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Intramuscular extended-release naltrexone: current evidence

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Extended-release naltrexone (XR-NTX; Vivitrol®), developed to address poor adherence in addictive disorders, is approved for use in alcohol and opioid-dependence disorders. In alcohol-dependent adults with ≥4-day initial abstinence, XR-NTX increased initial and 6-month abstinence. An fMRI study found that XR-NTX attenuated the salience of alcohol visual and olfactory cues in the absence of alcohol, and *post hoc* analyses demonstrated efficacy even during high cue-exposure holiday periods. Safety and tolerability have generally been good, without adverse hepatic impact or intractable acute pain management. XR-NTX use appears feasible in primary care and public systems, and retrospective claims analyses have found cost savings and decreased intensive service utilization relative to oral agents. In opioid dependence, following detoxification, XR-NTX shows efficacy for maintaining abstinence, improving retention, decreasing craving, and preventing relapse. Trials are also exploring its use for the treatment of stimulant dependence. XR-NTX appears compatible with counseling and self-help attendance. While more research is needed, current findings suggest that a formulation of naltrexone that was sought beginning over three decades ago is fulfilling its promise as an extended-release pharmacotherapeutic.

Keywords: alcohol dependence; opioid dependence; naltrexone; extended-release naltrexone; Vivitrol®

Medications for alcohol dependence

Alcohol dependence continues to be a serious problem in the United States and around the world. Almost 4% (about 8 million people) of the adult U.S. population is dependent on alcohol.[1] The effects of alcohol dependence on both the individual and society are well documented in terms of morbidity, mortality, healthcare costs, and lost work productivity.[2–6] If anything, worldwide use of alcohol is increasing, particularly in developing countries, and age at first drink is decreasing, suggesting that there will be an even greater need for effective treatments for alcohol dependence in the future.[7–9]

Although most individuals with alcohol dependence who seek treatment receive either psychosocial counseling or participate in self-help groups without the use of pharmacological interventions,[10] current practice guidelines recommend pharmacotherapy with behavioral treatments.[11] In the United States, Food and Drug Administration approved medications for alcohol dependence include disulfiram (Antabuse®) (introduced in 1948), oral naltrexone (ReVia®, Depade®) (approved in 1994), acamprosate Calcium (Campral®) (approved in 2004), and extended-release injectable naltrexone (XR-NTX; Vivitrol®) (approved in 2006). Despite these guidelines, only 16.2% of substance abuse treatment facilities in the United States report using disulfiram, 17.2% acamprosate, and 15.8% naltrexone (not broken down by oral vs. extended-release), and rates of adoption are growing very slowly.[10] There are likely multiple reasons for this, including the fact that the use of medications to reduce alcohol consumption is seen by some[12] as contrary to an emphasis on complete abstinence, as well as known problems, reviewed later in this chapter, with adherence to oral medications for alcohol dependence.

In order to address problems with adherence, extended-release medications are an option. The purpose of the current review is to present emerging data regarding extended-release injectable naltrexone. The primary focus of the review is on

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the use of XR-NTX as a treatment for alcohol dependence. This review examines the existing efficacy data for XR-NTX, including a focus on clinically meaningful subpopulations (those with prior abstinence; severely dependent individuals) and examination of the impact of XR-NTX on quality of life and health economics in addition to drinking outcomes. Studies that investigated other injectable formulations of naltrexone that have not received FDA approval are generally not reviewed. Data on the safety, tolerability, and other clinical concerns of XR-NTX are presented. Following a presentation of studies with alcohol-dependent patients, research evaluating XR-NTX for other disorders is also briefly described. To fully understand data on XR-NTX, it may be useful first to briefly review prior research on oral naltrexone.

Oral naltrexone

Naltrexone is a competitive antagonist at the μ-opioid receptors in the brain. While historically naltrexone has been described as an antagonist at the mu, delta, and kappa opioid receptors, more recent data have shown that it is a partial kappa agonist with no appreciable activity at delta receptors.[13] Naltrexone taken orally is quickly absorbed and undergoes first-pass metabolism in the liver where it is converted to its major metabolite, 6β-naltrexol.[14] After chronic administration, the mean serum elimination half-life for a 50 mg/d dose is 9.7 h for naltrexone and 11.4 h for 6β-naltrexol.[15]

Initially, naltrexone was investigated as a treatment for heroin addiction, receiving U.S. FDA approval in 1984 for opioid blockade. However, earlier animal studies had revealed that opioid antagonists blocked the ability of ethanol to increase dopamine release in pathways leading from the ventral tegmental area to the nucleus accumbens[16] and that naltrexone blocked the self-administration of alcohol in rhesus monkeys.[17] This work was followed by placebo controlled trials in alcohol-dependent humans showing that naltrexone reduced rates of relapse to heavy drinking.[18,19] Further research found that naltrexone blocked the subjective experience of a "high" from alcohol and reduced pleasure from drinking alcohol.[20–23] Oral naltrexone was approved in 1994 by the FDA for the treatment of alcohol dependence, and was also approved in a number of other countries (Australia, Canada, several European countries).

Although initial efficacy studies[18,19] of oral naltrexone for alcohol dependence were positive, subsequent reviews of a larger body of studies showed a more complex picture. To date, there have been five published meta-analyses/systematic reviews of the efficacy of oral naltrexone for alcohol dependence.[24–28] These reviews covered between 7 and 24 studies of oral naltrexone for alcohol dependence and, for the most part, reached similar conclusions. Across studies, oral naltrexone was superior to placebo or other control groups, but effect sizes were relatively small and there was substantial heterogeneity across studies. The most recent meta-analyses[27] found that across 24 randomized, double-blind, controlled studies of oral naltrexone with alcohol-dependent patients naltrexone was superior to control groups in regard to relapse to heavy drinking (28% vs. 42.5% relapsers), but not in failure of abstinence/return to drinking (59% vs. 65%). Furthermore, there were no significant differences between naltrexone and placebo on any secondary outcome measures, and 36% of patients treated with oral naltrexone discontinued treatment before 12 weeks. Results from a subsequent systematic (not a meta-analysis) review[28] reinforced these findings, documenting that almost 30% of trials showed no difference between drug and placebo, and the majority of studies failed to find evidence that oral naltrexone improves abstinence rates. Studies vary considerably in their methods of determining and assuring patient adherence; however, this may have been a critical factor compromising efficacy in some of these.[29]

The conclusion about the impact of adherence on efficacy is evident in the results of specific studies. For example, one study reported a nonsignificant difference between oral naltrexone and placebo on rates of returning to drinking.[30] This finding, however, was qualified by a statistically significant interaction of compliance with medication and relapse: relapse rates were only 14% in the medication-compliant (defined as taking pills on 90% or more of study days) naltrexone-treated patients compared to 52% in the medication-compliant placebo-treated patients.

Similarly, another study found oral naltrexone to be no better than placebo in the intent-to-treat analysis.[31] However, less than half of the sample was compliant. Among those who were compliant, oral naltrexone was found to be significantly superior to

placebo, with naltrexone-treated patients consuming half the amount of alcohol as placebo-treated patients. In summary, high compliance with oral naltrexone (pills taken on >80–90% of days) appears necessary to achieve efficacy.

Finally, a reanalysis of data from two studies in which oral naltrexone was not significantly better than placebo revealed that, in each study, medication adherence had a significant effect on improvement trends over time. For those who adhered to oral naltrexone, the odds of drinking on a particular day were one-third to one-half (depending on the study and the specific pattern of drinking over time into which patients were sorted) compared to those who were not adherent.[32]

In the "real world", outside of randomized clinical trials, however, compliance with many types of medications in general medicine is far from ideal.[33] Yet, when pharmacy claims of alcohol-dependent patients who were prescribed oral medications were analyzed for their refill rates with medications for other diseases, their persistence on alcohol-dependence medications (oral naltrexone and disulfiram) was poor (Fig. 1A), and substantially worse than for statins, antidepressants, or antipsychotics.[34] Several studies have directly assessed compliance with oral naltrexone in real-world clinical settings. Analysis of data from a commercial, community-based, claims database (Fig. 1B) revealed that over half of 1,138 patients with alcohol-related disorders who received a prescription for oral naltrexone did not refill the initial prescription, and 86% of these insured patients were not compliant (defined as having filled prescriptions for ≥80% of the duration) for a 6-month period.[35] Similarly, another claims database study of prescriptions for oral naltrexone (Fig. 1C) found that a typical patient who initiates oral naltrexone treatment uses the medication for a substantially shorter time period than the recommended guidelines (at least 3 to 6 months), with less than 10% continuing to have prescriptions filled for 6 months, and about half only filling only one prescription.[36] The healthcare utilization implications of noncompliance with oral naltrexone in real-world settings has also been empirically examined. Using claims data for the years 2000 to 2004, this study found that patients who were noncompliant for a 6-month course of oral naltrexone, compared to compliant ones, had significantly more hospital admissions, ER admissions, and alcohol detoxifications.[35]

Development and characteristics of XR-NTX

In the early 1970s, when naltrexone was first selected as a leading candidate to be developed for clinical use, it was recognized that a long-acting version of this medication was needed.[37] By 1981, only Phase II studies of oral naltrexone had been performed, yet the anticipated compliance problem with the medication was already evident.[38] Based on this early awareness that oral naltrexone would have limited clinical utility, the National Institute on Drug Abuse (NIDA) initiated a quest for a long-acting version of naltrexone, issuing six contracts in the early 1970s to separate research programs to develop new, long-acting delivery systems.

