HHS Public Access

Author manuscript

Addiction. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Addiction. 2017 October ; 112(10): 1861–1868. doi:10.1111/add.13868.

PPAR-gamma agonist pioglitazone modifies craving intensity and brain white matter integrity in patients with primary cocaine use disorder: A double-blind randomized controlled pilot trial

Joy M. Schmitz, Ph.D.[1], **Charles E. Green, Ph.D.**[1,2], **Khader M. Hasan, Ph.D.**[1], **Jessica Vincent**[1], **Robert Suchting, Ph.D.**[1], **Michael F. Weaver, M.D.**[1], **F. Gerard Moeller, M.D.**[3], **Ponnada A. Narayana, Ph.D.**[1], **Kathryn A. Cunningham, Ph.D.**[4], **Kelly T. Dineley, Ph.D.**[4], and **Scott D. Lane, Ph.D.**[1]

[1]McGovern Medical School, University of Texas Health Science Center at Houston

[2]UT-Houston Center for Clinical Research & Evidence-Based Medicine

[3]Virginia Commonwealth University

[4]Center for Addiction Research, University of Texas Medical Branch, Galveston

Abstract

Background and aims—Pioglitazone (PIO), a potent agonist of PPAR-gamma, is a promising candidate treatment for cocaine use disorder (CUD). We tested the effects of PIO on targeted mechanisms relevant to CUD: cocaine craving and brain white matter (WM) integrity. Feasibility, medication compliance, and tolerability were evaluated.

Design—Two-arm double-blind randomized controlled proof-of-concept pilot trial of PIO or placebo (PLC).

Setting—Single-site outpatient treatment research clinic in Houston, Texas, USA.

Participants—Thirty treatment-seeking adults with CUD. Mean [standard deviation (SD)] age was 47.8 (7.45), education was 12.7 (1.5), with 19.3 (7.8) years of reported cocaine use. Eighteen of the 30 participants (8=PIO; 10=PLC) completed diffusion tensor imaging (DTI) of WM integrity at pre/post-treatment.

Intervention—Study medication was dispensed at thrice weekly visits along with once weekly cognitive behavioral therapy for 12 weeks.

Measurements—Measures of target engagement mechanisms of interest included cocaine craving assessed by the Brief Substance Craving Scale (BSCS), the Obsessive Compulsive Drug Use Scale (OCDUS), a visual analog scale (VAS), and change in WM integrity. Feasibility

Correspondence concerning this article should be addressed to Dr. Joy M. Schmitz, Ph.D., Center for Neurobehavioral Research on Addiction, Department of Psychiatry & Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center – Houston, 1941 East Road, Houston, TX 77054. Telephone: 713-486-2867; Joy.M.Schmitz@uth.tmc.edu.

Conflict of Interest Declaration: None

CT.gov: NCT02774343

measures included number completing treatment, medication compliance (riboflavin detection), and tolerability (side effects, serious adverse events).

Findings—Target engagement change in mechanisms of interest, defined as a ≥ 0.75 Bayesian posterior probability of an interaction existing favoring PIO over PLC, was demonstrated on measures of craving (BSCS, VAS) and WM integrity indexed by fractional anisotropy (FA) values. Outcomes indicated greater decrease in craving and greater increase in FA values in the PIO group. Feasibility was demonstrated by high completion rates among those starting treatment (21/26 = 80%) and medication compliance (≥ 80%). There were no reported serious adverse events for PIO.

Conclusions—Compared with placebo, patients receiving pioglitazone show a higher likelihood of reduced cocaine craving and improved brain white matter integrity as a function of time in treatment. Pioglitazone shows good feasibility as a treatment for cocaine use disorder.

Keywords

Cocaine use disorder; PPAR-gamma; pioglitazone; target engagement; craving; white matter integrity; Bayesian statistics

INTRODUCTION

Over 3 million people worldwide stand to benefit from the development of safe and effective medications for the treatment of cocaine use disorder (CUD) (1, 2). Left untreated, individuals with CUD are more likely to incur societal and economic costs, especially related to hospitalization and emergency department visits (3). Advances in our understanding of key neurobiological mechanisms associated with chronic cocaine use have moved the field beyond classic neurotransmitter systems toward novel targets for the development of medication treatments (4). One emerging target for the treatment of CUD and other drug use disorders is the peroxisome proliferator-activated receptor (PPAR) pathway (5).

