RE: REVISED

Opioid Epidemic: Uses, Abuses, and Innovation: A New Method for Treatment of Opioid Use Disorder via Lorcaserin

Dear Dr. Glaser,

Thank you for your reply on April 19th with the peer reviews of our original manuscript. We were pleased to see the comments and have taken them all into consideration during the revising process. We have changed the recommendations as we see fit, and have described them as follows:

**Major Revisions**

[M.1] Reviewers 1 and 2 recommended adding more about the procedure of synthesizing lorcaserin. Though differentiating between supporting information and synthesis is important, methods for synthesizing lorcaserin is limited. Therefore, the supporting information will likely sound similar to our materials and methods. The materials and methods focus primarily on the structure of lorcaserin. Our supporting information section, explains the synthesis of lorcaserin with a full mechanism versus just a structure.

[M.2] Reviewers 2 and 3 recommended moving the IR information to supporting information. This change was made.

[M.3] Added End-notes to the paper as recommended by reviewers 1 and 2.

**Response to Reviewer 1**

[1.1] The wording of the abstract was revised to include more information about lorcaserin, and less of an introduction style. The image was made smaller and placed at the top before the abstract.

[1.2] Information in the introduction was added about how rats self-administer the opioid. This added clarity to how the experiment was conducted.

[1.3] Made grammatical correction to first line in “Results and Discussion.”

**Response to Reviewer 2**

[2.1] In our manuscript, we reported the results of lorcaserin in Table 1 and Table 2. There is additional text that explains the information in the tables as well.

[2.2] Through revising our abstract, the scheme gained significance.

[2.3] We added the drugs we are comparing to lorcaserin in our abstract.

[2.4] We rewored our abstract.

[2.5] The introduction was proof read, grammar errors were changed, and confusing wording was corrected to be clearer.

[2.6] We made sure the entire scheme and table titles were in bold.

**Response to Reviewer 3**


[3.2] The scheme in the abstract was made by Theodora Leventis using ChemDraw.

[3.3] Deleted the phrase “…lorcaserin use as a weight-loss drug” in some parts of the paper. This was to avoid repetition.

Sincerely,

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*Theodora Leventis,*

*Leigh Burdick*
Opioid Epidemic: Uses, Abuses, and Innovation: A New Method for Treatment of Opioid Use Disorder via Lorcaserin

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Abstract

Opioids are a category of drugs that include illegal drugs such as heroin and cocaine, synthetic opioids such as fentanyl, and prescribed pain relievers such as oxycodone, codeine, and morphine. When misused, opioids can often lead to addiction and overdose, which causes death. Naltrexone can reverse an opioid overdose when given right away. Another effective medication, methadone, also exists to treat opioid use disorders. Although these medications exist, a new drug with higher success rates for treatment and prevention of misuse is needed. This review discusses the synthesis and experimental results of lorcaserin fighting addiction and cravings in rats.
Introduction

Lorcaserin is commonly used as a weight-loss drug, however, it has been recently found to act as a possible opioid suppressant. In this experiment, rats were connected to pumps that administered oxycodone when they pulled a lever.¹ This process allowed rats to self-administer oxycodone and gave a way for information to be collected about how often the rats craved the oxycodone. Rats that were treated with lorcaserin showed reduced use and dependence of the oxycodone. Lorcaserin has also been shown to curb opioid and nicotine cravings, even when tested in tempting, relapse-prone environments.¹ When compared to rats that didn’t get the lorcaserin treatment, rats that received treatment were less likely to take oxycodone and exhibit addictive behaviors.

A couple existing drugs used to decrease opioid tendencies are naltrexone and methadone. Naltrexone, an opioid antagonist, helps prevent opioids from working in the body by reversing the effects.² The drug must be injected immediately at the signs of opioid overdose to reverse the damage.³ Methadone, on the other hand, is an opioid that blocks the high achieved from other opioids. Methadone provides a similar feeling and prevents withdrawal symptoms by replacing the opioids in the system with milder effects.²

Here, we report the results of lorcaserin use to treat opioid addiction. Lorcaserin was administered to rats who had been taking oxycodone.³ Once injected with lorcaserin, the rats showed less drug-seeking behaviors than the rats that did not receive the treatment. Even when exposed to cues such as lights and sound that the rats were conditioned to associate with oxycodone, they still showed resistance to the opioid.³ This finding is significant in that it
provides a more effective alternative to opioid addiction treatment such as naltrexone and methadone.

