The exploration of pioglitazone's potential as a pharmacotherapy option for drug addiction

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ABSTRACT

Pioglitazone is a selective agonist for peroxisome proliferator-activated receptor gamma (PPAR γ) that is currently used for the treatment of type 2 diabetes mellitus. However, recent evidence suggests that the PPAR γ pathway may be a promising novel target for drug addiction therapy. There has been considerable evidence with preclinical models of addiction that support pioglitazone's therapeutic potential for opioid, alcohol, methamphetamine, and cocaine dependence. Although the precise mechanisms remain unclear, these preclinical studies suggest that pioglitazone blocks the excitation of ventral tegmental area dopamine signaling, which is associated with the addictive properties of abused drugs. Recently, clinical studies have also emerged to investigate the role of pioglitazone for drug addiction in humans. Clinical evidence supports preclinical findings that pioglitazone may indeed be beneficial for the treatment of cocaine dependence. Other clinical evidence suggests that pioglitazone may also be effective for nicotine addiction. Further clinical research is needed to investigate pioglitazone's effects in opioid, alcohol, and methamphetamine addiction. Pioglitazone also has a favourable and safe profile. These findings suggest that pioglitazone may be a novel treatment option for drug dependence in the future. Due to its status as a medication approved by the Food and Drug Administration, there is a potential for accelerated establishment of pioglitazone as an addiction treatment method.

INTRODUCTION

Pioglitazone is a widely used oral prescription medication for type 2 diabetes mellitus.¹ Pioglitazone belongs to the thiazolidinedione class of drugs and is a selective agonist of the nuclear transcription factor, peroxisome proliferator activated receptor gamma (PPAR γ).² PPAR γ signaling is implicated in the transcription of proteins involved in the metabolism of carbohydrates and lipids.³ Pioglitazone elevates the expression of these proteins that ultimately improves glycaemic control and insulin sensitivity.³ Clinical evidence suggests that the drug is effective in type 2 diabetes patients and that it has a safe tolerability profile.¹ In addition to its uses as an anti-diabetic medication, evidence suggests that pioglitazone can cross the blood-brain barrier and improve various neurological conditions.⁴⁻⁷

Current research suggests that PPAR γ agonists may be a promising novel treatment option for drug addiction treatment.⁸ Specifically, the therapeutic benefits of pioglitazone in drug addiction has been investigated in both preclinical and clinical experiments.^{2,9-16} The present review will investigate the current preclinical and clinical evidence supporting the therapeutic

potential of pioglitazone in the prevention of drug addiction development and relapse. This review will also explore the potential mechanisms underlying the anti-addictive properties of pioglitazone and its side effects.

OVERVIEW OF DRUG ADDICTION

Drug addiction is a chronic condition where sufferers experience compulsive desires for a drug and demonstrate persistent drug-taking behaviour despite negative consequences.^{8,17} The development of drug addiction begins with initial exposures to the drug, leading to rewarding effects and subsequent positive reinforcement for abuse.¹⁸ Consistent drug consumption causes neurological modifications that result in gradual increases in tolerance for the drug.¹⁸ Users accommodate for the decrease in the rewarding drug effects by increasing their drug usage.¹⁸ Many addictive drugs also induce withdrawal symptoms that can be relieved through repeatedly increasing drug consumption. These effects create a cycle that is detrimental to one's well-being.¹⁸

Current evidence suggests that the addictive properties of abused drugs are due to their effects on the dopaminergic systems in the brain.⁸ Nearly all addictive drugs produce their reinforcing effects through one common pathway: the mesolimbic dopamine system.^{8,19} The mesolimbic dopamine system is comprised of dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc).¹⁹ Previous findings indicate that the rewarding effects of addictive drugs are associated with amplified dopaminergic signaling in this pathway.²⁰ However, the precise underlying processes involved in addiction remain unclear.²¹

Currently, there are no pharmacological addiction treatments that are completely effective when administered alone.¹⁸ Pioglitazone, through its activation of PPAR γ , presents a promising potential treatment option for drug addiction.

PRECLINICAL EVIDENCE OF PIOGLITAZONE'S BENEFICIAL EFFECTS IN DRUG ADDICTION

Using animal models of addiction, several preclinical studies have demonstrated the anti-addictive properties of pioglitazone. One study investigated the effect of oral pioglitazone administration on voluntary alcohol consumption in Marchigian Sardinian (msP) rats, which are genetically selected rats with high alcohol preference.⁹ The PPAR γ agonists pioglitazone and rosiglitazone both decreased alcohol consumption while water consumption was unchanged.⁹ Interestingly, intra-cerebroventricular infusions of GW9662, a selective PPAR γ antagonist, blocked these effects.⁹ This suggests that the attenuation of alcohol consumption by pioglitazone and rosiglitazone is coordinated through PPAR γ

signaling in the brain. A subsequent study explored the combined effects of pioglitazone with naltrexone, a medication approved by the Food and Drug Administration for alcohol dependence treatment.^{10,22} It was reported that both pioglitazone and naltrexone treatment alone significantly decreased alcohol consumption in mP rats.¹⁰ Interestingly, the combined treatment with pioglitazone and naltrexone produced a greater inhibition of alcohol consumption compared to the administration of either drug alone.¹⁰

