The Need for Psychosocial Interventions to Facilitate the Transition to Extended-Release Naltrexone (XR-NTX) Treatment for Opioid Dependence: A Concise Review of the Literature

Susan E. Ramsey[1–3], Dan Rounsaville[4], Randall Hoskinson[5], Tae Woo Park[1,2], Evan G. Ames[1], Victor D. Neirinckx[1] and Peter Friedmann[5]

[1]Rhode Island Hospital, Providence, RI, USA. [2]Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University, Providence, RI, USA. [3]Department of Medicine, The Warren Alpert Medical School of Brown University, Providence, RI, USA. [4]VA Boston Healthcare System, Brockton, MA, USA. [5]Baystate Health, Springfield, MA, USA.

ABSTRACT: Given the increase of opioid dependence and opioid-related morbidity and mortality, improving treatment options for individuals with opioid dependence warrants increased attention. This article provides a concise review of work in this area. Remission from opioid dependence can be very difficult to sustain, particularly in the absence of opioid replacement or opioid antagonist therapy. For those who wish to transition from opioid use or opioid replacement therapy to opioid antagonist therapy, a significant challenge can be the period of withdrawal symptoms that must be endured prior to the initiation of opioid antagonist therapy. Studies that have incorporated psychosocial interventions into detoxification protocols have found that they can result in improved treatment outcomes. Interventions based on Acceptance and Commitment Therapy have shown promise in the treatment of clinical disorders that present with symptoms similar to those of opioid withdrawal and have been found to positively impact outcomes among those tapering from methadone. However, the use of an Acceptance and Commitment Therapy-based intervention has yet to be studied among opioid-dependent patients transitioning to XR-NTX, and its value to those transitioning to XR-NTX is currently unknown.

KEYWORDS: opioid dependence, XR-NTX, Acceptance and Commitment Therapy

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CORRESPONDENCE: Susan_Ramsey@Brown.edu

Introduction

Improving treatment for opioid dependence is increasingly important as rates of abuse and dependence have risen over the past decades, largely due to increased prescription opioid abuse.[1] The costs of opioid dependence to the individual and society are significant, including numerous negative medical consequences, overdose, health care and law enforcement costs, and damage to family and social relationships.[2,3] In the U.S., in 2011, 426,000 individuals were diagnosed with heroin abuse or dependence, and another 1,768,000 were dependent on or abused prescription opioid pain relievers. The number of persons with nonmedical pain reliever dependence increased 50% from 2002 to 1.4 million in 2011, but only 51% of those individuals received adequate addiction treatment. Rates of emergency department visits associated with pharmaceutical misuse or abuse increased 114% between 2004 and 2011, with over 420,000 involving opioid analgesics in 2011 alone.[4] Between 1999 and 2010, more than 125,000 people in the U.S. died from an overdose involving an opioid analgesic, which outnumbers overdose deaths involving all illicit drugs combined.[5] It is estimated that prescription opioid abuse cost the U.S. $55.7 billion in 2007 alone.[6] Opioid analgesics were involved in 30% of drug overdose deaths in 1999, compared to nearly 60% in 2010.

Achieving successful remission from opioid dependence is difficult. Individuals seeking to become opioid free have very low success rates without the assistance of medications that mitigate or block the reinforcing effects of opioids. Opioid agonist agents, otherwise known as opioid replacement agents, attach to the opioid receptors. At low doses, opioid agonists prevent withdrawal symptoms, and, at higher doses, they block the euphoric effects of any opioids that might be self-administered. In contrast, opioid antagonists attach to the opioid receptors but do not activate the receptors, and they prevent opioids from attaching to the receptors. Opioid antagonists are effective and are

