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Open-label Study of Injectable Extended-release Naltrexone (XR-NTX) in Healthcare Professionals With Opioid Dependence

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Objectives: Healthcare professionals (HCPs) with opioid dependence are at risk for relapse and death, particularly in the first year of recovery; however, maintenance treatment with opioid agonists is controversial in this safety-sensitive group. We evaluated long-term safety, tolerability, and treatment outcomes of injectable, intramuscular, extended-release naltrexone (XR-NTX) in opioid-dependent HCPs.

Methods: This single-arm, multisite, open-label study was conducted in opioid-dependent HCPs who had been detoxified from opioids for at least 2 weeks. Subjects received monthly XR-NTX injections for up to 24 months, combined with counseling via intensive outpatient substance abuse treatment programs. Assessments included monthly urine opioid drug tests and routine safety assessments, along with a trimonthly short form (36) Health Survey, opioid craving questionnaire, and Treatment Satisfaction Questionnaire for Medication.

Results: Of 49 opioid-dependent HCPs screened, 38 enrolled and received at least 1 XR-NTX injection. Most were female (n = 31) and nurses or nursing assistants (n = 30). More than half (n = 21; 55.3%) received at least 12 injections. Seven discontinued due to adverse events (3 anxiety, 2 headache, 1 injection-site mass, 1 derealization). None experienced relapses to opioid dependence necessitating detoxification, overdose, or death during treatment. At 24 months, mean opioid craving fell by 45.2%, and short form (36) mental component scores improved by 31.1% from baseline and approached normal levels. Of 22 unemployed subjects at baseline, 45.5% improved employment status at 24 months.

Conclusions: Long-term (2 years) XR-NTX was associated with no new safety concerns, and, compared with shorter-term studies in the general population, similar or better rates of retention, opioid-negative urines, opioid craving reduction, mental health functional quality of life improvement, and re-employment.

Key Words: extended-release naltrexone, healthcare providers, injectable naltrexone, opioid dependence, prescription opioids

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Opioids are the second most common drug of abuse (after alcohol) among healthcare professionals (HCPs), who appear to have a greater risk for opioid dependence compared with a matched general population (McLellan et al., 2008; Cottler et al., 2013). Clinical risk factors for this population are comparable with those of the general population, although the risk of death (~1%) is lower than that in the general population (Domino et al., 2005; McLellan et al., 2008; Berge et al., 2009). However, ready access to substances of abuse in the healthcare environment may contribute to a greater risk of relapse (Berge et al., 2009), and approximately 25% of HCPs in treatment for substance use disorders relapse at least once in the 5-year time frame, with 58% (43 of 74) of first relapses occurring within the first year (Domino et al., 2005).

Opioid agonists (eg, methadone, buprenorphine) and an opioid antagonist (oral naltrexone and extended-release naltrexone [XR-NTX]) are US Food and Drug Administration (FDA)-approved and recognized pharmacotherapy options for opioid dependence (oral naltrexone is approved for opioid blockade). For dependent HCPs, opioid agonist treatments, in particular, are controversial and stigmatized, and are prohibited in some US states (McLellan et al., 2008; Hamza and

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Conflicts of interest: Dr Earley is a paid consultant to Alkermes, Inc; Drs Memisoglu and Silverman are employees of Alkermes, Inc; and Dr Gastfriend and Ms Zummo were employees of Alkermes, Inc when the study and analyses were conducted.

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Bryson, 2012). Consequently, most health programs for dependent HCPs rely on nonagonist treatment protocols combined with close monitoring of performance as part of a comprehensive, long-term approach (Washton et al., 1984; Merlo and Gold, 2008; DuPont et al., 2009a; Earley, 2009; Hamza and Bryson, 2012). In a longitudinal study of 904 physicians in treatment for substance use disorders, opioid-based treatment was least preferred, with only 1 physician choosing methadone treatment, whereas more HCPs preferred naltrexone treatment (6%) (McLellan et al., 2008). Potential privacy and legal consequences of agonist-based treatment may also be contributing factors (Merlo and Gold, 2008; Berge et al., 2009).