In another series of experiments, the potential of pioglitazone for opioid dependence treatment was investigated. One study found that oral administration of pioglitazone decreased the motivation for heroin in rodent models of heroin self-administration.² This effect was blocked by pre-treatment with GW9662, which suggests that pioglitazone does indeed attenuate the motivation for heroin through PPAR γ activation.² In a follow-up study, the effect of pioglitazone on opioid withdrawal and relapse was examined in opioid dependent rats. Oral treatment with pioglitazone significantly diminished the exhibition and manifestation of morphine withdrawal behaviours.¹¹ Additionally, pioglitazone significantly reduced susceptibility of relapse to heroin.¹¹

Pioglitazone's effects on psychostimulant drug dependence have also been studied. Specifically, these experiments explored the role of pioglitazone on behavioural sensitization – a model to study drug addiction that is generated by repeated exposure to stimulants.²³ In mice studies, intra-cerebroventricular pioglitazone has been found to prevent methamphetamine-induced behavioural sensitization.¹² Rat studies also demonstrated that pioglitazone inhibits the formation of cocaine-induced behavioural sensitization and diminished reactivity to cocaine-linked cues that can trigger relapse.¹³

These preclinical findings suggest that pioglitazone may be a promising treatment method for the dependence of alcohol, opioids, and psychostimulants such as methamphetamine and cocaine.

POTENTIAL MECHANISMS UNDERLYING PIOGLITAZONE'S ANTI-ADDICTIVE PROPERTIES

While the above experiments studied the effects of systemically administered pioglitazone on addiction behaviour, its effects at the neuronal and molecular levels have also been investigated. As explained previously, the addictive properties of drugs of abuse are due to the excitation of the mesolimbic dopamine system that releases dopamine from the VTA to the NAc.⁸ Accordingly, increases in extracellular dopamine were observed in the shell region of the NAc (NASH) as a result of chronic heroin administration.² Interestingly, this effect was blocked by pre-treatments with oral pioglitazone.² Ex vivo electrophysiology experiments further revealed that bath application with pioglitazone blocks morphine-induced excitation of VTA dopamine neurons.² This effect was dependent on the inhibitory GABA projections from the rostromedial tegmental nucleus (RMTg), to the VTA dopamine neurons.² To verify that these effects were mediated by PPAR γ activation in the RMTg, immunohistochemistry was used to verify that PPAR γ is indeed expressed in the RMTg.² These findings, together with the fact that PPAR γ colocalizes with GABA neurons,

suggest that pioglitazone produces its anti-addictive effects through RMTg inhibitory GABA signaling onto VTA dopamine cells via PPAR γ agonism.^{2,24} In support of this, behavioural experiments demonstrated that intra-RMTg infusions of pioglitazone inhibit self-administration of heroin in heroin-sensitized rats.²

An interesting implication from the above findings is that pioglitazone may potentially produce the same effects in the NAc. The NAc and the RMTg are similar in that they both send inhibitory GABA projections to the VTA and that PPAR γ is expressed in both regions.^{2,25} Therefore, intra-NAc pioglitazone may similarly inhibit VTA dopamine excitation through the NAc inhibitory GABA projections to the VTA. Future studies are necessary to validate this potential mechanism.

CLINICAL EVIDENCE OF PIOGLITAZONE'S BENEFICIAL EFFECTS IN DRUG ADDICTION

In addition to preclinical experimentation of pioglitazone, more recent studies have investigated its efficacy in clinical studies. In individuals with cocaine use disorder (CUD), pioglitazone treatment abated cravings for cocaine according to self-reported measures.¹⁴ In the same study, pioglitazone treatment also induced improvements in white matter integrity – a mechanism that is impaired in individuals with CUD and implicated in addiction.¹⁴ Another study examined the effects of pioglitazone on the addictive properties of nicotine in heavy smokers. The study revealed that pioglitazone significantly decreased craving for nicotine.¹⁵ Interestingly, pioglitazone did not have any significant effects on the abuse potential of the opioid oxycodone in nondependent users of prescription opioids.¹⁶ It is important to note, however, that this may have been due to the fact that the sample population were not opioid-dependent.¹⁶ This data may be inconsistent with previously mentioned preclinical studies with opioids because animal models are representations of stronger opioid dependence.^{2,11,16}

The above clinical findings support the potential of pioglitazone in cocaine and nicotine dependence. However, further research is required to validate its therapeutic properties for opioid and alcohol dependency as demonstrated in preclinical models.

