioid overdose mortality is often associated with mixing opioids with other substances, particularly sedatives, the overall etiology of opioid-related deaths is complex and multi-factorial.(10) The varied risk factors and causes do not mitigate the significant mortality from untreated opioid addiction.(2,4-7,11-12).

Treatment of substance addiction is both life-saving, and cost-effective. (13, 14) When co-morbid conditions, such as complex chronic pain are present, health benefits and cost-savings are expected. (1,15). This review of opioid dependence (Addiction) associated with Chronic Opioid Therapy (COAT) for Chronic Pain aims to further research which will better determine prevalence of opioid addiction in pain patients on COAT. Perhaps when prevalence is better appreciated, clinical outcomes will improve.

**Background**

**Diagnostic Criteria for opioid addiction (dependence):**

DSM-III & IV criteria are the commonly cited criteria for opioid addiction. Newer DSM 5 criteria have eliminated the criteria associated with physical dependence. These newer criteria have not been adequately validated or tested for reliability. Based on DSM-IV TR criteria, longstanding reliability has been established through structured diagnostic interviews**.**(16-17) While the structured interview provides the “gold standard” for research purposes, clinical judgment remains important in establishing a diagnosis. The worksheet provided in Table 1 provides for a formal evaluation of opioid addiction based on the DSM-IV TR criteria.

Addiction is a primary, chronic disease of brain reward, motivation, learning and related circuitry. It entails brain dysfunction that is not necessarily secondary to another disease. DSM-IV TR criteria are consistent with International Classification of Diseases (ICD -9 -CM) guidelines. DSM-IV TR and the upcoming ICD-10 guidelines were revised in a coordinated effort among researchers worldwide to develop criteria that were as consistent with one another as possible.(18,19) The definitions of addiction such as those established by consensus of the American Academy of Pain Medicine, American Pain Society, and American Academy of Addiction Medicine (<http://www.asam.org/for-the-public/definition-of-addiction>) are consistent with DSM-IV TR criteria.

DSM V, as already mentioned, changes the criteria, and compared to DSM-IV TR, it groups substance abuse and dependence disorders into Substance Use Disorders (SUDs). This reflects the growing appreciation of a continuum of severity in addictive disorders. These DSM V changes are expected to make it easier to establish a diagnosis for an opioid use disorder in pain patients on COAT. The merits of this facilitation are likely to be debated for some time. Rather than embrace or wait for these new criteria to be validated, this paper uses the well-established DSM-IV TR criteria. The research associated with these criteria and the previous similar DSM III criteria for opioid addiction are significant. Further research, aimed at establishing reliability and validity, is needed to relate current research findings to any new diagnostic labels or criteria. This is especially true given that criteria for opioid addiction are still not without controversy.(18,19)

In addition to the established criteria for diagnosing of opioid addiction, there are also addiction screening and assessment tools (20, 21). A difficulty in, or a failure to making an accurate diagnosis of opioid addiction reflects many possible factors such as poor diagnostic tools or skills, lack of objective markers, cultural beliefs, legal ambiguities, lack of adequate management options, etc..

Even when there is a lack of current use, signs, or symptoms opioid addiction can be diagnosed by a professional interview that focuses on the patient’s history. As is the case with many diseases, serious clinical consequences arise when a patient’s history is not adequately taken.

Perhaps the best readily available definition for addiction is on the American Society of Addiction Medicine’s (ASAM) website (<http://www.asam.org/for-the-public/definition-of-addiction>). ASAM lists five (ABCDE) features common in most addiction:

1. Inability to consistently Abstain;
2. Impairment in Behavioral control;
3. Craving; or increased “hunger” for drugs or rewarding experiences;
4. Diminished recognition of significant problems with one’s behaviors and interpersonal relationships; and
5. A dysfunctional Emotional response.

Note these five features are not intended to be used as “diagnostic criteria” for determining if addiction is present or not. Although these characteristic features are widely present in most cases of addiction, regardless of the substance in question, each feature may not be equally prominent in every case. Consequently, ASAM recommends a professional assessment for a diagnosis of addiction.

In the context of COAT for pain, a recent discussion of addiction was offered by Ballantyne et al.(37) As already noted, the current criteria for an addiction diagnosis do not include findings from the physical exam, laboratory, or imaging markers. The criteria are, however, well established and have validity and reliability. Furthermore, the diagnosis of opioid addiction is associated with meaningful prognostic and therapeutic findings. Perhaps the physiological basis for opioid addiction is better understood than the majority of chronic diseases? (See below) Until improved criteria are supported by the literature, the DSM-IV TR criteria continue to be recommended.

**The Nature & Physiology of Opioid Addiction**

Addiction correlates with powerfully conditioned behaviors. The development of opioid addiction involves repetitive exposure to opioids, in the context of exposure being contingent on situational variables. The situational variables are associated with pharmacologically induced dopamine surges in the nucleus accumbens. (22) Potent “memories” are laid down. This physiological “conditioning” is what is thought to be the basis of addiction. This physiological conditioning, and its association with long term memory helps explain why addiction, whether treated or not, is expected to be a chronic condition. All addictions, indeed all forms of higher learning, may involve dopamine surges in the nucleus accumbens (NA). Furthermore, all substances demonstrated to be addictive in animal models, are thought to pharmacologically induce the release of dopamine in the NA.(23-25)

“The understanding of addiction requires understanding of a broader network of neural connections involving forebrain as well as midbrain structures. Selection of certain rewards, preoccupation with certain rewards, response to triggers to pursue certain rewards, and motivational drives to use alcohol and other drugs and/or pathologically seek other rewards, involve multiple brain regions outside of reward neurocircuitry itself.” (ASAM statement on the physiological nature of addiction at http://www.asam.org/for-the-public/definition-of-addiction)

Substance addiction is only considered in remission when the patient has not misused the substance for a 12 month period. When a patient is being medically managed with opioid agonists and taking their medications as directed, they are considered opioid addicted on agonist therapy.

The disease of addiction is relapsing. Similar to other mental conditions, relapses are to be expected, and lifetime therapy is indicated to prevent or minimize relapses. Continuing maintenance is indicated even in the context of normal or “better than normal” functioning. Hence, recovery from addiction consists of a “one day at a time” process, as is suggested in 12 step programs such as Alcoholics Anonymous.

Clinicians may associate the presence of addiction as being reflected in the signs and symptoms of end stage disease. It is often not appreciated that opioid addicted patients can be stabilized, even for a lifetime, on a fixed amount of a properly administered agonist agent.(11-12,14,29) Time in treatment is highly associated with outcomes and agonist treatment is known to help achieve this objective.(6,7, 11-12, 29)

Similar to other chronic diseases, the signs and symptoms of untreated opioid addiction may vary significantly over time. The disease may also appear to be cyclic in nature. Indeed, in milder or partially treated cases there may be extended periods of time with no apparent signs or symptoms of addiction.