The PPARs constitute a family of nuclear receptor transcription factors that modulate gene expression involved in key cell functions, including metabolism and inflammation (6). Activation of the PPAR gamma (PPAR-γ) isoform is the mechanism of action used in therapy to treat type-2 diabetes (7, 8). Importantly, PPAR-γ agonists exert a wide range of anti-inflammatory and anti-oxidative effects that have been shown to promote neuroprotection in models of neurodegenerative diseases such as Parkinson's and Alzheimer's disease (9–11).

Current data suggest at least two mechanisms through which PPAR-γ agonists may affect CUD. First, PPAR-γ activation enhances cognition by modulating extracellular signal-regulated kinases (ERK), a protein involved in hippocampal learning and memory consolidation, including memories for drug cues (12, 13). Recently, the PPAR-γ agonist pioglitazone (PIO) was shown to attenuate cocaine cue reactivity in rats; an effect that was accompanied by normalization of ERK activity in the medial prefrontal cortex (PFC) and hippocampus (14). Second, PPAR-γ activation may confer neuroprotection against drug-induced neurotoxicity. Evidence for cocaine neurotoxicity comes from many different forms

of neuroimaging (15, 16), one of which is white matter (WM) integrity as measured by diffusion tensor imaging (DTI). Multiple studies, both preclinical (17, 18) and human (19–21) show impaired WM integrity is associated with functional consequences, including impulsivity (19), decision making (22) and relapse (23). Importantly, emerging evidence implicates WM integrity across a range of psychiatric disorders and cognitive processes relevant to addiction (24, 25). Based on (1) modulation of cocaine cue reactivity in animal models via PPAR-γ agonism, and (2) evidence for neuroprotective effects of PPAR-γ agonism, we sought to identify analogous effects of PIO treatment in individuals with CUD.

Here we define target engagement as the ability of treatment to exact change on key mechanisms of interest underlying a particular disorder. Beyond the prototype measure of receptor occupancy, biobehavioral domains linked to other aspects of treatment efficacy, such as cocaine craving and WM integrity proposed here, have been recognized as targetable mechanisms (26, 27). Consistent with this experimental therapeutics approach (26), the aims of this study were to (1) compare PIO with placebo (PLC) on change in measures of cocaine craving intensity and WM integrity; and (2) compare PIO with PLC on measures of feasibility, including retention, medication compliance, and tolerability. While this project was not designed or powered as a test of clinical efficacy, measures of cocaine use were collected for exploring potential clinical outcomes.

METHODS

Design

We conducted a 12-week, two-arm, double-blind, randomized controlled pilot trial of PIO versus PLC on measures of craving and WM integrity as indexed by fractional anisotropy (FA) value (ClinicalTrials.gov identifier: NCT02774343). In keeping with recommendations of Leon et al (28), sample size for this pilot trial was based primarily on pragmatics of recruitment and the necessities for examining feasibility. We pre-specified and planned to conduct a Bayesian final analysis to obtain probability estimates of effect sizes along with uncertainty. We did not plan to conduct any significance testing and as such, power analysis was not warranted.

Participants

Major inclusion criteria were age (18 – 60 years old) and meeting DSM-IV criteria for cocaine dependence (29). Patients with current dependence on any drug except cocaine, alcohol, nicotine, and cannabis were excluded. Physiological dependence on alcohol requiring medical detoxification was exclusionary. Patients with medical conditions contraindicating PIO pharmacotherapy or using medications that would adversely interact with PIO were excluded, as were medical contraindications to MRI scans (see Appendix S1).

Procedures

Eligible subjects underwent a 1-week baseline period to obtain pretreatment measures of target domains. Randomization was performed by the blinded study coordinator using a standard random number generator as programmed using SAS 9.3. Following

randomization, subjects assigned to PIO underwent a two-week dose titration period until reaching the target dose of 45 mg/d by Week 3. Subjects assigned PLC received identical capsules on the same schedule. Thrice weekly attendance during treatment included cognitive-behavioral therapy 1 hour per week and prize-based contingency management for attendance.

Measurement of Target Domains

Craving—On a weekly basis, patients completed the Brief Substance Craving Scale (BSCS)(30) and the Obsessive Compulsive Drug Use Scale (OCDUS) in the treatment clinic (31). Every two weeks, visual analog scale ratings of craving (VAS craving) consisting of 100 mm line, anchored by 0 “not at all” and 100 “extremely,” were used to assess cocaine craving right now, craving on average in the past week, and the worst craving in the past week. Data were analyzed as a total score across the three questions.

