

Individualizing Opioid Use Disorder (OUD) Treatment: Time to Fully Embrace a Chronic Disease Model

Richard Gustin^{1*}, Jake Nichols¹ and Peter R. Martin²

¹Pharmaceutical Industry Education and Research, FL, USA

²Department of Psychiatry and Pharmacology, Vanderbilt University Medical Center, Nashville, TN, USA

*Correspondence to:

Richard Gustin, PhD
Medical Science Liaison
Boynton Beach, FL, USA
Tel: +1-561-809-0489
E-mail: gustinrm@gmail.com

Received: January 28, 2015

Accepted: February 17, 2015

Published: February 19, 2015

Citation: Gustin R, Nichols J, Martin PR. 2015. Individualizing Opioid Use Disorder (OUD) Treatment: Time to Fully Embrace a Chronic Disease Model. *J Reward Defic Syndr* 1(1): 10-15.

Copyright: © Gustin et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY) (<http://creativecommons.org/licenses/by/4.0/>) which permits commercial use, including reproduction, adaptation, and distribution of the article provided the original author and source are credited.

Published by United Scientific Group

Disclaimer: All opinions expressed by Richard Gustin, Ph.D. and Jake Nichols, PharmD, MBA in this article and journal are solely their own opinions. This article was prepared by Richard Gustin, Ph.D. and Jake Nichols, PharmD, MBA in their own personal capacity. The opinions expressed in this article do not necessarily reflect the view of their employer.

Abstract

The current opioid epidemic in the United States is changing our perceptions of the face of addiction. Opioid Use Disorder (OUD) has become pervasive and is affecting all ethnicities, races, socioeconomic classes, the young and the old. In 2015, 46 people will lose their life each day to a chronic brain disease that is going unnoticed and undertreated. Over the last five decades, numerous scientific and clinical breakthroughs have allowed for a better understanding of the mechanisms underlying addiction, and the development of medications that can help support a patient's long-term recovery. All of those that have contributed to these advancements have aided in redefining addiction as a primary, chronic disease of the brain reward, motivation, memory and related circuitry; however, our treatment strategies have not necessarily advanced to the same extent as our current understanding of the disease. This commentary will explore how personal philosophies can bias treatments strategies and definitions of treatment success, and prevent adoption of chronic disease treatment models that would significantly improve the quality of life of those suffering with OUD. This is a challenge to consider how our views and stigma can impact a patient's recovery. We are currently losing a battle with a disease that is taking the lives of 46 individuals daily; it is time to fully embrace a chronic disease model which comprises an integrated pharmacopsychosocial approach for treating the biopsychosocial disorder that is addiction to reverse these trends.

Keywords

Opioid Use Disorder (OUD), Buprenorphine, Naloxone

Introduction

Addiction to prescription and illicit opiates has reached epidemic proportions in the United States, to the point where commonly cited statistics seem almost fictional. Ninety-nine percent of the world's hydrocodone and 80% of the world's supply of opioids overall are consumed in the U.S. [1]; and in 2008, the number of overdose deaths due to prescription pharmaceuticals surpassed that of traffic accidents [2]. The statistics speak to how invasive this issue has become. The over prescription of opioid pain medication in the U.S. has led to levels of heroin addiction not seen since the Vietnam War era [3, 4].

The time has come to reach a consensus in our approach to the treatment of opioid use disorder (OUD). Achieving this goal will require a great deal of effort from the treatment community, requiring many to put aside their individual philosophies and biases. When discussing the opioid addiction epidemic, as advocates for the many who suffer from addiction, we must have a shared voice and demonstrate a sense of urgency to compel our healthcare system, politicians, and society as a whole to take action in halting and reversing these opioid addiction