All chronic diseases have a continuum of severity based on individual susceptibilities, genetic variables, environmental factors, initiating factors, available medical care, as well as other often unrecognized or under-appreciated variables. Similarly, opioid addiction has a continuum of severity. The notion of individual susceptibility is highlighted by the estimates that only one in four individuals exposed to heroin eventually become opioid addicted.(26)

Compared to alcohol addiction for which abstinence is generally considered optimal, opioid addicted patients have a poor prognosis with abstinent based therapy. (6-7,11-12,27-30) The degree of neuro-apoptosis (neural cell death) or mu receptor degradation which occurs with repeated opioid administration is still being studied. The full mu receptor agonist methadone is well known to improve prognosis in opioid addicted patients. The partial agonist buprenorphine is also FDA approved for treating opioid addiction. The mu receptor antagonist naltrexone has also demonstrated efficacy. These pharmacological therapies are important in predicting a favorable prognosis for opioid addicted patients. (6, 12, 27-33)

For most patients opioids result in physical dependence when used continuously over time. As noted above, physical dependence alone does not mean addiction. Conversely, some clinicians assume that addiction requires evidence for physical dependence. This emphasis on physical dependence is misleading. Only two of the seven DSM-IV TR criteria for addiction involve physical dependence i.e.: tolerance and withdrawal. At least three criteria need to be met to establish addiction. Consequently, the diagnosis of opioid addiction can be readily met without evidence for physical dependence. When an opioid addicted patient is free of symptoms and signs for some time their tolerance does return to normal. It is frequently an addicted patient’s loss of tolerance that contributes to drug overdoses.(34) Hence, an opioid addicted patient may die from their disease even when they are not currently physically dependent on an opioid.

Whether receiving agonist therapy (some call it substitution therapy) or not, a diagnosed opioid addicted patient can function normally as well as feel normal without symptoms or signs. Just as with diabetes and other chronic diseases the diagnosis of opioid addiction does not establish disability or invariably predict a poor prognosis. This is particularly true when the disease is being adequately treated or is in remission. The lack of current signs and symptoms must not therefore dissuade the clinician from at least entertaining a diagnosis of opioid addiction. Any 12 month period in the patient’s lifetime when three criteria are met is adequate to establish the diagnosis. Addicted patients who are drug free or sober for years are not to be considered cured. Like the cancer patient, the longer an addicted patient remains without a “relapse” the better their prognosis.

A patient’s age, genetic, and environmental factors are all known to influence the risk of opioid addiction. What percentage of the population is at risk? Who are at highest risk? Does third party coverage matter? This question may be quite relevant because in Washington State more than 50% of the opioid overdose deaths were in Medicaid clients.(4) Are there objective factors to determine or predict severity? Answers to these questions while clinically relevant are not well researched.

**Opioid Addiction in Pain Patients on COAT**

The above introduction of the diagnostic and clinical attributes of opioid addiction has implications for pain patients on COAT. As already mentioned, the lack of apparent signs or symptoms of opioid addiction does not preclude the diagnosis. With regards to addiction in the context of COAT for pain, a brief discussion of pseudo-addiction is warranted. The wide acceptance of the pseudo-addiction concept may partially explain the failure of some clinicians to make an opioid addiction diagnosis in pain patients on COAT.

**The Issue of Pseudo-Addiction**

The term “pseudo-addiction” was coined to describe the behavior of undertreated pain patients with behavior resembling addictive behavior. (35) Patients with unrelieved pain may become focused on obtaining medications, may “clock watch,” and may exhibit “drug seeking” behavior. Even behaviors involving illicit drug use and deception can understandably occur during a pain patient’s efforts to obtain adequate pain relief.

Pseudo-addiction is a descriptive term, and not a diagnosis per se. (5 pp.56) It is believed that pseudo-addiction can be readily distinguished from true addiction in that the behaviors resolve when the pain is effectively treated. While this common belief is based on what might be considered common sense, clinical dilemmas commonly arise as a result. For example, the average patient who is withdrawing from opioids will start to experience painful muscles. It could be expected because of the anxiety and sleeplessness associated with the withdrawal, that pain stemming from any etiology would increase. This “withdrawal pain” would also be relieved by adequate opioid administration. The clinical dilemma arises: is new or worse pain stemming from withdrawal or is it reflective of another etiology? Does it reflect an acute change in nociception? Does it reflect progressive chronic nociception? How can a clinician effectively differentiate the pain of withdrawal from the expected ups and downs of complex chronic pain?

Other problematic clinical questions arise: Does increased pain arise because of opiate induced hyperalgesia(OIH)? (36) When does it relate to an unrecognized medical or psychiatric disorder, or even common situational stressors? More to the point, pain can be of a nociceptive origin in addicted patients as well as non-addicted patients. How then could one really be confident that providing a higher dose of an opiate and relieving pain is secondary to pain relief rather than simply a more robust treatment of an opiate addiction with agonist treatment. It is well established that opiate addicted patients often require much higher levels of opiates to be stabilized even when they don’t have pain. In my opinion any patient who requires more than a 60mg equivalent of methadone per day for adequate pain management for chronic non-cancerous pain is very likely to be opiate addicted. That is, there brain has been altered significantly in such a way as to require long term chronic agonist therapy for stable brain function and optimal outcomes.

Concerns about the concept of pseudo-addiction were recently reviewed in a commentary by Ballantyne et al.(37) The authors state that a premise of pseudo-addiction is that the drug seeking behavior will go away when an adequate dose is employed, but that this is not necessarily apparent in the long term treatment of chronic pain. These authors also discuss the possibility that diagnoses, other than opioid addiction, must be entertained. They suggest the term “complex persistent opioid dependence” to acknowledge the common dependence seen in COAT for pain. The authors acknowledge that regardless of diagnostic labels, the effective clinical response is likely to be similar to the opioid addicted patient. This would include extra support, structure, and monitoring.

Experienced pain practitioners acknowledge it is clinically problematic to ascertain a clear etiology for pain behavior in complex pain patients. The differential diagnosis is even more complex in patients with a substance use disorder.

Based on the above discussion any astute clinician must be highly cautious when applying the label of pseudo-addiction. Nonetheless, there is likely a small subset of patient whose behavior might best be properly attributed to the descriptive term pseudo-addiction. Perhaps the label is particularly valid in patients who have established etiologies for rapidly progressive nociception such as patients with terminal cancer or in the context of an acutely painful condition?