Success in the development of a long-acting preparation of naltrexone was 30 years in the making. Ideally, a sustained-release delivery system for naltrexone would be easy to inject or implant, pharmacologically stable, would not cause adverse tissue reaction, would release the drug at a relatively constant rate for at least 30 days, and would biodegrade within a short time afterward.[39] Early preparations, such as one consisting of 1.5-mm diameter molded beads of lactic/glycolic copolymer naltrexone mixture, achieved some of these properties, but the then-available technologies could not circumvent the problem of residual solvents associated with the manufacturing process, and thus no extended-release preparation could progress to FDA approval until this challenge could be resolved, three decades later.

Following the FDA approval of oral naltrexone for the treatment of alcohol dependence (in 1994), the lack of success in developing a long-acting preparation led the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and NIDA to facilitate progress on such development. The Institutes approved two Small Business Innovation Research grants, one in 2000 and another in 2001, to see the development of an extended-release preparation of naltrexone designed to be administered by intramuscular gluteal injection once a month.

The technology for XR-NTX involves embedding of the drug molecule within a polymeric matrix of microspheres made of poly(DL-lactide-co-glycolide) (PLG).[40] PLG is a common biodegradable

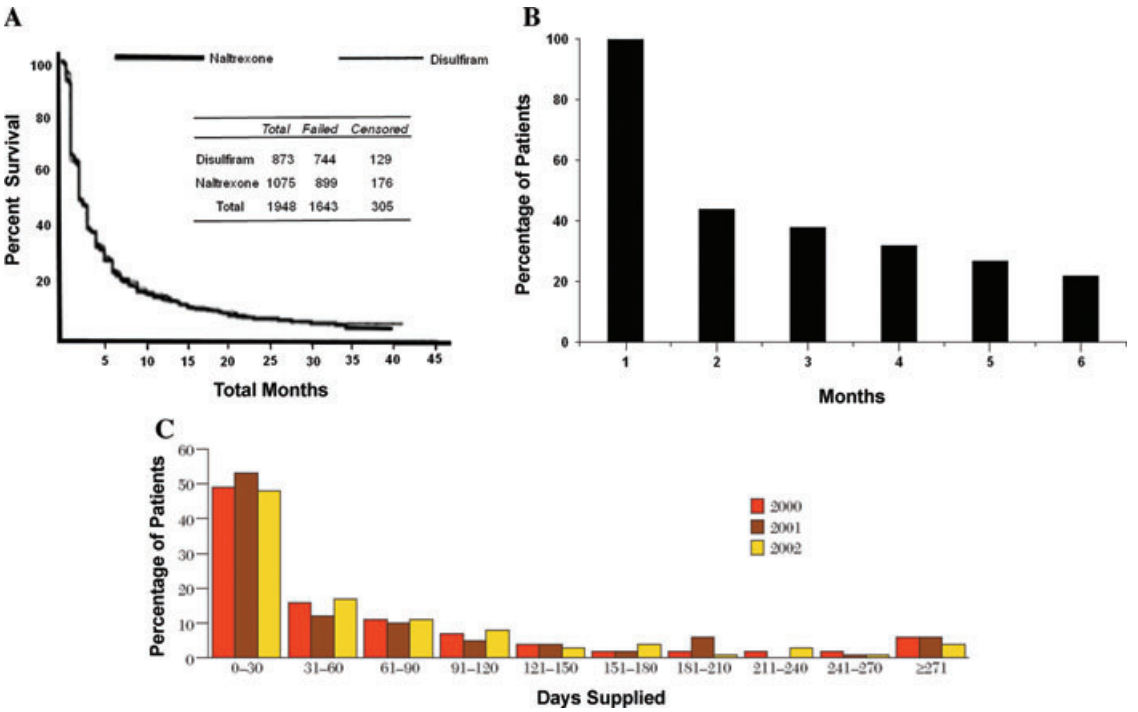

Figure 1. Survival curves from three retrospective pharmacy claims database analyses showing patients' adherence to refilling covered alcohol dependence medications over time. Panel 1A: Months per treatment episode for disulfiram and oral naltrexone in a U.S. Veterans population.[34] Panel 1B: Oral naltrexone refills from a multicommercial insurer database.[35] Panel 1C: Oral naltrexone refills across three consecutive 1-year periods.[36]

copolymer that has been used safely in humans for a variety of applications, including sutures, orthopedics, bone plates, and extended-release pharmaceuticals. The biodegradable polymers can be fabricated into small diameter, injectable microspheres (<100 μm) that provide release of drugs for predetermined time periods ranging from days to months. The release of the drug from PLG microspheres is influenced by water uptake, diffusion of the bioactive molecule from the microsphere surface, pores and polymer matrix, and the biodegradation of the polymer.

Pharmacokinetic studies of XR-NTX in animals[41] and humans[42–44] indicated that the extended-release formulation of naltrexone maintained stable, pharmacologically relevant plasma levels of naltrexone for at least 28 days, in addition to meeting the other criteria for a long-acting naltrexone preparation that were specified by Olson and Kincl.[39]

The mean *pK* characteristics of single-dose XR-NTX 380 mg versus oral naltrexone 50 mg are as follows: C_{max}: 12.9 vs. 10.6 ng/mL; t_{max} (median): 7.0 days versus 1.0 h; AUC_{∞}: 144 versus 30 ng·d/mL, and $t_{1/2}$: 4.95 days versus 3.9 h.[43] Several pharmacological characteristics appear to be unique to XR-NTX over a month of dosing: (1) For the patient, extended-release over 1 month ameliorates the daily adherence challenge; (2) for providers and significant others, the same extended-release feature provides an automatic "self-monitoring" effect, confirming that all dosing has been received for the month; (3) XR-NTX avoids first-pass hepatic metabolism, and this results in approximately one-fourth the monthly dose of XR-NTX (i.e., 380 mg), sufficing for treatment in contrast to oral naltrexone 50 mg (i.e., 1,500 mg per month); (4) avoidance of first-pass metabolism yields a markedly greater proportion of the active primary agent, naltrexone, in blood relative to the principal metabolite, 6β-naltrexol; (5) intramuscular administration also yields a plasma area-under-the-curve monthly plasma accumulation of naltrexone that is approximately four-times that achieved with daily oral naltrexone, that may have clinical

relevance, given that investigators have believed there may be a clinical dose-response effect for oral naltrexone and, accordingly, recent studies have used 100 mg/day rather than 50 mg/day of oral naltrexone;[45] and (6) it has been postulated that there may be effects of XR-NTX's continuous dosing as compared to oral naltrexone's pulsatile daily dosing, which may derive either pharmacologically—for example, with diurnally varying endorphin secretion—and/or psychologically—for example, with ever-changing internal cues, affective states, and expectancies.[46]

XR-NTX for alcohol dependence

Primary efficacy study

In April of 2006, the FDA approved XR-NTX for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with XR-NTX. This approval was based upon the prior evidence and approval for oral naltrexone, the preclinical and early phase clinical research on XR-NTX, and a single pivotal phase III efficacy study of XR-NTX. This efficacy study was a randomized, placebo-controlled trial with alcohol-dependent patients that was conducted at 24 centers across the United States.[47] Efficacy was evaluated across 24 weeks of monthly injections with XR-NTX 380 mg, XR-NTX 190 mg, or placebo. All patients also received 12 sessions of low intensity psychosocial therapy. The greatest treatment effect, found among patients defined a priori as those with $\geq$7 days of abstinence prior to treatment initiation, formed the basis of the FDA approval of XR-NTX for alcohol-dependent patients who are able to abstain from alcohol prior to treatment initiation and who are not actively drinking at the time of treatment initiation.

Efficacy in those with prior abstinence

A subsequent *post hoc* analysis of data from the primary efficacy trial revealed more details about treatment response in a subgroup of 83 patients who had at least four days of abstinence immediately prior to treatment initiation, which was not evident among the subset of patients who were actively drinking at the time of treatment initiation.[48] The 4-day lead-in abstinent interval is both a common threshold inclusion criterion in the literature (e.g., the COMBINE study[45]) and the median length of stay for completed detoxification episodes in the United States.[49] In patients with $\geq$4 days of prior abstinence, XR-NTX 380 mg resulted in nearly three-times as many patients with sustained abstinence for all 24 weeks compared with placebo (32% vs. 11%, $P = 0.02$) as well as a significantly greater proportion of responders (70% vs. 30%, $P = 0.006$) (responder = no more than 2 heavy drinking days in any consecutive 28-day period). In addition, patients receiving XR-NTX 380 mg had a significantly increased initial abstinence, that is, time to first drink (median durations of 42 vs. 12 days, $P = 0.02$) and time to first heavy drinking event (181 vs. 20 days, $P = 0.04$) (Fig. 2). Patients treated with XR-NTX 380, compared with placebo, also had significantly fewer drinking days per month (0.7 vs. 7.2, $P = 0.005$) and fewer heavy drinking days per month (0.2 days vs. 2.9 days, $P = 0.007$). The 190 mg dose of XR-NTX (not FDA-approved) consistently resulted in intermediate effects, indicating a dose-effect response. Thus, among patients who are initially abstinent for 4 or more days, XR-NTX 380 mg shows robust, large, and clinically meaningful improvements over placebo across a variety of outcome parameters. For patients receiving XR-NTX 380 mg, time to first drink was more than three times longer, time to first heavy drink was nine times longer, and number of heavy drinking days per month was less than one-tenth of that observed for those taking placebo.

