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The effects of pioglitazone, a PPAR γ receptor agonist, on the abuse liability of oxycodone among nondependent opioid users

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Abstract

Aims—Activation of PPAR γ by pioglitazone (PIO) has shown some efficacy in attenuating addictive-like responses in laboratory animals. The ability of PIO to alter the effects of opioids in humans has not been characterized in a controlled laboratory setting. The proposed investigation sought to examine the effects of PIO on the subjective, analgesic, physiological and cognitive effects of oxycodone (OXY).

Methods—During this investigation, nondependent prescription opioid abusers (N=17 completers) were maintained for 2–3 weeks on ascending daily doses of PIO (0 mg, 15 mg, 45 mg) prior to completing a laboratory session assessing the aforementioned effects of OXY [using a within-session cumulative dosing procedure (0, 10, and 20 mg, cumulative dose = 30 mg)].

Results—OXY produced typical mu opioid agonist effects: miosis, decreased pain perception, and decreased respiratory rate. OXY also produced dose-dependent increases in positive subjective responses. Yet, ratings such as: drug “liking,” “high,” and “good drug effect,” were not significantly altered as a function of PIO maintenance dose.

Discussion—These data suggest that PIO may not be useful for reducing the abuse liability of OXY. These data were obtained with a sample of nondependent opioid users and therefore may not

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Declaration of Interests

Conflicts of Interest: Only the authors listed are responsible for the content and preparation of this manuscript. Over the past three years SDC, MAS, SM, and JMM have received compensation (in the form of partial salary support) from investigator-initiated studies supported by Reckitt-Benckiser Pharmaceuticals, Schering-Plough Corporation, Johnson & Johnson Pharmaceutical Research & Development, Endo Pharmaceuticals, and MediciNova. SDC also served as a consultant to the following companies: AstraZeneca, Camurus, CliniLabs, Guidepoint Global, Janssen, Mallinckrodt, Orexo, Pfizer, and Salix.

Disclosures

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be applicable to dependent populations or to other opioids. Although PIO failed to alter the abuse liability of OXY, the interaction between glia and opioid receptors is not well understood so the possibility remains that medications that interact with glia in other ways may show more promise.

Introduction

Until recently, the abuse liability of opioids was thought to be mediated primarily through neuronal processes. However, emerging evidence indicates that immunocompetent cells (glia) may contribute significantly to opioid pharmacology. Glial cells constitute over 50% of the cells in the central nervous system [CNS (1)]. Once thought to be the passive “glue” that fills the space between neurons, it is now recognized that glia play key roles in many neuronal processes and disease states (2, 3, 4, 5).

Research on the interaction between opioids and glia began over 30 years ago (6). Although this research has revealed that immune cells express opioid receptors and the mRNA to produce them, there remains vigorous debate over how opioids affect glia (7, 8, 9). Opioid use typically increases vulnerability to infection, suggesting that opioids are immunosuppressive (10). Much of the laboratory research seeking to investigate this hypothesis has examined the effects of the prototypic opioid, morphine. Several studies have shown that acute or chronic morphine exposure suppresses antibody response (11), macrophage activity (12), B-cell activity (13), T-cell activity and cytokine release (14; see also 15 & 16 for reviews).

Alternatively, it has been shown that opioids cause direct glial cell activation in a non-classical opioid receptor fashion, possibly via opioid-induced activation of a class of pattern recognition receptors referred to as toll-like receptors (17). For example, chronic morphine administration has been associated with an increase in proinflammatory cytokine protein and/or mRNA (18), glial fibrillary acid protein (19, 20), and proliferation (astrogliosis) and migration of astrocytes (21, 22, 23, 24, 25).

Although the cause of these discrepant findings is still under debate, investigators have begun to study opioid and glial interactions as a means to separate the beneficial effects of opioids (analgesia) from their detrimental effects (abuse potential). Preclinical research into the behavioral effects of opioid-glia interactions has found that selectively increasing glial (astrocyte) activity in the NAcc and intracingle cortex results in significantly greater preference for morphine-associated cues relative to vehicle-associated cues [morphine-induced conditioned place preference (CPP)]. Investigators were able to attenuate this effect with a glial activity inhibitor (26).