This discussion also confirms the importance of clinical judgment and professional assessments in complex clinical settings. Pseudo-addiction and a further discussion of its origins and history can be found in an earlier paper by Ballantyne et al. which reviewed opioid addiction in pain patients on COAT. (38)

The term problematic opioid use (POU) perhaps is a better label for the behavior which could be associated with the concept of pseudo-addiction. The adjective problematic has advantages over the terms aberrant behavior or pseudo-addiction. Aberrant behavior may inappropriately shame a patient and in some clinical contexts “aberrant” behavior can be actually quite common. The term problematic opioid use assumes no etiology and may be less judgmental. It also encourages effective solutions to be sought. Thankfully, there are effective ways to address problematic behavior associated with COAT and pain management, even when opioid addiction or risk factors for same are present. (5, 39-44)

**Prognosis and Treatment Recommendations related to opioid addiction in the context of COAT for pain:**

What are the differences in properly managing opioid addiction in association with COAT for pain from opioid addiction stemming from heroin use? Or in other words: If patient A has pain and is addicted to Heroin and patient B has pain and is addicted to prescription opiates, how should treatment differ for patients A & B? Furthermore, what differences remain between patients A & B once significant confounding variables are eliminated? (27) Until the clinical trials to answer these question are done, it is suggested we assume that the differences are negligeable.

Variability is common both in the severity and response to treatment for opioid addiction.(28) In addition to variables already mentioned there are other variables to be considered: pharmacology of substance(s) used, routes of administration, co-morbid conditions, etc.. When risk factors for opioid addiction are present and uncertainties about pain etiology exist, a clinical response based on a risk assessment is required. (40, 43, 45). Patients in high-risk groups likely require different therapy compared with low-risk persons. (5, 39-41) Which opioids are best? Are long acting opioids or only those effective for opioid addiction best? What is the role for breakthrough or “as needed” opioid prescriptions? In what context can they be prescribed safely? What behavioral support is indicated and when is it necessary or simply better? On what reliable basis can we assess the severity of an addiction? Which clinical factors best determine the nature and intensity of therapeutic options? When acute nociception is present, such as after surgery or a fresh injury, what role do risk factors play in establishing proper pain management? Unfortunately, many of these important clinical questions have presently little but expert opinions to guide the clinician.

Therapy based on expert opinions with understandings of the pathophysiology of complex chronic pain and opioid addiction are likely to have the best outcomes pending further guiding research. Hence, it must be assumed a pain patient with opioid addiction is likely to do best on agonist therapy with a long acting opioid. In this context, avoidance of breakthrough or symptom contingent dosing is best limited.(46)

Long acting medications, such as methadone or buprenorphine are the current preferred medications (FDA approved) for agonist therapy for opioid addicted patients. Perhaps, given their demonstrated efficacy in treating pain, these are the agents of choice for opioid addicted patients on COAT for pain? In methadone maintenance clinics the average daily dose of methadone is 80-150mg day. (47) This range of methadone is likely to be the one also effective for stabilizing some complex pain patient who are also opioid addicted. Note, however, that effective pain management with methadone often requires more than once daily dosing. Note the possibility that long acting morphine (SROM) could be an effective management option for some patients who are mildly opioid addicted.(46)

The above reflect a few examples of meaningful recommendations despite the lack of formal answers regarding the management of high risk patients. Unfortunately, barriers to effective management of opioid addiction are common, even outside of the context of COAT for pain (15). Cultural, legal, regulatory, as well as financial barriers are prevalent.

The above was provided as background to appreciate how a failure to make the diagnosis of opioid addiction in patients on COAT is likely to be relatively common.

**Prevalence of the failure to make a diagnosis of opioid addiction.**

**Clinical observations**

Clinical observations suggest a high rate of false negatives (failure to make the diagnosis) of opioid addiction is present in pain patients on COAT. Experienced clinicians (45) corroborate that establishing or formally excluding the diagnosis of opioid addiction in a pain patient on COAT is problematic but often the opinions of pain specialists is that opioid addiction is relatively rare. This opinion is provided with little effort to provide a formal and specialized workup for addiction in pain patients on COAT. Consultants expressing concerns regarding the use of opioids will typically use phrases such as “This is high risk patient” or “This patient needs further psychiatric evaluations”, or “This patient must be taken off of their pain medications”, “This patient is a drug seeker”, “This patient exhibits aberrant behaviors,” or “There is no good reason for this patient to be on this dose of opioids.” In contrast one rarely encounters a clinical report such as: “Patient meets (or does not meet) the criteria for opioid addiction”.

On occasion, tools that screen for high risk patients are referenced. But these tools can only help clinicians predict and assess the likelihood of aberrant drug related behaviors (ADRBs) in patients on chronic opioid therapy. Evidence for their validity, however, is limited (48) and it can be argued that they should not replace efforts to establish or exclude the important diagnosis of opioid addiction.

The contents of current debates about the relevance of morphine equivalent doses and their relative risks for complications in pain patients on COAT (49) further suggest a denial of the importance of recognizing and effectively managing co-morbid conditions, including opioid addiction in pain patients on COAT. In Washington State legislation was passed based on morphine equivalent doses. In part this was supported by a linear relationship between doses and the likelihood of complications. Nonetheless, 50% of the opioid overdose cases in Washington State were in Medicaid clients.(4) This is in the context of probably less than 10% of prescribed opioids being prescribed to Medicaid clients in Washington State. These factors with the additional evidence that privately insured patients are prescribed similarly high doses of opioids (50) speaks to undisclosed variables other than morphine equivalent doses, as likely representatives of better predictors for opioid complications. Current evidence supports that the number of painful conditions, age, mental health conditions, and substance use disorders as being good predictors of higher opioid dosing in pain patients (50) It is reasonable to assume these variables are even more important predictors for COAT complications in that they predict the higher doses in the first place!

The focus on higher morphine equivalent doses as the primary concern for preventing opioid complications (49, 51), is consistent with many pain specialists assuming the diagnosis of opioid addiction is rare. It attributes the risk to the dose or the medication used rather than attributing the risk to patient diagnoses and management of underlying substance use disorders or other co-morbid medical and psychiatric conditions.

Extensive experience in an outpatient specialized pain and addiction clinic (45) supports our hypothesis that the diagnosis of opioid addiction is often not entertained, let alone established. Furthermore, when the diagnosis is entertained in high risk patients, the diagnosis of opioid addiction, based on DSM-IV TR criteria, is likely to be established.

**Informal literature review**

In addition to a search of the addiction literature, the search included the titles and abstracts of articles published in the pain literature. Some articles were found by reviewing the publications of acknowledged leaders in the field. (Ballantyne, Fine, Katz, Passik, Portenoy, Shnoll, and Webster) Other papers were found through searches including the terms chronic pain, opioid dependence and addiction.

None of the literature directly addressed the question: “What is the failure rate to make or exclude the diagnosis of opioid addiction (dependence) in pain patients on COAT?” The current literature does, however, attempt to address questions related to incidence or prevalence of opioid use disorders in pain patients on COAT:

* In1997 a study of 125 chronic pain clinic patients, 69.]6% were on opioid analgesics (including codeine) and 17.]6% were on benzodiazepines. 12% of these patients were diagnosed as having psychoactive substance abuse or dependence disorder using DSM-III-R criteria (52).