Although the FDA approval of XR-NTX was based upon the subset of patients with prior abstinence, the same treatment effects were not evident among the subset of patients ($n = 571$, 92% of the total study population) who were actively drinking at the time of treatment initiation. The overall sample in this pivotal trial consisted of 624 patients, of whom 91.2% were nonabstinent during the week prior to their first injection and 57% did not have a treatment goal of abstinence. In this overall sample, the 380 mg group was found to be significantly more effective than placebo (plus psychosocial therapy) in reducing the rate of heavy drinking events over 24 weeks. In terms of the event rate of heavy drinking days, the 380 mg group showed a 25% greater decrease versus placebo ($P = 0.03$) with the 190 mg of naltrexone intermediate, at a 17% decrease ($P = 0.07$); in terms of heavy drinking days, the XR-NTX 380-mg group showed a 48% median reduction in heavy drinking days versus the placebo injection group. A treatment-by-gender interaction

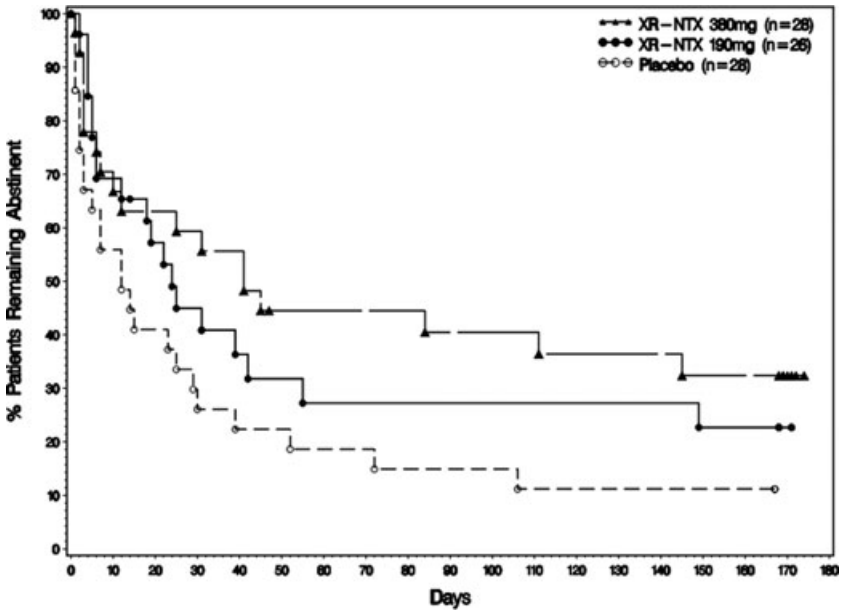

Figure 2. **Kaplan–Meier analysis of time to first drink among patients abstinent (≥4 days) prior to treatment initiation: duration of initial abstinence was significantly greater for XR-NTX 380 mg compared with placebo (42 vs. 12 days; $P = 0.02$) and the percent of patients with sustained abstinence at the conclusion of the trial was also significantly greater for XR-NTX 380 mg compared with placebo (32% vs. 11%; $P = 0.02$), with the XR-NTX 190 mg group showing results that are intermediate for both parameters.[48]**

was found in this study, in which the treatment effect was not significant in women; however, women represented a minority of subjects and the study was not powered to detect effects in women. The literature on oral naltrexone generally has not identified a differential gender effect. Efficacy in this study did not appear to be influenced by age, race, employment status, lead-in drinking, treatment goal, self-help meeting attendance, depression, use of antidepressants, smoking status, or body mass index. Maximum plasma concentration for naltrexone with XR-NTX 380 mg has previously been found to be approximately 30% lower in females, however, AUC was similar between genders.[43] One difference in this trial, however, is that women showed a stronger response to counseling plus placebo, compared to men.

Time course of treatment efficacy: early onset

In a further analysis,[50] the time course was examined to determine when the onset of effect occurred. During the first month following injection, patients receiving XR-NTX 380 mg had 37% fewer heavy drinking days versus placebo ($P < 0.01$). A significant reduction in the median number of drinks consumed per day was observed for the XR-NTX group versus placebo by day 2 ($P < 0.05$), and significant reductions in the percentage of patients reporting heavy drinking occurred by day 3 ($P < 0.05$). A dose-response effect was observed, with intermediate results for XR-NTX 190 mg. These findings are consistent with the pharmacokinetic release profile of XR-NTX, but more importantly, an early onset of efficacy may have important clinical implications for adherence and initial treatment engagement.

Time course of treatment efficacy: durability over 18 months

Given that alcohol dependence is a chronic disorder with multiple episodes of relapse and recurrence,[51] XR-NTX patients from the full sample who completed the 6-month pivotal trial were offered continuation on XR-NTX to evaluate its durability of effect over a 12-month open-label extension period.[52] For the 6-month double blind trial, the overall median rate of heavy drinking at baseline was 19 days per month. Patients who received 380 mg of XR-NTX decreased to a median of 3.1 days of heavy drinking. At the end of the 12-month open label extension period, the median patient receiving continuous XR-NTX since intake reported only 1.6 days of heavy drinking per month. Thus, although effects of

differential patient dropout could not be accounted for in this open-label phase, the effects of XR-NTX appeared durable over a total of 18 months.

Adherence in efficacy trial

Concerns about adherence with oral naltrexone were the impetus for the development of XR-NTX. But how well do patients adhere to regular monthly injections of XR-NTX? Adherence in the Garbutt *et al.*[47] trial with XR-NTX appears excellent when placed in the context of adherence to study medications in general, and oral medications for alcohol dependence in particular. A total of 64% of patients randomly assigned to receive XR-NTX received all six injections during the 24-week double-blind study period. This adherence is particularly noteworthy when considered against the nature of the trial sample: a vast majority of patients (91.2%) were still drinking during the week before their first injection, and more than half were not seeking to achieve abstinence. In many studies of oral naltrexone, all patients are abstinent for at least 4 days at the initiation of treatment. This inclusion criterion in most oral naltrexone studies likely preselects for more highly motivated and potentially compliant patients.

One concern with the results of many clinical trials is that a high rate of adherence may have been influenced by intensive research procedures. However, at the end of the trial, when patients still in the trial were offered the medication on a "compassionate use" open label basis for an additional 12 months without the intensive research procedures, 88% of the patients asked to continue on the medication and of these, 42% received all 13 doses of XR-NTX.[53] Moreover, approximately 10% of the originally randomized patients continued on XR-NTX for 3 to 4 years.[53]

Changes in quality of life

Heavy drinking of alcohol is associated with impairments in health-related quality of life (QOL), particularly mental health and social functioning.[54,55] Disorder-related impairments in quality of life and the ability of a new medical intervention to restore adequate QOL have been of increasing focus of research on medical and psychiatric disorders. The extent to which XR-NTX improves the QOL of alcohol-dependent patients was explored in a reanalysis[56] of data from the primary efficacy trial.[47] At baseline, the SF-36[57] showed impairment in the health-related QOL domain of mental health that was about 1 standard deviation below the U.S. population norm. Other specific domains (i.e., social functioning, problems with work or other daily activities due to emotional problems) also showed similar large impairments relative to U.S. norms. Over the course of 6 months of treatment, XR-NTX 380 mg was associated with significantly ($P < 0.05$) greater improvements from baseline in mental health, social functioning, general health, and physical functioning, compared to placebo. Furthermore, reductions from baseline in drinking (percentage of days drinking and percentage days of heavy drinking in past 30 days) were significantly ($P < 0.02$) correlated with improvements in QOL. Most subscales of physical functioning did not show significant treatment differences; however, these were not subnormative at baseline. Although this secondary analysis should be confirmed with additional studies and may not generalize to all alcohol-dependent individuals, given that co-occurring unstable medical and psychiatric conditions were excluded, with regard to mental health and social functioning patients treated with XR-NTX improved their QOL to an average score that was very close to the U.S. population norm.