trends. Growing knowledge around the neurobiology [5], genetic predisposition [6-8], and efficacy studies related to medication assisted treatment [9] provide an evidence-base which, in turn, has aided in the development of treatment guidelines; however, these effective treatment approaches have not been adopted as mainstream treatment options and are not offered to the majority of patients. There are currently greater than 2.5 million people suffering with OUD, with less than half of this population on medication assisted treatment [10]. In fact, less than half of private sector treatment facilities offer medication assisted treatment, and of those that do, only 34.4% of patients have access to this treatment [11]. Most clinicians would agree that a “one size fits all” treatment approach is ineffective for the majority, and tailoring a patient’s treatment plan to the specific needs of that patient is the most effective approach to achieving positive long-term outcomes and sustained recovery. Even with this understanding, we have allowed social stigma and discrimination to bias our treatment approaches. Patients suffering from addiction have been battling this stigma and discrimination for decades. The common social sentiment, “Why don’t these people stop doing drugs,” is not just sewn into the fabric of our society, but has also permeated our healthcare system, treatment models, and our definitions of ‘successful’ treatment [12]. These beliefs are centered on a misguided understanding, which assumes that if a patient stops taking the opioid, then they are cured; however, this is not supported by the available evidence concerning detoxification and abstinence based treatment [13-16]. Additionally, buprenorphine/naloxone maintenance therapy has been shown to reduce rates of relapse, increase retention in treatment [17], and engage patients in psychosocial recovery models [18].

The situation is daunting. There has been a relative lack of education and research initiatives dedicated to exploring and understanding effective strategies for treating patients suffering from OUD. The consequences are a reduced percentage of patients sustaining long-term recovery, and a higher risk for overdose and premature death. This commentary should be considered a challenge for each clinician, researcher, and layperson to consider how their personal philosophies can influence and affect a patient’s long-term recovery. It is no longer enough to change our semantics in discussing OUD as a chronic disease; we truly need to approach the treatment of OUD as a chronic disease.

Measuring Treatment “success”

The American Society of Addiction Medicine (ASAM) defines addiction as a primary, chronic disease of brain reward, motivation, memory and related circuitry. There has been a concerted effort to put addiction treatment on par with the rest of medicine, highlighting addiction as a chronic illness. Yet, do we approach treatment of addiction as a chronic disease as the definition suggests, or do our personal philosophies bias our approaches? As any chronic disease with biological, genetic, and physiological bases, addiction should be managed by integrating a combination of treatment paradigms personalized to the specific needs of the patient in order to ensure the best possible outcomes for the individual, namely an integrated pharmacopsychosocial approach to treatment [47]. Treatments for OUD must include medical,

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. *Tolerance, as defined by either of the following:
 - a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
 - b. A markedly diminished effect with continued use of the same amount of an opioid.
11. *Withdrawal, as manifested by either of the following:
 - a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal).
 - b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

* Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.

The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013)

Figure 1: DSM-V diagnostic criteria for opioid use disorder.

psychosocial, and behavioral management of the disease. In too many instances we are ineffective in coordinating this comprehensive approach. Additionally, the clinical criteria defining successful addiction treatment is often based on the patient becoming free of both the drug of abuse and pharmacotherapy that has facilitated abstinence. This begs the question, “Why is OUD not held to the same standards of other chronic diseases, e.g. diabetes, wherein insulin treatment continues indefinitely?” For instance, medical management of OUD with buprenorphine/naloxone or methadone is often perceived as substituting one addiction for another. This misunderstanding of the contribution of medications to the overall management of OUD can lead to premature discontinuation of medication to the detriment of the patient, and thus, high rates of relapse [19, 15, 16, 20]. Consider the Diagnostic and Statistical Manual of Mental Disorders criteria for the diagnosis of OUD (Figure 1). Assessing patients’ symptomatology prior to and after initiation of medication assisted therapy, demonstrates how effective appropriately administered medications can be at supporting a patient’s remission. The potential benefits of utilizing medications in patients with OUD include: assisting the patient in achieving remission from the disease, allowing the individual to engage in active recovery [18], and increasing retention in treatment

[19, 15]. For example, take the case of a patient who has been stable on buprenorphine/naloxone for an extended period, and over the course of 3 years that individual became employed, found stable housing, regained custody of his/her children, yet is still being maintained on low doses of buprenorphine/naloxone. Shouldn't this be considered a treatment success? Or, are we allowing misconceptions of the role of medication in the process of recovery to bias how we direct patients through treatment? It is time we promoted individualized care, and to begin to consider whether discontinuing a medication that has allowed the patient to rebuild his/her life from the depth of their addiction is worth the risk of destroying the quality of life due to relapse. There are many other examples of similar decision making in medicine—we know that depression can lead to suffering and suicide and that elevated blood pressure is associated with increased rates of myocardial infarction, stroke, and renal failure and so we continue patients on antidepressants or antihypertensives throughout a lifetime with little hesitation.