SIDE EFFECTS OF PIOGLITAZONE

Although pioglitazone is considered to have a favorable safety profile, there are some negative effects and risks associated with its use.²⁶ One of the main concerns of pioglitazone treatment is weight gain. However, accumulating evidence suggests that pioglitazone decreases fat build-up in the abdominal area and primarily increases subcutaneous fat storage. Other main negative effects of pioglitazone usage include the development of peripheral edema and increased vulnerability to bone fractures, although the latter is mostly seen in older women.^{26,27}

Pioglitazone also appears to have a positive effect on cardiovascular health.²⁸ Previous findings indicate that pioglitazone may decrease the risk of major adverse cardiovascular events and myocardial infarction.²⁸ However, some evidence suggests that pioglitazone treatment may increase the risk of heart failure.²⁸ Further studies are required to validate this potential association

between pioglitazone and increased heart failure risk as there have been inconsistent results regarding the topic.²⁸

Importantly, many clinical studies that investigate the adverse effects of pioglitazone use a sample population of diabetes patients that are known to have increased risk for cardiovascular disease.²⁶⁻²⁸ Future investigation is needed for pioglitazone's potential for cardiovascular risks in drug addiction patients without diabetes.

CONCLUSION

The therapeutic role of PPAR γ in drug addiction is currently an emerging research topic.¹⁴ However, there is considerable evidence supporting the therapeutic properties of pioglitazone for addiction through PPAR γ activation. Preclinical and clinical research support its potential in drug addiction for various drugs of abuse including opioids, alcohol, psychostimulants, and nicotine.^{2,9,10,12-14,15} More research is needed to determine the efficacy of pioglitazone compared to current treatment methods. However, as previously mentioned, there is evidence that pioglitazone may be effective as an adjunctive treatment for drug addiction.¹⁰ Additionally, pioglitazone is known to have a favourable safety profile and can be easily ingested orally.¹ Together, this suggests that pioglitazone may be a promising adjunctive treatment option for drug dependence.

REFERENCES

- Desouza C, Shivaswamy V. Pioglitazone in the Treatment of Type 2 Diabetes: Safety and Efficacy Review. *Clinical Medicine Insights: Endocrinology and Diabetes*. 2010;3:CMED.S5372. <https://doi.org/10.4137/CMED.S5372>
- de Guglielmo G, Melis M, De Luca M et al. PPAR γ Activation Attenuates Opioid Consumption and Modulates Mesolimbic Dopamine Transmission. *Neuropsychopharmacology*. 2014;40(4):927-937. <https://doi.org/10.1038/npp.2014.268>
- Smith U. Pioglitazone: Mechanism of action. *Int J Clin Pract Suppl*. 2001;(121):13-18.
- Grommes C, Karlo J, Caprariello A et al. The PPAR γ agonist pioglitazone crosses the blood-brain barrier and reduces tumor growth in a human xenograft model. *Cancer Chemother Pharmacol*. 2013;71(4):929-936. <https://doi.org/10.1007/s00280-013-2084-2>
- Jones J, Sullivan M, Manubay J et al. The effects of pioglitazone, a PPAR γ receptor agonist, on the abuse liability of oxycodone among nondependent opioid users. *Physiol Behav*. 2016;159:33-39. <https://doi.org/10.1016/j.physbeh.2015.10.006>
- Roohafza H, Shokouh P, Sadeghi M et al. A Possible Role for Pioglitazone in the Management of Depressive Symptoms in Metabolic Syndrome Patients (EPICAMP Study): A Double Blind, Randomized Clinical Trial. *Int Sch Res Notices*. 2014;2014:1-9. <https://doi.org/10.1155/2014/697617>
- Iranpour N, Zandifar A, Farokhnia M et al. The effects of pioglitazone adjuvant therapy on negative symptoms of patients with chronic schizophrenia: a double-blind and placebo-controlled trial. *Human Psychopharmacology: Clinical and Experimental*. 2016;31(2):103-112. <https://doi.org/10.1002/hup.2517>
- Foll B, Ciano P, Panlilio L, et al. Peroxisome Proliferator-Activated Receptor (PPAR) Agonists as Promising New Medications for Drug Addiction: Preclinical Evidence. *Curr Drug Targets*. 2013;14(7):768-776. <https://doi.org/10.2174/1389450111314070006>
- Stopponi S, Somaini L, Cippitelli A et al. Activation of Nuclear PPAR γ Receptors by the Antidiabetic Agent Pioglitazone Suppresses Alcohol Drinking and Relapse to Alcohol Seeking. *Biol Psychiatry*. 2011;69(7):642-649. <https://doi.org/10.1016/j.biopsych.2010.12.010>
- Stopponi S, de Guglielmo G, Somaini L et al. Activation of PPAR by Pioglitazone Potentiates the Effects of Naltrexone on Alcohol Drinking and Relapse in msP Rats. *Alcoholism: Clinical and Experimental Research*. 2013;37(8):1351-1360. <https://doi.org/10.1111/acer.12091>
- de Guglielmo G, Kallupi M, Scuppa G, et al. Pioglitazone attenuates the opioid withdrawal and vulnerability to relapse to heroin seeking in rodents. *Psychopharmacology (Berl)*. 2016;234(2):223-234. <https://doi.org/10.1007/s00213-016-4452-1>
- Maeda T, Kiguchi N, Fukazawa Y, et al. Peroxisome Proliferator-Activated Receptor Gamma Activation Relieves Expression of Behavioral Sensitization to Methamphetamine in Mice. *Neuropsychopharmacology*. 2006;32(5):1133-1140. <https://doi.org/10.1038/sj.npp.1301213>
- Miller W, Fox R, Stutz S et al. PPAR γ agonism attenuates cocaine cue reactivity. *Addict Biol*. 2016;23(1):55-68. <https://doi.org/10.1111/adb.12471>
- Schmitz J, Green C, Hasan K et al. 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. *Addiction*. 2017;112(10):1861-1868. <https://doi.org/10.1111/add.13868>
- Jones J, Comer S, Metz V et al. Pioglitazone, a PPAR γ agonist, reduces nicotine craving in humans, with marginal effects on abuse potential. *Pharmacology Biochemistry and Behavior*. 2017;163:90-100. <https://doi.org/10.1016/j.pbb.2017.10.002>
- Jones J, Sullivan M, Manubay J et al. The effects of pioglitazone, a PPAR γ receptor agonist, on the abuse liability of oxycodone among nondependent opioid users. *Physiol Behav*. 2016;159:33-39. <https://doi.org/10.1016/j.physbeh.2015.10.006>
- Treatment Approaches for Drug Addiction. Drugabuse.gov. <https://www.drugabuse.gov/publications/drugfacts/treatment-approaches-drug-addiction>. Published 2018. Accessed August 3, 2018.
- Potenza M, Sofuoglu M, Carroll K, et al. Neuroscience of Behavioral and Pharmacological Treatments for Addictions. *Neuron*. 2011;69(4):695-712. <https://doi.org/10.1016/j.neuron.2011.02.009>
- Nestler E. Is there a common molecular pathway for addiction?. *Nat Neurosci*. 2005;8(11):1445-1449. <https://doi.org/10.1038/nn1578>

