Johns Hopkins Medicine - eForm A

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1. Abstract

(Copied from the grant application without changes.)

This grant has funded human laboratory studies examining the pharmacological characteristics of tramadol, an atypical opioid analgesic. Results show tramadol exerts psychoactive effects, these effects differ from both placebo and a prototypic mu agonist opioid, but under chronic dosing conditions tramadol can produce opioid physical dependence. This provides an evidence base supporting the idea that tramadol may have therapeutic efficacy beyond its use as a non-controlled opioid analgesic. Specifically, these studies provide a foundation supporting the potential utility of this medication for the treatment of opioid withdrawal. It is important to acknowledge that the use of medically supervised withdrawal from opioids (aka detoxification) has limited effectiveness for many patients with opioid dependence. Especially for patients with longer histories of opioid addiction and those with higher levels of physical dependence, detoxification is often a short-term intervention that simply leads to subsequent relapse to drug use. However, there are populations for which detoxification may be preferred or indicated (e.g., persons with relatively short histories of opioid addiction, patients with a lower level of physical dependence, younger patients, and those with early physical dependence on opioids). The Drug Addiction Treatment Act of 2000, which is currently limited in its application to the use of buprenorphine, does not specifically mention buprenorphine – thus allowing other medications to be developed for office based opioid dependence treatment. This is a proposal to study tramadol as an agent for short-term opioid withdrawal treatment. A randomized, double blind clinical trial comparing the efficacy and safety of the extended release form of tramadol to clonidine and buprenorphine in the short-term treatment of opioid withdrawal will be conducted. Opioid dependent participants will be treated on a residential unit. There are three primary phases to the project: an initial stabilization on morphine (to establish a common level of physical dependence, with a naloxone challenge during this phase with results from that challenge used as one stratification variable); a withdrawal period with one of the three medications; and, a transition to double-blind oral naltrexone at the end of the residential stay. The use of tramadol in this way is novel and innovative. In addition, the study includes CYP2D6 genotyping of participants, which will be used as a stratification variable given tramadol's metabolism by 2D6. The primary outcome measure is opioid withdrawal symptoms during the second phase of the study.

2. Objectives (include all primary and secondary objectives)

The primary objective of this study is to compare the efficacy and safety of tramadol ER to clonidine and buprenorphine in the treatment of opioid withdrawal.

In addition, the study will examine secondary outcomes related to CYP2D6 genotyping, which will allow a stratification of subjects, and subgroup analyses to better characterize treatment outcome as a function of drug metabolism.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

INTRODUCTION

Tramadol is a mild to moderate opioid agonist that has low affinity for mu, kappa and delta receptors (Hennies et al. 1988), as well as possible agonist effects at non-opioid receptors (Marincsak et al. 2008), and monoamine reuptake blockade (Driessen et al. 1993; Gobbi and Mennini 1999; Sevcik et al. 1993). It is generally regarded as having a low abuse potential (Cami et al. 1994; Cicero et al. 1999; Epstein et al. 2006; Knisely et al. 2002; Preston et al. 1991). Because of this low abuse potential, review of tramadol in the United States resulted in its approval as an unscheduled opioid medication. However, there are numerous reports of tramadol abuse and of persons who have evidence that they developed physical dependence on tramadol (Brinker et al. 2002; Leo et al. 2000; Liu et al. 1999; Senay et al. 2003; Tjaderborn et al. 2009; Yates et al. 2001). Tramadol's relatively mild agonist effects at the mu opioid receptor suggest two important implications in its development for the treatment of opioid dependence. First, while it may be abused, this potential is considerably lower than other mu agonist opioids such as buprenorphine and methadone – so that it may be an ideal medication to use in office-based treatment settings. And second, its use may be restricted to patients with lower levels of physical dependence, given its mild to moderate efficacy as a mu agonist. While the former effect (low abuse potential) is an attractive feature to this medication, it is recognized that the latter (moderate maximal efficacy at the mu receptor) may be a liability, and the present study will help to determine if there is a reasonable degree of utility for this medication in the treatment of opioid dependence and withdrawal.

PRECLINICAL STUDIES OF TRAMADOL'S EFFECTS

Tramadol's effects can be attributed to both the parent compound (tramadol) and one of its several metabolites, mono-O-desmethyltramadol (commonly referred to as M1). This metabolite accounts for a significant proportion of the effects produced when tramadol is ingested, and in the subsequent discussion references to "tramadol" will encompass effects by the parent compound, M1, and other metabolites as well, unless otherwise specified.

Tramadol has two primary neurochemical effects. First, it binds to and activates opioid receptors (Gillen et al. 2000; Hennies et al. 1988; Raffa et al. 1992); the M1 metabolite shows a higher affinity for the mu receptor than the parent compound (Gillen et al. 2000), and M1 has an affinity for the mu receptor that is about one-tenth of that seen for morphine (Frink et al. 1996). While tramadol also binds to kappa and delta opioid receptors, it has higher relative affinity for mu receptors (Lai et al. 1996; Raffa et al. 1992). Tramadol's activity at opioid receptors has been demonstrated in studies showing that it displaces naloxone binding (Hennies et al. 1988), although it is considerably less effective than morphine, and its antinociceptive effects are blocked by opioid antagonists (Friderichs et al. 1978; Raffa et al. 1992), although this blockade is not always complete. These binding and interaction studies provide good evidence for tramadol's activity as a mu receptor agonist.

While binding studies show evidence that tramadol has a primary effect at the mu opioid receptor, animal studies that have examined the potential for chronic administration of tramadol to produce typical opioid physical dependence have yielded mixed results. There is some evidence that naloxone administration will precipitate very mild withdrawal in monkeys maintained on high doses of tramadol (Yanagita 1978), although such effects were not seen at lower maintenance doses for monkeys. Studies

in rats and mice have generally found minimal or no naloxone precipitated withdrawal following tramadol maintenance (Miranda and Pinardi 1998; Murano et al. 1978; Nickel and Aledter 1987). Tramadol does not suppress signs of opioid withdrawal in monkeys maintained on morphine (Yanagita 1978), consistent with its function as having relatively mild opioid agonist effects. However, tramadol has been shown to substitute for morphine in a drug discrimination paradigm, and furthermore, naltrexone blocks this effect (Ren and Zheng 2000). Conversely, morphine will substitute for tramadol when rats are trained to discriminate tramadol from saline (while a variety of other medications with other pharmacological actions do not substitute for it), and naloxone attenuates this discrimination (Filip et al. 2004). Because tramadol has an unusual profile of opioid effects, it might be possible to explain some of these effects by a partial agonist profile of mu receptor activation. However, tramadol is generally not characterized as a partial opioid agonist; it either does not precipitate withdrawal in opioid dependent animals (Friderichs et al. 1978), or produces only very mild withdrawal effects (Yanagita 1978).