**Materials and Methods**

*Preparation of Materials*

The synthesis of oxycodone starts with thebaine and undergoes oxidation followed by a hydrogenation of the carbon-carbon double bond.\(^4\) The structures of thebaine and oxycodone are shown in Scheme 1. Further information about the synthesis of oxycodone can be found in supporting information.

**Scheme 1: Structures of Thebaine and Oxycodone**

![Scheme 1: Structures of Thebaine and Oxycodone](image)

The structures of the starting material, 2-(4-chlorophenyl)ethanamine and resultant product lorcaserin can be found in Scheme 2. For further details on synthesis, see supporting information.\(^2\) Lorcaserin is originally known as a commercial weight loss drug. However, it has been found that it can also be used to treat opioid addiction.
Scheme 2: Structures of Starting Material and Lorcanerin

Naltrexone is an opioid antidote and is used to reverse an opioid overdose. Naltrexone works within minutes once injected and may also be combined in opioid pills to decrease the risk of misuse. Methadone, on the other hand, is a narcotic that is used to treat pain, however, it is not euphoric which also decreases the risk of misuse. Methadone can also be used to treat opioid addiction (Scheme 3).

Scheme 3: Structures of Naltrexone and Methadone
Results and Discussion

Naltrexone is typically used as an antidote to opioids. Similarly, methadone is sometimes used to help abusers overcome addiction.\(^1\) This is because methadone does not cause euphoria. Success rates of patients treated with naltrexone and methadone are much higher than those that went through programs without using drugs to help with abuse disorder.\(^4\) While these current drugs increase success rates, it is important to continue to improve drugs for opioid abuse disorder that have less side effects and higher success rates.

Successful recovery rates are difficult to achieve with people that have opioid abuse disorder. In order to produce higher success rates it is important to find alternative drugs that help reverse opioid addiction and keep people in recovery.\(^3\) Lorcaserin is typically used as a weight loss drug; however, a recent study suggests lorcaserin may be used to treat opioid abuse disorder. Lorcaserin increases the serotonin in the brain which affects the body’s sense of feeling full.\(^2\) This is how lorcaserin could prove to work towards both preventing and reversing opioid abuse. Though lorcaserin has not been tried in humans for the treatment of opioid abuse, the study performed on rats showed a high success rate in the ability to recover from opioid abuse disorder.\(^1\) Table 1 shows the success rate of naltrexone and methadone used in humans as the treatment of opioid abuse versus the success of lorcaserin to treat opioid abuse in rats.
Table 1: Success Fates of Opioid Abuse Disorder Drugs

<table>
<thead>
<tr>
<th>Opioid Abuse Disorder Drugs</th>
<th>Percent of patients positive for opioids w/ drug</th>
<th>Percent of patients positive for opioids w/o drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone</td>
<td>35%</td>
<td>90%</td>
</tr>
<tr>
<td>Methadone</td>
<td>28%</td>
<td>63%</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>4%</td>
<td>93%</td>
</tr>
</tbody>
</table>

The rats in this lab acquired self-administration of oxycodone. Success rates regarding the reversing of oxycodone addiction were collected based on the number of times the rats pressed a lever to self-administer the oxycodone. After the rats acquired addiction, rats were randomly assigned into a control group and a trial group with an equal number of rats in each group. The rats in the trial group were given lorcaserin 15 minutes prior to self-administration sessions. The number of lever presses were obtained in total for each group during self-administration sessions. The control group showed an increase of about 100 lever presses over the 12-session period. This shows signs of tolerance development in the rats, thus they are intaking more oxycodone to achieve the same reinforcement feeling before developing tolerance. On the other hand, the rats that received lorcaserin prior to the self-administration sessions pressed the lever much less. When the sessions started, the rats were considered to be equally addicted to the oxycodone. After just one session of treatment, the rats in the trial group were proving to be much less reliant on the oxycodone when compared to the control group. The results of this trial can be found in Table 2.