Use of XR-NTX with severely dependent patients

An ongoing clinical challenge has been the treatment of individuals who are severely dependent on alcohol. More severely dependent patients, compared to those at lower severity levels, have been found to have higher levels of craving, worse symptoms of tolerance and withdrawal, higher and more abnormal values on biomarkers of alcohol dependence, higher rates of tobacco use and psychiatric symptoms, and more impaired QOL.[57–61]

There has been uncertainty about the efficacy of pharmacological interventions for this subgroup of severely dependent individuals. Oral naltrexone was found not to be significantly different from placebo in a large randomized clinical trial conducted with chronic, severe alcohol-dependent veterans.[62] Another study found oral naltrexone superior to acamprosate for alcohol-dependent patients with low severity but no different from acamprosate and placebo for those with high severity of alcohol dependence.[63] High severity of alcohol dependence has also been found to be associated with being more

likely to drink spirits (rather than wine or beer), which occurred more often in patients who showed lower compliance to oral naltrexone or topiramate treatments (in conjunction with psychosocial therapy) for alcohol dependence.[64]

The efficacy of XR-NTX for patients with a relatively greater degree of severity of alcohol dependence was investigated in another secondary analysis of data from the primary XR-NTX efficacy trial. For these analyses,[65] severely alcohol-dependent patients, defined by a relatively elevated score on the Alcohol-Dependence Scale[66] ($N = 97$), who received XR-NTX 380 mg had significantly fewer heavy drinking days ($\geq$5 drinks/day for men, $\geq$4 for women) than those who received placebo. When severity was defined in term of engaging in detoxification prior to randomization ($N = 26$), a significant ($P = 0.004$) difference between XR-NTX 380 mg and placebo also emerged (reductions from baseline of heavy drinking days of 48.9% for XR-NTX 380 mg and 30.9% for placebo). In addition, patients with lead-in abstinence—those for whom XR-NTX is specifically indicated ($N = 56$)—were significantly ($P = 0.002$) more likely to be severely dependent. Thus, in contrast to conclusions reached in the literature on oral naltrexone, XR-NTX appears to be useful in the treatment of individuals with severe alcohol dependence.

Understanding XR-NTX effects on abstinence: cue-response in the laboratory and in the environment

While reviews of the efficacy of oral naltrexone have generally attributed its benefit to reduction in heavy drinking rather than to promotion of abstinence, studies of XR-NTX have shown significant efficacy with maintenance of initial abstinence,[48] sustained abstinence, [48] and abstinence in the context of cue-rich environments.[67] This latter finding may aid our understanding as to the mechanism of how XR-NTX might benefit abstinence.

Diminished reactivity to alcohol-related cues has been found to predict longer latency to relapse, reduced reinstatement of dependence, and reduction in the quantity of alcohol consumed in alcohol-dependent individuals.[68] Alcohol-related cue reactivity was examined using BOLD fMRI to determine if it is attenuated by XR-NTX.[69] Visual and olfactory cues of patients' favorite alcoholic beverages were delivered in real time to detoxified alcohol-dependent subjects over a 28-minute exposure period. At baseline, there was a profound pattern of brain response to alcohol-related visual and olfactory cues, relative to neutral cues, in multiple brain regions including orbital and cingulate gyri, inferior frontal gyrus, middle frontal gyrus, and visual cortex (for visual images). Two weeks after injection with XR-NTX or placebo, BOLD signal activation in these regions was significantly and substantially different in XR-NTX-treated individuals compared to the placebo-treated individuals. The data suggest that, in the absence of alcohol consumption, XR-NTX attenuated the salience of cues that are associated with alcohol. In the clinical use of XR-NTX, such attenuation of cue reactivity may interrupt the processes that precede "slips" and relapse and thus may contribute to the maintenance of abstinence.

A real-world analog to this human laboratory finding that XR-NTX attenuates alcohol cue reactivity is the drinking response to the naturalistic, cue-enriched environment surrounding U.S. national holidays. One of the barriers to maintaining abstinence among alcohol-dependent individuals is the tendency for culturally accepted cues to trigger more frequent (and heavy) drinking. This especially occurs in regard to holidays.[70] The effect of XR-NTX treatment combined with psychosocial support on alcohol consumption during holiday and nonholiday periods was examined using data from the 6-month XR-NTX Phase III efficacy trial,[47] focusing on those alcohol-dependent patients who had maintained at least 4 days of continuous abstinence before receiving their first treatment. This *post hoc* analysis of our pivotal study[67] examined the 10 leading holidays for alcohol-related traffic fatalities, as monitored by the National Highway Traffic Safety Administration. Results indicated that XR-NTX 380 mg significantly ($P < 0.05$) increased abstinence and reduced risky drinking, heavy drinking, and drinks per day during such holidays compared with placebo (Fig. 3). During holiday periods (which ranged from single days to 3-day weekends), the median percent of nonabstinent days was 0% for XR-NTX-treated patients compared to 19% for placebo-treated patients. Similarly, the median percent of heavy drinking days during such holidays was 0% for XR-NTX and 11% for placebo. XR-NTX 380 mg also significantly ($P < 0.05$) reduced drinking during nonholiday periods in this same population,

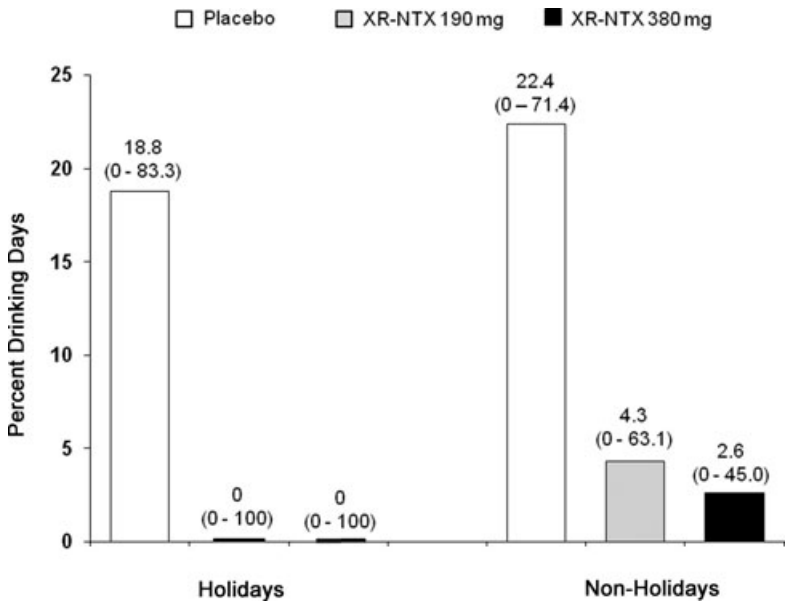

Figure 3. Median percent drinking days among patients with initial abstinence (≥4 days) during holiday and nonholiday periods for percent drinking days. Numbers in parentheses represent ranges for each category. Placebo, $N = 27$; XR-NTX 190 mg, $N = 26$; XR-NTX 380 mg, $N = 27$. Data analyzed by Wilcoxin test: $^{*}P < 0.05$; $\dagger P < 0.01$.[67]

compared to placebo. It should be noted, however, that this was a *post hoc* analysis for which holiday drinking trends prior to baseline were not available.

Safety, tolerability, and other potential concerns about use of XR-NTX

Adverse events

In the phase III trial of XR-NTX, the most common adverse events reported by patients who received XR-NTX were injection site reaction, nausea, headache, and fatigue.[47] The majority of these adverse events occurred during the first month of treatment. Pain at the injection site occurred for about 12% of patients who received XR-NTX and 9% for those who received placebo injections. More patients discontinued XR-NTX 380 mg (14.1%) due to adverse events (primarily nausea and headache) compared to placebo (6.7%). There were two serious adverse events (eosinophilic pneumonia and interstitial pneumonia) in this trial that were judged to be possibly related to XR-NTX 380 mg. Both of these resolved with treatment. Subsequent to the phase III trial, based on postmarketing reports of severe injection site reactions requiring surgical intervention, the FDA issued an alert, noting that XR-NTX should not be administered intravenously, subcutaneously, or inadvertently into fatty tissue.[71]

Hepatic safety

A detailed analysis of potential impact of XR-NTX on liver enzymes has been reported.[72] This close look at hepatic safety issues was prompted by the concern about the administration of excessive doses of oral naltrexone, or administration to patients with active liver disease, which resulted in a boxed warning in the package insert for oral naltrexone in relation to hepatotoxicity. The warning was prompted by studies reporting hepatotoxicity at high dosages of oral naltrexone (350 mg/d) in obese patients and those with senile dementia.[73] Within the recommended dosage range (50 mg/d), the evidence supports the safety of oral naltrexone.