White matter integrity—DTI scans were acquired on a Philips Integra 3T magnet (parameters in the Appendix S2). DTI analysis, including segmentation and regions of interest (ROI) determination, followed atlas-based methods and quality assurance protocols for serial stability (32–34). These methods, critical in small-N samples, are ordered, anchored for motion and stability, and alternating to reduce cross terms and maximize signal-to-noise. Due to incidental finding of a brain abnormality (N=1), and scanner maintenance interruption (N=1), only 18 subjects were scanned at both pre- and post-treatment (10 = PLC, 8 = PIO). ROI analyses of FA focused on WM ROI based on several previous studies of WM integrity in cocaine dependence: (1) commissural fibers: the genu and splenium of corpus callosum (CC); (2) projection fibers: the anterior and posterior thalamic radiations; and (3) association fibers: the cingulum and the external capsule (18, 19, 22, 23, 35, 36).

Feasibility Measures

Treatment retention was determined by clinic visit attendance and total number of study weeks completed. Medication adherence was determined by urinary riboflavin levels (37) and self-reports of taking capsules. Medication safety assessments included adverse event (AE) reports and weekly rating scale for side-effects.

Cocaine use Measures

Urine samples collected at each visit were analyzed for benzoylecgonine at a concentration of 300ng/mL. Self-reported cocaine use throughout the study period was assessed using a modified Timeline Followback (TLFB) procedure (38).

Statistical analyses

Descriptive statistics were used to summarize baseline characteristics of the sample. All analyses were conducted on a modified intent-to-treat sample of randomized participants who received at least one capsule (per-protocol; 14 = PLC, 12 = PIO). Multilevel models were used to test the interaction of time and treatment on craving and cocaine use outcomes, while regression models for residual change scores were used for DTI outcomes. Simple

effects and the posterior probabilities that these effects existed were performed as follow-up tests for interpreting interactions. Statistical analyses were performed using SAS 9.3, R 3.1.1 (R Core Team, 2016), and OpenBUGS 3.0 (2007).

Bayesian statistical reasoning was used to quantify the evidence for change in mechanisms of interest (target engagement). This approach is recommended over conventional Frequentist statistics in the context of hypothesis testing in decisions to carry forward the development of a candidate medication based on target engagement (39–42). Bayesian statistics provide a direct estimate of the probability of the alternative hypothesis (H1) existing, given the data. Here we defined H1 as a treatment group-by-time effect, favoring PIO over PLC. A posterior probability of ≥ 0.75 for the existence of an effect was considered sufficient evidence to warrant further investigation. This reasoning is consistent with previous probability thresholds stipulated for decision-making in existing medication trials; these thresholds were chosen *a priori* (43–47). Vague, neutral priors were used to maximize the influence on the posterior estimates (see Appendix S3).

RESULTS

Sample description

Forty-two cocaine users were screened to obtain a sample of 30 subjects who were randomized to treatment (see Appendix S4 for CONSORT). The two groups were similar in demographic and substance use characteristics, as shown in Table 1. Most participants (n = 26, 86%) met diagnostic criteria for alcohol use disorder (AUD) as well.

Mechanisms of interest

Table 2 provides outcomes of the Bayesian analyses for the primary target variables and cocaine use outcomes (see Appendix S5 and S6 for corresponding tabular and graphic presentation of outcomes). For comparison purposes, Frequentist solutions to these models are provided in Appendix S7.

Craving—For the BSCS, there was a 0.97 posterior probability of a treatment by time interaction existing with simple effects indicating a high likelihood that for every additional week in treatment, craving was reduced by a factor of 0.24 for participants receiving PIO compared to 0.09 for participants receiving PLC. For the VAS, there was a >0.99 posterior probability of an interaction, with regression coefficients indicating a decrease in craving by a factor of 3.84 for PIO versus 1.34 for PLC for every additional biweekly period in treatment.