Is Tapering off Buprenorphine Maintenance Therapy an Achievable Goal for All Patients?

The most commonly utilized medication for the treatment of OUD is buprenorphine/naloxone. There has been a great deal of debate, as well as conflicting studies, relative to how long patients should be treated in order to achieve optimal outcomes and avoid relapse. Frequently, time limits are set on duration of treatment with buprenorphine/naloxone, and this leads to the question, “Why are some patients rushed through certain aspects of recovery, namely medication assisted therapy?” This is contrary to our understanding that long-term recovery is a day-to-day, life-long commitment that evolves over time and requires the ability to adapt to situations. As a field we can fixate on questions related to identifying the optimal length of buprenorphine/naloxone maintenance treatment, and attaining guidance in how we can get patients off buprenorphine/naloxone. The answer is relatively simple: it is dependent upon the individual patient's needs, their attitude toward recovery, and their overall stability. A fixed dose reduction or tapering schedule will not be effective for the majority of patients. This is best highlighted in the detoxification literature, with roughly 88% of patients being detoxified over a period of 7 or 28 days relapsing within a 90 day period [16]. While evaluating the individual patient's needs, a specific treatment plan can be constructed – one that takes advantage of all treatment modalities that both the patient and physician agree will be essential for continued success [21]. In many settings, this approach is not being utilized, specifically as it relates to buprenorphine/naloxone maintenance therapy. There are a number of standardized protocols that individual physicians, clinics, rehabs, and treatment centers utilize. On many occasions we have heard comments such as, “I just want my patients off these drugs” when referring to buprenorphine/naloxone”, or “I stabilize patients on buprenorphine/naloxone and over the course of X amount of time I taper my patients off of the medication.” Research, clinical practice, and experience tell us that this is an ineffective approach for most individuals with OUD. We need to start thinking of treatment in terms of a “Treatment Clock” versus a “Time Clock”. If a patient's goal is to be medication free, there are some characteristics that may

increase the likelihood of success. We need further research dedicated to understanding how to effectively identify these characteristics and taper their medication more appropriately. Based on observations and feedback from physicians, the primary characteristic is that a patient expresses his/her desire to be taken off the medication. Allowing a patient to take the lead in his or her treatment plan is empowering, and can help reestablish control in one's life. Moreover, it is important not to be judgmental with patients who prefer to continue taking buprenorphine/naloxone as it makes them feel safe and comfortable in their recovery. These patients typically have a long period of negative toxicology results from all drugs of abuse, including alcohol, marijuana, cocaine, and benzodiazepines. Patients that continue to take the medication in a strictly adherent manner in treatment or have successfully tapered off the medication, have engaged and embraced some form of psychosocial recovery, and have renewed pleasure in activities not associated with drug use. Associated with this is the patient's understanding that relationships formed around their drug use cannot be maintained, and they need to develop a positive network of family and friends to support their desire to become medication free, along with their recovery. Lastly, and often times over looked, is the appropriate diagnosis of other behavioral health and medical issues that need to be addressed. We know that patients with substance use disorders exhibit relatively high rates of co-morbid psychiatric disorders [22-25], and it is naive to think that long-term recovery is achievable if these issues are not adequately addressed. If we were to approach the treatment of OUD from the standpoint of treatment goals versus a fixed duration of treatment, we could greatly improve upon treatment outcomes. As a field, if we are serious about treating this illness as a chronic disorder, we need to start approaching treatment more cohesively. Expounding that OUD is driven by brain mechanisms, and is not the consequence of a morally compromised individual, is no longer enough if we truly intend to make an impact on this epidemic.