The examination of hepatic safety using data from the XR-NTX phase III trial revealed no significant differences in alanine aminotrasferase, aspartate aminotransferase, or bilirubin levels between the XR-NTX 380 mg, XR-NTX 190 mg, or placebo groups at baseline or at any of the 6 monthly assessments.[72] Gamma-glutamyltransferase levels in the XR-NTX 380 mg group were actually significantly lower than in the placebo group at several assessments, most likely because of the reduction

in drinking alcohol in the XR-NTX 380-mg group. High (>3 times the upper limit of normal) values for liver chemistry tests and other hepatic-related adverse events were infrequent for both XR-NTX and placebo-treated patients. There was also no evidence of elevated liver function tests or hepatic-related adverse events in either of the XR-NTX group compared to placebo within clinically meaningful subgroups such as those drinking heavily throughout the study or obese subjects. Furthermore, although concerns have previously been raised about concomitant use of nonsteroidal antiinflammatory drugs (NSAIDs),[74–79] this study found no evidence of elevated liver function tests or hepatic-related adverse events in patients taking NSAIDs. Thus, the available evidence supports the hepatic safety of XR-NTX, at least at the approved dosage and for the types of patients represented in this study. In addition, an earlier small open-label study found no clinically meaningful changes in hepatic enzymes following a single dose of 190 mg of XR-NTX given to patients with mild or moderate hepatic impairment.[44] The long-term (beyond 6 months) hepatic safety of XR-NTX, as well as the hepatic safety of XR-NTX in the elderly, in whom liver function may be compromised, remains to be examined in future research.

Pain management: basic science findings and clinical implications

The clinical research program on XR-NTX has administered injections exceeding 600 patient-years of exposure. During this time, there were no reports of serious adverse events, such as emergency room admission or hospitalization secondary to unmanageable pain.[80] In a preclinical experiment, rats were studied in a pain-analgesia paradigm using the hot plate test to determine whether opioid analgesics could override the blockade of XR-NTX and whether the analgesic response would be accompanied by excessive respiratory depression or signs of sedation. The competitive opioid receptor blockade of XR-NTX was overcome with higher doses of opioids that were sufficient to achieve analgesic responses to the pain stimulus, however, compared to placebo, these doses did not show further effects on respiratory depression or locomotor activity.[81] The relevance of animal research to the human clinical setting, however, is unclear. Therefore, it has been suggested that the management of patients with pain when reversal of XR-NTX blockade is required can include regional analgesia or use of nonopioid analgesics (Vivitrol® Package Insert). If opioid therapy is required as part of anesthesia or analgesia, such patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure; and such therapy should be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation, with close monitoring by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Impact of XR-NTX on reported pleasure from daily activities

As mentioned earlier, blocking opioid receptors with naltrexone leads to less alcohol-induced pleasure.[23] These subjective effects are thought to be mediated by the effects of naltrexone in reducing the alcohol-stimulated dopamine output in the nucleus accumbens.[82,83] Because the nucleus accumbens is involved in the rewarding aspects of other behaviors, such as eating[84] and sex,[85] a question arises as to whether naltrexone might interfere with pleasure from other activities, not just drinking alcohol. Several studies have in fact demonstrated an impact of opioid antagonists (oral naltrexone, naloxone) on the hedonic effects of physical exercise,[86] gambling,[87] eating,[88] sex,[89] and shopping.[90] A clinical concern with the use of extended-release naltrexone has been that patients would experience a broad reduction in experienced pleasure to a wide range of activities.

The extent to which long-term treatment with XR-NTX affects hedonic response in alcohol-dependence patients has been recently investigated.[91] In this cross-sectional study exit survey, 74 alcohol-dependent patients who had received XR-NTX for a mean duration of 3.5 years reported that pleasure from drinking alcohol was significantly ($P < 0.05$) less than pleasure experienced from listening to music, sex, reading, being with friends, eating good food, eating spicy food, and playing video/card games (Fig. 4). Pleasure derived from gambling and shopping was rated relatively low and not significantly different from pleasure

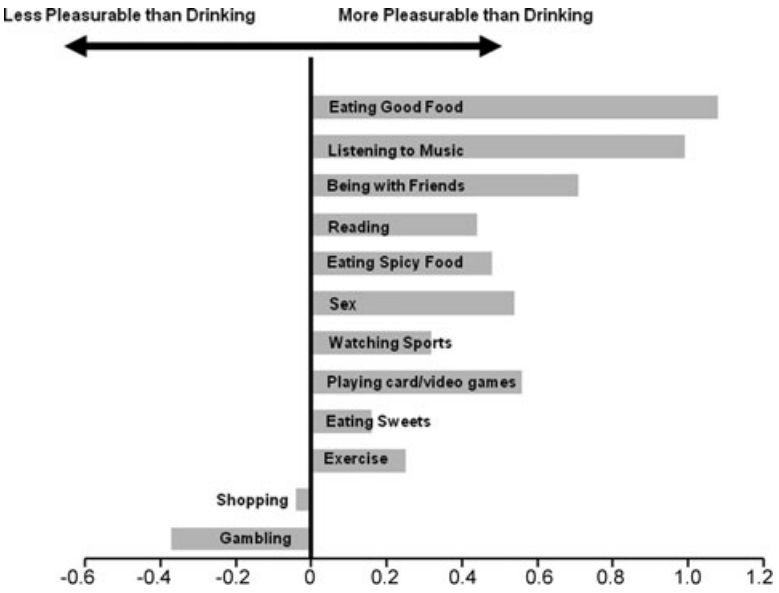

Figure 4. Hedonic response to everyday activities: among patients (total $N = 74$) with 3.5 years mean duration of continuous XR-NTX treatment; effect sizes for ratings of pleasure in past 90 days, in contrast to drinking alcohol, were positive for a wide range of activities including eating good food, sex, and exercise. Negative effect sizes were found for gambling and shopping (adapted from O'Brien *et al.*, in press [91]).

derived from drinking. These data are suggestive that long-term use of XR-NTX selectively reduces pleasure from drinking alcohol, and may also reduce pleasure from shopping and gambling, compared to the pleasure obtained from many regular daily activities. However, interpretation of the data must take into account the study limitations, for example, the sample was a select group of patients who had maintained use of XR-NTX for several years and no baseline data on hedonic response to daily activities was available.

Feasibility of using XR-NTX in the "real world"

Adoption by addiction specialty treatment programs

Health services research indicates that real world adoption of XR-NTX started in treatment programs that specialize in alcohol-dependence treatment. Within the first 2 years after XR-NTX was approved by the FDA, a nationally representative survey asked 345 addiction specialty treatment programs about their adoption of the new agent.[92] The study found that 16% of programs had adopted the use of the agent, with greater likelihood of adoption predicted by larger organizational size, having a staff that included a physician, having had prior use of an alcohol-dependence pharmacotherapy, and having a higher proportion of patients with commercial insurance. The study, although limited in being an administrative survey rather than tracking actual pharmacy claims, found that XR-NTX is addressing the patient compliance barrier, as demonstrated by 70% of these patients receiving at least 2 months of the medication.

Use of XR-NTX in primary care

Data on the use of XR-NTX in a variety of real-world clinical settings are beginning to emerge. One recent open-label study examined 3-month treatment retention, patient satisfaction, and alcohol use among alcohol-dependent patients in two public hospital primary care clinics.[93] Patients were offered 3 monthly XR-NTX injections along with physician-delivered medical management that reviewed medication side effects, encouraged abstinence, and supported use of mutual help and counseling resources. Recruitment for this study was good, with only about half of patients needing to be recruited through advertising. Retention was reasonably good, with 90% (65 of 72) of eligible patients receiving the first XR-NTX injection, 75% of those initiating treatment receiving a

second XR-NTX injection, and 62% of those initiating treatment receiving the third injection. Those that received all three injections reduced their drinks per day from a median of 4.1 at baseline to 0.5 at month three. Limitations of this study included the lack of a control group and the presence of research supports including free care and medication. Nevertheless, these preliminary data suggest that it is feasible to treat patients with XR-NTX in the context of a primary care practice.

A pilot demonstration project in the medical setting examined the feasibility of using XR-NTX to treat homeless individuals who are dependent on alcohol.[94] A hospital system in a small city found that this subpopulation was its most costly subgroup, with some patients having 50–100 emergency room visits per year and accruing over $200,000 per year in total costs due to ambulance, social services, medical, and law enforcement involvement. Considering that adherence to oral medications among the homeless might be low, the hospital initiated an open-label demonstration project with XR-NTX. The project found that numerous challenges needed to be addressed and was successful in doing so by securing a hospital budget to support the pharmacy so that XR-NTX could be stocked and provided at no charge to uninsured homeless individuals; coordinating with a detoxification facility so that treatment is initiated once the patient becomes abstinent; collaborating with healthcare for the homeless outpatient medical clinics elsewhere in the community for continuity of care; securing state funding to those clinics for continued XR-NTX administration; and providing training to homeless clinic nurses in injection administration. With these steps in place, the typical patient received 2–3 months of treatment with XR-NTX. Staff noted that patients became more likely to make their appointments, for example, for housing, and ER utilization declined to less than one visit per month for the majority of patients treated with XR-NTX. The project reported that these policy, funding, and logistical procedures proved feasible and effective in integrating care for a particularly complex and needy population.