**Comment:** Because of the mix of prescriptions and the non-specificity of the findings regarding opioid addiction, little can be gleaned, but this study highlights the lack of formal assessments for opioid addiction in studies reporting prevalence or incidence.

* A 2005 American study demonstrated that 2-5% of chronic pain patients were addicted to opioids. (53) The definition they used for addiction was: “addiction means the pursuit of such substances for no medical purpose despite resulting physical or psychological harm.”

**Comment:** The definition of addiction used would likely exclude many patients who are opioid addicted and are receiving adequate therapy. These “treated” patients on prescribed COAT would not be expected to present with aberrant behavior or overt illicit behavior. Furthermore by excluding craving and other criteria generally appreciated to be consistent with addiction, the expected sensitivity for establishing opioid addiction would be limited. What’s more, since they did not include the use of opioids to help manage opioid addiction, it reflects potentially strong prejudices in the pain community about opioid addiction. Opioids are medically helpful not only for painful conditions, but as already discussed, are frequently essential and potentially life-saving in patients who are opioid addicted.

* In 2006 Mehta et al. quote a 3–16% rate of addiction in patients who complain of pain, albeit in diverse pathological conditions, and using different definitions of addiction. (54)

**Comment:** This group is not formally comparable to patients on COAT for pain. The study does highlight a significant concern about addiction in patients with pain complaints and implies the usefulness of formal assessments for addiction in patients with chronic pain, regardless of COAT status.

* In 2007 Ballantyne et al. review the pain literature as it pertains to the diagnosis of opioid addiction in patients on COAT. (38) The authors provide confirmation that diagnosing iatrogenic opioid addiction is more problematic than when the opioid use is associated with longstanding illicit drug use. The authors express a lack of satisfactory means of differentiating “true addiction” from problematic behavior secondary to factors other than addiction.

**Comment:** Rather than considering one disorder that presents in a variety of ways and depends on severity and context, the authors suggest additional distinct explanations for the observed “problematic” behavior. In their discussion, no formal diagnosis is typically established to explain the “problematic” behavior. As already discussed, the phenomenon of pseudo-addiction is often provided as the common reason for problematic behavior. In addition to not formally addressing the question of false negatives, the review by Ballantyne et al. supports a wide variance in reported prevalence of opioid addiction in pain patients on COAT. This is consistent with the hypothesis that formal and reliable assessments are lacking.

* In 2007 another study involved 801 chronic pain patients who received opioid therapy from their primary care physician. (55) The point prevalence of current (DSM-IV criteria in the past 30 days) substance abuse and/or dependence was 9.]7% (n=78) and 3.]8% (46) for an opioid use disorder.

**Comment:** This represents a significant number of opioid addicted patients on chronic opioid therapy for pain. It also limited the assessment to the past 30 days which, as previously mentioned, would clearly limit the number of potential patients who meet diagnostic criteria. Such a potential reduction in addiction diagnoses interferes with meaningful prevalence determinations. Indeed, the validity and reliability of the findings are not discussed.

There was no reported attempt to address the rate of false negatives. This lack of determining the “False Negative” is typical of the current literature that explores prevalence rates of opioid disorders in pain patients. False negatives must be important in these populations. It is well recognized that self-reporting is problematic in populations being prescribed opioids.(56) Nonetheless, the diagnosis is most often not entertained even in specialized pain management settings.

* A 2007 European review paper reported the prevalence of addiction varied from 0% up to 50% in chronic non-malignant pain patients, and from 0% to 7.]7% in cancer patients. The rates depended upon the sub-population studied and the criteria used. (57)

**Comment:** The variability in prevalence rates reported in this review calls for further studies to formally assess prevalence of opioid addiction in various subgroups of patients. Note that the findings did not require patients to be on COAT but simply to have chronic non-malignant pain. The findings of addiction were not reported to be specific to opioid addiction. Nonetheless, their findings provide supportive evidence that opioid addiction is likely to be significantly prevalent in patients with chronic non-malignant pain. It could be argued that those who are on COAT are even more likely to be opioid dependent. Patients on COAT for pain commonly meet at least 2 out of the 3 required DSM-IV TR criteria.

* In their 2007 book, *Avoiding Opioid Abuse while Managing Pain*, Webster and Dove(58) state:

“The prevalence of addiction in pain patients has almost certainly been underestimated in the recent past. In truth, the prevalence of drug abuse and addiction in patients treated with opioids for chronic pain has not been established because of the lack of prospective studies.”

They quote statistics that suggest that having chronic pain whether managed by opioids or not, is associated with substance abuse in the 10-18% range. This rate is similar or slightly higher than the general rate of addiction in the general population.

**Comment:** There were admittedly no studies which directly and formally address opioid addiction prevalence. If 10-18% of the general population have substance abuse problems, and patients on COAT for pain inevitably meet two (tolerance and withdrawal) out of the three meet DSM-IV TR criteria for opioid addiction, a fair percentage of patients on COAT for pain are probably opioid addicted. Given the lack of observed opioid addiction diagnoses being made, these statistics support a common failure to make the diagnosis of opioid addiction in pain patients on COAT.

The authors state in the next chapter that “True opiate addiction that results from long-term opioid therapy is relatively rare”. (58, pp. 30) One must agree that long term opioid therapy is not by itself the sole cause. Genetics, age, environmental, and co-morbid conditions all contribute to the possibility of disease initiation and progression. The statement, however, is misleading. By focusing on the question of incidence as the direct or unique result of COAT, it sidesteps the more important clinical question of the prevalence and incidence of opioid addiction in pain patients on COAT, regardless of causes.

* In the 2011 study “Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting” (59) Brown et al conclude: “there was a tendency for investigators to assign lower risk levels than those that were protocol-specific, suggesting a need for better understanding of factors influencing investigator decisions.”

**Comment:** While they did not specifically address the question of prevalence or incidence of opioid addiction, their findings support our hypothesis that even seasoned clinicians tend to minimize the risks for opioid addiction in their patients on COAT.

* In 2011 Morosco et al. spoke in more generic terms of Substance Use Disorders in patients with CNCP. (2)

**Comment:** While the importance of recognizing-morbid SUDs is stressed, they did not formally address the question of prevalence of opioid addiction in patients with Chronic non-Cancerous pain. This study too was performed in primary care setting. Studies to compare incidence and prevalence in primary care setting vs. specialized settings such as emergency rooms, orthopedic clinics, or pain management specialists would be helpful.

- In 2012 Monozzi et al. published *Development of dependence following treatment with opioid analgesics for pain relief: a systematic review*.(60) Qualifying studies for analysis included 3 systematic reviews, 1 randomized controlled trial (RCT), 8 cross-sectional studies, and 4 uncontrolled case series. Most studies involved adult patients with chronic non-cancer pain, two also included patients with cancer pain, but only one included patients with a previous history of dependence. Minozzi et al. found that the incidence of addiction reported across the various studies ranged from 0% to 24% (median 0.5%), while prevalence ranged from 0% to 31% (median 4.5%). There was a significant variation among the studies in terms of design, definitions of addiction, data collection, and other factors, so a data meta-analysis could not be conducted. The researchers rated the evidence as being overall of very low quality.