WM integrity—Table 2 provides outcomes of Bayesian analyses on WM integrity as measured by fractional anisotropy (FA) values. Across the specified ROIs, four regions revealed a Bayesian posterior probability > 0.75 bilaterally of PIO after controlling for baseline FA values: the genu of the CC (gCC = 0.99), the splenium of the CC (sCC = 0.99), the anterior thalamic radiation (left ATR = 0.95, right ATR = 0.96), and the posterior thalamic radiation (left PTR = 0.99, right PTR = 0.98). Controlling for baseline FA, gCC, sCC, ATR, and PTR FA values increased from week 0 to week 12 in PIO (positive *b*

parameter estimates) relative to PLC. Probabilities across hemispheres for the cingulum and external capsule (EXTC) did not meet the posterior probability threshold, with the exception of the left hemisphere of the EXTC.

Cocaine use

On the TLFB, there was a 0.99 posterior probability of an interaction, with simple effects indicating a 0.99 posterior probability of a reduction in the odds of reporting cocaine use for every additional day in treatment for PIO (O.R. 0.74, 95% CrI = 0.66–0.85) relative to an 89% posterior probability for PLC (O.R. 0.94, 95% CrI = 0.84–0.1.04). For cocaine positive urines, there was a 0.75 posterior probability of an interaction existing, with a greater chance of having decreased cocaine-positive urines in PIO (Posterior Probability = 0.36, O.R = 1.05, 95% CrI = 0.45–1.47) versus PLC (Posterior Probability = 0.10, O.R = 1.24, 95% CrI = 0.88–1.78).

Feasibility

Regarding retention, 30 subjects enrolled and four (PLA, n = 1; PIO, n = 3) dropped out of the trial before starting medication. Of the 26 subjects who started treatment, 21 (PLC, n = 11; PIO, n = 10) completed all 12 weeks (80%). Regarding medication adherence, mean compliance levels based on riboflavin were 95.4% (PLC) and 96.2% (PIO). Self-reported medication compliance was 86.9% (PLC) and 84.1% (PIO). The most frequently reported side effects were sleep disruption, diarrhea, stomach pain, cough, and increased urination; all rated mild (see Appendix S8).

DISCUSSION

The results of this study provide preliminary evidence of therapeutically targetable mechanisms of PIO. For patients with CUD, there was a > 75% posterior probability that PIO conferred benefit over PLC in reducing cocaine craving over a 12 week treatment period. This effect was found on two commonly used brief self-report measures (BSCS, VAS). On the second target domain of WM integrity, we found evidence suggesting that PIO improved FA value versus PLC by the end of treatment. Findings also provide evidence that PIO can be applied in a CUD population with adequate acceptability and tolerability.

Target domains (craving and WM integrity) in this proof-of-principle study were selected based on prior work suggesting these domains might be modifiable by PIO. Specifically, craving is a well-known trigger of relapse (48, 49), and stress induces heightened reactivity and craving to drug cues thereby increasing relapse risk (50–52). Notably, PIO was effective in reducing drug intake in a preclinical model of stress-induced relapse (53). Thus, one avenue to reduced craving in the PIO group may be via decreases in stress-induced craving. We posit that this will be an important mechanism to examine in future work.

More than a decade of preclinical and human research shows an association between chronic cocaine exposure and alterations in WM integrity. These alterations may have functional consequences associated with impulsivity (19, 54), decision making (22), and time to relapse (23). Notably, WM alterations are emerging as key factors in impaired cognitive functions and are prevalent in several psychiatric and neurological disorders, including addiction (24,

55). Because of the documented anti-inflammatory and potential neuroprotective effects of PPAR-γ agonists, multiple clinical trials are investigating PIO as a neuroprotective agent (56–61). Accordingly, we hypothesize that the change in FA values observed in the PIO group may correspond to improved cognitive and daily life functions. Comprehensive measurement of these variables and their association with changes in WM integrity provide key opportunities for further scientific progress.

This initial project was limited by several factors, including: (1) small sample size; (2) restricted measurement battery with regard to potential key variables (e.g., stress, inflammation, executive cognitive function, overall life/health function); (3) a sample of co-morbid CUD and AUD patients, obscuring the relative role of each substance in the outcomes (see Appendix S9 Alcohol Consumption); (4) examination of single dose (45 mg); (5) for the DTI data, the Bayesian parameter estimates of the variance in the simple effects may be underestimated (62, 63); and (6) the degree to which pioglitazone's therapeutic potential generalizes to other substances of abuse remains unknown.