Lapses are Lessons

It is an unrealistic expectation to think that patients will not have lapses and relapses to drug use while attempting to achieve long-term recovery. It is a struggle for patients to deal with stressors, cues, and cravings that lead to their brain telling them, “This can all go away if you just use again.” Is it therefore appropriate for a clinician to demand that a patient submit to routine urine drug screens and that the results are negative from the first day of treatment? Urine drug screens should not be used to ‘catch’ patients using drugs and ultimately throw them out of treatment. Instead, these tests should be used to evaluate vulnerabilities that the patient is continuing to struggle with, and use these test results as teachable moments for both patients and physicians to work on identifying and addressing triggers of relapse. Removal of a patient out of treatment leads to one inevitable outcome - relapse. In fact, the outcome of a positive urine drug test results should be to assist the patient in his/her time of need and provide more intensive treatment; after all, presumably both the patient and the clinician want the same thing for the patient, namely to stop the slide into active addiction.

Is Sustainable Long-Term Recovery Possible without Addressing other Mental Health Co-Morbidities?

As mentioned previously, understanding the patient's complete medical and psychiatric history is crucial for developing the optimal treatment strategy. Rates of physical and mental abuse, as well as behavioral health issues are relatively high in patients suffering with OUD [26-30]. It is rare to observe that someone addicted to opioids is only struggling with the drug itself. When an individual enters a detox or abstinence based program, the cravings and withdrawals deter the patient from fully engaging in all aspects of a comprehensive treatment program. In many instances, these patients would be well served by integrating buprenorphine/naloxone into their treatment plan. The medication helps to reduce cravings and withdrawal symptoms, and more importantly, allow clarity of thought to enable the patient to comprehend and commit to the psychosocial aspects of their recovery. This includes learning relapse prevention techniques and dealing with the stressors and cues that they will inevitably encounter. Moreover, clinicians can have the time to identify and treat the behavioral health issues that often times are being self-medicated by the opioid of abuse.

The Drug Addiction Treatment Act of 2000 (DATA 2000) provided an immediate necessity to the community by expanding access to treatment for patients who otherwise would not have likely pursued recovery. Over the past decade, this has had an unintended side effect. Most addiction treatment is administered by physicians who, while passionate and motivated, are not thoroughly trained in addiction medicine or psychiatry. There is an incomplete understanding of how to diagnose and treat contributing mental health conditions. We need to formulate creative methods that ensure that patients with OUD have the psychosocial support and behavioral health treatment they require, not only acutely, but throughout their lifetime. Just as access to buprenorphine/naloxone needs to be expanded, it is imperative that appropriate psychosocial treatment paradigms are individually developed and tailored to each patient in order to maximize the benefits of the medication in fully engaging the patient in the recovery process. Appropriate use of the medication within the rubric of effective psychosocial treatment, which must begin with a clear diagnosis of psychiatric co-morbidities, is the only acceptable and comprehensive approach to patient management that will improve outcomes. For any individual patient, this would likely include enhanced compliance with treatment plans and active engagement in the long-term recovery process [31, 18, 32].

Conclusion

The fields of addiction medicine and psychiatry have been proactive in disseminating the message that substance use disorders are chronic, relapsing brain diseases with underlying biological, genetic, and psychosocial mechanisms. It is time that the field fully accepts these facts and adopts treatment approaches that address each aspect of the disease in a comprehensive rather than piecemeal manner. We must acknowledge what the data has told us thus far about treatment, medication assisted therapy, and the use

of psychosocial support, while simultaneously limiting the bias our personal philosophies may have on approaches to treatment. Changing the stigma caused by social intolerance toward addiction and its treatment begins with a commitment to healthcare provider education. Our educational systems need to be dynamic, such that education around emerging diseases and trends can be integrated into the curriculum, and that healthcare providers are adequately informed and able to curtail epidemics like the one we find ourselves in the midst of today [33]. Interestingly, 72.1% of attending and resident physicians would be willing to prescribe buprenorphine for the treatment of OUD if given appropriate training and support [34]. This is not just an issue within medical education. It is also apparent in counselor and psychologist training, as well as most other healthcare disciplines [35]. In settings where counselors are appropriately trained on the benefits and utility of buprenorphine, acceptance is significantly greater [36]. The clinicians responsible for treating patients utilizing psychosocial treatment modalities need to be educated on the biology and genetics of addiction and how medication can be a useful tool in achieving their objectives. There has to be a commitment to comprehensive management of patients with substance use disorders utilizing chronic disease models of treatment. To insure that we are doing the best we can for the majority of patients, we must no longer downplay the necessity for psychosocial interventions, or continue to stigmatize the use of medications such as buprenorphine/naloxone, but use these two approaches in an integrated manner [37].