**Comment:** The authors did not comment on how they defined incidence or prevalence and the tables discussed frequencies. Frequency, particularly in the context of opioid addiction, does not readily translate to standard definitions for incidence or prevalence. The wide ranges of addiction incidence (0%-24%) and prevalence (0%-31%) reported by the researchers are consistent with a lack of reliability or validity in the methods used to assess opioid addiction. Estimates of median values —0.5% incidence and 4.5% prevalence — cannot be reliably used to denote the extent of addiction in patients receiving opioid analgesics for pain. The usefulness of the median statistic can be compromised by a large variation from the established mean. Median values also have limited value in estimating rates when the measures used are not established to be valid or reliable.

Time exposed to opioids varied greatly in the various studies. Only 11 of 17 studies reported on length of opioid treatment, which ranged from 3 days to 81 months. Most studies were of short duration. Since time and intensity of exposure are related to the likelihood of developing an addiction, studies of short duration are less likely to demonstrate development of addiction. As previously explained, if attempts were not made to formally assess evidence for opioid addiction in the past, prevalence data for the diagnosis of opioid addiction is uncertain. As would be predicted, indirect evidence from logistic regression analyses in 3 studies found that prior substance abuse/dependence was a strong predictor of addiction during opioid analgesic therapy.

- In 2015 Kevinn E. Vowles et al publish in Pain*: Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis.(68)* Rates of problematic use were quite broad in COAT, ranging from <1% to 81% across studies. Rates of addiction averaged between 8% and 12% (range, 95% Cl: 3%-17%). In none of the studies reviewed were there formal and systematic attempts to diagnose opiate dependence based on DSM IV criteria but rather on some current consensus definitions. In an accompanying commentary, (68) Ballantyne commented: “But could rates of addiction have been underestimated because these there cannot be clear distinctions between misuse and addiction, despite the apparent clarity of the definitions?” Ballantyne also comments that it may be impossible to understand what addiction actually is when it arises during pain treatment with opioids.

**Comment:** When it comes to problematic opioid use associated with COAT for pain, it seems that there are significant barriers to using standard and established definitions of addiction based on their established validity and reliability. This resistance was codified in the newer DSM V criteria where the diagnosis of opioid use disorders are to have different criteria in the context of the medical management of pain. While there is little or no literature to support these new criteria and the assumptions are arguably problematic based on our current understandings of the disease of opioid addiction, they are likely to endure until studies are designed and performed to address the questions.

- Most recently in 2015 Degenhardt L. et al. published a most important paper looking at the prevalence of opiate addiction and use disorders in Australian patients on COAT for chronic non-cancer pain. (70)

It was a cohort study and compared prevalence of opioid dependence and use disorders using DSM IV, DSM V, ICD-10, and proposed ICD-11 criteria. They used the well-established Composite International Diagnostic Interview, a structure interview, to explore the rates of opiate addiction in the population studied. The population was recruited generally with median duration of pain 10 years, strong opiates used for a median of 4 years, and mean age 58. (1422 participants)

While their findings are worth reviewing in detail, for the purposes of this review they found in the population studied an 8-10 % lifetime prevalence of opioid addiction with a DSM V rate of 21% if mild opioid use disorder criteria were used, and conditional exclusions present. (ie: tolerance and withdrawal criteria excluded). Of note they found men were more likely to meet criteria for opiate dependence with an odds ratio of approximately 1.5.

Their discussion of the different criteria and their agreement showed an excellent agreement between ICD-10, ICD-11, and DSM IV. There was only fair to moderate agreement between ICD-I0, DSM IV, and DSM 5 use disorder criteria. Based on their “model fit” the definition for dependence in the draft ICD-11 worked best, and the worst was DSM-5.

**Comment:** The results of this paper no longer allows a prescriber of COAT for a patient with chronic non-cancerous pain to assume that opioid use disorders are rare. As a result, their findings have huge clinical implications. The intent for writing this review was to promote studies, such as this one! The next step is to tease out the rates of opioid use disorders in patients who are likely to be at high risk: those with comorbid major psychiatric diagnoses and substance use disorders, age of onset before age 25, disability status, PTSD or sexual trauma in the past, family history, etc.. (See next Review)

It is also likely that the rates are different in different clinical contexts. Even more importantly it is time we recognize how frequently the diagnoses are missed in the various clinical contexts, that is, to explore formally the failure rates of making an appropriate opioid addiction diagnosis in pain patients on COAT. While Degenhardt L. et al., based on their findings, would seem to prefer the draft ICD-11 criteria, I would predict the DSM-IV criteria are equally suitable. The DSM IV criteria also have a robust and established research base as it relates to prognosis and effective therapy.

- In conjunction with the above large Australian Cohort study, Cambell G et al published an article in Pain Medicine in 2015. This article examines pharmaceutical opioid dose and dependence and examines the correlates of each.(71) Multivariate analysis found past-year dependence was independently associated with being younger, male, unemployed, unmarried, exhibiting more aberrant behaviors (most commonly early requests for refills or requests for higher doses) and having a history of benzodiazepine dependence. Patients who were opioid dependent were also more likely to report past year depression, GAD, and PTSD or other substance abuse disorders. A greater daily opiate milligram equivalent (OME) consumption was also associated with higher odds of multiple physical and mental health issues, aberrant opioid use, problems associated with opioid medication, and opioid dependence.

They like many reviewers seemed to be concerned about the opiate doses prescribed and the selection process for same. They commented: “The term “adverse selection” has been coined to describe this apparent contradiction in which the likelihood of a patient receiving opioid therapy increases as the number of risk factors for adverse outcomes increases; this study found strong evidence for this, whereby those consuming higher levels of opioids were clearly those with a more complex picture of physical and mental health problems, as well as social disadvantage.”

**Comments:** The correlates found confirm clinical experience and the literature.(72,73) in terms of higher morbidity and risk factors for having an opioid use disorder. A most pertinent question remains: when patients have one or more established risk factors, what is the actual likelihood that they have a significant opiate use disorder? If multiple risk factors are present we might expect a greater likelihood of a significant opiate use disorder. If this is true, a possible implication is that the complications seen as the result of higher doses of OEMs may simply be a failure to recognize and properly manage opiate use disorders in COAT patients. As previously noted opiate addicted patients, even those who do not have chronic non-cancerous pain, require higher doses of stabilizing opiates to avoid complications and assure the best clinical outcomes. One must appreciate that opioid use disorders must be considered life time disorders. The diagnosis must be considered when criteria are met during any 12 month period, not just the most recent 12 month period as in this study. So the 8-10% prevalence of opiate addiction in the past year doesn’t necessarily accurately reflect the true prevalence of the disease in this cohort.