Antagonist-based treatments combined with psychosocial management are alternatives that avoid some of these barriers. The use of oral naltrexone is well supported in highly motivated populations or in treatment settings with diligent monitoring to ensure compliance with the oral formulation (Washton et al., 1984; Roth et al., 1997; Merlo et al., 2011; Minozzi et al., 2011). Acknowledging the need to improve treatment adherence, the National Institute on Drug Abuse called for the development of a long-acting naltrexone preparation (Willette, 1976). In 2010, the US FDA approved once-monthly, intramuscular injectable, XR-NTX for the prevention of relapse in opioid-dependent individuals (VIVITROL, 2015). XR-NTX releases naltrexone from microspheres composed of polylactide-co-glycolide, a polymer used in dissolvable surgical sutures. A multicenter, placebo-controlled study demonstrated the efficacy of XR-NTX for the prevention of relapse after detoxification in a general population of opioid-dependent patients (Krupitsky et al., 2011). In that 6-month study, patients treated with XR-NTX had a median of 90% confirmed (via urine drug screen) abstinent weeks versus 35% for placebo. Prior studies (Garbutt et al., 2005; O'Malley et al., 2007; Gastfriend, 2011) demonstrated the effectiveness of XR-NTX in the treatment of alcohol dependence as well; XR-NTX is also approved for the treatment of alcohol dependence in abstinent patients (VIVITROL, 2015).

There have been no prospective studies of an extended-release opioid antagonist in the treatment of opioid dependence among HCPs. The primary objective of the present study was to evaluate the tolerability and long-term safety of XR-NTX for prevention of relapse among opioid-dependent HCPs who were enrolled in standard intensive outpatient care. Secondary aims were to evaluate the duration of treatment adherence, rates of confirmed opioid abstinence, changes in craving for opioids, and quality of life over the course of 24 months.

METHODS

This study was a prospective, single-arm, multisite, open-label evaluation of long-term safety, tolerability, retention, and treatment outcomes with up to 24 months of XR-NTX treatment for prevention of relapse to opioid dependence among HCPs. The study was conducted from June 1, 2009 to May 8, 2012 at 8 US sites. An institutional review board at each participating site approved the protocol. All study sites were independent intensive outpatient treatment centers (American Society of Addiction Medicine level 2.1). Participation in the study was voluntary and subjects could withdraw from the study at any time. Subjects provided written, informed consent and might or might not have been mandated to treatment under voluntary license supervision agreements; this information was not required or tracked by the study, nor did the study sponsor disclose information related to study participation or study outcomes to any monitoring agencies.

Subjects

Subjects were HCPs (nurses, doctors, pharmacists), 18 years of age or older, who had enrolled in outpatient treatment for opioid dependence. We excluded those with current clinically significant medical or psychiatric comorbid conditions; current dependence (past 12 months) on any drugs other than prescription opioids, heroin, benzodiazepines, caffeine, marijuana, alcohol, or nicotine based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria; and a positive urine drug test, positive naloxone challenge test, or self-reported opioid use at screening (ie, patients had to have already completed detoxification).

Study Design and Assessments

After the baseline evaluation, medical staff at the sites administered XR-NTX as a gluteal intramuscular injection once monthly for up to 24 months. All subjects also participated in intensive outpatient treatment programs, which typically offered individual and group drug counseling, encouragement to attend self-help meetings, and regular monitoring of drug use.

Safety assessments consisted of reports of adverse events (AEs), vital signs, and injection-site reactions, made by site investigators during the monthly visits for XR-NTX injections. An additional posttreatment visit was conducted 1 month after the final injection.

Retention was evaluated in terms of number of injections received. Urine drug tests for opioids were performed at each of the monthly visits. If drug use was suspected at any visit, at the investigator's discretion, a naloxone challenge test (using the short-acting antagonist) was performed, and the subject was withdrawn if the test was positive (which would indicate relapse to physiologic opioid dependence). In addition, 3 standard self-report assessments were administered at baseline and at every third visit: a standard and widely used quality-of-life measure of health-related functioning (Short Form [36] Health Survey) (Ware et al., 2000), an opioid craving questionnaire (Heinz et al., 2006), and the Treatment Satisfaction Questionnaire for Medication (TSQM) (Atkinson et al., 2005). The TSQM comprises 11 questions assessing a patient's satisfaction with their medication related to effectiveness, side effects, convenience, and global satisfaction with possible computed values ranging from 0 to 100. Each monthly visit also assessed self-reported change in employment and professional licensure status, and attendance at psychosocial treatment sessions offered within the outpatient program or at mutual peer-support meetings.