In addition to these effects at the mu opioid receptor, there also is considerable evidence that tramadol inhibits the reuptake of serotonin and norepinephrine (Bamigbade et al. 1997; Driessen and Reimann 1992; Driessen et al. 1993; Filip et al. 2004; Giusti et al. 1997; Raffa et al. 1992; Rojas-Corrales et al. 1998). Tramadol's analgesic efficacy appears to be due to the combination of mu receptor activation and monoamine reuptake inhibition (Kayser et al. 1992; Sevcik et al. 1993). Interestingly, tramadol's effects on monoamine reuptake suggest that it may have antidepressant qualities as well, and there is preclinical evidence to support this hypothesis (Rojas-Corrales et al. 2002; 2004; Rojas-Corrales et al. 1998; Yalcin et al. 2007).

STUDIES OF TRAMADOL'S ANALGESIC EFFECTS IN HUMANS

Tramadol is approved and marketed in the United States as an oral, non-scheduled analgesic. The mechanism of tramadol's analgesic effects appears to derive from its dual actions as both an opioid agonist and monoamine blocker, and one advantage to its use as an analgesic is that it has a relatively mild side effect profile. Numerous clinical trials have examined tramadol's antinociceptive effects in humans, and this section briefly reviews some of these studies. This work is particularly helpful for understanding tramadol's relative analgesic efficacy compared to other commonly used opioid medications. Tramadol's efficacy in the treatment of acute, and then chronic, pain will be considered here. There have been (and continue to be) numerous studies reporting on the relative efficacy of tramadol as an analgesic, and representative studies are summarized here.

Studies of tramadol's use in acute pain conditions have compared it to placebo (Moore et al. 1998; Stamer et al. 1997; Tarradell et al. 1996; Ugur et al. 2008), as well as a variety of active medications including codeine (Jeffrey et al. 1999; Moore et al. 1998), dextromethorphan (Ali et al. 2008), ketorolac (Ali et al. 2006), meperidine (Tarradell et al. 1996), morphine (Erolcay and Yuceyar 2003; Gritti et al. 1998; Houmes et al. 1992; Pang et al. 1999; Stamer et al. 1997; Wilder-Smith et al. 1999a), nalbuphine (Barsoum 1995), non-steroidal anti-inflammatory medications (Hogger and Rohdewald 1999; Pagliara et al. 1997), and propoxyphene combined with acetaminophen (Sunshine et al. 1992). Studies of tramadol for acute pain have varied with respect to route of administration (primarily oral versus parenteral dosing), mechanisms of administration (fixed doses versus use in a patient controlled analgesia (PCA) system), and the doses used. Such variations in the experimental procedures can make interpretation of study results problematic at times – comparisons using a very low dose of tramadol to an effective dose of a control compound such as morphine could bias a study toward concluding that tramadol was ineffective. While most studies of tramadol for acute pain have shown it be superior to placebo and as effective as moderate doses of other commonly used analgesics such as meperidine (Demerol) and pentazocine (Talwin) (Lee et al. 1993), occasional studies have failed to demonstrate such effects (Mehlisch 1998; Stubhaug et al. 1995). However, a meta-analysis that compared tramadol to placebo and other analgesics for the treatment of acute, postoperative pain concluded that tramadol was superior to placebo and comparable to codeine (60 mg) with aspirin (650 mg), or propoxyphene (100 mg) with acetaminophen

(650 mg) (Moore and McQuay 1997). While not the focus of the present application, there have also been numerous studies testing the relative analgesic efficacy of tramadol combined with acetaminophen, showing it is effective as well (McQuay and Edwards 2003).

The efficacy of tramadol has also been studied in the treatment of chronic pain conditions. These studies differ from acute pain studies – not only in the target conditions typically being treated (e.g., arthritis versus post operative pain management), but also in the dosing paradigms employed and settings in which they are conducted (i.e., studies of chronic pain usually employ oral dosing of tramadol in outpatient clinics). Like the acute pain studies reviewed above, these studies have also compared tramadol (or tramadol combined with acetaminophen in some cases) to a variety of active medications, including codeine with acetaminophen (Rauck et al. 1994), dihydrocodeine (Wilder-Smith et al. 2001), morphine (Grond et al. 1999; Wilder-Smith et al. 1999b; Wilder-Smith et al. 1994), non-steroidal anti-inflammatory medications (Pavelka et al. 1998), pentazocine (Bird et al. 1995), placebo (Bennett et al. 2003; Ruoff et al. 2003; Sindrup et al. 1999; Vorsanger et al. 2007; Vorsanger et al. 2008), and propoxyphene (Jensen and Ginsberg 1994). Overall, these studies show that tramadol is an effective analgesic for chronic painful conditions, and its relatively mild side effect profile makes it an attractive medication to use compared to other analgesics such as non-steroidal anti-inflammatories and opioids (Katz 1996).

These clinical trials that have examined the efficacy and safety of tramadol for the treatment of pain – either acute or chronic – have shown that it is generally more effective than placebo, that it can be at least as effective as a medication such as propoxyphene or codeine, and that in some circumstances it can be equally effective as morphine (in mild to moderate pain, for example) (Lee et al. 1993; Lewis and Han 1997). In addition, the efficacy of tramadol occurs with less side effects than comparable analgesics – specifically, fewer gastrointestinal problems than the non-steroidal anti-inflammatory medications, and less constipation and risk of respiratory depression than the opioids (Budd 1994; Katz 1996; Lee et al. 1993). Based upon these results, it can be concluded that tramadol is a safe and effective analgesic for moderate levels of pain, and that it is comparable in efficacy to propoxyphene (Darvon).

TRAMADOL'S METABOLISM

Tramadol is metabolized in the liver, with formation of the active M1 metabolite primarily mediated by the CYP 2D6 enzyme (Gan et al. 2007; Halling et al. 2008; Subrahmanyam et al. 2001). (However, other isoenzymes are also involved in tramadol's metabolism, such as 3A4 and 2B6, although these appear to have a primary role in the formation of non-active metabolites (Subrahmanyam et al. 2001).) Allelic variations in 2D6 can account for alterations in the metabolism of tramadol and other drugs that are substrates for the CYP 2D6 enzyme (Dalen et al. 1999). Mutant alleles can result in a lack of 2D6 enzymatic activity (poor metabolizers, PM), while increasing numbers of functional alleles in the 2D6 gene produce corresponding increases in enzymatic activity (intermediate, extensive, and ultrarapid metabolizers – IM, EM, and UM, respectively). Notably, 2D6 genotype (metabolizer status) influences tramadol disposition and potential efficacy, such that persons who are UM may be more prone to rapid conversion of tramadol to the active M1 metabolite (Kirchheiner et al. 2008; Stamer et al. 2007). This suggests that some between subject differences noted with tramadol may be due to genetic variations in hepatic enzymatic activity. In order to better control for such differences, the present study will stratify subjects based on genotyping of CYP 2D6 activity.