Another pilot study examined alcohol-dependent patients with serious mental illness, that is, schizophreniform disease and bipolar mood disorder. This study was an open-label, randomized, prospective 12-week trial of monthly injections of XR-NTX 380 mg or monthly dispensing of a 30-day supply of oral naltrexone 50 mg tablets; with weekly motivational counseling.[95] Eight patients who received XR-NTX attended an average of 84% of possible weekly visits and were administered 83.3% of possible monthly XR-NTX injections. In contrast, four patients who received oral naltrexone attended an average of 65.8% of weekly visits, were dispensed 75% of possible monthly bottles of oral NTX, and reported taking 40.5% of possible oral NTX doses. Although this was a very preliminary study, the findings appear to support the feasibility of using XR-NTX in patients with serious mental illness. XR-NTX may address the compliance difficulties found with this population of patients with cooccurring alcohol dependence and serious mental illness.

Use of XR-NTX in driving under the influence (DUI) and drug courts

Alcohol is known to be a significant risk factor for criminal behavior, with about 40% of all violent crimes involving alcohol,[96] which substantially exceeds the percent for all drug-related crime. In part, this is because individuals with this disease may often continue drinking, even when faced with long jail terms, and therefore pose a serious public health threat. Many individuals who commit crimes while under the influence of alcohol or drugs are increasingly being managed in DUI and drug courts, which use a team approach, combining personnel from the district attorney, public defender, and probation offices, as well as treatment providers, all under the leadership of a judge.

A preliminary study evaluated the feasibility of XR-NTX with supportive therapy in a case series of 10 DUI-sentenced repeat offenders with alcohol dependence who received at least one injection (seven received all three injections). Subjects reported significant within-subject decreases of 77% from pre-treatment in average drinks per day (from 3.0 to 0.69; $P < 0.01$), 39% decreases in drinks per drinking day (from 6.6 to 4.0; $P = 0.04$), and 31% increases in abstinent days (from 56.8 to 81.96; $P = 0.02$), with biomarker measures that were consistent with reduced drinking. This patient cohort also had breath alcohol interlock devices installed on their motor vehicles and their percentage of vehicular failures-to-start due to elevated breath alcohol dropped by more than half (from 3.1% to 1.29% of tests; $P =$ NS).[97]

A larger pilot study of XR-NTX examined outcome data on 64 alcohol-dependent clients recruited from two drug or DUI courts in Michigan and one in Missouri, 32 of whom were treated with XR-NTX and 32 were matched controls who received psychosocial treatment without XR-NTX.[98] Treatment with XR-NTX was open-label, voluntary, and was delivered in addition to psychosocial treatment. Treatment with XR-NTX was associated with a reduction in the primary outcome of annualized rearrest rate (8% vs. 26% for treatment as usual; $P < 0.05$) while under drug court supervision (relative risk reduction = 62%), with nonsignificant reductions in the component outcomes of rate of the number of missed drug court sessions (relative risk reduction = 57%), the rate of positive drug and alcohol tests (relative risk reduction = 35%), and the proportion of individuals with >25% overall positive alcohol or drug tests (relative risk reduction = 33%). Although further studies are needed with randomized and larger samples to establish causality, treatment with XR-NTX appeared to be feasible and was associated with a consistently large treatment effect across multiple outcomes relevant to a drug court setting. The findings from this project resulted in a policy initiative in Missouri, where the single-state agency for substance abuse treatment issued a mandate to all publicly funded treatment programs that, as of January 1, 2010, they must provide access for all medication-assisted therapies, including XR-NTX, or risk-losing state and federal block grant funding.[99]

Health economic studies of XR-NTX

Alcohol use disorders are known to result in elevated costs to individuals and society, with an estimated $185 billion in healthcare costs, lost wages, and property damage in the United States annually.[100] XR-NTX was developed in order to address the compliance problem with oral naltrexone. By improving compliance and maintaining abstinence or reducing episodes of heavy drinking, it would be expected that individuals treated with XR-NTX would have reductions in the heathcare-related costs of alcohol dependence.

The clinical significance of the pivotal trial efficacy results for XR-NTX among those with lead-in abstinence was examined in a previous review article that converted the results into number-needed to treat (NNT) statistics.[101] For XR-NTX, the data indicate that it takes four patients to demonstrate a significant improvement over placebo. This is in contrast to 13 patients treated with an alternative extended-release naltrexone formulation not pursued for further commercial development,[102] and 20 patients treated with oral naltrexone in the COMBINE study.[45]

A preliminary study has examined healthcare cost reductions following treatment with XR-NTX.[103] Using a claims database from a commercial insurer, this study compared the costs of alcohol-related hospitalizations, total medical costs, and total pharmacy cost in the 6 months prior to the initiation of XR-NTX to the 6 months following termination of XR-NTX treatment. For 48 patients, the average duration of XR-NTX treatment was 3 months. Alcohol-related hospitalizations were found to decrease by 52% from before to after treatment with XR-NTX; total medical costs decreased by 34%; total pharmacy costs decreased by 36%; and the combined pharmacy and medical costs decreased by 49%. While difficult to interpret without a comparison group, these data are suggestive that XR-NTX may be associated with significant healthcare cost reductions and prompted the insurer to initiate a prospective disease management program.

A larger study using a different commercial insurer claim database has looked at the healthcare utilization and costs associated with alcohol-dependence pharmacotherapy.[104] Using propensity score matching on demographic and baseline clinical and healthcare utilization variables, alcohol-dependent patients who had received an FDA-approved medication for alcohol dependence ($n = 2{,}977$) were compared with those who had not received such medication ($n = 2{,}977$) on 6-month healthcare utilization rates. In addition, comparisons were made among those who received oral naltrexone ($n = 663$), disulfiram ($n = 2{,}076$), acamprosate ($n = 883$), or XR-NTX ($n = 295$). Results indicate that patients who received alcoholism medications spent less time in detoxification and alcoholism-related inpatient care and had fewer emergency department visits. XR-NTX was associated with significantly ($P < 0.05$) less time spent in detoxification (224 days per 1,000 patients) than oral naltrexone (552 days) or acamprosate (525 days), and a significantly ($P < 0.05$) lower rate of alcohol-related hospitalization than acamprosate (2.3% vs. 4.5%) (Fig. 5). As a nonrandomized study,

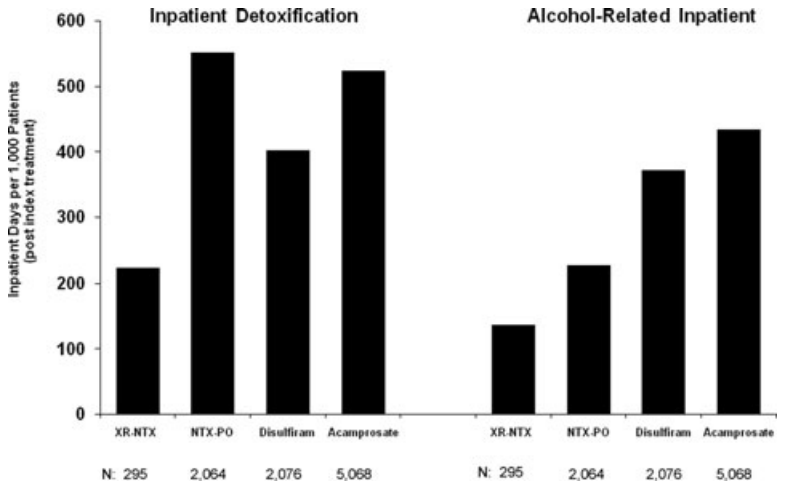

Figure 5. **Retrospective insurance claims analysis with propensity score matching: Four-way comparison of intensive health care utilization for the 6-month period following an index medication dose, showing greater reduction in detoxification days per 1,000 patients for XR-NTX vs. disulfiram ($P = 0.049$), oral naltrexone ($P = .003$), and acamprosate ($P < 0.001$), and greater reduction in alcohol-related hospital days per 1,000 patients for XR-NTX vs. disulfiram ($P = 0.004$), oral naltrexone ($P =$ NS), and acamprosate ($P < 0.001$)(adapted from Ref. 104).**

unmeasured variables, such as severity of dependence, may be responsible for the observed differences between medications. However, if patients with greater severity are more likely to receive a long-acting injectable medication, a severity bias would be expected to decrease the likelihood of finding cost advantages for XR-NTX. Assuming no confounds, XR-NTX appears to show a cost advantage over other oral medications for alcohol dependence.