Statistical Analyses

The safety population included all subjects who received at least 1 injection of XR-NTX. Incidence of AEs was summarized descriptively. Time to study discontinuation

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic	Enrolled Subjects (N = 38)
Female, n (%)	31 (81.6)
Age, y, mean (SD)	42.4 (±10.4)
Ethnicity/race, n (%)	
White	37 (97.4)
Black	1 (2.6)
Employment/licensure status*, n (%)	
Practicing, no restrictions	12 (31.6)
Practicing, some restrictions	4 (10.5)
Voluntarily stopped working	19 (50.0)
License revoked	3 (7.9)
Duration of opioid use, y, mean (SD)	6.6 (6.3)
Positive drug test, n (%)	
Benzodiazepines	1 (2.6)
Marijuana	1 (2.6)
Amphetamines, cocaine, or opioids	0
Opioid craving questionnaire total score, mean (SD)	3.1 (±1.3)
SF-36 score, mean (SD) [US Norms = 50]	
Mental component score	36.3 (±13.6)
Physical component score	52.2 (±7.8)
Negative naloxone challenge, n (%)	38 (100)

*This category reflects the HCP's status regarding his/her professional license.

was presented graphically using Kaplan-Meier plots. Rates of opioid-negative urine drug tests were reported descriptively. No other imputation was performed, and all other analyses were based on observed data. Descriptive summary of scores for self-report assessments and for employment data was performed at scheduled time points.

RESULTS

Subject Characteristics and Disposition

Of 49 subjects screened, 38 (77.6%) enrolled in the study and received at least 1 injection of XR-NTX. Reasons for not enrolling included lost to follow-up (n = 5), not fulfilling study inclusion or exclusion criteria (n = 4), withdrew consent (n = 1), or other (n = 1). Of 38 enrolled patients, 15 (39.5%) remained in the study for 24 months. Reasons for early termination were AEs (n = 7), loss to follow-up (n = 7), withdrawal of consent (n = 5), other (n = 2), investigator decision (n = 1), and subject relocated (n = 1).

Most of the 38 enrolled subjects were women (n = 31) and nurses or nursing assistants (n = 30), with an average age of 42.4 years (range = 23–64 years) (Table 1). Four subjects (10.5%) were physicians, 1 was a pharmacist, 1 was a substance misuse treatment counselor, and 2 had unspecified healthcare occupations. Although only 3 (7.9%) had their licenses to practice revoked, half of the subjects had stopped working voluntarily (n = 19). At baseline evaluation, subjects also reported histories of depression (44.7%), hypertension (23.7%), insomnia (21.1%), seasonal allergy (21.1%), headache (18.4%), migraine (18.4%), drug hypersensitivity (18.4%), anxiety (15.8%), major depression (15.8%), back pain (15.8%), and gastroesophageal reflux (15.8%).

Safety

Overall, 37 of the 38 subjects who received an injection experienced at least 1 AE (Table 2), all of which were consistent with prior study experience with XR-NTX treatment (Krupitsky et al., 2011). The most common AEs (>15%) were nausea (42.1%), injection-site pain (36.8%), anxiety (28.9%), headache (26.3%), upper respiratory tract infection (21.1%), arthralgia (18.4%), and dizziness (15.8%). Two cases of injection-site mass, and 1 case each of injection-site pain, nausea, anxiety, and neuralgia were coded as "severe"; all other events listed were coded as "mild" or "moderate."

The median duration of treatment-emergent AEs was 6.0 days for "mild" AEs, 7.5 days for "moderate" AEs, and 10.5 days for "severe" AEs. Among 37 subjects who had at least 1 TEAE, the distribution of TEAE severity was similar among completers and noncompleters (Fisher exact probability test; $P = 0.17$). Of the 7 subjects (18.4%) who discontinued due to AEs, 1 subject had an AE of "severe" anxiety after 64 days in treatment, which resolved in 7 days, and another subject had an AE of "moderate" anxiety after 57 days in treatment, which was not resolved before treatment discontinuation; all other AEs lasted 3 to 14 days and were "mild" (injection-site mass [1]) or "moderate" (derealization [2], anxiety [1], headache [2]).

There were 2 serious category AEs (a head injury due to a motor vehicle accident and a suicide attempt); both were judged by the investigator to be unrelated to study drug, and neither led to discontinuation of treatment. No overdoses were reported, and no deaths occurred during the study and up to 1 month post treatment (or after treatment).