TRAMADOL'S ABUSE POTENTIAL AND USE FOR THE TREATMENT OF OPIOID DEPENDENCE AND WITHDRAWAL

As tramadol produces an agonist effect at the mu opioid receptor, it would be predicted that it should have abuse potential. It is unusual that this medication was approved in 1994 by the Food and Drug Administration (FDA) in the United States as an unscheduled opioid agonist analgesic, given this profile of effects. However, it is also notable that tramadol had been used in Europe for many years with

minimal diversion and abuse. As part of the FDA approval, the sponsor of tramadol agreed to fund a number of initiatives designed to monitor for tramadol abuse (coordinated by an Independent Steering Committee, the "ISC"). Reports by this committee suggest that diversion and abuse of tramadol has been relatively uncommon (Cicero et al. 1999; Cicero et al. 2005).

Despite this finding, there is considerable anecdotal evidence that tramadol can produce opioid physical dependence in humans. It is important to note that there had been no well-controlled studies assessing tramadol's ability to produce physical dependence in humans (e.g., maintenance on different doses of tramadol with either abrupt, double-blind cessation or antagonist challenges) prior to work conducted under the sponsorship of this grant (Epstein et al. 2006). There have been numerous case reports of patients with evidence of physical dependence upon tramadol, as manifested by withdrawal symptoms with cessation of tramadol use (Barsotti et al. 2003; Ehrenreich and Poser 1993; Freye and Levy 2000; Leo et al. 2000; Meyer et al. 1997; Reeves and Liberto 2001; Ritvo et al. 2007; Rodriguez Villamanan et al. 2000; Soyka et al. 2004; Thomas and Suresh 2000; Yates et al. 2001), and since 1995 there have been a small but steady number of FDA adverse event reports for tramadol dependence, abuse or withdrawal (Brinker et al. 2002). One early study of patients with chronic pain maintained on daily doses of tramadol and challenged with intramuscular naloxone found virtually no opioid withdrawal effects produced (Richter et al. 1985), although a report of 219 patients presenting for treatment of tramadol abuse found mild opioid withdrawal symptoms and moderate rates of craving for tramadol with cessation of tramadol use (Liu et al. 1999). The most extensive effort to monitor possible tramadol abuse and withdrawal, conducted by the ISC noted above, investigated 422 cases of tramadol withdrawal, and found the overwhelming majority of these cases had typical opioid withdrawal symptoms associated with stopping tramadol use (Senay et al. 2003).

There have been a small number of human laboratory studies examining the pharmacological characteristics and abuse potential of tramadol. One important early study in this regard examined acute, single parenteral doses of tramadol (75, 150 and 300 mg) compared to morphine (15 and 30 mg) and placebo in non-dependent opioid abusers, and found that the lower doses of tramadol were placebo-like (Preston et al. 1991). While the highest dose of tramadol had some opioid agonist-like effects, these were small in magnitude and not consistently present across all measures (as compared to the morphine control condition). A second study compared higher acute doses of tramadol (up to 700 mg, given orally) to oxycodone (20 and 40 mg) and placebo in a similar population of subjects (Jasinski et al. 1993). In this study, 700 mg of tramadol producing effects similar to 40 mg of oxycodone, although effects of tramadol peaked later and had a longer duration of action. Finally, a study assessing the acute effects of parenteral tramadol (100 and 300 mg) compared to placebo in methadone maintained subjects, found tramadol produced placebo-like effects (Cami et al. 1994). However, this study did not include opioid agonist or antagonist control conditions, making interpretation of the results somewhat problematic.

As described in more detail in the Progress Report section of this application, the first funding period of this grant has supported several studies examining the acute and chronic effects of tramadol in humans. In brief, the first of these studies showed that tramadol can exert psychoactive effects in opioid dependent persons undergoing spontaneous opioid withdrawal, for oral doses of 200 and 400 mg of tramadol (Lofwall et al. 2007). While these were not typical opioid agonist effects, these higher doses of tramadol did show evidence of suppressing opioid withdrawal. A second report of two studies characterized the acute effects of tramadol in methadone and hydromorphone maintained volunteers (Carroll et al. 2006). Results from these studies showed that tramadol did not exert acute opioid antagonist effects (consistent with the Cami report noted earlier, but differing from that study by including naloxone control conditions). Furthermore, there was some evidence that tramadol might exert mild opioid agonist effects (consistent with the Lofwall study). Finally, another study examined whether chronic dosing with tramadol would produce opioid physical dependence (Lanier et al. 2008). This study showed that opioid dependent volunteers maintained on 200 mg per day and 800 mg per day of tramadol

demonstrated naloxone precipitated withdrawal. However, maintenance on tramadol did not produce significant blockade effects when challenged with hydromorphone.

Taken together, the studies supported by this grant and the literature on tramadol's potential for opioid agonist effects suggest it is not devoid of abuse liability, and that there are some patients who develop physical dependence upon tramadol. Given this evidence, it is somewhat surprising that there has not been an extensive literature on the use of tramadol as a treatment agent for opioid dependence. There have been three such reports, all from the Cleveland area and from the same group.

The first of these was a chart review study that compared outcomes for 20 patients treated with buprenorphine versus 44 treated with tramadol for opioid withdrawal (Tamaskar et al. 2003). This was not a randomized or blinded study. Buprenorphine was given subcutaneously over four days, with the maximum dose 2.4 mg on the first day. Tramadol was also given over four days, with the maximum dose 600 mg on the first day. In general, outcomes for the two groups were very similar, as shown by maximum CINA scores and length of stay. However, it appears that there was more supplemental clonidine use in the tramadol versus buprenorphine group. The second study was also a chart review (i.e., non-blind, non-randomized), and compared tramadol (59 patients) to clonidine (85 patients) (Sobey et al. 2003). In this case, tramadol was used over six days (again, a maximum dose of 600 mg on the first day), while clonidine was only used over five days (with a maximum dose of 0.6 mg on days 1 and 2). Patients treated with tramadol had a lower risk of leaving against medical advice (by day 4, 12% versus 41% for tramadol and clonidine groups, respectively), and had lower scores on a withdrawal scale used. Finally, another retrospective, non-randomized analysis compared tramadol (n=70) to buprenorphine (n=45) treated patients (Threlkeld et al. 2006). Doses of tramadol were administered over five days (again, the maximum dose was 600 mg on the first day), and buprenorphine was also administered over five days (with a maximum dose of 2.4 mg subcutaneously on the first day). Patients could also receive other medications (e.g., clonidine). Outcomes for the two groups were similar, with non-significant differences in retention (71% and 56% completing detoxification for tramadol and buprenorphine groups, respectively), although tramadol treated patients had higher withdrawal scores (although there may be a baseline difference between the groups, this is not clear in the report). For all three of these reports, there were no significant adverse events associated with tramadol use.