Reduced healthcare utilization costs for XR-NTX have also been found in an analysis of an Aetna Behavioral Health claims database.[105] In the 6 months after ending medication treatment for alcohol dependence, compared to the 6-month period prior to initiating the medication treatment episode, patients receiving XR-NTX ($n = 133$) had reduced emergency room visits (–13%), compared to no change for disulfiram ($n = 1{,}006$) and increases for acamprosate (+12%; $n = 3{,}012$) and oral naltrexone (+12%; $n = 1{,}135$). Approximately twice as many patients had continued on XR-NTX, compared to acamprosate, disulfiram, or oral naltrexone, at 3, 4, 5, 6, and 9 months after beginning treatment. Thus, the increased persistence found with XR-NTX appears associated with reduced healthcare utilization and other benefits. On the basis of these findings, Aetna reported initiating a national disease management model with XR-NTX for alcohol dependence, similar to what it had previously introduced for antidepressant management of major depressive disorder.[105]

Studies of XR-NTX with other populations

Opioid dependence

In 2010, the FDA approved XR-NTX for prevention of relapse to opioid dependence in detoxified patients. Because oral naltrexone was originally approved for the blockade of opioids, the testing of XR-NTX as a treatment for opioid dependence was a natural direction. The feasibility and safety of XR-NTX for opioid dependence was first established in an open-label sample of 121 patients with opioid dependence, some of whom who also were diagnosed with alcohol dependence.[106] A double-blind study of a different, unapproved XR-NTX preparation (Biotek, Inc.), found a better rate of confirmed abstinence over an 8-week period, compared to placebo injection.[107] Another study of this unapproved preparation examined the feasibility of recruiting, treating, and retaining opioid-dependent individuals, currently under supervision in the criminal justice system (i.e., on probation or parole), within the context of a 6-month trial of injectable extended-release naltrexone.[108] Six-month outcomes indicated that patients who completed treatment had significantly fewer opioid-positive urines and were less likely to have been incarcerated than those who had not completed treatment.

A multicenter phase III randomized, double-blind, placebo-controlled, 24-week, clinical trial evaluating the efficacy of the FDA-approved (for alcohol dependence) XR-NTX preparation as a treatment for opioid dependence has been conducted in Russia.[109] In this study, monthly injections of XR-NTX 380 mg ($n = 126$) or placebo ($n = 124$) were combined with 12 biweekly sessions of drug counseling. Clinically meaningful and statistically significant differences between XR-NTX 380 mg and placebo were evident in this study on both the primary efficacy measure of confirmed abstinence as well as with secondary ones, including craving, naloxone challenge tests, and retention. The primary efficacy outcome was the response profile based on each patient's rate of confirmed opioid-free weeks during the last 20 weeks of the 24-week double-blind treatment period, imputing dropout and missing urines as not confirming opioid abstinence. The rate of opioid-free weeks was calculated as a percent of the 20-week period of observation. The response profile was generated for each group by calculating the cumulative percentage of patients achieving each observed value of the rate of opioid-free weeks. Overall, the median patient taking XR-NTX had confirmed abstinence during 90% of study weeks 5–24, compared to 35% for placebo ($P = 0.0002$). With XR-NTX, 36% of patients maintained complete abstinence for weeks 5–24 versus 23% of placebo patients ($P = 0.02$). XR-NTX-treated patients also had significantly more self-reported opioid-free days ($P = 0.0004$; median percentage of days opioid-free = 99.2% for XR-NTX, 60.4% for placebo), less craving ($P < 0.0002$), less relapse to physiological dependence as documented by positive naloxone challenge ($P < 0.0001$), longer median retention ($P = 0.0042$; >168 days vs. 96 days for placebo), and significant benefits on health outcomes such as reduced HIV drug risk (but not sex risk) behavior, and normalized mental health functional scores (although physical health function, which was normative at baseline, did not show significant differences). Prevalences were high in this sample for hepatitis C (88.8%) and HIV infection (41.2%). Transaminase elevations were more frequently elevated with XR-NTX than placebo, with mean maximal increases from baseline ALT levels of 61 IU/L versus 48 IU/L with placebo, and from baseline AST levels of 40 IU/L versus 31 IU/L with placebo. Liver enzyme elevations were isolated and transient, and there was no evidence of hepatic injury. In the XR-NTX group, serious adverse events most commonly consisted of infectious processes, including AIDS/HIV, in 2.4% of XR-NTX patients and 3.2% of placebo patients. Attempts by patients to overcome XR-NTX blockade pose a danger of overdose death, however, in this study there were no overdose events, suicide attempts, or deaths reported.

XR-NTX has begun to be studied in opioid dependence among other populations as well, including health professionals and young adults. Health professionals with opioid dependence have emerged as a subgroup with unique risks and obstacles to treatment.[52] Anesthesiology appears to be the medical specialty with the highest risk for opioid dependence and also with the most stringent requirements for treatment and reentry—with many states concluding that a recovering anesthesiologist should probably never be allowed to return to the operating room. However, a review of the experience with programs that incorporated a combination of initial residential treatment, regular behavioral monitoring, aggressive testing of hair and fingernails for high-potency opioids, and required administration of XR-NTX, found strikingly better results than with other approaches at rehabilitation.[110]

Young adults and adolescents are another high-risk group, with a rapidly rising incidence for opioid dependence but, paradoxically, limitations in available treatment options, for example, due to federal guidelines and parental concerns with opioid agonist maintenance. In a case series using clinical chart abstractions from a convenience sample of 15 such patients, several observations were made regarding treatment with XR-NTX.[111] XR-NTX reportedly showed good feasibility as a standard treatment and was easily integrated with counseling in a community treatment program. Patients and families accepted XR-NTX, with some parents even preferring it because of its extended-release formulation. Although this was a limited size sample and a naturalistic, open-label, uncontrolled study, treatment with XR-NTX was suggested as a promising treatment for this population.

Stimulant dependence

The reinforcing effects of amphetamine are thought to primarily occur through stimulation of the dopamine system.[112] The μ-opioid system,

however, is thought to modulate brain dopamine.[113] Because of this connection between the μ-opioid system and the dopamine system, there may be a role for a μ-opioid antagonist like naltrexone in the treatment of stimulant dependence. In humans, oral naltrexone has been found to attenuate the subjective effects of amphetamines in both healthy volunteers[114] and amphetamine-dependent individuals.[115] In addition, one placebo-controlled trial found efficacy for oral naltrexone in the treatment of amphetamine dependence.[116]

No studies using XR-NTX in humans with amphetamine dependence have yet appeared. However, one study has compared the effects of naltrexone administered acutely (orally or subcutaneously) versus XR-NTX on the reward-enhancing effects of amphetamine in rats.[117] XR-NTX was found to result in significant attenuation of amphetamine-enhanced brain stimulation reward, but such attenuation was not observed with acute administration of naltrexone despite the fact that naltrexone plasma levels were comparable across all naltrexone-treated rats. The mechanism for this differential effect between XR-NTX and oral naltrexone is not known.[117] Human clinical studies are currently underway in Stockholm, Reykjavik, and San Francisco with XR-NTX for amphetamine dependence and methamphetamine dependence; results may shed light on any possible future role in stimulant disorders treatment.

Combination with psychosocial management

The FDA-approved indication for XR-NTX, and indeed all recommendations and study designs to date, have used it in combination with behavioral management. Thus, rather than thinking of these trials as XR-NTX versus placebo, in fact it is more accurate to think of them as studies of counseling without pharmacotherapy versus XR-NTX added to counseling. Studies have employed different approaches, however, and it is of some interest to consider which ones have been used and have been shown to be effective.

The pivotal trial of XR-NTX for treatment of alcohol dependence utilized 12 sessions of the BRENDA model (biopsychosocial, report, empathy, needs, direct advice, and assessment), which employs a session duration of intermediate length and has been previously validated in alcohol-dependent patients.[118] A more intensive approach is individual drug counseling (IDC),[119] which was adapted for use in the XR-NTX pivotal trial for opioid dependence.[109] IDC is a full 50-minute session length, manualized counseling model that incorporates both twelve-step abstinence and relapse prevention approaches, and in this study it was delivered by psychiatrists. Both of these studies reported beneficial effects for the placebo-plus-counseling condition, suggesting that the psychosocial treatment model itself was meaningfully effective, as was found in prior studies of each model.[118,120] In the open-label naturalistic study in two primary care medical settings in lower Manhattan, a more limited psychosocial treatment was used, medical management (MM). MM has a focus on supporting either reduced drinking or abstinence and medication adherence, without formal therapeutic approaches such as twelve-step facilitation, motivational interviewing, or cognitive behavioral therapy.[121] MM is a brief-session length model that was delivered in this study in nonstandardized fashion by the treating internal medicine physicians during routine follow-up outpatient medical visits.[93] The fact that clinically meaningful outcomes were found for XR-NTX in all three of these studies, despite considerable variance in their intensity, provider specialty, provider skills, and content, suggests that while XR-NTX should be delivered in combination with psychosocial management there are no data as yet to specifically recommend different counseling models.

The most intensive psychosocial management model reportedly used to date with XR-NTX has been contingency management. This behavioral treatment was specifically examined in one prospective, random-controlled study that used contingency management for promoting XR-NTX persistence with a reinforcer of paid employment in unemployed heroin-dependent adults.[122] Preliminary analysis indicated that, compared to an employment opportunity provided without contingency, the rate of acceptance of XR-NTX was significantly better with contingency management, especially in the long term. Results were also suggestive that naltrexone adherence may be correlated with opiate abstinence, but this finding was tentative.