Study Outcomes

Nearly three-fourths (28; 73.7%) of subjects voluntarily received at least 6 months of XR-NTX treatment, more than half (21; 55.3%) received 12 or more monthly injections, and 14 (36.8%) subjects received all 24 available injections. Fifteen of the 38 subjects (39.5%) completed 24 months of assessments in the study (16 completed 18 months and 18 completed 12 months), yielding a median time to discontinuation of XR-NTX for all 38 subjects of 404.0 days, or 13.3 months (lower bound of 95% confidence interval [CI]: 183.0 days; upper bound exceeded study duration) (Fig. 1). However, 5 subjects discontinued after 1 injection. For the 23 subjects who discontinued treatment before 24 months, the median time to discontinuation was 183.0 days, or 6 months.

TABLE 2. Adverse Events Occurring in >10% of Subjects

Adverse Event	Subjects, n (%)
At least 1 adverse event	37 (97.4)
Nausea	16 (42.1)
Injection-site pain	14 (36.8)
Anxiety	11 (28.9)
Headache	10 (26.3)
Upper respiratory tract infection	8 (21.1)
Arthralgia	7 (18.4)
Dizziness	6 (15.8)
Bronchitis	5 (13.2)
Depression	5 (13.2)
Diarrhea	5 (13.2)
Sinusitis	5 (13.2)
Vomiting	5 (13.2)
Decreased appetite	4 (10.5)
Fatigue	4 (10.5)

Discontinued treatment due to adverse events 7 (18.4).

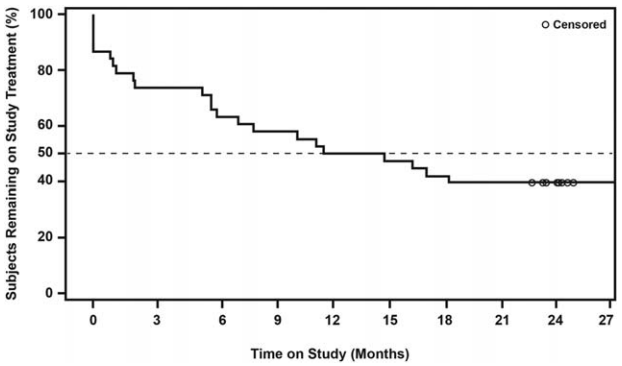

FIGURE 1. Retention of the HCP population (Kaplan-Meier plot) over the 24-month study period with XR-NTX treatment.

Psychosocial treatment in this study was treatment as usual; thus, its nature and frequency were not characterized. However, nearly all subjects attended counseling (92.1%), or attended mutual support meetings (94.6%) over the course of treatment; the frequency and duration of care varied. In the last study month, 66.7% of completers (n = 10) attended a psychosocial treatment session, and 80% had attended a mutual support meeting in the prior month.

Urine drug tests were conducted at each scheduled monthly medication visit for all subjects. Of all the scheduled and unscheduled (as determined by the specific program requirements) urine drug tests conducted after initiating XR-NTX (n = 519) completed over 24 months, 4 subjects tested positive for opioids (3 subjects had only 1 positive urine drug screen each). No subject required opioid detoxification after initiating XR-NTX.

Craving for opioids decreased rapidly over the first 6 months of treatment and remained reduced for the subsequent 18 months, with an overall decrease in mean total score from 3.1 to 1.7 on the 7-point scale (45.2% improvement) (Fig. 2A). SF-36 physical component scores were normative at baseline and remained so across treatment (all monthly mean scores from 50 to 55, Fig. 2B). The mental component score of the SF-36 indicated increased function over time (Fig. 2C). At baseline, the mean mental component score for all subjects (36.3) was more than 1 standard deviation (SD) less than US population norms (ie, 50 on the 100-point scale), and improved to 47.6 at 24 months (31.1% improvement); these results were consistent

