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Relapse to opioid use disorder after inpatient treatment: Protective effect of injection naltrexone

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ABSTRACT

Background: Opioid use disorder is often treated with short term hospitalization and medically supervised withdrawal from opioids followed by counseling alone without medication assisted treatment (MAT). More evidence is needed to confirm the expectation that the rate of relapse would be high after short term inpatient treatment and withdrawal from opioids without follow-up MAT.
Objective/methods: To examine relapse to opioid use disorder in a randomized, multi-site effectiveness trial of extended-release injection naltrexone (XR-NTX) vs community-based treatment as usual (TAU) without medication, as a function of the type of clinical service where treatment was initiated—short-term inpatient (N = 59), long-term inpatient (N = 48), or outpatient (N = 201). Inpatients typically were admitted to treatment actively using opioids and had completed withdrawal from opioids before study entry. Outpatients typically presented already abstinent for varying periods of time.
Results: One month after randomization, relapse rates on TAU by setting were: short-term inpatient: 63%; long term inpatient: 14%; outpatient: 28%. On XR-NTX relapse rates after one month were low (<12%) across all three settings. At the end of the 6 month trial, relapse rates on TAU were high across all treatment-initiation settings (short term inpatient 77%; long term inpatient 59%; outpatient 61%), while XR-NTX exerted a modest protective effect against relapse across settings (short term inpatient: 59%; long term inpatient 46%; outpatient 38%).
Conclusions: Short term inpatient treatment is associated with a high rate of relapse among patients with opioid use disorder. These findings support the recommendation that medically supervised withdrawal from opioids should be followed by medication assisted treatment.

1. Introduction

Inpatient or residential treatment is a time-honored intervention for substance use disorders. Beneficial features of this approach include medically supervised withdrawal from substances of abuse, removal of the individual from the natural environment in which substance use was taking place, and initiating and setting the stage for ongoing psychosocial treatment and self-help group participation on an outpatient basis after discharge.

Until recently, many if not most inpatient and residential treatment programs did not routinely offer initiation of medications for maintenance of abstinence and prevention of relapse. However, this approach is problematic for opioid use disorder. Medications for opioid use disorder—methadone (an opioid agonist), buprenorphine (an opioid partial agonist), and injection naltrexone (an opioid antagonist)—are highly effective at maintaining abstinence and preventing relapse (Hser et al., 2014; Krupitsky et al., 2011; Mattick, Breen, Kimber, & Davoli, 2014). The risk of relapse to opioid use disorder is uniquely high because of death from overdose. This risk is in theory especially high after a period of abstinence, such as after inpatient or residential treatment, because of loss of tolerance. Correspondingly, large

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observational studies have shown a spike in opioid overdose deaths after release from controlled settings such as prison or inpatient treatmen (Binswanger et al., 2007; Bird & Hutchinson, 2003; Ravndal & Amundsen, 2010; Seaman, Brettle, & Gore, 1998).

Despite these concerns, the evidence-base on the outcome of opioid use disorder after an episode of inpatient or residential treatment remains limited. A handful of studies of clinical course of opioid use disorder after inpatient treatment are available, showing high rates of relapse, but also that a proportion of patients reduce their drug use or sustain abstinence (Broers, Giner, Dumont, & Mino, 2000; Chutuape, Jasinski, Fingerhood, & Stitzer, 2001; Gossop, Green, Phillips, & Bradley, 1989). Most controlled trials of medication treatments for opioid use disorder have been based in outpatient settings (Hser et al., 2014; Mattick et al., 2014; Weiss et al., 2011). The pivotal trial demonstrating the effectiveness of injection naltrexone (XR-NTX) for opioid use disorder, conducted in Russia, initiated active or placebo injections among inpatients, and then followed them as outpatients for 6 months. XR-NTX produced significantly more abstinence and retention in treatment over 6 months, compared to placebo (Krupitsky et al., 2011). Still, on placebo about 30% of patients were retained in treatment and predominantly abstinent (Nunes et al., 2015). To initiate naltrexone, a patient must be fully withdrawn from opioids, in order to avoid precipitated withdrawal. Thus, inpatient units, as utilized in the Russian trial, are an ideal setting for initiating naltrexone, because medically supervised withdrawal from opioids can be accomplished in a protected setting. An outpatient initiating naltrexone must have already achieved and sustained abstinence for at least a week or more, which might suggest a greater level of control and lower risk of relapse over the long term.

