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Original Research Article

Evaluation of dependence on pregabalin, tramadol and codeine

Soumia Tehami [a,b*], Oumnia Hafsi [c], Dounia Filali [c], Rahma Boumehdiou [c]

[a] *University 3 of Constantine, faculty of Medicine, department of Pharmacy, Constantine, 25000, Algeria*

[b] *Process Engineering for Sustainable Development and Health Products*

[c] *University 1 of Constantine, Department of Biology, Constantine, 25000, Algeria*

Abstract

This study examines pregabalin addiction, a medication prescribed for the treatment of disorders such as epilepsy and neuropathic pain. However, there is ongoing debate regarding the potential for pregabalin addiction. Some studies suggest that long-term use of pregabalin may lead to physical dependence and tolerance, meaning that higher doses are required to achieve the same effects. To assess whether pregabalin causes dependence, using tramadol and codeine for comparison, the conditioned place preference test was employed, a commonly used method to study preferences associated with drug administration over 12 days. The test was conducted using a device divided into two main chambers: a neutral compartment and another associated with drug administration.

Tramadol and codeine, selected for comparison with pregabalin in the test results, were chosen due to their addictive effects, which may be more similar to those of pregabalin, as well as their comparable reasons for use, such as their low cost, which makes them "drugs of the poor," and their easy accessibility. The results indicated that pregabalin has a higher potential for dependence than these substances. This difference in addictive effects emphasizes the importance of considering the specific characteristics of each drug when prescribing and using them.

Keywords:
Addiction; pregabalin; tramadol; codeine

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*Corresponding author
Email address: tehamisoumia25@gmail.com (Soumia Tehami)

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I.Introduction

Addiction to psychoactive substances represents a major public health issue due to its significant health, social, and economic consequences. Among the medications associated with substance use disorders, analgesics such as tramadol and codeine, as well as substances like pregabalin, have drawn increasing attention due to their addictive potential. While these compounds are widely used for their therapeutic efficacy, particularly in pain management and anxiety disorders, their misuse is steadily increasing.

Pregabalin, an anticonvulsant also used as an analgesic, tramadol, a step-2 opioid, and codeine, a weak opioid, share mechanisms of action that involve neurochemical effects on the central nervous system, potentially fostering psychological and/or physical dependence.

This article aims to explore and compare the addictive potential of these three substances through in vivo studies. By leveraging behavioral and neurobiological models, this evaluation seeks to enhance understanding of the risks associated with their use and contribute to improved prescription practices to mitigate the risk of abuse.

II. Materials and methods

II.1. Materials

II. 1.1. Animal

In this experiment, we employed Albino Wistar rats, weighing between 180 and 300 g, bred in the animal facility of Frères Mentouri Constantin 1 university.

A total of 20 rats, consisting of 5 males and 15 females, were housed in three separate cages.

The temperature, maintained between 18 and 22°C, and the humidity, ranging from 45% to 70%, were monitored using an analog thermo-hygrometer. The rats were provided with specialized food and water.

II.1.2. Substances

Saline solution (NaCl) was utilized for the control group, as well as for the dilution and preparation of solutions. Pregabalin was used in its crystallized powder form (raw), while tramadol was provided in powdered form (raw). Codeine was administered in combination with paracetamol in tablet form. Additionally, mint and cinnamon were also included in the study.

II.1.3 Instruments

The experiment used grid cages specifically designed to house the rats. Laboratory glassware was employed for solution preparation, and an analytical balance was used for the precise weighing of powdered substances. A coarse balance was used to measure the body weight of the rats. A magnetic stirrer facilitated the homogenization of solutions, while 5 ml syringes were used for administration. Additionally, a feeding probe was utilized for oral delivery.

II.1.4. Experimental set-up

The conditioned place preference (CPP) paradigm was assessed using a custom-made wooden device specifically designed for this purpose.

The apparatus consists of three chambers, each measuring 35 cm in height and 40 cm in length, separated by small doors. Each chamber is visually distinct (figure 1):

- **First chamber:** Interior walls feature black and white stripes.
- **Second chamber (middle):** Entirely white interior walls.
- **Third chamber:** Interior walls display black and white aspirin patterns.

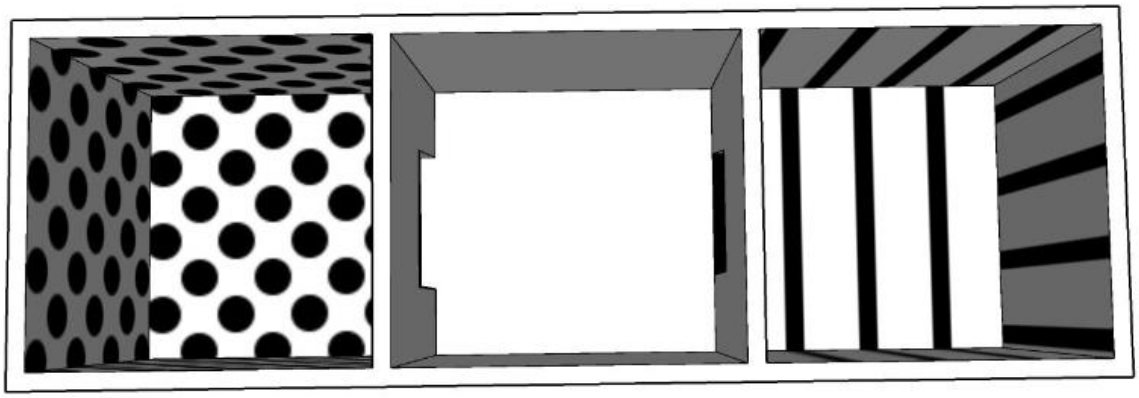

Figure 1. Illustration of PPC (Home Designer Professional) experimental device.