As a logical extension of this work, there is a growing body of literature examining whether pharmacological modulators of glial cells may show some clinical utility to reduce the abuse potential of opioids (see reference 26 for a review). Ibudilast (AV411), minocycline, pentoxifylline and propentofylline are medications that suppress opioid-induced increases in immune factors (27, 28, 29). Furthermore, these glial modulators are hypothesized to decrease the rewarding effects of opioids. Ibudilast co-administered with morphine significantly reduced the magnitude of opioid-induced dopamine release in the NAcc (30),

and ibudilast, propentofylline, and minocycline reduce or completely block opioid-induced CPP (17, 26, 3).

Another glial modulator being investigated in this respect is the peroxisome proliferator-activated gamma receptor (PPAR γ) agonist, pioglitazone (or Actos). In the central nervous system, PPARs are expressed in neurons, oligodendrocytes, and astrocytes (32, 33, 34, 35). PPAR γ agonists have been shown to inhibit the expression of cytokines by monocytes/macrophages and microglia (36). Preclinical research further showed that PPAR γ activation by pioglitazone (PIO) attenuated development of opioid tolerance (38) reduced heroin self-administration under a fixed-ratio and progressive-ratio schedule of reinforcement and heroin-induced increases in extracellular dopamine in the nucleus accumbens (39).

The ability of PIO to alter the effects of opioids in humans has not been characterized in controlled, clinical laboratory settings. As such, the primary aim of the current study was to examine the subjective effects of oxycodone (OXY) under maintenance on various doses of PIO [0 (placebo), 15, and 45 mg] in nondependent, prescription opioid abusers. Oxycodone was chosen because it is one of the most commonly prescribed and abused opioid analgesics (40, 41, 42). The PIO doses employed in this study are currently used clinically for the treatment of insulin resistance and type 2 diabetes (43, 44). The secondary aims of the study were to examine the influence of PIO on the analgesic, cognitive, and physiological effects of OXY. Based on preclinical evidence, we hypothesized that pioglitazone would decrease the positive subjective effects of oxycodone while potentiating its analgesic properties. If this hypothesis is supported, regulation of PPAR γ may represent a new pharmacotherapeutic strategy to reduce the abuse of opioid drugs.

Methods

Participant Screening and Selection

Participants were recruited from the New York City metropolitan area through various print media advertisements. Respondents who met study inclusion/exclusion criteria, based upon the initial telephone interview, were scheduled to come to the New York State Psychiatric Institute for additional screening procedures. Screening consisted of both self-report and clinical interviews administered by a team of research assistants, psychologists, nurses, and physicians. Assessments were made of drug use, general health, and medical history, and multiple laboratory tests (hematology, blood chemistry panel, liver and thyroid functioning, urinalysis, and syphilis serology) were performed. Rapid urine drug screens assessed recent use of opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines. Naloxone (0.2–0.8 mg) was administered intramuscularly during screening to determine if individuals were currently physiologically dependent on opioids.

Participants were required to be physically and mentally healthy recreational users of prescription opioids between the ages of 21 and 55 years. Potential participants were excluded from the study if they were seeking treatment for their drug use, had chronic pain, or had a severe Axis I psychiatric diagnosis. Potential participants were also excluded if they were physiologically dependent on opioids, alcohol or illicit drugs, with the presence of physiological withdrawal used as the principal criterion. As compensation, participants were

paid \$25/day with a \$25/day bonus for completing the study. All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute (study # 6106).

Study Design

This within-subjects investigation was placebo-controlled and conducted under single-blind conditions. Participants who passed the physiological and psychological screening were maintained on PIO (or placebo) throughout the ≈ 7 –9 week study. For approximately 2–3 weeks participants were stabilized on each dose of PIO (0, 15, 45 mg) in ascending order. At the end of each maintenance period, the subjective, analgesic, physiological and cognitive effects of oral OXY (0 mg, 10 mg, 20 mg = cumulative dose of 30 mg) were examined. Cumulative dosing of opioids has been demonstrated to be an efficient and reliable strategy for assessing dose response within a single session. Data have also shown that cumulative opioid challenge drug dosing, conducted over time, produces reliable results with no evidence of habituation (45, 46, 47, 48, 49).