Indeed, the impetus of this paper is the clinical impression that the failure to make the diagnosis and assure proper care for an opiate use disorder is common amongst COAT patients. Such a failure may well be the primary reason for the higher complications associated with the higher OEM doses. Another possibility is the relatively poor management of the other co-morbid psychiatric problems, let alone the socio-economic stressors, and the overall adverse selection process (72-75).

With almost all strong pharmaceuticals, when predicting good outcomes, proper patient selection and monitoring for potential side effects and complications is essential. Most often the selection and monitoring is more important than the actual dose of medicine prescribed.

The author is concerned that the emphasis on OEM doses often represents a Post Hoc fallacy. In other words, the association between higher OEM doses and complications does not necessarily imply that higher OEMs are the primary cause of the complications.

**General Comments on Review Articles**

Minozzi et al’s along with Vowles et al’s reviews were, until the Degenhardt L. et al’s cohort study, the most exhaustive evidence gathering and review process on this subject to date. With the findings of Degenhardt L. et al, the contention that addiction is not a “major risk” associated with COAT can be rejected. As already discussed, opioid therapy alone is not likely to be a significant risk, but when it is coupled with other risk factors, the prevalence and incidence for opioid addiction is expected to be even greater than the 9-10% noted in the general cohort of COAT chronic non-cancerous pain patients.

Until Degenhardt L.et al.’ findings, there was a lack in the literature of valid and reliable opioid addiction assessments for a large cohort of chronic complex pain patients on COAT. Conclusive evidence regarding incidence and prevalence of opioid addiction will likely come from prospective clinical studies which use the “gold standard” of structured interviews, as found in the Degenhardt L. et al study.

Another possibility is that “objective biomarkers” will soon be able to establish the diagnosis of opioid addiction, as is now being considered with Major Depressive Disorders. Biomarkers might readily overcome subjective biases and other inherent barriers which make the diagnosis of opiate use disorders difficult to formally establish.

This is particularly true when the disease of opiate addiction is clinically mild, intermittent, or in remission, whether from agonist therapy for pain or addiction, or through abstinence based approaches. Until such biomarkers have been validated and found to be reliable, the patient history, expert clinical evaluation, and the appreciation of risk factors will remain essential to help prevent the serious complications in patients with chronic non-cancerous pain who receive COAT.

The variable rates of addiction reported above and elsewhere reflect a heterogeneous group of settings and patients who take opioids for chronic pain. Given this, along with the variety of definitions used, and the lack of clear objective markers, the challenges and controversies in establishing the prevalence or incidence of the diagnosis of opioid addiction are likely to continue.

Patients at risk for substance abuse are not expected to be reliable reporters. This makes self-reported criteria further suspect. The clinical significance of false negatives in the population of pain patients on COAT has not gone unnoticed. Due to the clinical uncertainties in identifying problematic use, abuse, or dependence, Urine Drug Testing (UDT) has become standard in specialty clinics prescribing COAT for pain. If not sought for or screened for, drug abuse and adherence concerns are commonly missed, even by the most experienced practitioner. (9, 56, 61-62)

Clinicians may also falsely label patients as “drug seekers” or “addicts”. In addition to the concept of pseudo-addiction as discussed above, another confounder is that adherence problems are common in most chronic conditions, particularly those with prescribed regimens requiring regular dosing. Hence, problems of adherence do not only occur only in pain patients suffering from an addiction or substance abuse. Perhaps the rates of adherence problems in pain patients with addictive disorders are similar in magnitude to those with other chronic diseases such as diabetes, hypertension, or asthma? Indeed, most chronic diseases have similar relapse rates to that of addictive disorders. (65)

Lastly, one must acknowledge that abuse, addiction, or diversion are not the only reasons for adherence problems in a specific COAT patient. Other explanations need to be always entertained by the astute clinician when confronted by an adherence concern, whether for a low or high risk patient.

**Conclusion**

Three lines of evidence support a common failure to diagnose opioid addiction in pain patients on COAT.

1. The established pathophysiology of opioid addiction and the risks inherent with repeated exposure to potent opioids. In addition to the repeated exposure to opioids, there are a significant number of patients who are known to be at high risk for having or for developing addiction.
2. Clinical observations.
3. Informal review of the literature.

How common these failures are requires further study but the findings of Degenhardt L. et al. have already documented a likely significant failure by prescribers to establish or rule out opioid use disorders. A prevalence of 10% which is likely much higher in certain subgroups or cohorts, is not a rare or even uncommon diagnosis.

This paper provides support for the importance of clinical research to help resolve the question of prevalence and incidence of opioid addiction in pain patients receiving COAT. We encourage formal screening for opioid use disorders in all pain patients on COAT, in particular those with risk factors, for which higher OEM doses is just one of many.

Based on established morbidity and mortality rates the consequences for the lack of formal screening for opioid addiction in pain patients prescribed COAT are serious and predictable. Until there are better criteria for establishing the diagnosis for opioid addiction, with research confirming their validity and reliability, the currently established criteria for opioid addiction based on DSM-IV TR or perhaps with time the new draft ICD-11 criteria will be found to be best.

**Summary**

Once incidence and prevalence of opioid addiction in pain patients on COAT are more widely appreciated, effective preventive and therapeutic measures are likely to follow. Hopefully, as the new DSM V criteria for substance use disorders become established, there will be a further appreciation that opioid addiction, as is the case with most chronic diseases, has a continuum of severity and morbidity. Unrecognized and or poorly treated opioid addiction may be a common explanation for the recent spate of opioid overdose deaths. (64)

As physicians better appreciate the common neuro-psychological findings present in patients with chronic complex pain and addictive disorders, they will be better prepared to address and treat addictions in patients with chronic pain disorders. Physicians might also better utilize some of what is known in treating addictions to improve their management of complex pain patients. (65, 66)

**Competing Interests:** None

**Author’s Information:**

JKR has been the medical director of a private outpatient pain and addiction clinic for over ten years. He is board certified in Addiction Medicine and is a diplomat of the American Academy of Pain Management. He has a long time interest in Public Health and is a Fellow of the American College of Preventive Medicine.

**Acknowledgements:**

Ian Buttfield, M.D. was most helpful in reviewing the transcript. Dr. Buttfield also provided ongoing motivation with regard to the effort to complete and have published this review.

**References**

[1.] Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as

a neurological disease and parallels with other chronic disease states. Pain Med.

2011 Jul;12(7):996-1004.

[2.] Morasco BJ, Corson K, Turk DC, et al., Association between Substance Use Disorder Status and Pain-Related Function Following 12 Months of Treatment in Primary Care Patients with Musculoskeletal Pain J Pain. 2011 March ; 12(3): 352–359.]

[3.] CDC. Vital Signs: Overdoses of Prescription Opioid Pain Relievers—United States, 1999-2008. MMWR 2011; 60: 1-6.