preferred by some individuals seeking treatment for opioid dependence.[7] While there are limited data regarding the percentage of those seeking treatment for opioid dependence who prefer antagonist therapy, two recent studies have found that this percentage may be as high as 32%–52%.[8,9] However, in order to transition from opioid use or opioid replacement therapy to opioid antagonist therapy, one must first withdraw from all opioid agonists in order to avoid the sudden onset of potentially severe opioid withdrawal. Withdrawal symptoms are extremely unpleasant, even with comfort medications. Symptoms include vomiting, tremors, aches, fatigue, weakness, restlessness, and insomnia as well as the psychological symptoms of intense depression and anxiety.[10] Many opioid users expend great energy obtaining opioids to avoid withdrawal. In addition, prolonged use of opioids can cause hypersensitivity to the unpleasant physical and mental symptoms of withdrawal.[11] Tolerating the symptoms of withdrawal is one of the earliest barriers that treatment-seeking individuals must confront and is thought to be one of the primary reasons for detoxification dropout.[12–14]

Transitioning to XR-NTX

Once detoxification has occurred, extended-release injectable naltrexone (XR-NTX), a long-acting opioid antagonist, is an effective means of preventing relapse. The Food and Drug Administration approved XR-NTX in October 2010 to treat opioid dependence. The extended-release injectable form lasts 30 days, preventing patients from impulsively discontinuing the medication. XR-NTX provides opioid-dependent patients the opportunity to take effective medication monthly, as opposed to the daily dosing required by other opioid dependence medications (ie, methadone, buprenorphine, oral naltrexone). Although the evidence-base is less extensive than for agonist therapy, XR-NTX is an effective, evidence-based practice for opioid dependence.[7,15,16]

Before patients can initiate XR-NTX, they must first completely detoxify from opioids. Chronic opioid-dependent individuals tend to have maladaptive coping behaviors and often cannot tolerate the high levels of physical and mental discomfort from withdrawal.[10,11] Physical and psychological withdrawal symptoms may be more extreme for chronically opioid-dependent individuals.[11] Chronic opioid use can result in hypersensitivity to physical pain,[17] as well as greater fear of anxiety and anxiety-related sensations.[18]

Opioid detoxification has high rates of dropout and relapse to opioid abuse.[19,20] While rates of success vary widely between programs, studies have found that an average of 30% or fewer patients are abstinent at the end of detoxification.[21,22] A multisite study of outpatient Suboxone detoxification found that only 29% of participants were opioid free at the end of treatment.[23] Briefer detoxification programs have reported lower success rates ranging from 9%[24] to 21%.[25] In a review of 28 buprenorphine detoxification studies, the range of patients who successfully completed treatment was from 22% to 51%.[21] These low rates of successful detoxification, which itself is only the first step in recovery from opioid dependence, indicate that improvements to the detoxification process are needed. Programs that incorporate psychosocial interventions into detoxification protocols have improved program completion and opioid abuse rates.[26] However, few of these interventions have focused on tolerance and acceptance of the withdrawal symptoms as their primary therapeutic target.

Acceptance and Commitment Therapy may Assist with Transition to XR-NTX

A relatively recent innovation in cognitive behavioral therapy is the development of theoretical and clinical approaches to experiential acceptance.[27] Hayes et al. developed a specific treatment approach, Acceptance and Commitment Therapy (ACT),[28] to produce acceptance behaviors aimed at private events that have interfered with accomplishing life goals, such as the symptoms of nicotine withdrawal preventing an individual from quitting smoking. The interest in acceptance stems from literature supporting interventions that disrupt experiential avoidance of negative sensations.[29] This paradigm, which is a departure from traditional cognitive behavioral therapies focused on controlling thoughts and feelings, is highly suited to the acceptance and tolerance of aversive symptoms associated with opioid withdrawal.