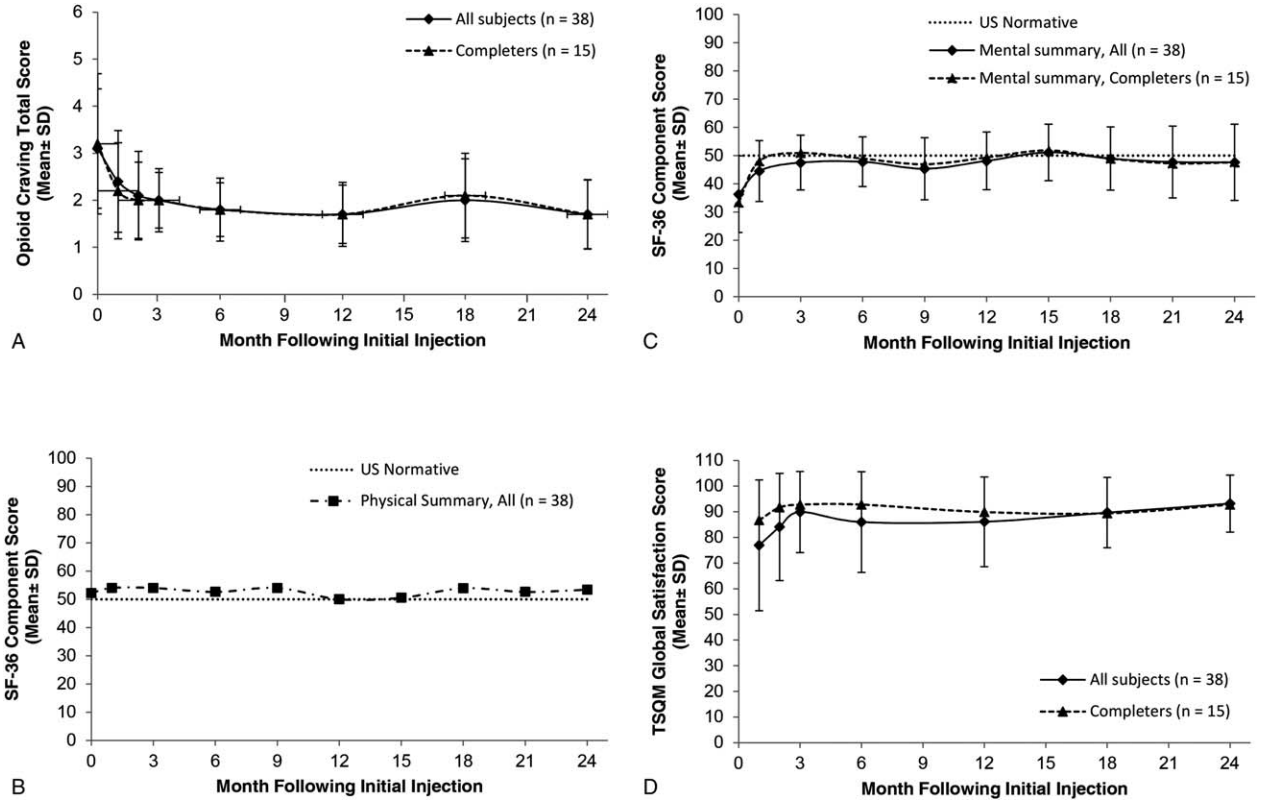

FIGURE 2. Outcomes of the HCP population over the 24-month study period with XR-NTX treatment. (A) Opioid craving scores (all subjects and completers). Total score on the opioid craving scale ranges from 1 to 7; higher scores = more craving. (B) SF-36 physical component scores (all subjects and completers). Higher scores = greater function; scores (ranging from 0 to 100) are adjusted such that 50 = normative for healthy US populations and 10 points = 1 standard deviation. (C) SF-36 mental component scores (all subjects and completers). Higher scores = greater function; scores (ranging from 0 to 100) are adjusted such that 50 = normative for healthy US populations and 10 points = 1 standard deviation. (D) TSQM global satisfaction scores (all subjects and completers). Scaled scores were derived for global satisfaction from TSQM questions assessing patient satisfaction with medication. Scores ranged from 0 to 100, with higher scores indicating greater satisfaction.

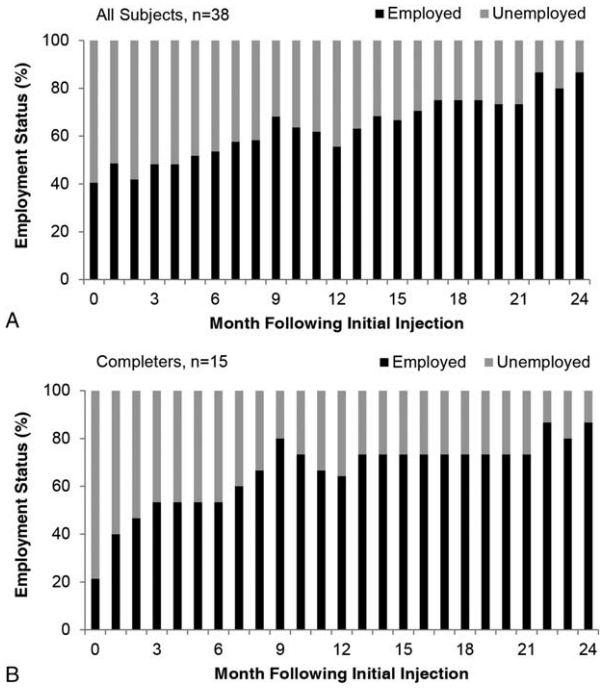

FIGURE 3. Employment status of HCPs over the 24-month study period with XR-NTX treatment. Represents employment as an HCP or otherwise.