[4.] Coolen P, Best S, Sabel J: Overdose Deaths Involving Prescription Opioids Among Medicaid Enrollees --- Washington, 2004--2007. *MMWR .* 2009; 58(42):1171-1172.5

[5.] Tip 54 - Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders. Available at: www.kap.samhsa.gov/products/manuals/tips/pdf/TIP54.pdf; p. 71. Accessed April 20, 2012.

[6.] Kakko J, Svanborg KD, Kreek MJ, et al. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet.* 2003 Feb 22;361(9358):662-8.

[7.] Clausen T, Waal H, Thoresen M, Gossop M, Mortality among opiate users: opioid maintenance therapy, age and causes of death*. Addiction*. 2009 Aug;104(8):1356-62.

[8.] Wu LT, Woody GE, Yang C, et al.. How Do Prescription Opioid Users Differ From Users of Heroin or Other Drugs in Psychopathology: Results From the National Epidemiologic Survey on Alcohol and Related Conditions *J Addict Med*. 2011 March:5(1):28-32.5

[9.] American Pain Society. Guideline for the Use of Chronic Opioid Therapy in Chronic

Noncancer Pain: Evidence Review. Glenview, IL: American Pain Society; 2009.

[10.] Webster, L. R., Cochella, S., Dasgupta, N., et al.. An Analysis of the Root Causes for Opioid-Related Overdose Deaths in the United States. Pain Medicine. 2011 12: S26–S32.5

[11.] Ward J, Hall W, Mattick RP, Role of maintenance treatment in opioid dependence. *Lancet* 1999; 353: 221–26.

[12.] Kreek, MJ. Methadone-related opioid agonist pharmaCOATherapy for heroin addiction. History, recent molecular and neurochemical research and future in mainstream medicine. [*Ann N Y Acad Sci.*](http://www.ncbi.nlm.nih.gov/pubmed/10911931)2000;909:186-216.

[13.] Miller T, Hendrie D. *Substance Abuse Prevention Dollars and Cents: A Cost-Benefit Analysis*, *DHHS Pub. No. (SMA) 07-4298.* Rockville, MD: Center for Substance Abuse Prevention, Substance Abuse and Mental Health Services Administration, 2008.

[14.] National Institute on Drug Abuse. *Principles of Drug Addiction Treatment – A Research-Based Guide.* NIH Publication No. 09-4180, 2009, pp. 12.

[15.] Dubois MY, Gallagher RM, Lippe PM et al. Pain Medicine Position Paper. *PAIN MEDICINE*. 2009 10(2) 972-1000.

[16.] First, MB, Williams JB, Spitzer RL, et al. *Structured Clinical Interview for DSM-IV TR Axis I Disorders, Clinical Trials Version (SCID-CT).* New York: Biometrics Research, New York State Psychiatric Institute, 2007.

[17.] Zanarini MC, Skodol AE, Bender D, et al. The Collaborative Longitudinal Personality Disorders Study: reliability of axis I and II diagnoses. *J Personal Disord* 2000 Winter;14(4):291-9

[18.] Babor, T.F. Substance-related problems in the context of international classificatory systems. In: Lader, M.; Edwards, G.; & Drummond, D.C., eds. *The Nature of Alcohol and Drug Related Problems*. New York: Oxford University Press, 1992.

[19.] Schuckit, M.A. DSM-IV: Was it worth all the fuss? *Alcohol and Alcoholism*.(Supp. 2):459-469, 1994.

20. Selection of a substance use disorder diagnostic instrument by the National Drug Abuse Treatment Clinical Trials Network. *J Subst Abuse Treat.* 2004 July; 27(1): 1–8.

[21.] Miller T, Hendrie D. Substance Abuse Prevention Dollars and Cents: A Cost-Benefit Analysis, *DHHS Pub. No. (SMA) 07-4298.* Rockville, MD: Center for Substance Abuse Prevention, Substance Abuse and Mental Health Services Administration, 2008.

[22.] Di Chiara G, Bassareo V, Fenu S, et al. Dopamine and drug addiction: The nucleus accumbens shell connection. Neuropharmacology, Vol 47(Suppl1), 2004, 227-241.

[23.] Willuhn I, Wanat M, Clark JJ, et al., Dopamine Signaling in the Nucleus Accumbens of Animals Self-Administering Drugs of Abuse. Behavioral Neuroscience of Drug Addiction. *Current Topics in Behavioral Neurosciences 3*, Springer‐Verlag Berlin Heidelberg 2009, published online 15 September 2009, <http://faculty.washington.edu/pemp/pdfs/pemp2010-07.pdf>.

[24.] Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*.2006;29: 565-598.

[25.] Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*.2001;24(2):97-129.

[26.] Anthony JC, Helzer JE. Epidemiology of drug in dependence. In: Tsuang MT, Tohen M, Zahner GE, eds. *Textbook in psychiatric epidemiology*. New York: Wiley-Liss, 1995: 361–406.

[27.] Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry. 2011; 68(12):1238-46

[28.] Ling W, Wesson DR, Charuvastra C et al., A Controlled Trial Comparing Buprenorphine and Methadone Maintenance in Opioid Dependence. *Arch Gen Psychiatry*. 1996;53(5):401-407

[29.] Mattick RP, Breen C, Kimber J, Davoli M., Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD002209.

[30.] Washington State Agency Medical Directors’ Group (Ed). Washington State’s Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain. <http://www.agencymeddirectors.wa.gov/opioiddosing.asp> Accessed 4/18/2012. 2007.

[31.] Sees KL, Delucchi KL, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence a randomized controlled trial. *JAMA* 2000;283:1303-1310.

[32.] National Institute on Drug Abuse. *Principles of Drug Addiction Treatment – A Research-Based Guide.* NIH Publication No. 09-4180, 2009, pp. 2-22.5

[33.] Haastrup S, Jepsen PW. Eleven year follow-up of 300 young opioid addicts.*Acta Psychiatrica Scandinavica* 1988; 77:22-26.

[34.] Morse GR: Loss of tolerance and overdose mortality with detoxification-Abstinence is a valid choice.*BMJ*. 2003:16; 327(7411):393–394.

[35.] Weissman DE, Haddox JD: Opioid pseudo-addiction—An iatrogenic syndrome. *Pain.* 1989;*36*(3):363–366.

[36.] Mao, J: Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. *Pain. 2002;100:*213–217.

[37.] Ballantyne JC, Sullivan MD, Kolodny A, Opioid Dependence vs. Addiction: A Distinction Without a Difference?. *Arch Intern Med.* 2012 Aug 13:1-2. doi: 10.1001/archinternmed.2012.3212.

[38.] Ballantyne JC, LaForge KS: Opioid dependence and addiction during opioid treatment of chronic pain. *Pain. 2007* 129(3): 235-52.5

[39.] Gourlay DL, Heit HA. Universal Precautions Revisited: Managing the Inherited Pain Patient. *Pain Medicine.* 2009; 10(S2):S115-S123.