Acceptance can be defined as the act of approaching psychologically aversive or troubling internal stimuli while behaving adaptively;[30] it involves actively engaging in the process of experiencing feelings, thoughts, and sensations without attempting to avoid or change the experiences and without allowing them to influence one's behavior in negative ways.[28] One key ACT concept is that a reliance on avoidance and control coping strategies produces psychological inflexibility, which manifests as constrained behavioral repertoires in response to negative internal stimuli.[28] The problematic consequence of these avoidance and coping strategies is that they can interfere with more goal-directed, adaptive behaviors. Hence, the negative internal stimuli are not a problem in and of themselves; they become problematic when they result in destructive, values-inconsistent behaviors.[31] This process is evident in substance dependence where drugs are used to avoid unpleasant internal stimuli and then become the source of unpleasant stimuli through withdrawal and other problems associated with opioid dependence.[32] Acceptance interventions acknowledge the impossibility of completely preventing negative thoughts, feelings, and sensations. Treatment components from ACT that have been developed to facilitate adaptive responses to negative affect and other negative internal stimuli include acceptance, defusion, values clarification, commitment, self-as-context, and willingness.[28] ACT is particularly apt to address withdrawal as opioid-dependent patients are more likely to engage in avoidance-based coping through drug use[32] and have heightened sensitivity to physical and psychological discomfort.[10,11,17,18]

ACT has been found to be an effective treatment for many common clinical disorders, including substance dependence, in which recovery requires learning adaptive ways to adjust to uncomfortable symptoms.[32,33] Studies have successfully used ACT for smoking cessation,[34–37] alcohol dependence,[38] and methadone maintenance.[32,39] Hayes et al.[31] conducted the first study examining the efficacy of ACT for substance use. They compared ACT with a time-matched Twelve-Step Facilitation intervention and a treatment as usual control condition among polydrug-abusing methadone clinic patients. Those assigned to the ACT condition had lower rates of objectively measured opioid use and total drug use and lower subjective measures of total drug use compared to control participants. The Twelve-Step Facilitation participants had results similar to the ACT participants; however, intention-to-treat analyses of the objective total drug use measure supported the superiority of ACT over control but not the superiority of Twelve-Step Facilitation over control. In addition, ACT has been used successfully to treat disorders with symptoms that overlap with opioid withdrawal, including affective and anxiety disorders[40] and chronic pain.[41–43] In one study[44] examining the efficacy of ACT for chronic pain, ACT was found to result in significant improvements not only in the area of pain but also in depression, pain-related anxiety, disability, medical visits, work status, and physical functioning; effect sizes for all domains were in the medium to large range. Intense physical discomfort and symptoms of depression and anxiety are among the typical symptoms of opioid detoxification.

An intensive ACT-based program has been developed to facilitate methadone dose reduction during methadone maintenance treatment.[39] This intervention consists of 24 weekly sessions over the course of 6 months while participants taper their methadone. The ACT intervention was modified to address issues specific to methadone treatment and was compared to a drug counseling (DC) protocol that encouraged abstinence without addressing coping skills. Although this small study ($n = 56$) did not detect statistically significant differences between the conditions, 60% of the individuals who received ACT completed treatment compared to 46.2% in the DC condition. In addition, 36.7% of the ACT group was considered successful compared to 19.2% of the DC group, with treatment success defined as having an opioid-negative urine drug screen at the end of treatment without having reenrolled in methadone treatment. ACT also reduced fear of detoxification compared to the DC condition. Rates of opioid use during detoxification were similar across conditions. This study demonstrates the potential of ACT-based interventions to target the physical discomfort associated with opioid withdrawal, as well as the accompanying negative mood symptoms.

Conclusions

XR-NTX is an effective treatment for opioid dependence. However, before treatment with XR-NTX can be initiated, patients must completely detoxify from opioids. The physical and mental discomfort experienced during the withdrawal process causes many patients to relapse to opioid use prior to completing the detoxification process. The incorporation of psychosocial interventions into detoxification protocols has been found to improve outcomes. Interventions rooted in ACT have shown promise in the treatment of other clinical disorders characterized by the presence of uncomfortable symptoms. The use of ACT-based interventions to facilitate the transition to XR-NTX treatment warrants investigation; the contribution of this type of intervention to the XR-NTX transition process is currently unknown.