with those for completers. Treatment satisfaction as measured by the TSQM increased over time, with the greatest levels of global satisfaction measured in the final 6 months of the study; these satisfaction ratings were consistent in both the all-subjects and completers analyses (Fig. 2D).

Of the 22 individuals at baseline who were unemployed (voluntarily or due to revoked license), 10 (45.5%) reported improved employment status by the study's end. Of those who were employed at baseline (n = 16), only 2 (12.5%) reported worse employment status at the study's end. Of those who completed the study (n = 15), unemployment in the healthcare professions fell from 78.6% (11/14) at baseline to 13.3% (2/15) by 24 months (Fig. 3). For those who completed the study, the mean (SD) number of paid hours of employment per week increased from 9.8 (19.6) hours at baseline to 28.9 (15.9) hours by end of study.

DISCUSSION

This is the first report of XR-NTX treatment of opioid dependence in HCPs and the longest treatment duration reported with this medication to date for opioid dependence. The safety profile of XR-NTX was consistent with the randomized clinical trials (Garbutt et al., 2005; Krupitsky et al., 2011), and no new or unexpected safety concerns were evident. Although injection-site reactions are not uncommon with XR-NTX, only 1 subject discontinued treatment because of this AE. The long duration of XR-NTX treatment, a median 404 days, is also noteworthy. Treatment satisfaction was high, retention was good, and rates of opioid-positive urines were low. Mental health-related quality of life improved, and completers showed an approximate tripling in the number of hours of paid work per week.

This study was open-label, conducted in the United States, and of predominantly female HCPs who were dependent on oral prescription analgesics, unlike the multisite randomized controlled trial of XR-NTX, which recruited primarily men with a high rate of injectable opioid use (Krupitsky et al., 2011). For purposes of comparison, the 6-month retention rate in the present study (73.7%) was greater than that in the pivotal study of XR-NTX (57.9%; N = 126) (Krupitsky et al., 2011). Double-blind study design and treatment setting in Russia, where agonist-based treatments are unavailable, are important differences between the pivotal study and the present one. Treatment completion rates in clinical studies for opioid dependence vary considerably (Timko et al., 2016), and the completion rates for the present study are consistent with other medication-assisted treatment options. Among patients with opioid dependence, low acceptance of medication-assisted treatment has been a prevailing barrier and remains an important factor that can influence treatment retention rates (Uebelacker et al., 2016). Regardless, both studies retained a majority of subjects through 6 injections, with comparable sustained reductions in craving (approximate 50% decrease from baseline) and improvements in quality-of-life outcomes (approximate 1.5-SD improvement in SF-36 mental health function scores). Additional studies have confirmed the impact of XR-NTX and reduced craving in the heroin-dependent patient population (Sullivan et al., 2013; Langleben et al., 2014; Wang et al., 2015).

Almost all patients in the present study participated in psychosocial treatments and mutual support groups, and participation rates remained high at 24 months. Many profession-specific monitoring programs track ongoing treatment and support group attendance; these data suggest that XR-NTX maintenance was compatible with recovery-oriented treatment regimens. Similarly, previous research has indicated that XR-NTX treatment for alcohol dependence is compatible with participation in psychosocial therapy and mutual support groups (Cisler et al., 2010). A health economic analysis found that XR-NTX-treated opioid-dependent patients had similar or greater numbers of outpatient psychosocial visits than those treated with oral naltrexone, methadone, or buprenorphine (Baser et al., 2011). The present data are consistent with these previous findings and extend them to the use of XR-NTX in opioid-dependent HCPs.

Limitations of the present study include an open-label and uncontrolled study design and a relatively small sample consisting predominantly of white women. Larger placebo-controlled trials with additional types of HCPs are needed to better evaluate the efficacy of XR-NTX in this group of safety-sensitive employees.