In its current clinical indications (diabetes mellitus type 2 and non-alcoholic steatohepatitis) a PIO effect typically takes 2 weeks to be observed (50). The dose order of PIO was not randomized due to the possibility of PIO carryover effects among the conditions. Although the current design also allows for the possibility of carryover effects, in this case they would have increased our likelihood of seeing a signal of PIO's effects. As the first clinical investigation into this drug for this indication, the investigators thought the latter was more important. The study was conducted on an outpatient basis with participants making 3–5 daily visits per week to the New York State Psychiatric Institute to receive study medication (administered and observed by a research nurse), provide a urine sample, and complete various study questionnaires (described below). Laboratory tests for blood glucose, liver function, and complete blood count, were performed weekly. Participants were provided with take-home PIO doses over the weekend, with pill counts and compliance assessments performed at each study visit. On the day of the lab session, participants were required to have not used alcohol recently (confirmed by breathalyzer) and provide a negative drug urine toxicology (Utox) the day of the lab session. Some exceptions were made for marijuana, because it remains detectable in the urine for such a long duration, as long as the reported use was not recent (within 2 days) based on self-report, and the participant appeared not to be acutely intoxicated. No other exceptions were made, and no lab sessions needed to be rescheduled due to the presence of other drugs of abuse.

The subjective effects of OXY (cumulative dose of 30 mg) were tested under each PIO maintenance condition. The daily maintenance dose of PIO was given on the day of the session 45 min prior to the OXY challenge doses (Table 1). Laboratory sessions typically began at 1000 hrs and took approximately 5–6 hours to complete. After the lab session, participants completed a field sobriety test and were sent home via a taxi or car service.

Maintenance Phase Monitoring and Measures

During each outpatient visit, participants met with a research assistant and a nurse for study medication dispensing and monitoring (described below). Participants completed a number

of assessments of: general health, PIO side effects, and outpatient drug use. Participants generally completed 3–5 study visits per week. Participants were given take-home doses over the weekends, and for days that they did not appear at NYSPI for an outpatient visit. Participants were instructed to bring all of their study medication to each outpatient visit so that pill counts could be conducted by a research nurse in order to evaluate medication compliance.

Adverse medication effects were assessed at each visit using the SAFTEE (51). The SAFTEE queries participants concerning up to 30 possible adverse events (e.g., fever, gas, insomnia, palpitations, dry mouth, etc. ...) and rates their: severity (1=mild, 2=moderate, 3=severe), relationship to study medication, any action taken by medical staff, and outcome. At each visit nurses also measured body weight, and drew blood weekly for blood chemistry (LFT, CBC, blood glucose, and BMP). After meeting with the nurse, participants provided a urine sample for 11-panel DrugCheck® urine dipstick analysis (w/pregnancy test). They also completed the Alcohol Use Disorders Identification Test (AUDIT-C) to assess alcohol use during the preceding week (52), a locally derived assessment of the type and frequency of other recreational drug use, and assessment of drug craving (opioids, alcohol, marijuana and tobacco) from ‘Not at all’ (0 mm) to ‘Extremely’ (100 mm).

Laboratory Session Measures

Subjective Effects—Two questionnaires were used to assess subjective drug effects and opioid withdrawal symptoms. A Visual Analog Scale (VAS) was used to assess subjective and physiological drug effects such as “I feel a good drug effect” and “I feel high”. Participants rated each item on the scale from ‘Not at all’ (0 mm) to ‘Extremely’ (100 mm). The second questionnaire was a modification of the Single Dose Questionnaire, which assessed for the presence of a number of potential drug effects by indicating “1” for True, or “2” for False (53, 54).