While these three reports have limitations (all are retrospective chart reviews, there is no randomization or blinding of medications, and baseline differences between groups may be present), they do provide interesting evidence from clinical practice that tramadol can be used for the treatment of opioid withdrawal – and, that it is being so used. They provide evidence of effectiveness, and also support the need for more controlled studies that can test the efficacy and safety of tramadol in the use of opioid withdrawal.

USE OF OPIOID MEDICATIONS FOR OPIOID DEPENDENCE TREATMENT

A highly significant change in the opioid addiction treatment system for the United States occurred in October of 2000, when the Drug Addiction Treatment Act (DATA) was signed into law. DATA was clearly designed with buprenorphine in mind (which was approved by the FDA for the treatment of opioid dependence in late 2002), and set out the circumstances under which medications could be used for the treatment of opioid addiction outside the traditional Opioid Treatment Program (OTP) system. However, DATA did not specify buprenorphine, and opens the possibility for the development of other medications that can be used in office-based settings for the treatment of opioid dependence.

The availability of buprenorphine in office-based settings is clearly an important and valuable step forward in the treatment of opioid addiction. Buprenorphine is mainstreaming addictions treatment, and familiarizing physicians with use of medications for this indication. Providing other medications such as tramadol for the treatment of opioid addiction should further advance this goal – doctors will have another prescription option besides buprenorphine. As more medication options become available, the physician

is not left thinking that if buprenorphine is not effective with a patient then they have no other choices for treatments.

While it is recognized that tramadol may be most appropriate for either patients with lower levels of physical dependence or as a withdrawal agent, this suggests that there may be a particular niche that it can occupy with respect to treatment indications. In a model of stepped medication treatment for office-based opioid dependence treatment, tramadol may be a good first choice for the physician. Its relative ease of use (oral dosing), apparent lower abuse potential compared to other opioids, and mild opioid agonist effects should make it a good and effective initial treatment option that has a high likelihood of patient adherence. It may also be possible that tramadol could serve as an effective bridge agent, transitioning a person from a full or partial mu agonist to an opioid antagonist. Thus, patients might transition from methadone at a clinic to buprenorphine in an office setting, then from buprenorphine to tramadol followed by a taper off tramadol with subsequent treatment with oral naltrexone. This might then be converted to extended-release naltrexone administered in the office setting.

In addition to these possibilities, patients addicted to prescription opioids may be good candidates for tramadol treatment, either as a maintenance agent with a low abuse potential, or as a transition agent from the abused opioid to eventual drug free treatment. In the outpatient office-based setting, tramadol also may be useful as an initial withdrawal agent for a new patient – again, its lower abuse potential would make it an attractive first option for newer patients with whom a physician may be relatively unfamiliar. In a model of stepped care, those patients who are not successfully treated with tramadol would then step up to another pharmacotherapy such as buprenorphine. If buprenorphine were not effective, then patients might progress to methadone treatment as yet an even more intensive treatment option.

The opportunity for opioid addiction treatment in the office setting provides an expansion in the treatment system, but also requires flexibility in the medications that can be used in this setting. In a choice of medications that is currently composed of buprenorphine, methadone, and naltrexone, tramadol has the potential to be a very useful addition to the options that can be used by physicians for this disorder.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

OVERVIEW

This is an approximately four-week double-blind randomized controlled trial that enrolls opioid dependent volunteers seeking medically supervised withdrawal. The study will be conducted on the BPRU's Residential Research Unit (RRU), which is a contained environment designed for conducting substance abuse research. There are three phases for each participant's time on the RRU. During the first phase (lasting between 7-10 days), they are maintained on subcutaneous morphine four times per day. Two primary events occur during this phase: genotyping of CYP 2D6 is obtained, and a naloxone challenge is conducted. Results from these assessments are used as stratification variables at the end of the first phase. Participants are then randomly assigned to one of three medication groups: sublingual buprenorphine, oral clonidine, or oral tramadol ER. Dosing of medication is double blind and double dummy (i.e., a combination of oral and sublingual dose formulations). The second phase of a volunteer's time on the RRU lasts seven days, and during this time the medication is withdrawn. The final phase of the volunteer's time on the RRU lasts ten days, and during this time they continue on placebo forms of the medications. During the last three days on the RRU, participants will be administered a second naloxone challenge. Those who are interested will be given the opportunity to start on oral naltrexone. Volunteers will then be discharged to the BPRU's outpatient clinic, where they will be offered continued drug abuse counseling, urine testing, and oral naltrexone if desired.

FIRST PHASE: MORPHINE DOSING

There are several goals for the first phase of the study, which lasts 7-10 days. The immediate goal upon admission to the RRU is for the participant to be stabilized on morphine, 30 mg subcutaneously (SQ) four times per day. Doses of morphine will be administered at 0700, 1200, 1700, and 2200. The decision for this total daily dose of morphine and the time of administrations is described below. Subjects who have evidence of excessive opioid agonist effect (e.g., nodding) will be assessed and considered for study discharge if they do not appear to have opioid physical dependence. Participants who have evidence of opioid withdrawal will be given symptomatic aids in an effort to achieve comfort on this dose of morphine. The goal is for participants to have at least four days of morphine dosing (30 mg SQ qid) before the naloxone challenge session. Another goal for this first phase is to obtain an assessment of the participant's level of physical dependence based upon a naloxone challenge session. Participants will receive an intramuscular dose of 0.4 mg naloxone during this session; this dose of naloxone was selected based upon a recently completed study we conducted, in which opioid dependent volunteers maintained on 30 mg SQ qid morphine had a 0.4 mg naloxone challenge (Tompkins et al. 2009). Participants in that study showed evidence of opioid precipitated withdrawal that was measurable and tolerable. Naloxone will be administered 1100 on test session days (i.e., 4 hours after the morning dose of morphine). The 1200 dose of morphine will be administered at 1330 on test session days. Results from this challenge session are used as one of four stratification variables. This phase of the study also provides a window of time during which CYP 2D6 genotyping results will be obtained; these will also be used for stratification purposes. Finally, at the end of this phase, participants are randomly assigned to buprenorphine, clonidine, or tramadol ER conditions. An urn randomization procedure will be used, and stratification variables will be: gender, race, 2D6 genotype (UM, EM, IM, PM), and response to naloxone challenge (based upon a Clinical Opioid Withdrawal Scale [COWS] peak score of ≤8 versus >8). On the last day of morphine dosing, the last two doses of morphine will be placebo doses, to ensure that subjects are experiencing mild opioid withdrawal prior to the first dose of study medication. This design feature is to minimize the risk of buprenorphine-related precipitated withdrawal (Rosado et al. 2007; Strain et al. 1992; 1995).