[40.] Fishman SM. Strategies for selecting treatment and mitigating risk in patients with chronic pain. J Clin Psychiatry. 2011 Jan;72(1):e)02.

[41.] Fishbain DA, Johnson S, Webster L, et al.: Review of Regulatory Programs and New Opioid Technologies in Chronic Pain Management: Balancing the Risk of Medication Abuse with Medical Need. *J Manag Care Pharm.* 2010; 16(4):276-287.

[42.] Kircher S, Zacny J, Apfelbaum SM, Passik S, Kirsch K, Burbage M, Lofwall M.

Understanding and treating opioid addiction in a patient with cancer pain. *J Pain.* 2011 Oct;12(10):1025-31.] Review.

[43.] Passik SD, Kirsh KL. Addictions in pain clinics and pain treatment. *Ann N Y*

*Acad Sci.* 2011 Jan;1216:138-43.

[44.] Weaver MF, Schnoll SH. Opioid treatment of chronic pain in patients with addiction. J Pain Palliat Care PharmaCOATher. 2002;16(3):5-26.

[45.] Rotchford, JK: The OPAS Experience—An Outpatient Model for At-Risk Chronic non-Malignant Pain Patients. *The Pain Practitioner*. 2007; 4(1): 40-42.] <http://www.aapainmanage.org/library/pain-practitioner/2007-q4-winter.pdf>

[46.] Jegu J, Gallini A, Soler P, et al., Slow-release oral morphine for opioid maintenance treatment: a systematic review. Br J Clin Pharmacol. 2011 June; 71(6): 832–843.

[47.] Ries RK, Fiellin DA, Miller SC, et al. (eds): *Principles of Addiction Medicine*, Philidelphia: Lippincot Williams and Wilkins, 2009 pp 121.

[48.] Chou R, Fanciullo GJ, Fine PG, et al. 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. *Journal of Pain. 2009;10*(2):131–146.

[49.] McCarberg W, Hahn KL, Twillman RK, et al. A Role for Opioids in Chronic Pain Management. *ARCH INTERN MED*. 2012 172(10) 824-822.5

[50.] Edlund MJ, Martin BC, Fan MY, et al. An Analysis of Heavy Utilizers of Opioids for Chronic Non-Cancer Pain in the TROUP Study. *Pain Symptom Manage*. 2010 August; 40(2): 279–289.

[51.] Washington State Agency Medical Director’s Group*, Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An educational aid to improve care and safety with opioid therapy.* 2010 <http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf> 1-59.

[52.] Kouyanou K, Pither CE, Wessely S: Medication misuse, abuse and dependence in chronic pain patients. *J Psychosom Res*. 1997; 43: 497-504.

[53.] Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005 Nov-Dec; 6(6):432-42.

[54.] Mehta V, Langford RM: Acute pain management for opioid dependent patients. *Anaesthesia*. 2006; 61(3):269-276.

[55.] Fleming MF, Balouse SL, Klessig CL, et al: Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. *The Journal of Pain. 2007; 8(7): 573-582.*

[56.] Gourlay DL, Heit HA, Ballantyne JC, et al.(Eds.): Compliance monitoring in chronic pain management., In Bonica’s management of pain (4thed.). Baltimore: LippinCOATt Williams & Wilkins. 2009.

[57.] Højsted J, Sjogren P: Addiction to opioids in chronic pain patients: A literature review. *European Journal of Pain.* 2007; 11(5):490–518.

[58.] Webster LR, Dove B: *Avoiding Opioid Abuse while Managing Pain: a Guide for Practitioners*, Sunrise River Press, North Branch, MN 55056, 2007 pp 19.

[59.] Brown J, Setnik B, Lee K, et al.. Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting*. J Opioid Manag.* 2011 Nov-Dec;7(6):467-83.

[60.] Minozzi S, Amato L, Davoli M. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. Addiction. 2012(Oct18); online ahead of print.

[61.] Heit HA, Gourlay DL: Clinical Pearls in Urine Drug Testing. *J Pain Symptom Manage*. 2004:27(3):260-267.

[62.] Gourlay DL, Heit HA. Universal Precautions Revisited: Managing the Inherited Pain Patient. Pain Medicine. 2009; 10(S2):S115-S123.

[63.] National Institute on Drug Abuse. (2009). Principles of Drug Addiction Treatment – A Research-Based Guide. NIH Publication No. 09-4180, 2009 pp. 11-12.

[64.] Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States*. Pain Med.* 2011 Jun;12 Suppl 2:S26-32.5

[65] Savage SR, Kirsh KL, Passik SD. Challenges in using opioids to treat pain in

persons with substance use disorders. *Addict Sci Clin Pract*. 2008 Jun;4(2):4-22.5

[66.] Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse*. Clin J Pain*. 2006 Feb;22(2):173-81.

[67.] Vowles KE, McEntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. PAIN, 2015 April;156(4): 569-575.

[68.] Ballantyne, JC. Assessing the prevalence of opioid misuse, abuse, and addiction in chronic pain. Pain, 2015 April; 156(4): 567-68.

[69.] Billelo JA, Thurmond LM, Smith KM, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. J Clin Psychiatry, 2015 Feb; 76(2)” e199-206. <http://www.psychiatrist.com/jcp/article/Pages/2015/v76n02/v76n0211.aspx>

[70.] Degenhardt L, Bruno R, Lintzeris N, et al. Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study. The Lancet Psychiatry 2015;2:314-22. [http://www.thelancet.com/pdfs/journals/lanpsy/PIIS2215-0366%2815%2900005-X.pdf#.Vavkqcq0pjA.email](http://www.thelancet.com/pdfs/journals/lanpsy/PIIS2215-0366%2815%2900005-X.pdf%23.Vavkqcq0pjA.email)

[71] Campbell G, Nielsen S, et al. Pharmaceutical Opioid Use and Dependence among People Living with Chronic Pain: Associations Observed within the Pain and Opioids in Treatment (POINT) Cohort. Pain Med 2015; doi: 10.1111/pme.12773 1526-4637. <http://onlinelibrary.wiley.com/doi/10.1111/pme.12773/abstract>

[72] Cochran BN, Flentje A, Heck NC, et al. Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: mathematical modeling using a database of commercially-insured individuals. Drug Alcohol Depend 2014;138:202–8.

[73] Sullivan MD. Who gets high-dose opioid therapy for chronic non-cancer pain? Pain 2010;151:567–8.

[74] Rogers KD, Kemp A, McLachlan AJ, Blyth F. Adverse selection? A multi-dimensional profile of people dispensed opioid analgesics for persistent non-cancer pain. PloS One 2013;8:e80095.

[75] Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use

after major surgery: Population based cohort study. BMJ (Clin Res Ed) 2014;348:g1251.