A recently completed, U.S.-based trial demonstrating the effectiveness of injection naltrexone for treatment of opioid use disorder (Lee et al., 2016) offered the opportunity to further examine relapse after inpatient treatment for opioid use disorder, since some of the patients initiated the trial during short-term inpatient stays, some during long-term residential treatment, and some initiated the trial as outpatients having already achieved abstinence. Participants were randomly assigned to receive either community-based treatment as usual (TAU) consisting mainly of psychosocial treatment without medication, or TAU + monthly injection naltrexone (XR-NTX) for 6 months. We hypothesized that the rate of relapse in the TAU condition would be highest, and the protective effect of XR-NTX (i.e. the difference in relapse between the XR-NTX + TAU versus TAU conditions) greatest among those initiating treatment as inpatients.

2. Methods

2.1. Overview

This report is secondary analysis of a 6-month, multi-site, randomized, controlled effectiveness trial of monthly injection naltrexone (XR-NTX) (brand name: Vivitrol) for prevention of relapse among patients with a history of opioid use disorder as well as recent criminal justice involvement. Details of the methods (Lee et al., 2015) and primary outcome analyses (Lee et al., 2016 NEJM) have been reported previously. The study was reviewed and approved by the Institutional Review Boards at each of the participating sites, and all participating patients gave written informed consent. The present analysis focuses on comparing outcomes between patients initiating the trial on short term inpatient/residential units, versus long-term inpatient/residential units, versus outpatient settings.

2.2. Participants and settings

Participants had a lifetime history of opioid use disorder (heroin or prescription opioids), and criminal justice involvement, but were not currently prisoners. Rather, they were either under community supervision (parole or probation) or had some other form of criminal justice involvement, such as an arrest, within the last 12 months. Though having a lifetime history of active opioid use disorder and thus at risk for relapse, participants had to have a stated goal of opiate-free treatment (i.e. not seeking agonist maintenance treatment with buprenorphine or methadone), and be currently abstinent and able to pass a challenge test with the short acting opioid antagonist naloxone, confirming their readiness to start naltrexone.

Participants were recruited from 5 sites across the eastern U.S., in Philadelphia, PA, Baltimore, MD, Providence, RI, and New York, City (two sites, one at New York University Medical Center, and one at Columbia University Medical Center). Two of those sites (New York University Medical Center, and Providence) recruited exclusively outpatients who had already achieved abstinence from opioids at some point in the last 6 months. One site (Baltimore, MD) recruited mainly inpatients who had been admitted to either short term (up to 4 weeks) or long term (up to 6 months) inpatient/residential treatment programs. Two sites (Pennsylvania and Columbia University Medical Center) recruited a mixture of outpatients and inpatients. For the purposes of the present analysis, participants were classified according to whether they entered the trial as either: 1) outpatient; 2) short term inpatient-residential, defined as an expected residential stay of 4 weeks or less; 3) long-term inpatient-residential, defined as a longer expected stay, typically 3 to 6 months.

2.3. Procedures

Prospective participants first underwent a psychiatric and medical evaluation to confirm eligibility, and had to be abstinent from all opioids, with an opioid negative urine toxicology and able to pass a naloxone challenge test, in order to be randomized. Participants were randomly assigned to either treatment as usual (TAU) in the community, typically consisting of some form of counseling without study medication, or TAU plus monthly injections of injection naltrexone (XR-NTX) (Vivitrol), for a 6 month trial. All participants, across both conditions, received regular follow-up visits with a medical clinician (weekly, then biweekly) throughout the trial. At each follow-up visit, participants provided a urine sample that was tested for opioids and other substances, and self-reported substance use with the time-line follow-back calendar method.

2.4. Data analysis

The primary outcome measure was Relapse (time to relapse) to regular opioid use, operationalized as either two consecutive opioid positive urines or at least seven consecutive days of self-reported opioid use with missing urine tests imputed as positive. Relapse is considered a clinically meaningful outcome among patients with opioid use disorder in abstinence-based treatment, because once regular opioid use is resumed it is typically sustained and requires either another medically supervised withdrawal, or medication treatment (such as methadone or buprenorphine maintenance) to get it back under control. Patients on naltrexone treatment typically do not take opioids regularly while the medication is present at adequate blood levels (except for occasional 'testing of the blockade'), and the typical failure mode is to stop taking the medication (miss a scheduled dose) after which the blockade wears off. Relapse to regular opioid use at that point requires another withdrawal from opioids to re-establish abstinence before naltrexone can be re-initiated.

The data analysis evaluated time to Relapse in an 2 treatment condition (TAU vs TAU + XR-NTX) by 3 setting type (outpatient, vs short term inpatient, vs long term inpatient) design. The original plan was to use survival analysis with Cox models. However, with the 2 by 3 design, the proportional hazards assumption was not confirmed. We therefore fit separate logistic regressions for the binary outcomes of Relapse (yes/no) at 5 weeks after randomization to capture rapid relapse,

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