SECOND PHASE: BUPRENORPHINE, CLONIDINE, OR TRAMADOL ER DOSING

Participants will receive oral capsules four times per day and sublingual tablets once per day during the second phase of the study. Dosing of medications will occur at 0700, 1200, 1700, and 2200; sublingual tablet administrations will occur at 0700. Assessments will be collected prior to each dose, and at 0900, 1400, and 1900. The timing of dosing and assessments has been selected to provide clonidine over a 15 hour period (at 5 hour intervals), using the same times at which morphine is administered in the first phase. In addition, the timing of assessments is designed to collect measures over the course of the day while not unduly imposing upon when participants sleep. All dosing will occur on the RRU, with doses administered under supervision by nursing staff.

Buprenorphine/naloxone will be administered in the form of the small (2/0.5 mg) tablets. All participants will receive four of these tablets each day, with a combination of active and placebo tablets used to maintain the blind. Clonidine and tramadol ER will be administered in identically appearing capsules prepared by the BPRU's pharmacy. Capsules are administered four times per day, but only the clonidine group receives active doses of medication at any time other than 0700.

The dose schedules of medications used during phase 2 of the study are shown in the below table:

Dosing Schedule During Phase 2 of the Study*

Day during phase 2	Buprenorphine	Clonidine**	Tramadol ER
1	4/1	0.4	300
2	8/2	0.8	600
3	6/1.5	0.6	400
4	6/1.5	0.6	400
5	4/1	0.4	300

6	4/1	0.4	300
7	2/0.5	0.2	200

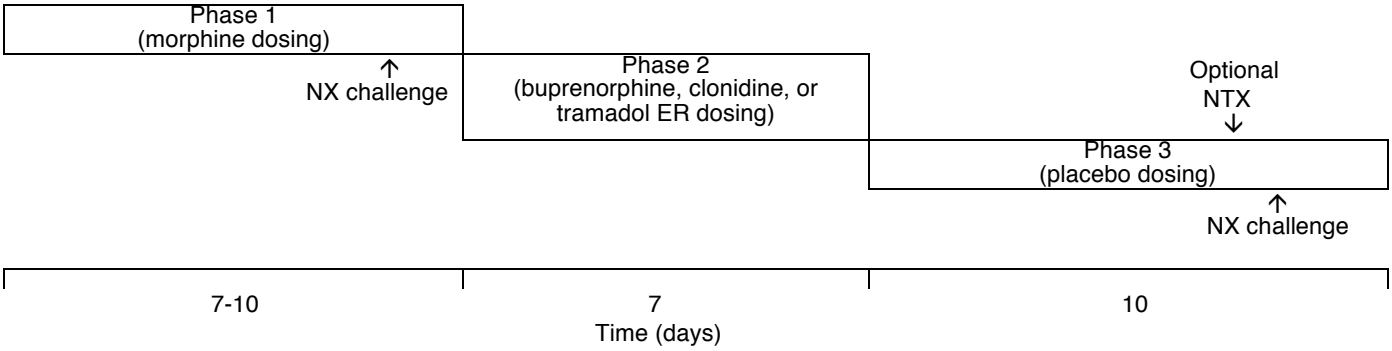
* all doses are in mg; buprenorphine is the buprenorphine/naloxone formulation
** total daily dose of clonidine, which is divided and administered four times per day

THIRD PHASE: PLACEBO DOSING

At the end of the second phase of the study, all study participants are switched to placebo tablets and placebo capsules. Placebo administrations continue for an additional ten days at the same times as the second study phase, and assessments continue at the same times as well. For blind staff and study participants, there is no distinction between the second and third phases. Three to five days prior to the end of the study (the fifth to seventh day of the third phase), all participants undergo a second 0.4 mg IM naloxone challenge. Participants who desire to be treated with oral naltrexone will receive the first dose on the eighth day of the third phase, assuming they have shown minimal or no opioid withdrawal in response to the naloxone challenge. If a participant does have opioid withdrawal with the naloxone challenge, oral naltrexone dosing will be delayed by 1-2 days (depending upon the degree of opioid withdrawal produced in response to naloxone).

Participants may experience opioid withdrawal symptoms while stabilizing on morphine during the first phase of the study, or during the third study phase when active medications end and they receive double-blind placebo dosing. It is also possible that subjects may experience some withdrawal symptoms during the second study phase. Medical staff not involved in the study as an investigator, and blind to condition assignments and the distinction between the second and third study phases, will be available to assess participants and order symptomatic aids as clinically indicated. No opioid medications may be ordered, nor may clonidine or benzodiazepines be used.

STUDY TIMELINE



(NX = naloxone, NTX = naltrexone)

b. Study duration and number of study visits required of research participants.

Study duration is approximately four-weeks for each volunteer. The study involves admission to the BPRU's RRU, where participants will reside for the active phase of the study.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

All drugs are administered under double blind conditions. The blinding of these procedures is to ensure that expectations of investigators, staff, or participants do not influence study results.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants will receive medications that have been previously used for the treatment of opioid withdrawal (buprenorphine, clonidine, or tramadol). In addition, they will be in a supervised environment. The proposed period on the RRU (approximately four weeks) is a longer duration than typically provided by inpatient withdrawal programs (e.g., the Bayview Chemical Dependency Unit's average length of stay for opioid withdrawal is three days).

e. Justification for inclusion of a placebo or non-treatment group.

There is no placebo or non-treatment group in this study.

f. Definition of treatment failure or participant removal criteria.

Participants can also be discharged from the study for medical reasons (e.g., if the subject develops a medical condition that requires immediate attention related or unrelated to the study medication, they may be discharged early). Subjects can also be discharged from the BPRU for violating the residential unit rules. These written rules are reviewed with the volunteers at the time of admission, and the volunteers provide their signature agreeing to abide by the rules. These rules prohibit such activities as verbal abuse of staff or other volunteers, stealing, violating protocol requirements, and sexual activity.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

At the end of the third study phase, or if a participant is discharged early from the study, subjects are discharged from the RRU and can continue in outpatient treatment at the BPRU's outpatient research/treatment clinic. This service includes counseling, urine testing, and continued oral naltrexone dosing. Volunteers who wish to continue in treatment elsewhere will be assisted in the transfer of care to alternate sites.