Analgesic Effects—The analgesic effects of OXY were evaluated with experimentally induced pain using the cold pressor test (CPT), a commonly used and well-established model for producing pain (55). Crushed ice was added to a cold tank, and warm water was placed in a warm tank. The temperature was maintained at 4°C in the cold tank (additional ice was added, if necessary) and 37°C in the warm tank. Each participant was asked first to immerse the hand in the warm tank for 2 min (to equalize baseline skin temperature across participants). Next, they were asked to immerse the same hand in the cold tank for up to 2 min. Standard instructions were read to each participant before administration of the CPT. During the cold water immersion, subjective ratings of pain were measured. Immediately following the CPT, subjective ratings of pain again were measured using the MPQ (CPT-MPQ) and the Pain Intensity/Bothersome Scales (‘Not at all’ (0) to ‘Extremely’ (10)) during which participants were asked to rate the ‘Intensity’ and ‘Bothersomeness’ of the acute pain experienced during immersion in cold (4°C) water during the CPT. Objective dependent measures included: pain threshold (time in seconds to the first report of pain) and pain tolerance (time until removal of the hand from water).

Physiological Measures—Miosis was assessed as a physiological indicator of mu agonist effects using a NeurOptics™ Pupillometer (Neuroptics INC. Irvine, CA) under ambient lighting conditions. For safety, a pulse oximeter continuously monitored oxygen saturation (%SpO₂) during sessions, while respiration (breaths per minute), heart rate, and blood pressure (systolic and diastolic) were measured and recorded every 5 minutes. Supplemental oxygen was also provided throughout the session.

Pharmacokinetic Measures—Oxycodone plasma concentrations (ng/ml) were assessed throughout the lab session (Table 1). Blood (≈8 ml/sample) was collected from an intravenous catheter into tubes containing 15% EDTA and centrifuged. Blood samples collected at +165 minutes post PIO dosing were used to assess PIO levels. Plasma was separated from blood and frozen at −70°C. Frozen plasma samples were batched and transferred to the Analytical Psychopharmacology Laboratories at the Nathan Kline Institute for analysis.

Drugs

Pioglitazone tablets (15 mg) were provided by the OMEROS Corporation (Seattle, WA). Each daily dose consisted of 3 capsules of active drug and/or lactose-filled placebo, depending on the final target dose (e.g. 45 mg = 3 × 15 mg tablets; 15 mg = 1 × 15 mg tablet + 2 placebo tablets; 0 mg = 3 placebo tablets). During weekly study visits, the 3 tablets were administered to participants by a research nurse. For weekend dosing, participants were provided with a separate bottle that contained the 3 tablets for each day. Back-up doses were also provided in this manner, in case participants missed a study visit. All drug over-encapsulation and packaging was performed by the New York State Psychiatric Institute Pharmacy.

Oxycodone HCL tablets (5 mg) were purchased from TYCO Healthcare (Princeton, NJ). For blinding, tablets were over-encapsulated and participants were given 4 capsules consisting of active drug and/or lactose-filled placebo.

Naloxone HCl (Narcan) for IM injection was obtained from the International Medication System Limited Amphastar (South Elmonte, CA).

Statistical Analyses

Continuous and categorical demographic variables and adverse events reports were summarized descriptively. Regarding data collected during the maintenance phases, univariate analyses of variance (ANOVA) tests were employed to examine changes in drug use and drug craving as a function of PIO maintenance dose (summed across each of the 3 periods). When analyzing the data from the lab sessions, a repeated-measures ANOVA was used to compare the time course of drug effects over the various time points throughout the session for each of the PIO maintenance doses (Main effects: PIO Dose & Time). Because of the cumulative dosing procedure, this analysis allowed the investigators to evaluate the overall influence of PIO on the effects of the cumulative OXY dose (30 mg). In order to examine the effects of PIO on each individual OXY (0, 10, 30 mg) dose, planned comparisons were used to assess maximal drug effect (peak=increase or trough=decrease)

within the timeframe immediately prior to the next oxycodone administration. These planned comparisons of PIO dose failed to reveal any significant effects, and thus, for the sake of brevity were not included in this report. An α of $p < 0.05$ was considered statistically significant, while $p < 0.10$, was considered as trending towards significance. All data analyses were performed using SPSS version 18 (56) and SuperANOVA (57).