Within the restriction of these limitations, the combined potential to attenuate craving and preserve WM integrity in individuals with CUD suggests PIO may have a role as a pharmacotherapy for CUD. One function may be as an adjunctive treatment to reduce risk for relapse during the critical early phase of recovery when craving is prominent, and in the context of preserved cognitive/life functioning, which can impede efforts to maintain drug abstinence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported in parts by NIDA P50 DA 009262 (JMS, FGM, SDL, PAN, CEG), P20 DA 024157 (KAC, KTD, FGM, SDL), NIDA K05 DA020087 (KAC) and by funds from the Center for Addiction Research at the University of Texas Medical Branch.

Disclosure: KAC is a consultant for Arena Pharmaceuticals.

References

1. Reboussin BA, Anthony JC. Is there epidemiological evidence to support the idea that a cocaine dependence syndrome emerges soon after onset of cocaine use? Neuropsychopharmacology. 2006; 31(9):2055–64. [PubMed: 16482089]
2. U.N. United Nations Office on Drugs and Crime: World Drug Report 2015: United Nations. 2015
3. SAMHSA. Drug Abuse Warning Network 2005 National Estimates of Drug-related Emergency Department Visits, DAWN Series D-29. Rockville, MD: 2007. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. DHHS Publication. No (SMA) 074-4256. 2007
4. Le Moal M, Koob GF. Drug addiction: pathways to the disease and pathophysiological perspectives. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2007; 17(6–7):377–93. [PubMed: 17169534]
5. Le Foll B, Di Ciano P, Panlilio LV, Goldberg SR, Ciccocioppo R. Peroxisome proliferator-activated receptor (PPAR) agonists as promising new medications for drug addiction: preclinical evidence. Current drug targets. 2013; 14(7):768–76. [PubMed: 23614675]

6. Michalik L, Auwerx J, Berger JP, Chatterjee VK, Glass CK, Gonzalez FJ, et al. International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. Pharmacological reviews. 2006; 58(4):726–41. [PubMed: 17132851]
7. Kersten S, Desvergne B, Wahli W. Roles of PPARs in health and disease. Nature. 2000; 405(6785): 421–4. [PubMed: 10839530]
8. Kersten S, Wahli W. Peroxisome proliferator activated receptor agonists. Exs. 2000; 89:141–51. [PubMed: 10997287]
9. Neher MD, Weckbach S, Huber-Lang MS, Stahel PF. New insights into the role of peroxisome proliferator-activated receptors in regulating the inflammatory response after tissue injury. PPAR research. 2012; 2012:728461. [PubMed: 22481914]
10. Feinstein DL. Therapeutic potential of peroxisome proliferator-activated receptor agonists for neurological disease. Diabetes technology & therapeutics. 2003; 5(1):67–73. [PubMed: 12725709]
11. Feinstein DL, Galea E, Gavrilyuk V, Brosnan CF, Whitacre CC, Dumitrescu-Ozimek L, et al. Peroxisome proliferator-activated receptor-gamma agonists prevent experimental autoimmune encephalomyelitis. Annals of neurology. 2002; 51(6):694–702. [PubMed: 12112074]
12. Denner LA, Rodriguez-Rivera J, Haidacher SJ, Jahrling JB, Carmical JR, Hernandez CM, et al. Cognitive enhancement with rosiglitazone links the hippocampal PPARgamma and ERK MAPK signaling pathways. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2012; 32(47):16725–35a. [PubMed: 23175826]
13. Lu L, Koya E, Zhai H, Hope BT, Shaham Y. Role of ERK in cocaine addiction. Trends in neurosciences. 2006; 29(12):695–703. [PubMed: 17084911]
14. Miller WR, Fox RG, Stutz SJ, Lane SD, Denner L, Cunningham KA, Dineley KT. PPAR gamma agonism attenuates cue reactivity during forced abstinence from cocaine self-administration. Addiction biology. In press.
15. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nature reviews Neuroscience. 2011; 12(11):652–69. [PubMed: 22011681]
16. Hanlon CA, Dufault DL, Wesley MJ, Porrino LJ. Elevated gray and white matter densities in cocaine abstainers compared to current users. Psychopharmacology (Berl). 2011; 218(4):681–92. [PubMed: 21691942]
17. Narayana PA, Ahobila-Vajjula P, Ramu J, Herrera J, Steinberg JL, Moeller FG. Diffusion tensor imaging of cocaine-treated rodents. Psychiatry research. 2009; 171(3):242–51. [PubMed: 19217266]
18. Narayana PA, Herrera JJ, Bockhorst KH, Esparza-Coss E, Xia Y, Steinberg JL, et al. Chronic cocaine administration causes extensive white matter damage in brain: diffusion tensor imaging and immunohistochemistry studies. Psychiatry research. 2014; 221(3):220–30. [PubMed: 24507117]
19. Moeller FG, Hasan KM, Steinberg JL, Kramer LA, Dougherty DM, Santos RM, et al. Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. Neuropsychopharmacology. 2005; 30(3):610–7. [PubMed: 15637640]
20. Ma L, Hasan KM, Steinberg JL, Narayana PA, Lane SD, Zuniga EA, et al. Diffusion tensor imaging in cocaine dependence: regional effects of cocaine on corpus callosum and effect of cocaine administration route. Drug Alcohol Depend. 2009; 104(3):262–7. [PubMed: 19595517]
21. Ma L, Steinberg JL, Keyser-Marcus L, Ramesh D, Narayana PA, Merchant RE, et al. Altered white matter in cocaine-dependent subjects with traumatic brain injury: A diffusion tensor imaging study. Drug Alcohol Depend. 2015; 151:128–34. [PubMed: 25841982]
22. Lane SD, Steinberg JL, Ma L, Hasan KM, Kramer LA, Zuniga EA, et al. Diffusion tensor imaging and decision making in cocaine dependence. PLoS One. 2010; 5(7):e11591. [PubMed: 20661285]
23. Xu J, DeVito EE, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. White matter integrity is associated with treatment outcome measures in cocaine dependence. Neuropsychopharmacology. 2010; 35(7):1541–9. [PubMed: 20393459]
24. Fields RD. White matter in learning, cognition and psychiatric disorders. Trends in neurosciences. 2008; 31(7):361–70. [PubMed: 18538868]