5. Inclusion/Exclusion Criteria

Participants in this study will be males and females between the ages of 18 and 60 years. Applicants must be opioid dependent based upon the Structured Clinical Interview for DSM-IV (SCID); in addition, they must have an opioid positive urine during the screening process (or have evidence of opioid withdrawal). They must be healthy, with no significant medical illnesses (e.g., insulin dependent diabetes), and without significant psychiatric illness (e.g., schizophrenia) besides their drug dependence. Females will have a pregnancy test prior to study enrollment, and if found to be pregnant will be excluded and referred to a substance abuse program for pregnant women (the Center for Addiction and Pregnancy) on the campus. Volunteers will also be excluded if they have pre-admission hypotension (due to the use of clonidine in the study). Applicants with a history of seizures (including substance-related seizures, such as alcohol withdrawal related) will be excluded. Alcohol and/or sedative dependence will be specific

exclusionary criteria (given the small risk of seizures associated with tramadol use). Allergies to any of the study medications will be grounds for exclusion.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

TRAMADOL

Participants assigned to the tramadol ER condition will receive a single daily oral dose of tramadol ER in the morning, at the same time as buprenorphine dosing (0700). The schedule of tramadol ER dosing will be: 300 mg on day 1; 600 mg on day 2; 400 mg on days 3 and 4; 300 mg on days 5 and 6; and 200 mg on day 7. This schedule of dosing generally parallels that used for the buprenorphine and clonidine conditions, allowing for the fact that tramadol ER comes in dosage forms of 100, 200 and 300 mg. The highest dose of tramadol ER (600 mg) is equivalent to the highest total daily dose used in the reports of Sobey and Threlkeld, which was 600 mg per day (Sobey et al. 2003; Threlkeld et al. 2006). In previous studies of tramadol, we have safely tested acute doses of 400 mg of tramadol in opioid dependent subjects (Lofwall et al. 2007), and have safely maintained opioid dependent volunteers on 800 mg of daily total tramadol (Lanier et al. 2008). Tramadol appears to exert psychoactive effects in persons experiencing opioid withdrawal (Lofwall et al. 2007), and these effects appear to be dose related. In addition, tramadol appears to not exert opioid antagonist effects (unlike buprenorphine), suggested there is little risk of precipitating withdrawal with the first dose (Carroll et al. 2006). Finally, while tramadol has been noted to increase the risk of seizures, this appears to have occurred very rarely with oral dosing, although the risk may be increased when higher doses of tramadol (e.g., 300-700 mg) are administered relatively rapidly by the intravenous route (Epstein et al. 2006). While acute doses of oral tramadol can produce seizures, in general the risk of a tramadol seizure appears to be quite low, and more likely in persons with a history of a seizures or head trauma, in cases where a higher dose is ingested (greater than 500 mg), and when there is concurrent alcohol use (Gardner et al. 2000; Jovanovic-Cupic et al. 2006; Talaie et al. 2009). Interestingly, there is evidence to suggest that the risk of seizures associated with tramadol use is no greater than that seen with use of other analgesics (Gasse et al. 2000).

BUPRENORPHINE

The dosage form of buprenorphine that will be used in this study is the 2/0.5 mg buprenorphine/naloxone sublingual tablet. Active tablets and matching placebo tablets will be provided by the manufacturer of buprenorphine/naloxone (personal communication, R.E. Johnson, Pharm.D., Reckitt and Benckiser Pharmaceuticals, Richmond, VA; October, 2009). Participants will receive a single daily dose of buprenorphine/naloxone, with the following schedule of dosing: 4/1 mg on day 1; 8/2 mg on day 2; 6/1.5 mg on days 3 and 4; 4/1 mg on days 5 and 6; and 2/0.5 mg on day 7. These doses have been selected, in part, to parallel the dosing schedule that is used for the other two medication conditions. We and others have shown that the highest dose of buprenorphine (8 mg) in the buprenorphine/naloxone formulation is a well-tolerated dose when delivered sublingually in opioid dependent subjects (Stoller et al. 2001). A higher dose of buprenorphine could have been used, although a maximum daily dose of 8 mg sublingual buprenorphine has been commonly reported in other studies in which patients were undergoing short-term withdrawal (Amass et al. 1994; Oreskovich et al. 2005; Wright et al. 2007).

CLONIDINE

Participants assigned to the clonidine group will receive this medication four times per day, to lessen side effects such as hypotension that can be associated with a large single dose of this medication, and consistent with use of clonidine for opioid withdrawal (Cheskin et al. 1994; Gossop 1988; Strain 2006).

Clonidine will be administered at 0700, 1200, 1700, and 2200 (the same times at which morphine is dosed in the first phase of the study). Ideally, the dose of clonidine administered each day would parallel that used for the buprenorphine schedule. The first day's dose of clonidine is lower than the second day's dose, to ensure tolerability. The following schedule of clonidine dosing will be used for volunteers assigned to this condition: a total daily dose of 0.4 mg on day 1 (i.e., 0.1/0.1/0.1/0.1 mg); a total daily dose of 0.8 mg on day 2 (i.e., 0.2/0.2/0.2/0.2 mg); a total daily dose of 0.6 mg on days 3 and 4 (i.e., 0.15/0.15/0.15/0.15 mg); a total daily dose of 0.4 mg on days 5 and 6 (i.e., 0.1/0.1/0.1/0.1 mg); and a total daily dose of 0.2 mg on day 7 (i.e., 0.05/0.05/0.05/0.05 mg). This schedule is designed based upon several considerations. First, the average daily dose for the first two days (0.6 mg) is the same starting dose used in the study by Sobey et al., in which clonidine was compared to tramadol (Sobey et al. 2003). Second, the rate of dose reduction after the first two days of clonidine dosing matches the reductions in the buprenorphine schedule (i.e., both schedules have 25% dose decreases every two day period with the exception of the final reduction, which is a one day period). Importantly, if participants have evidence of clinically significant hypotension as identified by medical staff not involved in the study as an investigator, then a non-blind investigator will adjust the clonidine dosing (e.g., decrease the day 2 dose).

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Oral tramadol has been well tolerated and is generally safe. It is a widely used analgesic. High doses of tramadol administered intravenously (400 mg over 5 minutes) have produced seizures. After tramadol's release, the manufacturer reported 52 cases of seizures occurred among 3,460,000 patients exposed to tramadol. The majority of these cases (n=33) were in patients with a predisposing risk factor for seizures. The currently proposed study with tramadol involves only oral dosing – there is no parenteral dosing of tramadol in this study. We expect the doses of oral tramadol proposed in this study should be well tolerated and safe. Notably, this study is conducted on our residential research unit where subjects are under 24-hour nursing supervision. Applicants with any history of a seizure will be excluded from this study.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Not applicable.