Results

Participants

Between October, 2010 and August, 2013, 32 participants were enrolled into the study. Fifteen participants either voluntarily withdrew from the study or were dropped by the investigators due to a number of factors including: elevated liver function tests ($n = 1$), vasovagal episode during the lab session ($n = 2$), becoming opioid dependent during outpatient phase ($n = 1$), pulmonary embolism ($n = 1$, determined to be unrelated to the study), difficulty interacting with staff ($n = 1$), missing too many outpatient visits ($n = 7$) and misrepresenting age or drug use history ($n = 2$). Complete data sets were obtained from 17 participants for inclusion in this analysis. The average age of the participants was 35.0 years (± 9.0), including 15 men and 2 women. The racial breakdown of the completers was as follows: 8 African-American /Black, 4 Caucasian/White, 3 Multiracial, 1 Native-American or Alaskan, 1 not reported). Ethnically, 5 of the 17 completers considered themselves to be Hispanic/Latino.

All participants had recent histories of recreational use of Rx opioids (within the last year). The majority of participants used Rx opioids on a “Weekly” basis ($n = 9$), followed by “Monthly” use ($n = 4$), “Less than Monthly” ($n = 3$) and daily ($n = 1$, opioid use may have been over reported, since naloxone challenge indicated the participant was not physiologically dependent). All participants abused Rx opioids orally, with the exception of 2 who used via oral and intranasal routes. The mean duration of recreational opioid use was 4.1 years (± 3.5). In addition to their opioid use, 70% ($n = 12$) of the participants reported occasional alcohol use (weekly-monthly, ave 4.4 drinks/month), 56% ($n = 9$) were regular marijuana users (4 daily, 2 weekly, 3 monthly), 41% ($n = 7$) were regular tobacco smokers (daily-weekly use), and 30% used stimulants (cocaine or amphetamines) sporadically (monthly or less). The use of heroin, sedatives (benzodiazepines or barbiturates), club drugs (ecstasy, GHB, ketamine) and hallucinogens (LSD or PCP) was rare among this sample.

Maintenance Phase Measures

Prior to completing the OXY challenge testing, participants were maintained on PIO 0 mg for an average of 14.4 days (± 3.1), PIO 15 mg for 16.2 days (± 2.8) and PIO 45 mg for 15.6 days (± 3.2). Variability in dosing duration was the result of accommodation for scheduling (e.g., holidays and weekends) and participant variables (e.g., availability for scheduling sessions). The adverse events judged to be “possibly” related to the study medication and reported by multiple participants were: GI upset, gas, fatigue and drowsiness. The severity of these symptoms was rated as “mild to moderate.” Adverse effects reported less regularly included chills and sweating. During the maintenance phases, mean VAS ratings for “I Want: Opioids, Alcohol, Marijuana and Tobacco,” failed to significantly differ as a function of PIO

maintenance dose (Table 2). Additionally, the number of positive drug UTox samples and breathalyzer tests did not differ significantly across the three PIO maintenance phases.

Lab Session Measures

Positive Subjective Effects—VAS assessments of positive subjective effects including: “Liked the Choice (Figure 1: Upper Panel),” “High,” “Good Effect,” “Quality,” “Stimulated,” and amount participants “Would Pay” for the drug, increased as a function of Time (p 's < 0.001). For all measures, the maximal drug effect was observed between 180 and 210 minutes (i.e. ratings increased as a function of increasing OXY dose). For none of these measures was there a significant main effect of PIO dose, and no PIO X Time interaction. This same pattern of results was found for the ARCI measures of: “I Feel:” “High,” “Relaxed,” and “Drunken,” (Time, p 's < 0.05), and again with the more general indicators of drug effect, VAS “Potent,” and “Sedated” (p 's < 0.001).

Negative Subjective Effects—VAS ratings of “Irritable” significantly increased later in the session (Time, $p < 0.01$). In contrast, VAS ratings of overall “Bad Drug Effect” were minimal throughout the laboratory session, although the main effect of Time did approach significance ($p = 0.07$, shown in Figure 1: Lower Panel). ARCI ratings of “I Feel Nervous” did not significantly vary as a function of Time or PIO dose. None of these ratings varied as a function of PIO maintenance dose and no interaction was found. Significant drug effects were found on subjective measures of gastrointestinal (GI) upset. ARCI measures of “Turning Stomach,” and VAS assessment of “Nauseous” increased as the session progressed (Time, p 's < 0.001). Again, no effect of PIO or interaction was found on these measures.