Almost all states have profession-specific monitoring programs for physicians (DuPont et al., 2009a), and many also have programs for dentists, pharmacists, and nurses (American Society of Addiction Medicine, 2011). Such programs typically include an initial triage; an individualized treatment regimen; regulation regarding the types of approved treatment options; and particularly, long-term abstinence tracking using sophisticated drug screen analysis. Dependent HCPs are

directed to these programs, and employment and licensure is often contingent on continued participation in the monitoring program (including but not limited to remaining abstinent). The typically intensive, comprehensive, and long-term combination of treatment and monitoring is unusual and creates an excellent prognosis for HCP opioid addiction (Domino et al., 2005; McLellan et al., 2008; Skipper et al., 2009; Buhl et al., 2011). Indeed, the results from this treatment model have prompted suggestions that it become the standard for all addiction treatment in the entire population (Gastfriend, 2005; DuPont et al., 2009b).

Some HCPs are not successful in monitoring programs and relapse (Domino et al., 2005) or are legally or financially deterred from agonist-based treatments (Talbott et al., 1987; Berge et al., 2009). These HCPs may be especially vulnerable due to the ease of access to addictive substances that could produce conditioned cue craving (Talbott et al., 1987; O'Brien et al., 1990; Berge et al., 2009).

Extended-release opioid antagonist treatment could provide additional protection against cue-induced craving and relapse, and is consistent with the recovery-oriented approach favored by most professional societies governing the treatment of opioid-dependent HCPs (Skipper et al., 2009). Effective use of oral naltrexone among opioid-dependent HCPs requires consistent and voluntary self-administration, usually daily or at minimum at least 3 times per week. In general populations with opioid dependence, adherence to oral naltrexone is low, such that its efficacy has generally been no better than placebo (Minozzi et al., 2011).

However, in a study of highly motivated professionals, including HCPs, 74% of opioid-dependent physicians treated with 6 months of oral naltrexone were abstinent and returned to their practice in 12 months (Washton et al., 1984). The authors noted that naltrexone may have provided specific benefits to physicians' ability to focus on recovery and work, and also potentially ensured reduced suspicion and doubt within the legal community and among medical colleagues on return to work. In other structured programs with naltrexone (including XR-NTX), long-term abstinence rates of up to 94% have been observed (Roth et al., 1997; Merlo et al., 2011).

These promising findings among safety-sensitive HCPs argue persuasively for broader evaluation of XR-NTX in the large and growing population of opioid-dependent individuals, which has reached epidemic status (Han et al., 2015). It is noteworthy that only 8 of 519 urine drug screens revealed any opioid use in the present study. Among those who remained on XR-NTX, there were no relapses to opioid dependence over the 24-month period. The results of the present study are consistent with prior XR-NTX studies of 6-month efficacy and safety and add to the evidence for long-term safety and positive treatment outcomes for XR-NTX in opioid-dependent individuals for durations up to 24 months.

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REFERENCES

American Society of Addiction Medicine, 2011. Public policy statement on healthcare and other licensed professionals with addictive illness: an overview [American Society of Addiction Medicine web site]. Available at: http://www.asam.org/advocacy/find-a-policy-statement/view-policy-statement/public-policy-statements/2011/12/16/healthcare-and-other-licensed-professionals-with-addictive-illness-an-overview. Accessed February 11, 2015.

Atkinson MJ, Kumar R, Cappelleri JC, et al. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. *Value Health* 2005;8(Suppl 1): S9–S24.

Baser O, Chalk M, Fiellin DA, et al. Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care* 2011;17(Suppl 8):S235–S248.

Berge KH, Seppala MD, Schipper AM. Chemical dependency and the physician. *Mayo Clin Proc* 2009;84:625–631.

Buhl A, Oreskovich MR, Meredith CW, et al. Prognosis for the recovery of surgeons from chemical dependency: a 5-year outcome study. *Arch Surg* 2011;146:1286–1291.

Cisler RA, Silverman BL, Gromov I, et al. Impact of treatment with intramuscular, injectable, extended-release naltrexone on counseling and support group participation in patients with alcohol dependence. *J Addict Med* 2010;4:181–185.

Cottler LB, Ajinkya S, Merlo LJ, et al. Lifetime psychiatric and substance use disorders among impaired physicians in a physicians health program: comparison to a general treatment population: psychopathology of impaired physicians. *J Addict Med* 2013;7:108–112.

Domino KB, Hornbein TF, Polissar NL, et al. Risk factors for relapse in health care professionals with substance use disorders. *JAMA* 2005;293: 1453–1460.