7. Study Statistics

a. Primary outcome variable.

The primary outcome measure is the score on the Clinical Opioid Withdrawal Scale (COWS) from the second phase of the study.

b. Secondary outcome variables.

Secondary outcome variable include additional measures from the second phase (Subjective Opioid Withdrawal Scale [SOWS] scores, successful completion of this phase of the study, as well as results from the third study phase (e.g., COWS scores, SOWS scores, retention to the end of the study). In addition, the proportion of subjects who are successfully discharged on naltrexone, as a function of second phase medication condition, will be examined.

c. Statistical plan including sample size justification and interim data analysis.

POWER

A total of 150 subjects will be enrolled in this study. The target is to enroll an average of approximately three subjects per month.

Study completion is defined as successfully completing the second phase of the study, given that the primary study question is the relative efficacy of tramadol ER in the treatment of opioid withdrawal. Of the 150 enrolled, it is expected that approximately 20% (30 subjects) will drop out prior to study completion. Thus, 120 subjects are anticipated to complete the study. It is hypothesized that both tramadol ER and buprenorphine will be statistically superior to clonidine in the treatment of opioid withdrawal as measured by peak COWS score, and that buprenorphine will not be significantly superior to tramadol ER. This is consistent with the findings from the Sobey paper, which found tramadol superior to clonidine (Sobey et al. 2003), and also consistent with the paper by Threlkeld et al. (Threlkeld et al. 2006), which compared tramadol to buprenorphine. (While tramadol had higher peak withdrawal scores than buprenorphine in that study, it appears those higher scores represented a difference at baseline between the tramadol and buprenorphine groups, with the former having higher baseline scores. And, interestingly, tramadol was superior to buprenorphine in treatment retention in that study.)

There are limited studies that have compared tramadol to clonidine or buprenorphine in the treatment of opioid withdrawal. In the paper by Sobey and colleagues (Sobey et al. 2003), patients treated with clonidine or tramadol (not randomized) were assessed with a four point scale (0-3) for the degree of opioid withdrawal experienced. Peak scores for patients treated with clonidine were 1.82 (95% CI, 1.63-2.01), and those for patients treated with tramadol were 1.16 (95% CI, 0.95-1.36). This shows a relatively large effect size of f=0.39. However, this was a non-randomized sample, and biases such as expectancy effects (which may have contributed to the perception by patients that the new medication (tramadol) would be better than clonidine), and patient assignment to the drug thought to be best suited for a particular person may have contributed to this relatively large effect size. Assuming that the effect size would be somewhat diminished in a randomized, double blind study, the present design assumes an effect size f=0.29 (a more medium sized effect). For power=0.8 and alpha of 0.05, with an effect size of 0.29, the needed sample is then 120 for the current three group design.

DATA ANALYSES

Groups will be compared on baseline characteristics to ensure equal distributions for features that might be related to treatment outcome (e.g., gender, age). Continuous measures will be compared with ANOVA, and categorical measures with chi square analyses. If imbalances are found, subsequent analyses will include baseline characteristics as covariates in the analyses. Groups will also be compared on peak COWS scores in response to the first naloxone challenge (during the morphine phase of the study), and also for proportions of subjects by CYP 2D6 genotype to ensure balance in the randomization has occurred.

There are two periods of study interest related to this controlled clinical trial. The first is the seven days of active study medication dosing (buprenorphine, clonidine, or tramadol ER), and this period is the primary period of study interest. In addition, the third study phase during which placebo dosing occurs will also provide useful data about the immediate period of time following the end of active dosing of the study

medications, and the degree and time course of withdrawal that can occur following cessation of medication. This period is of secondary interest.

The primary outcome is COWS scores from the second study phase. We will consider using COWS scores from the naloxone challenge as a covariate in these analyses, to decrease individual subject variability in response during the active treatment phase of the study. Data from this phase for the COWS will be analyzed with three approaches – peak scores during the seven day period, area under the curve (AUC) for the full seven day period, and an analysis of score by time. Comparisons will be made with a one factor ANOVA in the case of peak and AUC scores (i.e., the three conditions), and a repeated measures regression for the time course analyses (i.e., condition x time). Rates of missing data are expected to be very low, given the study is conducted on a residential unit under constant staff supervision and data collection. Pairwise comparisons will be assessed with Tukey's post hoc procedure. Secondary measures of interest from this phase of the study (e.g., SOWS scores, successful completion of this phase of the study) will be analyzed following a similar approach. Subgroup analyses will also be conducted when indicated (e.g., genotype within a medication condition).

Results from the third study phase will be analyzed following a similar pattern to that used in the second study phase. That is, COWS scores (peak, AUC, and time course), as well as other measures (e.g., SOWS, retention to the end of the study) will be examined as a function of medication group, and using ANOVA and repeated measures regression. Peak COWS score results from the second naloxone challenge session will also be analyzed as a function of condition assignment. Finally, chi square analyses will examine the proportion of subjects who are successfully discharged on naltrexone, as a function of second phase medication condition.

d. Early stopping rules.

Volunteers in this study may choose to stop study participation at any time. Participants who demonstrate strong drug effects that are poorly tolerated may be discharged early from the study and treated outside the parameters of the protocol using routine clinical practice.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

There is essentially no risk to the nonpharmacological treatment delivery or the data collection procedures used in this study. The primary risks are associated with the pharmacologic interventions used. There are six medications used in this study, although no subject will receive all six. Three of the medications have an opioid agonist component of action (buprenorphine, morphine, and tramadol ER). A risk associated with the use of opioids such as buprenorphine, morphine, and tramadol ER is side effects from the medication (e.g., constipation); these effects are not unique to the proposed studies, but are usual for patients receiving opioid treatment medications. Doses have been selected for these medications that are within the range of prior administrations in other studies. Thus, for example, the dose of morphine used in the present study (30 mg SQ four times per day, for a total daily dose of 120 mg) is in the mid-range of doses used in studies of opioid dependence that were conducted at NIDA's Addiction Research Center (ARC) in the 1970s; those studies used total daily doses as low as 30 and as high as 240 mg. This dose of morphine has been successfully used in a recent study conducted at the BPRU (Tompkins et al., 2009), and was well tolerated. The doses of buprenorphine and tramadol ER have also been used in prior studies of opioid detoxification, as described in the research plan, and have been well tolerated.