Other Drug Effects—Assessments of: “Mellow,” “Restless,” and “Sleepy,” increased as a function of Time ($p < 0.001$, $p < 0.01$, & $p < 0.001$; respectively) but there were no significant main effects of PIO dose, and no PIO X Time interactions. There were no significant findings (Time, PIO, PIO X Time) on assessments of: “Alert,” “Anxious,” “Depressed,” “Energetic,” “Gooseflesh,” “Muscle Pain,” or “Talkative.”

Experimental pain/CPT—ANOVA revealed that as the laboratory session progressed (and the OXY dose increased) there were significant increases in the analgesic effects of oxycodone. Active doses of oxycodone doubled latency of participants to withdraw their hand from 4° water ($p < 0.001$, Figure 2: Upper Panel) and latency to report feeling pain ($p < 0.001$), while significantly decreasing self-reported “Bothersomeness” of the pain ($p < 0.01$). These ratings did not vary as a function of PIO maintenance dose.

Physiological Effects—The average pupil diameter, heart rate and breaths per minute decreased significantly as the session progressed (Time: $p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). However, no influence of PIO, or PIO x Time interactions were found.

Pharmacokinetic Measures—Mean plasma oxycodone levels significantly increased as function of Time ($p < 0.001$), but no effects of PIO or interactions were found (Figure 2, Lower Panel). Analysis of plasma samples also revealed that significantly higher levels of

plasma PIO were achieved following active PIO maintenance periods vs placebo periods (Shown in Table 2, $p < 0.01$).

Discussion

The current study sought to determine whether pioglitazone, a PPAR γ agonist and glial modulator, would alter the effects of oxycodone. In our sample of non-dependent recreational prescription opioid users, oral OXY produced typical mu opioid agonist effects, including miosis, decreased pain perception and respiratory rate, and mild cognitive impairment. Oxycodone also produced dose-dependent increases in reports of positive subjective effects with relatively minimal aversive effects. This subjective profile (which included mild GI upset) is similar to what has been previously reported by comparable participant samples (59, 60, 61). These data, once again, demonstrate the abuse potential common to most opioid analgesics, exemplifying the need to develop ways to alter these effects in order to deter recreational use that often leads to abuse and dependence (62). Unfortunately, our data revealed that an approximately 2-week period of PIO maintenance had no observable influence on the subjective, cognitive, analgesic, or physiological effects of OXY. Moreover, drug craving and recreational drug use did not vary as a function of PIO during the outpatient periods in between the testing sessions.

Pioglitazone dosing parameters (duration and mg amounts) were based on its clinical utility for treating diabetes, though these may not be related to its effects on glia (63). Although robust plasma concentrations of PIO were achieved, the lack of an observable PIO x OXY interaction may have been due to an inability of our dosing parameters to reduce levels of inflammatory markers. Unfortunately, the investigators did not include a measure of glial activation to test this hypothesis. The most relevant measurements of inflammatory markers would come from cerebrospinal fluid (CSF) but performing spinal taps on our participants would have significantly increased the risks associated with the study, and would have not been well-tolerated (64). Although measurements of inflammatory markers can also be found in plasma samples, previous research has demonstrated that plasma levels of inflammatory markers cannot be used to identify relative changes in the CSF (65).

The results of this study may also have varied if an opioid-dependent sample had been employed. According to the theory of opioid-induced glial activation and neuroinflammation; chronic opioid (ab)users may have higher tonic levels of glial activity upon which PIO could act (17, 29, 66). The use of a nondependent sample may also explain why the results of the current study are discrepant with preclinical studies on the efficacy of PIO for this purpose (39). Animal models may reflect a more severe state of opioid dependence.