Chronic disease models of treatment can be constructed by building patient-centric networks to integrate care addressing both substance use disorder and underlying or co-morbid medical and/or behavioral health issues. Staying abreast of emerging data will provide better understanding on how to manage patients with substance use disorder. Our knowledge of the genetics underlying predisposition to addiction [6-8], alterations in neurotransmitter tone [38, 39], and how reward deficiency is contributing to stress and relapse [40] will supply us with a more sophisticated and heuristically useful view of the patient's physiological condition and allow for a more individualized approach.

Medication assisted therapy, such as buprenorphine/naloxone, reduces rates of overdose and overdose death [41-43], reduces recidivism in emergency departments and within the criminal justice system [44, 45], increases compliance and adherence to other medical services [31, 32]. But most importantly, it helps put people on the path to recovery and enhances their quality of life [46, 47]. We are in the midst of an epidemic that is targeting teens and young adults, and we are losing this battle with a disease that is taking the lives of 46 individuals daily [48]. It is time we stop philosophizing over what treatment should look like, and start providing individuals with the chronic disease management that they need to be successful in recovery.

Disclosure

The authors are employed by Orexo US, Inc. and the opinions expressed in this article are entirely their own. The opinions expressed do not necessarily reflect the view of Orexo US, Inc.

Authors Contribution

Richard Gustin was the lead author. Jake Nichols and Peter Martin contributed equally in providing insight and development of the manuscript.

Conflict of Interest

Both Richard Gustin and Jake Nichols are employed by Orexco Pharmaceutical Corporation, USA.