25. Silveri MM, Dager AD, Cohen-Gilbert JE, Sneider JT. Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. Neuroscience and biobehavioral reviews. 2016
26. Insel TR. The NIMH experimental medicine initiative. World psychiatry : official journal of the World Psychiatric Association. 2015; 14(2):151–3.
27. Riddle M. Science of Behavior Change Working G. News from the NIH: using an experimental medicine approach to facilitate translational research. Translational behavioral medicine. 2015; 5(4):486–8. [PubMed: 26622921]
28. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. Journal of psychiatric research. 2011; 45(5):626–9. [PubMed: 21035130]
29. A, PA. Diagnostic and Statistical Manual of Mental Disorders, fourth. American Psychiatric Association; Washington, DC: 2000.
30. Mezinskis JP, Honos-Webb L, Kropp F, Somoza E. The measurement of craving. J Addict Dis. 2001; 20(3):67–85. [PubMed: 11681594]
31. Lievaart M, Erciyes F, van der Veen FM, van de Wetering BJ, Muris P, Franken IH. Validation of the cocaine versions of the Obsessive Compulsive Drug Use Scale and the Desires for Drug Questionnaire. Am J Drug Alcohol Abuse. 2015; 41(4):358–65. [PubMed: 26010120]
32. Hasan KM, Lincoln JA, Nelson FM, Wolinsky JS, Narayana PA. Lateral ventricular cerebrospinal fluid diffusivity as a potential neuroimaging marker of brain temperature in multiple sclerosis: a hypothesis and implications. Magnetic resonance imaging. 2015; 33(3):262–9. [PubMed: 25485790]
33. Hasan KM, Moeller FG, Narayana PA. DTI-based segmentation and quantification of human brain lateral ventricular CSF volumetry and mean diffusivity: validation, age, gender effects and biophysical implications. Magnetic resonance imaging. 2014; 32(5):405–12. [PubMed: 24582546]
34. Keser Z, Hasan KM, Mwangi BI, Kamali A, Ucisik-Keser FE, Riascos RF, et al. Diffusion tensor imaging of the human cerebellar pathways and their interplay with cerebral macrostructure. Frontiers in neuroanatomy. 2015; 9:41. [PubMed: 25904851]
35. Kaag AM, van Wingen GA, Caan MW, Homberg JR, van den Brink W, Reneman L. White matter alterations in cocaine users are negatively related to the number of additionally (ab)used substances. Addiction biology. 2016
36. Lim KO, Wozniak JR, Mueller BA, Franc DT, Specker SM, Rodriguez CP, et al. Brain macrostructural and microstructural abnormalities in cocaine dependence. Drug Alcohol Depend. 2008; 92(1–3):164–72. [PubMed: 17904770]
37. Mooney M, Sayre LL, Green C, Rhoades H, Schmitz J. Comparing measures of medication taking in a pharmacotherapy trial for cocaine dependence. Addict Disord Their Treat. 2004; 3:165–73.
38. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. J Consult Clin Psychol. 2000; 68(1):134–44. [PubMed: 10710848]
39. West R. Using Bayesian analysis for hypothesis testing in addiction science. Addiction. 2016; 111(1):3–4. [PubMed: 26487081]
40. Green C, Schmitz J, Lindsay J, Pedroza C, Lane S, Agnelli R, et al. The influence of baseline marijuana use on treatment of cocaine dependence: application of an informative-priors bayesian approach. Front Psychiatry. 2012; 3:92. [PubMed: 23115553]
41. Green CE, Moeller FG, Schmitz JM, Lucke JF, Lane SD, Swann AC, et al. Evaluation of heterogeneity in pharmacotherapy trials for drug dependence: a Bayesian approach. Am J Drug Alcohol Abuse. 2009; 35(2):95–102. [PubMed: 19322730]
42. Beard E, Dienes Z, Muirhead C, West R. Using Bayes Factors for testing hypotheses about intervention effectiveness in addictions research. Addiction. 2016
43. Intrinsic reward sensitivity and smoking cessation with varenicline or patch NRT. [Internet]. NCT02162849.
44. Varenicline and combined NRT for initial smoking cessation and rescue treatment in smokers [Internet]. NCT02271919.
45. Ketamine for treatment resistant late-life depression [Internet]. NCT02556606.