In light of the present data, we must also consider the possibility that the opioid effects studies here may not be modulated by its actions on glial cells. As previously mentioned, there is an alternative body of literature arguing that opioids are immunosuppressive. According to this dissenting opinion, the logic behind the proposed clinical utility of an opioid + glia inhibitor combination is flawed. Therefore, the lack of an interaction observed in the current study would be consistent with this line of research (16, 67). Due to the

primary limitation of this study (i.e., lack of a measure of glial activity), what the current data adds to this debate is limited.

The primary limitation of this study (i.e., lack of a measure of glial activity) reflects the difficulty in performing this type of animal-to-human translational research. Specifically, no viable tools are available in clinical settings to confirm the mechanism by which glial modulators, such as ibudilast, minocycline, or pioglitazone, may be producing their effects. Although, within the current parameters, PIO failed to alter the subjective effects of OXY, it may be more effective in treating other forms of drug dependences. PPAR agonists have been shown to decrease ethanol consumption, ethanol-seeking and reduce withdrawal severity and susceptibility to stress-induced relapse in rodents (68, 69, 70).

Although PIO failed to alter the abuse liability of OXY under the current parameters, the interaction between glia and opioid receptors is not well understood. Other glial modulators acting through different mechanisms may show more promise. The prevalence and serious adverse consequences of opioid abuse make it imperative that we continue to investigate novel interventions such as this.

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Figure 1. Mean ($\pm$ SEM) Visual Analog Scale (VAS) ratings of “Liked the Drug” and “Bad” drug effect, shown as a function of each preceding PIO maintenance condition ($n=17$).

Figure 2. Mean ($\pm$ SEM) amount of time participants ($n=17$) kept their hand immersed in cold water (4° C), and plasma oxycodone concentration (ng/ml), shown as a function of each preceding PIO maintenance condition.

Table 1**Laboratory Session Events**

Time points at which physiological, plasma, performance and subjective assessments were made throughout the testing session.

Time (min)	Event
–30	Begin continuous physiological monitoring, pupils, subjective effects, CPT, performance battery
0	Pioglitazone or Placebo
15	Subjective effects, pupils,
30	Subjective effects, pupils, blood, CPT
45	OXY 0 mg, PO
60	Subjective effects, pupils,
75	Subjective effects, pupils, blood, CPT
90	OXY 10 mg, PO: Subjective effects, pupils
105	Subjective effects, pupils,
120	Subjective effects, pupils, blood
135	OXY 20 mg, PO (cumulative dose of 30 mg): Subjective effects, pupils
150	Subjective effects, pupils,
165	Subjective effects, pupils, blood, CPT
180	Subjective effects, pupils, blood, CPT,
195	Performance battery
210	Subjective effects, pupils, CPT
255	Subjective effects, pupils, performance battery, CPT
315	Subjective effects, pupils, blood, CPT, performance battery

Table 2**Mean Maintenance Phase Measures**^a

Results of various study measures collected during the 3 PIO maintenance periods leading to laboratory testing.

	PIO 0 mg	PIO 15 mg	PIO 45 mg	F Value	Sig.
	Mean (SD)	Mean (SD)	Mean (SD)		
I Want Rx Ops (0-100)	6.4 (9.7)	3.9 (8.6)	4.2 (9.3)	1.4	0.9
I Want Marijuana	12.8 (28.2)	12.3 (21.1)	9.4 (15.9)	1.1	0.85
I Want Alcohol	5.1 (24.4)	4.5 (12.5)	3.3 (10.3)	0.79	0.78
I Want Tobacco	11.9 (27.8)	13.4 (23.0)	9.5 (16.9)	0.66	0.74
# of Opioid + UTtox ^b	0.71 (0.88)	1.1 (0.5)	1.3 (0.8)	0.74	0.47
# of Cocaine + UTtox ^b	2.0 (1.9)	3.6 (2.2)	3.8 (1.9)	0.32	0.22
Plasma PIO ^c (ng/ml)	0.0 (0.0)	514 (257)	1155 (514)	9.65	0.001

^a Only positive samples for cocaine, opioids, oxycodone and THC were found. THC is unreported because the drug's persistence in urine samples significantly confounds estimating separate positive samples.

^b Mean taken only from those participants who tested positive.

^c Obtained during the lab session following each maintenance/stabilization phase.