Contemporary Clinical Trials 51 (2016) 34–43

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Ethical and clinical safety considerations in the design of an effectiveness trial: A comparison of buprenorphine versus naltrexone treatment for opioid dependence

Edward V. Nunes MD [a,*], Joshua D Lee MD MSc [c], Dominic Sisti [d], Andrea Segal [d], Arthur Caplan [e], Marc Fishman [f], Genie Bailey [g], Gregory Brigham [h], Patricia Novo [b], Sarah Farkas [b], John Rotrosen MD [b]

[a] Columbia University Medical Center, New York State Psychiatric Institute, United States
[b] NYU School of Medicine, Department of Psychiatry, United States
[c] NYU School of Medicine, Department of Population Health, United States
[d] Perelman School of Medicine, University of Pennsylvania, United States
[e] NYU School of Medicine, Division of Medical Ethics, United States
[f] Johns Hopkins University School of Medicine, Mountain Manor Treatment Program, United States
[g] Warren Alpert Medical School of Brown University, Stanley Street Treatment and Resources, United States
[h] ADAPT, Roseburg, OR, United States

ARTICLE INFO

Article history:
Received 3 June 2016
Received in revised form 12 September 2016
Accepted 25 September 2016
Available online 28 September 2016

Keywords:
Ethics
Effectiveness
Clinical trial
Opioid dependence
Buprenorphine
Naltrexone

ABSTRACT

We examine ethical challenges encountered in the design of an effectiveness trial (CTN-0051; X:BOT), comparing sublingual buprenorphine-naloxone (BUP-NX), an established treatment for opioid dependence, to the newer extended-release injectable naltrexone (XR-NTX). Ethical issues surrounded: 1) known poor effectiveness of one possible, commonly used treatment as usual control condition—detoxification followed by counseling without medication; 2) the role of patients' preferences for treatments, given that treatments were clinically approved and available to the population; 3) differences between the optimal "usual treatment" clinical settings for different treatments making it challenging to design a fair comparison; 4) vested interest groups favoring different treatments exerting potential influence on the design process; 5) potentially vulnerable populations of substance users and prisoners; 6) potential therapeutic misconception in the implementation of safety procedures; and 7) high cost of a large trial limiting questions that could be addressed. We examine how the design features underlying these ethical issues are characteristic of effectiveness trials, which are often large trials that compare treatments with varying degrees of existing effectiveness data and familiarity to patients and clinicians, in community-based treatment settings, with minimal exclusion criteria that could involve vulnerable populations. Hence, investigators designing effectiveness trials may wish to remain alert to the possibility of similar ethical issues.

1. Introduction

Effectiveness trials constitute an important step in the translational spectrum of treatment development. Efficacy trials stress internal validity and address whether a new treatment can be shown to work under ideal conditions, often within research centers. Once efficacy is established, effectiveness trials take the next step, emphasizing external validity and addressing how a new treatment will perform under real-world clinical conditions and in comparison to current standards of care in the community.

The National Drug Abuse Treatment Clinical Trials Network (CTN), funded by the National Institute on Drug Abuse (NIDA), was founded in 1999, charged with the mission to conduct randomized, controlled effectiveness trials, in order to help move new efficacious treatments for substance use disorders out of research centers and into widespread clinical use. An Institute of Medicine report [1] had concluded that while a number of new treatments for substance use disorders had been developed through efficacy trials in research settings, these treatments were not being adopted into routine clinical practice, and that community-based effectiveness trials were needed to bridge this gap. The CTN provided a collaborative structure within which researchers could partner with community-based treatment programs and NIDA to conduct such effectiveness trials on new interventions and services for treating substance use disorders.

The first decade of experience in the CTN yielded a number of lessons learned about the design and analysis of effectiveness trials in the addictions field [2–6]. However, to date there has been relatively little inquiry around bioethical issues involved in the design and

* Corresponding author at: 1051 Riverside Drive (unit 51), New York, NY 10032, United States.
E-mail address: nunesed@nyspi.columbia.edu (E.V. Nunes).

http://dx.doi.org/10.1016/j.cct.2016.09.006
1551-7144/

implementation of CTN effectiveness trials. In this paper, we review the ethical issues encountered in the design of one CTN study, CTN-0051, "Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT)", led by several of us (JR, JL, EN). While the ethical framework for traditional efficacy trials is relatively well worked out, in the design of CTN-0051 we encountered issues that seemed related to the distinct aims and circumstances of a community-based effectiveness trial and comparative effectiveness research. We examine how these ethical issues relate to specific design features of CTN-0051 and the extent to which such design features may reflect general characteristics of community-based effectiveness trials. It is hoped that this may provide a useful framework for the design of future studies.

2. Methods

The CTN-0051 protocol development team was charged by NIDA to design a trial to evaluate the effectiveness of extended release injectable naltrexone (XR-NTX, Vivitrol®), a sustained-release injectable formulation of the opioid receptor antagonist naltrexone, for treatment of opioid dependence in real world, community-based treatment settings in the U.S. Oral naltrexone had been indicated and available for several decades for treatment of opioid dependence, but its effectiveness in practice had been limited by poor adherence [7–10]. Long-acting injected or implanted naltrexone has the potential to circumvent problems with adherence to daily pill taking. XR-NTX, which has a month-long duration of action, had received FDA approval for treatment of alcohol dependence in 2006, and for treatment of opioid dependence in 2010, and had seen limited clinical use at the time the present trial launched in 2014. Approval was based on a pivotal trial conducted in Russia among hospitalized, detoxified opioid dependent patients, which demonstrated that 51% of patients on active XR-NTX plus outpatient counseling had what could be considered a good clinical response–remaining in treatment for 6 months (6 monthly injections) with minimal evidence of opioid use–compared to 31% of patients treated with placebo plus outpatient counseling [11,12]. Other forms of long-acting, implanted naltrexone, had also shown efficacy compared to oral naltrexone, or to placebo [13–15].