Table 2: Number of Lever Presses of Control Group vs. Trail Group
**Conclusion**

Lorcaserin was given to rats to treat opioid use disorder. This drug is also a candidate for prevention of opioid use disorder. This means if a rat were to take oxycodone and lorcaserin simultaneously, its risk factor for addiction could be decreased. Lorcaserin also had a greater success rate for treatment of opioid use disorder, than naltrexone and methadone. This study has not yet been applied to humans. Based on this study with rats, lorcaserin could be used to treat and prevent opioid use disorder.

No other drug has been shown to prevent opioid use disorder. Naltrexone and methadone, the drugs of comparison, are only used to treat opioid use disorder. A drug that could prevent the addictive properties of opioids would be revolutionary. Patients could know their risk of addiction factor would decrease when using opioid pain medications, specifically oxycodone, with this drug, pending its results in human trials. One possible consequence of this drug being put in circulation would be that people started to view opioids as harmless if you take them with lorcaserin, however this is not what the study is about.
Supplementary Material Available

A thorough description of the process of the substrate, as well as its characterization can be found in the appendix.

Reference


(6) NIH, National Institute on Drug Abuse. “Medications to Treat Opioid Use Disorder” 2018.


Supporting Information

Opioid Epidemic: Uses, Abuses, and Innovation: A New Method for Treatment of Opioid Use Disorder via Lorcaserin

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Synthesis

The synthesis of oxycodone starts as thebaine. Since thebaine already has the desired backbone structure shared by all opioids, the first step is oxidation by m-CPBA in acetic acid-trifluoroacetic acid to 14-hydroxycodine. H_{2}O_{2} can be used, however it is more efficient to use m-CPBA. Oxycodone is only one step away, a hydrogenation of the carbon-carbon double bond in 14-hydroxycodine (Scheme S1).

Scheme S1: Synthesis of Oxycodone

Starting with 2-(4-chlorophenyl)ethanamine, lorcaserin can be synthesized by reaction with 2-chloropropionylchloride, then Friedel-Crafts alkylation reduction and chiral resolution
(Scheme S2). This method produces a 7.2% overall yield. While this is less than the yield using 2-(4-chlorophenyl)acetic acid, the latter requires an expensive condensing agent. One disadvantage to using 2-(4-chlorophenyl)ethanamine is it requires large amounts of aluminum chloride, which leads to a complicated step that reduces the yield. Although there are cons to both methods, the 2-(4-chlorophenyl)ethanamine method is preferred, as it is shorter.

**Scheme S2: Synthesis of Lorcaserin**
IR Information

According to the IRs, lorcaserin, methadone, and naltrexone share similarities. All three spectra commonly show a prominent carbonyl peak at roughly 1700 cm\(^{-1}\), a CH\(_2\) bend and a CH\(_3\) bend at roughly 1480 cm\(^{-1}\), a CH (sp\(^2\)) stretch at roughly 2900 cm\(^{-1}\), and a CH (sp\(^3\)) at roughly 3100 cm\(^{-1}\). However, in the lorcaserin IR analysis (Figure 1), the CH stretches are stronger than in the methadone (Figure 2) and naltrexone analyses (Figure 3), and there also appears to be an NH stretch at roughly 3500 cm\(^{-1}\). The stronger CH stretches in the lorcaserin may be due to the fact that it is a dietary drug unlike methadone which is a non-euphoric opioid and naltrexone which is an opioid antidote. The NH functional group may be the reason that the serotonin levels in rats increased. The similar functional groups amongst lorcaserin, methadone, and naltrexone lessened oxycodone cravings. However, the increased serotonin levels may have played an additional role in lessening addiction, thus making lorcaserin more successful.

Spectral Properties of Lorcaserin

![Spectral Properties of Lorcaserin](image-url)
Figure 1: IR spectrum of lorcaserin

Spectral Properties of Methadone

Figure 2: IR spectrum of methadone

Spectral Properties of Naltrexone
Figure 3: IR spectrum of naltrexone

Bibliography