Use of XR-NTX and psychosocial counseling and self-help attendance

Clinical guidelines encourage physicians to consider adding medication to psychosocial treatment

whenever a patient is diagnosed with active alcohol dependence or is abstinent but experiencing increasing craving.[11] Some clinicians might conceivably wonder, however, whether alcohol-dependent patients who receive medication might believe this is the only necessary treatment and be less motivated for psychosocial counseling or mutual-help programs like Alcoholics Anonymous (AA). Alternatively, those who become engaged in counseling or AA may be less compliant with medication. In fact, there are health care practitioners and members within the mutual-help recovery fellowships who are opposed to the use of medication for alcoholism.[123]

To address the question of whether receiving XR-NTX interferes with attendance at counseling or self-help programs, an analysis of such attendance data in the primary XR-NTX 6-month efficacy trial was conducted (Fig. 6).[124] The proportion of patients who completed all 12-study protocol counseling sessions was nonsignificantly greater for XR-NTX 380 mg (45%) than for placebo (39%). Similarly, the proportion of patients who attended couples or family counseling outside of the study (10% vs. 7%), and the proportion that attended self-help support groups (13% vs. 10%) was nonsignificantly higher in the XR-NTX 380 mg group compared to placebo. Furthermore, findings for the XR-NTX 190 mg group were intermediate. Since attending self-helps groups was significantly ($P = 0.04$) related to reduced heavy drinking, the data indicate that XR-NTX is compatible with counseling and support group participation in facilitating the treatment of alcohol dependence.

Counseling participation with XR-NTX has also been examined in naturalistic, real-world analyses of claims data from commercial insurance databases. Compared to the baseline period, XR-NTX was associated with increased utilization of outpatient counseling in the Aetna Behavioral Health sample[105] and in the Medstat Marketscan database analysis, across multiple insurers, a significantly greater percentage of patients on XR-NTX (68.6%) had an outpatient visit for substance abuse treatment than patients on oral agents (38.0% oral naltrexone, 40.2% disulfiram, 40.1% acamprosate; $P < 0.001$).[104] Thus, in both a randomized, controlled efficacy trial, and in naturalistic insurance database analyses, the evidence does not indicate that XR-NTX interferes with or is incompatible with participation in psychosocial management.

Future directions

Over the coming decade, research on XR-NTX is likely to expand in a number of directions. Given existing studies in substance dependencies, an obvious consideration is the use of XR-NTX for patients with concurrent dependence on multiple substances, for example, alcohol and opioids, and pending outcomes of current trials with XR-NTX for stimulant dependence, a second area might be concurrent alcohol or opioid dependence with stimulant dependence. Interest is growing in genetically based differences in response to oral naltrexone, although no data exist to date regarding unique genetic responses to XR-NTX. One obvious area of potential investigation is the use of XR-NTX in the treatment of other disorders that involve reinforcement/reward processes. Possibilities here include pathological gambling, smoking, binge eating, and addictive sun tanning, to name a few. Preliminary suggestions about whether XR-NTX might help with these disorders could be obtained from examination of subgroups (e.g., smokers) within samples of alcohol- or opioid-dependent patients treated with XR-NTX. Also, it may be worthwhile to examine whether improved medication adherence for substance dependence might yield other compliance behavior benefits, such as better adherence to anti-HIV regimens.

Future research will also need to further explore the role of psychosocial treatments in conjunction with XR-NTX. While past studies have used versions of standard drug counseling or medical management psychosocial administered along with XR-NTX, a more fruitful direction might be to develop psychosocial intervention strategies that are more directly targeted to patient acceptance of XR-NTX and persistence with ongoing injections. Such interventions targeted at engagement and compliance with XR-NTX could be delivered in addition to other counseling interventions that address other problems (e.g., interpersonal, legal, employment) that have occurred as a result of alcohol or drug addiction. More broadly, the role of XR-NTX in a coordinated disease management program for alcohol or opioid dependence needs to be

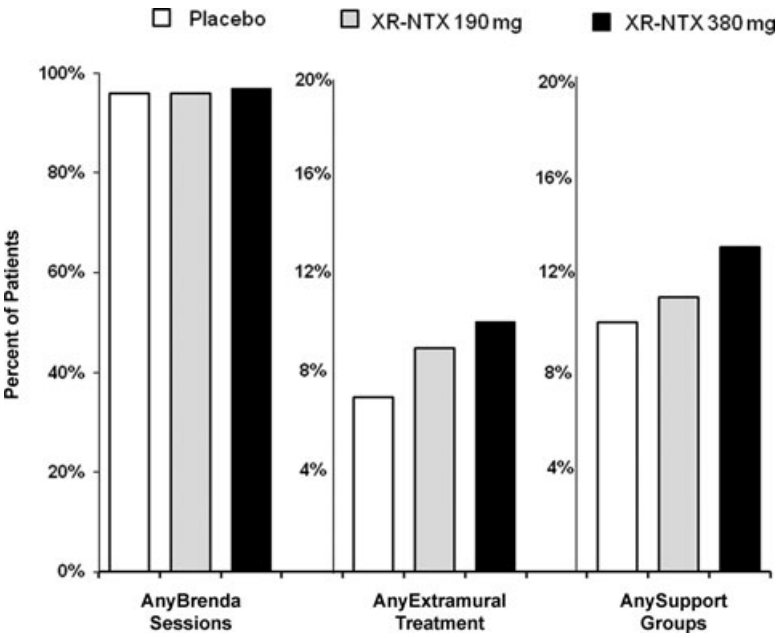

Figure 6. Compatibility of XR-NTX treatment with counseling and mutual help recovery activity, examined by comparing the percent of patients who attended: all 12-study protocol counseling (BRENDA) sessions vs. placebo (45% vs. 39%; P = NS); couples or family counseling outside of the study (10% vs. 7%; P = NS); and self-help support groups (13% vs. 10%; P = NS); findings for the XR-NTX 190 mg group were intermediate.[124]

investigated, particularly as it relates to possible cost savings.

Research should also explore the efficacy of combined XR-NTX with other pharmacological agents for selected patient populations. Given the primary μ-opioid antagonism provided by XR-NTX, it is conceivable that pretreatment with XR-NTX followed by buprenorphine, whose partial μ-agonist effects might thereby be blocked, essentially leaving a net pharmacodynamic effect of κ-opioid antagonism, might yield a viable treatment for cocaine dependence or even for treatment resistant major depression.[125]

An additional area of future research concerns the specifics of actually delivering XR-NTX. This includes research on the how to educate providers who will be explaining XR-NTX to patients, administering injections and counseling patients who are being treated with XR-NTX. In addition, health services studies need to investigate the impact of treatment setting, financing, and other logistical issues regarding the delivery of XR-NTX in various clinical settings. Given that disease management programs implementing XR-NTX are now being embarked upon by commercial and Medicaid-managed care entities, and single-state agencies are beginning to mandate its access and initiate public system initiatives, it will be important to systematically evaluate the outcomes of these efforts.

The identification of subgroups of patients who are particularly well-suited to XR-NTX treatment is another relevant topic for future research. For example, certain highly motivated individuals, such as health professionals, attorneys, and pilots, who are dependent on alcohol might be ideal candidates to accept XR-NTX treatment and persist with it. Some clinical evidence suggests this might be the case with anesthesiologists,[110] though controlled trials are needed. Motivation may not need to be internal, as externally motivated groups such as offenders in DUI/drug courts or those in prison and facing reentry may be important populations for further research. In contrast, there may be individuals who are relatively less motivated and are at an early stage of the addiction process who may need specific counseling approaches to address their motivational issues prior to initiating XR-NTX treatment, such as adaptations of motivational enhancement therapy for pharmacologic interventions. Interestingly, XR-NTX, because of its

extended-release and potent μ-opioid antagonism, may be a suitable probe for some research paradigms that previously have not been possible, for example, long-term outpatient studies of opioid receptor regulation or studies combining mixed agonists with XR-NTX.

Summary

The literature on XR-NTX indicates that this agent has fulfilled the proposed criteria[39] of a sustained-release delivery system for naltrexone that is easy to inject, is pharmacologically stable, is generally well-tolerated, releases the drug at a relatively constant rate for at least 30 days, and biodegrades over time. The initial phase III clinical trial results that formed the basis for FDA approval in the treatment of alcohol dependence have been followed by additional reports further demonstrating clinically meaningful superiority over counseling plus placebo among patients with lead-in abstinence and among those who have severe alcohol dependence. XR-NTX sustains its efficacy even in the face of culturally powerful cues to drink alcohol during holiday periods. Studies of the mechanism of action of XR-NTX have found that it attenuates the salience of cues associated with alcohol, and that long-term use of XR-NTX appears to relatively selectively reduce pleasure from drinking (and possibly gambling and shopping). Health economic studies indicate that there are healthcare cost saving that are evident for patients using XR-NTX compared to other pharmacological interventions for alcohol dependence. XR-NTX has also been found to be efficacious in the treatment of opioid dependence.

Despite promising results for XR-NTX within multiple clinical populations, there are several areas of investigation that either lack replication or existing studies are not methodologically rigorous. Furthermore, there are a number of potential clinical uses of XR-NTX that have yet to be explored. Thus, there is a wide range of future research that is needed to confirm early findings, test possible new indications for XR-NTX, and maximize the effectiveness of XR-NTX with alcohol-dependent individuals. A number of studies addressing these topics are currently underway around the world.

Conflicts of interest

The author declares no conflicts of interest.

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