The final design of CTN-0051 is a randomized, comparative effectiveness trial, in which individuals with opioid dependence, seeking treatment at community-based, short-term inpatient/residential addiction treatment programs, were offered the opportunity to consent to being randomly assigned to 6-months of treatment with either monthly injections of XR-NTX, or daily sublingual buprenorphine-naloxone (BUP-NX). Buprenorphine is a high-affinity, mu-opioid receptor partial agonist and kappa receptor agonist with well-established efficacy and effectiveness for the long-term, maintenance treatment of opioid dependence [16]. BUP-NX had been FDA approved for the long-term treatment of opioid dependence for 10 years at the time CTN-0051 was designed. The final design and its rationale is described in detail elsewhere [17].

Early in project development of CTN-0051, it became clear that several design issues were associated with bioethical concerns, some of them unfamiliar. What followed was a year-long process of design reconsiderations with input from investigators, the treatment community, the Sponsor (NIDA), the manufacturer of XR-NTX (Alkermes, Inc.), and an independent Protocol Review Board. In the process, the lead team engaged two bioethicists (DS and AC) to join the development team. In what follows we describe the design features with associated ethical issues encountered during the design of CTN-0051 and how these may relate to the general features of effectiveness trials.

3. Ethical issues encountered in the design process

3.1. Treatment as usual (TAU) control condition

Effectiveness trials often seek to compare a new treatment such as XR-NTX to existing treatments in use in the community, referred to as 'treatment as usual' (TAU) [2]. Therein lay the first and most difficult ethical rub in the design of CTN-0051, namely the choice of TAU control condition(s) that were scientifically appropriate, and ethically acceptable. Usual treatments, having already been in widespread clinical use, may already have substantial evidence characterizing their effectiveness and safety, or lack thereof. For CTN-0051, one of the potential control conditions in common use in community-based practice for opioid dependence, namely detoxification followed by counseling without maintenance medication, had evidence of being inferior and potentially dangerous.

Usual treatments for opioid dependence in the U.S. at the time included opioid agonist therapies, methadone maintenance or buprenorphine maintenance [18], which had substantial evidence from clinical trials for superiority over placebo with counseling alone [19,16]. Such trials typically showed rates of good clinical response retained throughout a 3 to 6 month course of treatment, predominant abstinence from opioids) of at least 40% to 50%. Observational studies also suggest agonist maintenance therapy protects against overdose death [20]. These could be considered gold standard treatments, and a trial comparing the effectiveness of the new treatment, XR-NTX, to methadone or buprenorphine maintenance, was straightforward from an ethical perspective. To date, no such comparisons of a long acting injected or implanted naltrexone formulation, compared to opioid agonist therapy, have been performed. Such a trial would ask how the new treatment, XR-NTX, compares to the gold standard.

However, another usual mode of treatment in the U.S., and many other parts of the world, consists of hospitalization for detoxification from opioids, followed by psychosocial, counseling-based treatment without medication, either on an outpatient basis or as part of long term residential treatment. There were significant concerns about high risk of relapse [21,22], and associated risk of overdose and overdose death after detoxification and discharge to outpatient status. Large observational studies have shown a spike in relapse deaths after discharge from controlled settings like prison without a maintenance medication [23]. The mechanism of this is well understood, namely that detoxification reverses tolerance, and patients are then more susceptible to the powerful respiratory depressant effects of opioids, at doses that would previously have been tolerated. Yet for numerous reasons this approach remains common in the U.S. [24,25]. Strong traditions or beliefs among both clinicians and patients favor a "drug-free" treatment, and certainly, some patients succeed in achieving long term recovery from opioid dependence with this route, although little is known about how to identify such good prognosis patients ahead of time. In particular, there is a tradition of considering inpatient rehabilitation treatments definitive, perhaps almost curative, by a process of psychological and spiritual epiphany. Significant stigma and lack of acceptability surround agonist treatments [26,27]. Agonist treatment is actually illegal in Russia, where the pivotal trial of XR-NTX was conducted [11]. Many parts of the U.S. simply lack sufficient methadone maintenance programs or physicians certified to prescribe buprenorphine for treatment of opioid dependence, leaving detoxification followed by counseling based treatment without medication as the only option.

Thus, the CTN-0051 design team faced the difficult decision whether or not to include, as a third arm, a TAU control condition consisting of inpatient detoxification, followed by counseling-based treatment without medication. To be considered ethically acceptable, a trial needs to address a question that is scientifically and clinically important and about which there is equipoise (uncertainty about the answer), risks need to be reasonable, and adequate protections in place [28]. For inpatient detoxification followed by counseling with no medication, there was, arguably, both absence of equipoise and serious risk. Despite this, a compelling argument in support of this TAU lay in the very fact that detoxification, followed by counseling without medication, remained a predominant standard of care in many if not most communities in the United States. Thus, there was a desire for a definitive trial to demonstrate the inferiority of this approach, especially within the very delivery