DuPont RL, McLellan AT, Carr G, et al. How are addicted physicians treated? A national survey of Physician Health Programs. *J Subst Abuse Treat* 2009a;37:1–7.

DuPont RL, McLellan AT, White WL, et al. Setting the standard for recovery: physicians' health programs. *J Subst Abuse Treat* 2009b;36:159–171.

Earley P. Physicians health programs and addiction among physicians. In: Ries R, Fiellin D, Miller S, Saitz R, editors. Principles of Addiction Medicine. Philadelphia, PA: Lippincott, Williams and Wilkins; 2009. p. 531–548.

Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005;293:1617–1625.

Gastfriend DR. Physician substance abuse and recovery: what does it mean for physicians: and everyone else? *JAMA* 2005;293:1513–1515.

Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. *Ann N Y Acad Sci* 2011;1216:144–166.

Hamza H, Bryson EO. Buprenorphine maintenance therapy in opioid-addicted health care professionals returning to clinical practice: a hidden controversy. *Mayo Clin Proc* 2012;87:260–267.

Han B, Compton WM, Jones CM, et al. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *JAMA* 2015;314:1468–1478.

Heinz AJ, Epstein DH, Schroeder JR, et al. Heroin and cocaine craving and use during treatment: measurement validation and potential relationships. *J Subst Abuse Treat* 2006;31:355–364.

Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011;377:1506–1513.

Langleben DD, Ruparel K, Elman I, et al. Extended-release naltrexone modulates brain response to drug cues in abstinent heroin-dependent patients. *Addict Biol* 2014;19:262–271.

McLellan AT, Skipper GS, Campbell M, et al. Five year outcomes in a cohort study of physicians treated for substance use disorders in the United States. *BMJ* 2008;337:a2038.

Merlo LJ, Gold MS. Prescription opioid abuse and dependence among physicians: hypotheses and treatment. *Harv Rev Psychiatry* 2008;16: 181–194.

Merlo LJ, Greene WM, Pomm R. Mandatory naltrexone treatment prevents relapse among opiate-dependent anesthesiologists returning to practice. *J Addict Med* 2011;5:279–283.

Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2011;CD001333.

O'Brien CP, Childress AR, McLellan T, et al. Integrating systemic cue exposure with standard treatment in recovering drug dependent patients. *Addict Behav* 1990;15:355–365.

O'Malley SS, Garbutt JC, Gastfriend DR, et al. Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent before treatment. *J Clin Psychopharmacol* 2007;27:507–512.

Roth A, Hogan I, Farren C. Naltrexone plus group therapy for the treatment of opiate-abusing health-care professionals. *J Subst Abuse Treat* 1997;14: 19–22.

Skipper GE, Campbell MD, Dupont RL. Anesthesiologists with substance use disorders: a 5-year outcome study from 16 state physician health programs. *Anesth Analg* 2009;109:891–896.

Sullivan MA, Bisaga A, Mariani JJ, et al. Naltrexone treatment for opioid dependence: does its effectiveness depend on testing the blockade? *Drug Alcohol Depend* 2013;133:80–85.

Talbott GD, Gallegos KV, Wilson PO, et al. The medical association of Georgia's impaired physicians program. Review of the first 1000 physicians: analysis of specialty. *JAMA* 1987;257:2927–2930.

Timko C, Schultz NR, Cucciare MA, et al. Retention in medication-assisted treatment for opiate dependence: a systematic review. *J Addict Dis* 2016;35:22–35.

Uebelacker LA, Bailey G, Herman D, et al. 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.

VIVITROL prescribing information. VIVITROL® (naltrexone for extended-release injectable suspension) prescribing information. Waltham, MA: Alkermes, Inc; 2015.

Wang AL, Elman I, Lowen SB, et al. Neural correlates of adherence to extended-release naltrexone pharmacotherapy in heroin dependence. *Transl Psychiatry* 2015;5:e531.

Ware JE, Kosinski M, Dewey JE. How to score version two of the SF-36 Health Survey. Lincoln, RI: Quality Metric; 2000.

Washton AM, Pottash AC, Gold MS. Naltrexone in addicted business executives and physicians. *J Clin Psychiatry* 1984;45(9 Pt 2):39–41.

Willette R, ed. Narcotic antagonists: the search for long-acting preparations [National Institute on Drug Abuse Research Monograph Series 4]; 1976. Available at: http://archives.drugabuse.gov/pdf/monographs/04.pdf. Accessed February 11, 2015.