46. Low reward sensitivity and behavioral activation therapy for smoking cessation [Internet]. NCT02697227.
47. Clinical trial of citalopram in cocaine dependence [Internet]. NCT01535573.
48. O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. The American journal of psychiatry. 2005; 162(8):1423–31. [PubMed: 16055763]
49. Serre F, Fatseas M, Swendsen J, Auriacombe M. Ecological momentary assessment in the investigation of craving and substance use in daily life: a systematic review. Drug Alcohol Depend. 2015; 148:1–20. [PubMed: 25637078]
50. Belin-Rauscent A, Fouyssac M, Bonci A, Belin D. How Preclinical Models Evolved to Resemble the Diagnostic Criteria of Drug Addiction. Biol Psychiatry. 2016; 79(1):39–46. [PubMed: 25747744]
51. Brady KT, Sinha R. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. The American journal of psychiatry. 2005; 162(8):1483–93. [PubMed: 16055769]
52. Sinha R, Shaham Y, Heilig M. Translational and reverse translational research on the role of stress in drug craving and relapse. Psychopharmacology (Berl). 2011; 218(1):69–82. [PubMed: 21494792]
53. Stopponi S, de Guglielmo G, Somaini L, Cippitelli A, Cannella N, Kallupi M, et al. Activation of PPARgamma by pioglitazone potentiates the effects of naltrexone on alcohol drinking and relapse in msP rats. Alcoholism, clinical and experimental research. 2013; 37(8):1351–60.
54. Romero MJ, Asensio S, Palau C, Sanchez A, Romero FJ. Cocaine addiction: diffusion tensor imaging study of the inferior frontal and anterior cingulate white matter. Psychiatry research. 2010; 181(1):57–63. [PubMed: 19959341]
55. Suckling J, Nestor LJ. The neurobiology of addiction: the perspective from magnetic resonance imaging present and future. Addiction. 2016
56. The effect of pioglitazone on neointima volume and inflammatory markers [Internet]. NCT00494559.
57. Pioglitazone hydrochloride in preventing radiation-induced cognitive dysfunction in treating patients with brain tumors [Internet]. NCT01151670.
58. NCT01931566 [Internet]. Biomarker qualification for risk of mild cognitive impairment due to alzheimer's disease and safety and efficacy evaluation of pioglitazone in delaying its onset.
59. AD-4833/TOMM40_303 Extension study of the saftey and efficacy of pioglitazone to slow cognitive decline in participants with mild cognitive impairment due to alzheimer disease [Internet]. NCT02284906.
60. Pioglitazone in alzheimer disease [Internet]. NCT00982202.
61. Neuroprotection of pioglitazone in acute ischemic stroke [Internet]. NCT02195791.
62. Gelman A. Prior distributions for variance parameters in hierarchical models. Bayesian Anal. 2006; 1(3):515–34.
63. Hox, JJ., Moerbeek, M., Van de Schoot, R. Multilevel analysis: Techniques and applications. 2. Routledge: Taylor & Francis; 2010.