References

1. Manchikanti L, Singh A. 2008. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 11(2 Suppl): S63-88.
2. Warner M, Chen LH, Makuc DM, Anderson RN, Miniño AM. 2011. Drug poisoning deaths in the United States, 1980-2008. *NCHS Data Brief* 81: 1-8.
3. American Society of Addiction Medicine. 2011. Definition of Addiction. Retrieved from <http://www.asam.org/for-the-public/definition-of-addiction>
4. American Psychiatric Association. 2013. Diagnostic and Statistical Manual of Mental Disorders (5th Edition). American Psychiatric Association, Washington, DC, USA. doi: 10.1176/appi.books.9780890425596
5. Koob GF, Simon EJ. 2009. The Neurobiology of Addiction: Where We Have Been and Where We Are Going. *J Drug Issues* 39(1): 115-132. doi: 10.1177/002204260903900110
6. Blum K, Chen AL, Oscar-Berman M, Chen TJ, Lubar J, et al. 2011. Generational association studies of dopaminergic genes in reward deficiency syndrome (RDS) subjects: selecting appropriate phenotypes for reward dependence behaviors. *Int J Environ Res Public Health* 8(12): 4425-4459. doi:10.3390/ijerph8124425
7. Blum K, Oscar-Berman M, Demetrovics Z, Barh D, Gold MS. 2014. Genetic Addiction Risk Score (GARS): molecular neurogenetic evidence for predisposition to Reward Deficiency Syndrome (RDS). *Mol Neurobiol* 50(3): 765-796. doi: 10.1007/s12035-014-8726-5
8. Blum K, Febo M, McLaughlin T, Cronje FJ, Han D, et al. 2014. Hatching the behavioral addiction egg: Reward Deficiency Solution System (RDSS)TM as a function of dopaminergic neurogenetics and brain functional connectivity linking all addictions under a common rubric. *J Behav Addict* 3(3): 149-156. doi: 10.1556/JBA.3.2014.019
9. Thomas CP, Fullerton CA, Kim M, Montejano L, Lyman DR, et al. 2014. Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatr Serv* 65(2): 158-170. doi: 10.1176/appi.ps.201300256
10. Volkow ND, Frieden TR, Hyde PS, Cha SS. 2014. Medication-assisted therapies-tackling the opioid-overdose epidemic. *N Engl J Med* 370(22): 2063-2066. doi: 10.1056/NEJMp1402780
11. Knudsen HK, Abraham AJ, Roman PM. 2011. Adoption and implementation of medications in addiction treatment programs. *J Addict Med* 5(1): 21-27. doi: 10.1097/ADM.0b013e3181d41ddb
12. Olsen Y, Sharfstein JM. 2014. Confronting the stigma of opioid use disorder and its treatment. *JAMA* 311(14): 1393-1394. doi: 10.1001/jama.2014.2147
13. Dunn KE, Sigmon SC, Strain EC, Heil SH, Higgins ST. 2011. The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review. *Drug Alcohol Depend* 119(1-2): 1-9. doi: 10.1016/j.drugalcdep.2011.05.033
14. Dreifuss JA, Griffin ML, Frost K, Fitzmaurice GM, Potter JS, et al. 2013. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. *Drug Alcohol Depend* 131(1-2): 112-118. doi: 10.1016/j.drugalcdep.2012.12.010
15. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 361(9358): 662-668. doi: 10.1016/S0140-6736(03)12600-1
16. Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, et al. 2009. Buprenorphine tapering schedule and illicit opioid use. *Addiction* 104(2): 256-265. doi: 10.1111/j.1360-0443.2008.02455.x.
17. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, et al. 2011. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry* 68(12): 1238-1246.
18. Parran TV, Adelman CA, Merkin B, Pagano ME, Defranco R, et al. 2010. Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. *Drug Alcohol Depend* 106: 56-60.
19. Fiellin DA, Moore BA, Sullivan LE, Becker WC, Pantalon MV, et al. 2008. Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. *Am J Addict* 17: 116-120.
20. Soyka M, Zingg C, Koller G, Kuefner H. 2008. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *Int J Neuropsychopharmacol* 11: 641-653. doi: 10.1001/archgenpsychiatry.2011.121
21. American Society of Addiction Medicine. 2014. The Standards of Care: For the Addiction Specialist Physician.
22. Becker WC, Sullivan LE, Tetrault JM, Desai RA, Fiellin DA. 2008. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: psychiatric, medical and substance use correlates. *Drug Alcohol Depend* 94(1-3): 38-47. doi: 10.1016/j.drugalcdep.2007.09.018
23. Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, et al. 2010. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction* 105:1776-1782. doi: 10.1111/j.1360-0443.2010.03052.x.
24. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. 2007. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain* 129(3): 355-362.
25. Goldner EM, Lusted A, Roerecke M, Rehm J, Fischer B. 2014. Prevalence of Axis-1 psychiatric (with focus on depression and anxiety) disorder and symptomatology among non-medical prescription opioid users in substance use treatment: systematic review and meta-analyses. *Addict Behav* 39(3): 520-531. doi: 10.1016/j.addbeh.2013.11.022.
26. Bartholomew NG, Rowan-Szal GA, Chatham LR, Nucatola DC, Simpson DD. 2002. Sexual abuse among women entering methadone treatment. *J Psychoactive Drugs* 34(4): 347-354. doi: 10.1080/02791072.2002.10399975
27. Bartholomew NG, Courtney K, Rowan-Szal GA, Simpson DD. 2005. Sexual abuse history and treatment outcomes among women undergoing methadone treatment. *J Subst Abuse Treat* 29(3): 231-235. doi: 10.1016/j.jsat.2005.07.003
28. Conroy E, Degenhardt L, Mattick RP, Nelson EC. 2009. Child maltreatment as a risk factor for opioid dependence: Comparison of family characteristics and type and severity of child maltreatment with a matched control group. *Child Abuse Negl* 33(6): 343-352. doi: 10.1016/j.chiabu.2008.09.009
29. Heffernan K, Cloitre M, Tardiff K, Marzuk PM, Portera L, et al. 2000. Childhood trauma as a correlate of lifetime opiate use in psychiatric patients. *Addict Behav* 25(5): 797-803. doi: 10.1016/S0306-4603(00)00066-6
30. Mills KL, Teesson M, Ross J, Darke S, Shanahan M. 2005. The costs and outcomes of treatment for opioid dependence associated with posttraumatic stress disorder. *Psychiatr Serv* 56(8): 940-945. doi: 10.1176/appi.ps.56.8.940
31. Cunningham CO, Sohler NL, Cooperman NA, Berg KM, Litwin AH, et al. 2011. Strategies to improve access to and utilization of health care services and adherence to antiretroviral therapy among HIV-infected drug users. *Subst Use Misuse* 46(2-3): 218-232. doi: 10.3109/10826084.2011.522840
32. Moatti JP, Carrieri MP, Spire B, Gastaut JA, Cassuto JP, et al. 2000. Adherence to HAART in French HIV-infected injecting drug users: the contribution of buprenorphine drug maintenance treatment. The Manif 2000 study group. *AIDS* 14(2): 151-155.

