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Extended-release naltrexone plus medical management alcohol treatment in primary care: findings at 15 months

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ABSTRACT

The feasibility of long-term extended-release naltrexone (XR-NTX) alcohol treatment is unknown. Following an initial 12-week, single-arm, observational trial of XR-NTX plus medical management (MM) in primary care, we offered 48 additional weeks of XR-NTX treatment (12 additional monthly injections) in two public primary care clinics as a naturalistic extension study. Of 65 alcohol dependent adults initiating XR-NTX treatment, 40 (62%) completed the initial 12-week XR-NTX observational trial, and 19 (29%) continued treatment for a median of 38 weeks total (range, 16–72 weeks; median 8 total XR-NTX injections). Among active extension phase participants, self-reported rates of drinking days (vs. last 30 days pre-treatment baseline) were low: median 0.2 vs. 6.0 drinks per day; 82 vs. 38% days abstinent; 11 vs. 61% heavy drinking days. Long-term XR-NTX treatment in a primary care MM model was feasible and may promote lasting drinking reductions or alcohol abstinence (clinical trial: NCT00620750).

1. Introduction

National health reform and current addiction treatment priorities align around the expansion of addiction and alcohol medications within primary care settings, including the patient-centered medical home (PCMH) and accountable care organizations (Buck 2011; Mechanic 2011). Within the PCMH, preventive services, disease management, and addiction and mental health care will be coordinated by teams of generalist and specialty providers (Kim et al. 2011). Effective alcohol medications and non-specialized counseling approaches surrounding decreased drinking and medication adherence clearly fit into primary care and PCMH models, yet widespread adoption of these interventions has not occurred (CSAT, 2009). This may be due in part to a lack of data on the routine and long-term use of alcohol medications in primary care settings.

Extended-release naltrexone (XR-NTX) is the newest FDA-approved pharmacotherapy for alcohol dependence in the United States. The medication's long-acting depot formulation produces a 4–5 week period of therapeutic plasma naltrexone levels, equivalent or superior to that seen with daily adherence to oral naltrexone (Garbutt 2009). The extended release formulation confers a potential advantage in effectiveness in treating alcohol dependence over the oral formulation, which is compromised by low rates of daily medication adherence as observed in clinical trials and commercial pharmacy data (Kranzler, Stephenson, Montejano, Wang, & Gastfriend 2008; Krystal, Cramer, Krol, Kirk, & Rosenheck 2001).

Medical management (MM) of alcohol use disorders, as adapted from the NIAAA-supported COMBINE and other addiction pharmacotherapy trials, consists of a provider–patient partnership surrounding the alcohol dependence diagnosis and effective medication treatment. In this model, the clinician provides brief counseling to reinforce the goals of abstinence or reduced alcohol use, encourages 12-step or other psychosocial treatment involvement, prescribes pharmacotherapies, and supports medication adherence (Anton et al. 2006). Previously, we have investigated and reported on the feasibility of an initial 12 weeks of XR-NTX for alcohol dependence in a primary care medical management model in a single-arm, open-label, observational treatment study (Lee et al. 2010). In this initial study, 92% of adult alcohol dependent participants eligible for XR-NTX initiated monthly injections, and 56% (40 of 72) of the total sample completed three consecutive injections. Self-reported drinking outcomes in-treatment demonstrated robust improvements from baseline levels, mirroring the pivotal 24-week efficacy study of XR-NTX for alcohol dependence (Garbutt et al. 2005).

Beyond 12 weeks the feasibility, acceptability, and effectiveness of alcohol treatment with XR-NTX are not well described in the 'real world' of primary care. Most naltrexone clinical trials have involved a 12–24 weeks of treatment, including the pivotal efficacy trial. Longer-

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term treatment data are important given the chronically relapsing nature of alcohol dependence. In addition, 12–24 week treatment phases may not adequately stabilize patients in terms of maintaining abstinence, avoiding heavy drinking, and consolidating the complex behavioral changes required for optimal treatment outcomes. We therefore conducted a naturalistic observational study of prolonged primary care-based alcohol treatment with XR-NTX for up to 48 additional weeks of active treatment (12 additional injections) among participants completing the initial 12-week trial. Outcomes of interest were rates of treatment retention, the quantity and frequency of self-reported alcohol use, engagement in other addiction related care including 12-step participation, and rates of adverse events.

2. Materials and methods

An open-label extended treatment phase followed an initial 12-week study evaluating the use of XR-NTX with MM among alcohol dependent adults in the primary care clinics of two public hospital facilities in lower Manhattan (Bellevue Hospital Center and Gouverneur Diagnostic and Treatment Center). Seventy-two participants provided written informed consent and were enrolled in the initial 12-week trial, the methods and results of which we have reported previously (Lee et al. 2010). Briefly, eligible participants were English- or Spanish-speaking adults (age ≥18 years) meeting *DSM-IV* criteria for alcohol dependence and stating a willingness to initiate XR-NTX treatment. Exclusion criteria were (a) pregnancy; (b) liver function tests (LFTs) greater than three times upper normal limits; (c) opioid dependence or an anticipated need for opioid analgesia, (d) record of recent missed visits in primary care (≥2 or last 3 scheduled visits) or no working phone number, and, (e) any serious uncontrolled medical or psychiatric disorders judged by the study physician to compromise the subject's ability to participate in the study (i.e., active psychosis, dementia).