Author Contributions

Wrote the first draft of the manuscript: SR, DR, RH, PF. Contributed to the writing of the manuscript: SR, DR, RH, TWP, EA, VN, PF. Agree with manuscript results and conclusions: SR, DR, RH, TWP, EA, VN, PF. Jointly developed the structure and arguments for the paper: SR, DR, RH, PF. Made critical revisions and approved final version: SR, DR, RH, TWP, EA, VN, PF. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend*. 2006;81(2):103–7.
2. Becker WC, Sullivan LE, Tetrault JM, Desai RA, Fiellin DA. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: psychiatric, medical and substance use correlates. *Drug Alcohol Depend*. 2008;94(1–3):38–47.
3. Clausen T, Waal H, Thoresen M, Gossop M. Mortality among opiate users: opioid maintenance therapy, age and causes of death. *Addiction*. 2009;104(8):1356–62.
4. Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
5. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers-United States, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60:1487–92.
6. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med*. 2011;12:657–67.
7. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet*. 2011;377(9776):1506–13.
8. Uebelacker LA, Bailey G, Herman D, Anderson B, Stein M. Patients' beliefs about medications are associated with stated preference for methadone, buprenorphine, naltrexone, or no medication-assisted therapy following inpatient opioid detoxification. *J Subst Abuse Treat*. 2016;66:48–53.
9. Ahamad K, Milloy MJ, Nguyen P, et al. Factors associated with willingness to take extended release naltrexone among injection drug users. *Addict Sci Clin Pract*. 2015;10:1–6.
10. Phillips GT, Gossop M, Bradley B. The influence of psychological factors on the opiate withdrawal syndrome. *Br J Psychiatry*. 1986;149:235–8.
11. White JM. Pleasure into pain: the consequences of long-term opioid use. *Addict Behav*. 2004;29(7):1311–24.
12. Eklund C, Hiltunen AJ, Melin L, Borg S. Abstinence fear in methadone maintenance withdrawal: a possible obstacle for getting off methadone. *Subst Use Misuse*. 1997;32(6):779–92.
13. Latowsky M. Improving detoxification outcomes from methadone maintenance treatment: the interrelationship of affective states and protracted withdrawal. *J Psychoactive Drugs*. 1996;28(3):251–7.
14. Milby JB, Hohmann AA, Gentile M, et al. Methadone maintenance outcome as a function of detoxification phobia. *Am J Psychiatry*. 1994;151(7):1031–7.
15. Cornish JW, Langleben DD, Nordeck CD, et al. Six-month depot naltrexone treatment reduces relapse in parolees formerly addicted to opioids. 51st National Meeting of the American College of Neuropsychopharmacology, Hollywood, FL, December 11, 2012. Poster presentation. *Neuropsychopharmacology* 2012; 38:S355.

16. Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. *Addiction*. 2013;108:1628–37.
17. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend*. 2001;63(2):139–46.
18. Lejuez CW, Paulson A, Daughters SB, Bornovalova MA, Zvolensky MJ. The association between heroin use and anxiety sensitivity among inner-city individuals in residential drug use treatment. *Behav Res Ther*. 2006;44(5):667–77.
19. Chutuape MA, Jasinski DR, Fingerhood MI, Stitzer ML. One-, three-, and six-month outcomes after brief inpatient opioid detoxification. *Am J Drug Alcohol Abuse*. 2001;27(1):19–44.
20. Magura S, Rosenblum A. Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. *Mt Sinai J Med*. 2001;68(1):62–74.
21. Dunn KE, Sigmon SC, Strain EC, Heil SH, Higgins ST. The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review. *Drug Alcohol Depend*. 2011;119(1–2):1–9.
22. Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. *Drug Alcohol Depend*. 2001;62(3):255–64.
23. Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction*. 2005;100(8):1090–100.
24. Gruber VA, Delucchi KL, Kielstein A, Batki SL. A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug Alcohol Depend*. 2008;94(1–3):199–206.
25. Lintzeris N, Bell J, Bammer G, Jolley DJ, Rushworth L. A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal. *Addiction*. 2002;97(11):1395–404.
26. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev*. 2011;9:CD005031.
27. Acceptance and change: reconsidering the goals of modern behavior therapy. In: Panel Discussion at the Annual Meeting of the Association for Advancement of Behavior Therapy; 1997, Miami, FL.
28. Hayes SC, Strosahl KD, Wilson KG. *Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change*. New York: The Guilford Press; 1999.
29. Pennebaker JW. Writing about emotional experiences as a therapeutic process. *Psychological Science*. 1997;8:162–6.
30. Gifford EV. Setting a course for behavior change: the verbal context of acceptance. In: Hayes SC, Jacobson NS, Follette VM, Dougher MJ, eds. *Acceptance and Change: Content and Context in Psychotherapy*. Reno, NV: Context Press; 1994:218–22.
31. Hayes SC, Luoma J, Bond F, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes, and outcomes. *Behav Res Ther*. 2006;44:1–25.
32. Hayes SC, Wilson KG, Gifford EV, et al. A Preliminary trial of twelve-step facilitation and acceptance and commitment therapy with polysubstance-abusing methadone-maintained opiate addicts. *Behavior Therapy*. 2004;35:667–88.
33. Hayes SC, Wilson KG, Gifford EV, Follette VM, Strosahl KD. Experiential avoidance and behavioral disorders: a functional dimensional approach to diagnosis and treatment. *J Consult Clin Psychol*. 1996;64:1152–68.
34. Brown RA, Lejuez CW, Kahler CW, Strong DR, Zvolensky MJ. Distress tolerance and early smoking lapse. *Clin Psychol Rev*. 2005;25:713–33.
35. Brown RA, Palm KM, Strong DR, et al. Distress tolerance treatment for early-lapse smokers: rationale, program description, and preliminary findings. *Behav Modif*. 2008;32:302–32.
36. Brown RA, Lejuez CW, Strong DR, et al. A prospective examination of distress tolerance and early smoking lapse in adult self-quitters. *Nicotine Tob Res*. 2009;11(5):493–502.
37. Gifford EV, Kohlenberg BS, Hayes SC, Antonuccio DO, Piasecki MM, Rasmussen-Hall ML. Acceptance theory-based treatment for smoking cessation: an initial trial of acceptance and commitment therapy. *Behav Ther*. 2004;35:689–706.
38. Heffner M, Eifert GH, Parker BT, Hernandez DH, Sperry JA. Valued directions: acceptance and commitment therapy in the treatment of alcohol dependence. *Cogn Behav Pract*. 2003;10:378–83.
39. Stotts AL, Green C, Masuda A, et al. A stage I pilot study of acceptance and commitment therapy for methadone detoxification. *Drug Alcohol Depend*. 2012;125(3):215–22.
40. Hayes, S. C. (1987). A contextual approach to therapeutic change. In N. S. Jacobson (Ed.), Psychotherapists in clinical practice: Cognitive and behavioral perspectives (pp. 327–387). New York, NY: Guilford.
41. Dahl JC, Wilson KG, Nilsson A. Acceptance and commitment therapy and the treatment of persons at risk for long-term disability resulting from stress and pain symptoms: a preliminary randomized trial. *Behav Ther*. 2004;35:785–801.
42. McCracken LM, Vowles KE, Eccleston C. Acceptance-based treatment for persons with complex, long standing chronic pain: a preliminary analysis of treatment outcome in comparison to a waiting phase. *Behav Res Ther*. 2005;43:1335–46.
43. Vowles KE, McCracken LM, Eccleston C. Process of change in treatment for chronic pain: the contributions of pain, acceptance, and catastrophizing. *Eur J Pain*. 2007;11:779–87.
44. Vowles KE, McCracken LM. Acceptance and values-based action in chronic pain: a study of treatment effectiveness and process. *J Consult Clin Psychol*. 2008;76:397–407.