20. Edens E, Massa A, Petrakis I. Novel Pharmacological Approaches to Drug Abuse Treatment. *Behavioral Neuroscience of Drug Addiction*. 2009;343-386. https://doi.org/10.1007/7854_2009_29
21. Herman M, Roberto M. The addicted brain: understanding the neurophysiological mechanisms of addictive disorders. *Front Integr Neurosci*. 2015;9. <https://doi.org/10.3389/fnint.2015.00018>
22. Anton R. Naltrexone for the Management of Alcohol Dependence. *New England Journal of Medicine*. 2008;359(7):715-721. <https://doi.org/10.1056/nejmct0801733>
23. Enayatfard L, Rostami F, Nasoohi S, Oryan S, Ahmadiani A, Dargahi L. Dual Role of PPAR γ in Induction and Expression of Behavioral Sensitization to Cannabinoid Receptor Agonist WIN55,212-2. *Neuromolecular Med*. 2013;15(3):523-535. <https://doi.org/10.1007/s12017-013-8238-x>
24. Domi E, Uhrig S, Soverchia L et al. Genetic Deletion of Neuronal PPAR γ Enhances the Emotional Response to Acute Stress and Exacerbates Anxiety: An Effect Reversed by Rescue of Amygdala PPAR γ Function. *The Journal of Neuroscience*. 2016;36(50):12611-12623. <https://doi.org/10.1523/jneurosci.4127-15.2016>
25. Russo S, Nestler E. The brain reward circuitry in mood disorders. *Nature Reviews Neuroscience*. 2013;14(9):609-625. <https://doi.org/10.1038/nrn3381>
26. Shah P, Mudaliar S. Pioglitazone: side effect and safety profile. *Expert Opin Drug Saf*. 2010;9(2):347-354. <https://doi.org/10.1517/14740331003623218>
27. Schernthaner G, Currie C, Schernthaner G. Do We Still Need Pioglitazone for the Treatment of Type 2 Diabetes? A risk-benefit critique in 2013. *Diabetes Care*. 2013;36(Supplement_2):S155-S161. <https://doi.org/10.2337/dcs13-2031>
28. de Jong M, van der Worp H, van der Graaf Y, et al Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials. *Cardiovasc Diabetol*. 2017;16(1). <https://doi.org/10.1186/s12933-017-0617-4>