Monthly treatment visits consisted of physician-delivered medical management and XR-NTX intramuscular administration. MM consisted of counseling in support of alcohol abstinence or reduction, medication adherence, developing sober behaviors, and accessing available 12-step programs (e.g. Alcoholics Anonymous) or specialized addiction treatment. MM clinicians also managed any adverse events or medical issues surrounding treatment (i.e., monitoring LFTs). A research coordinator led recruitment, conducted telephone pre-screens, and coordinated all visits and study assessments. Physicians and the research coordinator assisted interested patients in locating and evaluating 12-step and specialty addiction treatment services, but did not directly refer to or mandate the use of such resources.

In the extension phase study, up to 12 additional XR-NTX (with MM) visits were scheduled every 4 weeks (28 days), with telephone reminders of upcoming visits. Time in treatment varied due to missed visits and rescheduled injections in keeping with a naturalistic study: patients generally in contact with study staff and intending to continue treatment were allowed to complete the 15 injections over a total time in treatment of greater than 60 weeks; patients who dropped in and out of active treatment were discontinued from the study at 60 weeks (i.e., prior to completing the 15 possible injections). Patients received medication free of charge but were otherwise not offered compensation or visit incentives. The Institutional Review Board of the New York University School of Medicine approved both the initial 12-week study and the extension phase.

2.1. Assessments

A diagnostic interview and a written *DSM-IV* alcohol dependency checklist were completed by study physicians to document a diagnosis of alcohol dependence at baseline. A baseline survey measured demographics and medical, psychiatric, alcohol and substance misuse, and current (last 30 days) and lifetime alcohol and addiction treatment histories. A baseline 30-day timeline follow back (TLFB) followed by monthly serial TLFB (covering all days since the last visit) documented self-reported alcohol use over time (Sobell LC, Sobell MB, 1995). Participation in 12-step and specialty services were tracked at each visit. Adverse events (AEs) and serious adverse events (SAEs) were characterized by the study clinician as medication- or non-medication related. LFTs were monitored bi-monthly; urine pregnancy and urine drug screens were performed at each visit. A final exit interview was conducted in person at study close, or, the event of early drop-out, by telephone. In the event of drop-out the research coordinator asked open-ended questions concerning reasons for early drop-out, drinking status, AEs, and further treatment plans. All data were collected in writing by the research coordinator and physician during the MM visit.

2.2. Analysis

Analysis was primarily descriptive. Differences in baseline characteristics between extension study participants and those enrolling in the initial 12-week study and not participating in the extension study were analyzed using the Fischer's exact test or analysis of variance. The primary outcome was the median number of total XR-NTX injections completed during an observed time in treatment. Secondary outcomes of interest were rates of self-reported drinking from the TLFB and AEs. We did not perform regression analysis of baseline in-treatment factors associated with longer XR-NTX treatment given the small sample size. Analysis was performed in STATA/SE 10.0 (Stata Corp LP, College Station, TX).

3. Results

The initial 12-week study began in August, 2007. Regulatory approval and study drug supply were obtained for the extension phase by January 1, 2008. Twenty-two subjects completed the initial 12-week study before January 1, 2008; 10 of these received all three injections, and of these, 3 enrolled in the extension study following a lapse of 2 to 8 months between study phases. Fifty subjects completed the initial 12-week study after January 1, 2008; of these, 30 received all three injections, and 16 of these enrolled in the extension study (with no lapse in treatment) (Fig. 1). Among 72 participants consented, 65 initiated XR-NTX, 40 of 65 (62%) completed the 12-week study and 19 of 65 (29%) entered the extension phase. Of the 21 of 65 (32%) eligible participants not enrolling in the extension phase, 5 continued XR-NTX treatment with other providers, 3 switched to oral naltrexone, 1 declined further treatment while planning conception, 5 declined further medication treatment, and 7 were lost to follow-up. In total, 24 of 65 (37%) of those initiating treatment continued or intended to seek XR-NTX treatment beyond an initial 12 weeks.

We have previously reported detailed baseline characteristics and drinking histories for the initial 12-week study cohort ($N=72$; Lee et al. 2010). Extension phase participants were largely similar to the remaining sample, while better educated (Table 1). Extension phase participants reported higher rates of 12-step and outpatient specialty addiction treatment involvement at baseline, possibly an importance difference that was not statistically significant. Extension phase participants self-reported common alcohol dependence co-morbidities, including a history of hepatitis C (1 of 19, 5%), HIV (1, 5%), any lifetime mental health problem (12, 63%), and current active mental health treatment (6, 31%). None reported a history of cirrhosis or liver failure.

Regarding the primary outcome of the number of total monthly injections over time, extension phase participants completed a median eight XR-NTX injections (range, 4–15) over a median observed time in treatment of 38 weeks (range, 16–72) (Fig. 2). MM injection visits were scheduled every 28 days; the median interval between doses was 32 days (range, 28–125 days).