A specific risk associated with tramadol is the risk of seizures. As noted in the application, this risk appears to occur very rarely with oral dosing, although the risk may be increased when higher doses of tramadol (e.g., 300-700 mg) are administered relatively rapidly by the intravenous route (Epstein et al., 2006). While acute doses of oral tramadol can produce seizures, in general the risk of a tramadol seizure appears to be quite low, and more likely in persons with a history of a seizures or head trauma, in cases where a higher dose is ingested (greater than 500 mg), and when there is concurrent alcohol use. Interestingly, there is evidence to suggest that the risk of seizures associated with tramadol use is no greater than that seen with use of other analgesics. Potential participants who have a history of seizing, head trauma, or concurrent alcohol use will be excluded from this study.

A risk associated with the use of clonidine is hypotension. This is a well-described side effect of this medication. Participants with hypotension prior to study admission will be excluded and referred to community based treatment. Subjects in this study will have regular blood pressure checks (at least once daily, and thrice daily for the first three days at the start of the second phase of the study) throughout their stay. Subjects who have evidence of low blood pressure will have a double-blind dose reduction if they have been assigned to the clonidine group.

A risk for both clonidine and buprenorphine (and potentially morphine) is sedation and over medication. If a participant appears to be experiencing an excessive effect from any of the study medications (including tramadol), then a double-blind dose reduction will be made.

Finally, participants will also receive an acute dose of parenteral naloxone twice during the study. The first administration is expected to produce opioid withdrawal. We have considerable experience with naloxone precipitated withdrawal, and this is a generally short syndrome (typically resolving within 45-60 minutes) that is discomforting to opioid dependent persons but not severe. In the study by Tompkins et al. (2009), we followed the same procedures proposed here with respect to morphine and naloxone dosing, and participants tolerated the withdrawal produced with no significant problems.

Volunteers may elect to receive naltrexone at the end of their stay on the RRU. Oral naltrexone will be used following standard practice in the community (e.g., 50 mg per day of oral dosing). No adverse events are expected, especially as subjects will have a naloxone challenge first to ensure there is no residual evidence of opioid physical dependence.

Alternative treatment options include non-study opioid detoxification, and buprenorphine or methadone treatment. These options are available in the Baltimore area. The risk of routine detoxification is that relapse can occur if there is not comprehensive follow up treatment planned. Buprenorphine and methadone maintenance treatments have excellent outcomes, but some patients resist entering maintenance treatment and wish to first try supervised withdrawal. The services provided in this study, such as a residential stay for four weeks, are more intensive than standard community care. Other treatment services are available in the local community, and applicants to this study may apply for these other forms of treatment as an alternative to study participation.

b. Steps taken to minimize the risks.

The Behavioral Pharmacology Research Unit maintains strict confidentiality for all participants in studies. Records are maintained on-site and are only released with the written consent of the patient. The identity of participants is never revealed in written reports, and documents with subjects' names are shredded or incinerated before being disposed.

Medical evaluations are conducted by a member of the medical staff before the onset of study participation. Coverage for medical problems is always available. Pharmacy services include a registered pharmacist and her staff, procedures for preparation of sterile products, and appropriate equipment (e.g., a laminar flow hood). All medication administrations are by trained nursing staff. A code to break the drug

blinds is always available if needed, and appropriate medical supplies and equipment for emergency response are available on site.

Participants who have evidence of side effects possibly related to the study medications (e.g., hypotension from clonidine) will have a double blind dose reduction. If medical staff not involved in the study as an investigator recommend a participant's withdrawal from the protocol, then this will promptly occur. The investigators will always be attentive to the clinical outcomes and welfare of study participants.

Female patients will have a pregnancy test done prior to study entry and then weekly. If a patient becomes pregnant, she will be withdrawn from the active phase of her study protocol, and assisted in transferring to a local program that specializes in the treatment of pregnant drug users (available on the campus). If a subject develops a major medical illness unrelated to their study participation, then they too will be withdrawn from the study protocol and assisted in transferring to routine, community based addictions treatment and in obtaining appropriate medical care.

c. Plan for reporting unanticipated problems or study deviations.

All adverse events will be reported to the IRB and other relevant agencies (e.g., FDA, NIDA) as required. The Principal Investigator and Co-investigators are responsible for reporting such events.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Some information is collected as part of the intake and assessment process regarding illegal activities (especially drug use). This information is generally provided as a global report (yes/no, frequency) rather than with specific information about a given instance of criminal activity that could lead to prosecution. We do not believe that this type of information, if breached, could lead to legal consequences.

e. Financial risks to the participants.

None.

9. Benefits

a. Description of the probable benefits for the participant and for society.

This study provides four weeks of residential treatment for opioid dependence as well as outpatient follow up care. Study participation will directly benefit subjects through the treatment services provided. The study will provide important information about the efficacy of tramadol ER in the treatment of opioid dependence. In addition to the direct benefit to study participants, the scientific knowledge gained from this study will benefit society and be useful in determining if tramadol ER will be a useful medication for the treatment of opioid dependence.

Abuse of opioids in the United States is rising, including both heroin use and especially misuse of prescription opioids. There is interest in broadening the delivery of treatment of opioid addiction to include office-based treatment of this disorder, and the legislative changes in the Drug Addiction Treatment Act (DATA) of 2000 allow physicians to treat patients with opioid dependence in their offices. Use of buprenorphine appears to be gaining slow but steady acceptance in the medical community, with over 10,000 physicians now eligible to prescribe this medication.

While buprenorphine has been an extremely valuable addition to the limited number of addiction treatment medications available to physicians, other treatment options are needed. Medications for opioid dependence can be conceptualized as falling along a continuum, progressing from methadone to buprenorphine and then naltrexone. Tramadol could fall between buprenorphine and naltrexone, as a low efficacy opioid for targeted clinical indications and that may be a useful bridge to transitioning a patient to an opioid antagonist.

The risks associated with this clinical trial are slight, and precautionary measures have been built into the study. The knowledge gained from this line of work will be beneficial to the treatment community, and the development of tramadol for the treatment of opioid dependence would be complementary to buprenorphine's use and a further asset to physicians in office based practices who are currently limited in approved medications they can use to treat this disorder. Hence, the knowledge to be gained from this work is important and valuable to the research and treatment communities.

IND approval will be obtained for this study.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Subjects will be paid according to a schedule of reimbursement used in our residential studies. This includes a base rate per day and potential additional daily fees for chores and hygiene. To minimize the risk that financial earnings in this study will be used to support illicit drug abuse, our laboratory uses the policy that payments to volunteers are in small amounts spread out over a period of time and are paid to individuals only if they provide a urine sample that is free of illicit drugs. Total earnings for study participation will be approximately $700 per subject.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There are no costs to subjects for the study procedure or drugs administered to them.