33. Polydorou S, Gunderson EW, Levin FR. 2008. Training physicians to treat substance use disorders. *Curr Psychiatry Rep* 10(5): 399-404. doi: 10.1007/s11920-008-0064-8
34. Cunningham CO, Sohler NL, McCoy K, Kunins HV. 2006. Attending physicians' and residents' attitudes and beliefs about prescribing buprenorphine at an urban teaching hospital. *Fam Med* 38(5): 336-340.
35. Knudsen HK, Ducharme LJ, Roman PM, Link T. 2005. Buprenorphine diffusion: the attitudes of substance abuse treatment counselors. *J Subst Abuse Treat* 29(2): 95-106. doi: 10.1016/j.jsat.2005.05.002
36. Knudsen HK, Ducharme LJ, Roman PM. 2007. Research network involvement and addiction treatment center staff: counselor attitudes toward buprenorphine. *Am J Addict* 16(5): 365-371. doi: 10.1080/10550490701525418
37. Blum K, Gardner E, Oscar-Berman M, Gold M. 2012. "Liking" and "wanting" linked to Reward Deficiency Syndrome (RDS): hypothesizing differential responsivity in brain reward circuitry. *Curr Pharm Des* 18(1): 113-118. doi: 10.2174/138161212798919110
38. Gardner EL. 2011. Addiction and brain reward and anti-reward pathways. *Adv Psychosom Med* 30: 22-60. doi: 10.1159/000324065.
39. Kreek MJ, Levran O, Reed B, Schlussman SD, Zhou Y, et al. 2012. Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. *J Clin Invest* 122(10): 3387-3393. doi: 10.1172/JCI60390.
40. Clausen T, Anchersen K, Waal H. 2008. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. *Drug Alcohol Depend* 94(1-3): 151-157. doi: 10.1016/j.drugalcdep.2007.11.003
41. Degenhardt L, Randall D, Hall W, Law M, Butler T, et al. 2009. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend* 105(1-2): 9-15. doi: 10.1016/j.drugalcdep.2009.05.021
42. Romelsjö A, Engdahl B, Stenbacka M, Fugelstad A, Davstad I, et al. 2010. Were the changes to Sweden's maintenance treatment policy 2000-06 related to changes in opiate-related mortality and morbidity? *Addiction* 105(9): 1625-1632. doi: 10.1111/j.1360-0443.2010.02999.x
43. Baser O, Chalk M, Fiellin DA, Gastfriend DR. 2011. Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care* 17(8 Suppl): S235-248.
44. Magura S, Lee JD, Hershberger J, Joseph H, Marsch L, et al. 2009. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. *Drug Alcohol Depend* 99(1-3): 222-230. doi: 10.1016/j.drugalcdep.2008.08.006
45. Feelemyer JP, Des Jarlais DC, Arasteh K, Phillips BW, Hagan H. 2014. Changes in quality of life (WHOQOL-BREF) and addiction severity index (ASI) among participants in opioid substitution treatment (OST) in low and middle income countries: an international systematic review. *Drug Alcohol Depend* 134: 251-258. doi: 10.1016/j.drugalcdep.2013.10.011
46. Sittambalam CD, Vij R, Ferguson RP. 2014. Buprenorphine Outpatient Outcomes Project: can Suboxone be a viable outpatient option for heroin addiction? *J Community Hosp Intern Med Perspect* 4. doi: 10.3402/jchimp.v4.22902
47. Martin PR, Weinberg BA, Bealer BK. 2007. *Healing Addiction: An integrated pharmacopsychosocial approach to treatment*. Hoboken, NJ: John Wiley and Sons.
48. Center for Disease Control. 2014. Opioid painkiller prescribing where you live makes a difference. DCD Vital Signs. Retrieved from <http://www.cdc.gov/vitalsigns/opioid-prescribing/>