Table 1

Sample demographic characteristics; N = 15 per group.

	Placebo		Pioglitazone	
Variable	**N**	**%**	**N**	**%**
Female	4	26.7	4	26.7
Race				
Black	7	46.7	12	80.0
White	4	26.7	3	20.0
Hispanic	3	20.0	0	0
Other	1	6.7	0	0
Employed	6	40.0	7	46.7
Alcohol use disorder	12	80.0	14	93.3
	Mean	SD	Mean	SD
Age	47.4	7.8	48.3	7.1
Education	12.8	1.1	12.6	1.9
Cocaine use (past 30 days)	13.9	9.0	18.2	11.8
Lifetime cocaine (years)	17.7	8.0	21.0	7.7
Alcohol use (past 30 days)	13.9	9.9	21.7	8.6
Lifetime alcohol (years)	22.3	12.2	23.9	13.1

Table 2

Summary of results from Bayesian statistical analyses of craving measures, cocaine use outcomes, and DTI outcomes.

Outcomes for Clinical variables	**Variable**					
	BSCS	**VAS**	**OCDUS**	**Cocaine use (TLFB)**	**Cocaine Use (UDS)**	
Post prob: Treatment × Time	0.97	>0.99	0.60	0.99	0.75	
Post prob: Simple Effect of Time (PIO)	p(b<0) > 0.99	p(b<0) > 0.99	p(b<0) = 0. 64	p(O.R. < 1) > 0.99	p(O.R. < 1) = 0.38	
Estimate: Simple effect of Time (PIO)	b = −0.24 (−0.36–−0.12)	b = −3.84 (−5.22–−2.46)	b = −0.07 (−0.45–0.30)	O.R. = 0.74 (0.66–0.85)	O.R. = 1.05 (0.75–1.47)	
Post prob: Simple effect of Time (PLC)	p(b<0) = 0.98	p(b<0) > 0. 99	p(b>0) = 0. 77	p(O.R. < 1) = 0.89	p(O.R. < 1) = 0.10	
Estimate: Simple effect of Time (PLC)	b = −0.09 (−0.18–−0.01)	b = −1.34 (−2.19–−0.51)	b = 0.15 (−0.25–0.55)	O.R. = 0.94 (0.84–1.04)	O.R. = 1.24 (0.88−1.78)	
Outcomes for DTI variables	**gCC FA**	**sCC FA**	**ATR FA** (hemisphere)	**PTR FA** (hemisphere)	**EXTC FA** (hemisphere)	**CING FA** (hemisphere)
Post Prob: Treatment Controlling for Baseline FA	0.99	0.99	0.93 (L) 0.93 (R)	0.98 (L) 0.97 (R)	0.93 (L) 0.52 (R)	0.68 (L) 0.54 (R)
Estimate of Simple of PIO	b = 25.96 (4.84–45.05)	b = 29.12 (6.52–51.92)	b = 12.59 (L) (−4.84–30.16) b = 13.83 (R) (−5.26–32.99)	b = 15.29 (L) (1.19–29.42) b = 15.96 (R) (−1.06–33.10)	b = 8.86 (L) (−3.09–20.87) b = 0.27 (R) (−9.53–10.06)	b = 4.29 (L) (−14.61–23.42) b = 1.26 (R) (−27.60–30.18)

Note. Post Prob = posterior probability; PIO = pioglitazone; PLC = placebo; p = probability; b = beta coefficient (with 95% credible intervals); O.R. = odds ratio. BSCS = Brief Substance Craving Scale; VAS = visual analog scale; OCDUS = Obsessive Compulsive Drug Use Scale; TLFB = Timeline Followback; UDS = urine drug screen; FA = fractional anisotropy value; gCC = genu of corpus callosum; sCC = splenium of corpus callosum; ATR = anterior thalamic radation; PTR = posterior thalamic radiation; EXTC = External Capsule; CING = Cingulate.

* Coefficients are in the log-form.