II. 1.5. Hardware

A laptop computer and a camera were also used in the study.

II. 1.6.Software

SPSS (version 26) was used for statistical analysis of the results, while Home Designer Professional (version 2020) served as the architectural software for device illustration.

II. 2. Methods

- Study type: Experimental *in vivo* study
- Location: Animal house, Frères Mentouri Constantine-1 University
- Duration: From February to May 2023.

II. 2.1 Animal adaptation

Prior to beginning the experimental procedures, the rats underwent a one-month adaptation period to reduce stress and fear. During this time, they were acclimated to the sounds, the process of being moved between cages, and were provided with food (figure 2).

Figure. 2. Rat adaptation

II.2.2. Test performed

The conditioned place preference test is a technique used in experimental psychology to evaluate the preferences or associations between stimuli and conditioned responses. It is grounded in classical conditioning, a process through which an organism learns to associate a neutral stimulus with a significant one, triggering a specific response.

It is typically conducted in an experimental setup with two distinct compartments. During the learning phase, a stimulus (e.g., an odor, sound, or light) is introduced in one of the compartments, while the other compartment remains neutral or presents a different stimulus.

In our protocol, we used a device with clearly defined dimensions, divided into two compartments:

- A neutral compartment associated with the injection of physiological saline.
- A compartment linked to drug administration.

This test measures the time spent in each compartment, offering an indication of the preference developed by the animal after substance injection. The animal demonstrates its preference by spending more time in one of the compartments. Its choice helps determine whether a dependency on the substance has developed.

The same protocol was applied for all three tests (pregabalin, tramadol, and codeine paracetamol). The PPC test was initially conducted with pregabalin for 12 days, followed by a 15-day rest period for the rats. The test was then repeated with tramadol for 12 days at a dose of 100 mg/kg. After another rest period, the test was repeated with a lower dose of tramadol (50 mg/kg) for 12 days. Finally, the same test was performed over the same period, this time using codeine. The steps in the protocol are as follows:

- Pregabalin

➢ **Pre-test (habituation phase)**

On days 1, 2 and 3, each rat is placed in the starter box with both doors open to allow the rats to explore the conditioning chambers for 10 minutes.

The animal's exploration in the two conditioning chambers was recorded and the time spent in both chambers was calculated.

➢ **Testing(the conditioning phase)**

The conditioning phase lasted 8 successive days. The days of pregabalin administration were D4, D6, D8 and D10.

First, each rat received a 90mg/kg dose of pregabalin, by intraperitoneal injection, diluted in 250 ml of saline according to their body weight.

Then, after administration of the molecule, each batch was placed in the corresponding chamber (black and white striped compartment and to be sure of our experiment we added the odor factor by using mint as a cue, as rats rely much more on the sense of smell), for one hour.

Days: D5, D7, D9 and D11 are the days of administration of physiological water with the same doses of drug, then, after the injection, each batch they put in the other chamber (aspirin compartment with the odor index which is cinnamon), also for an hour.

Figure.3. Rats after injection in compartment 2 (aspirin). Rats after injection in compartment 1 (striped).

To assess the ability of pregabalin to induce dependence, as evidenced by the relatively long time spent in the black-and-white striped compartment with the smell of mint.

➢ The post-test (preference test)

For day 12, each rat is placed in the starter box and given free access
to both chambers for 10 minutes.
The rats' preference in the two chambers was recorded using a camera (post-conditioning test) and the time spent is also calculated.
The time spent in the drug compartment is compared with that spent in the neutral compartment for each batch, and a statistical analysis is then used.

Tramadol

➢ Pre-test (habituation phase)

On days 1, 2 and 3, each batch of rats was placed in the starter box with both doors open allowing them to explore the conditioning chambers for 10 minutes. Time spent in both chambers was calculated.

For tramadol, the PPC test was carried out twice, following the same steps as aboveThe first time, with a dose of 100 mg/kg.th
And for the 2nd, with a dose of 50mg/kg.

➢ The test (the conditioning phase)

The conditioning phase was carried out over 8 successive days.
The days of tramadol administration were D4, D6, D8 and D10.
First, each rat received a dose of (100mg/g ,50mg/kg) tramadol, by intraperitoneal injection, diluted in 250 ml saline, depending on their body weight.
After administration of the molecule, each batch was placed in the corresponding chamber (aspirin compartment using a cinnamon odor index), for one hour.
Days: J5, J7, J9 and J11 are the days of administration of physiological water with the same doses of drug, after the injection each batch they put in the other chamber (compartment to the stripes with the index of odor which is mint), also for an hour.
To assess the ability of tramadol to induce dependence, which is reflected in a
time spent in the aspirin compartment with the smell of cinnamon.

- **The post-test (preference test)**

On the twelfth day, each rat is placed in the starter box and given free access to both chambers for 10 minutes.

The preference of the rats in the two chambers was recorded using a camera (post-conditioning test) and the time spent is also calculated.

The time spent in the drug compartment is compared with that spent in the neutral compartment for each batch, and a statistical analysis is then used.

Codeine

- **Pre-test (habituation phase)**

D1, D2, D3: habituation of each batch to the device.

On days 1, 2 and 3, each batch of rats was placed in the starter box with both doors open to allow rats to explore the conditioning chambers for 10 minutes.

Animal exploration in both conditioning chambers was recorded and time spent in both chambers was calculated.

- **The test (the conditioning phase)**

The conditioning phase was carried out over 8 successive days.

The days of paracetamol-codeine administration were D4, D6, D8 and D10.

First, each batch received an oral dose of 400mg/kg of codeine paracetamol, diluted in 250 ml of distilled water, depending on their weight.

Then, after administration of the molecule, each batch was placed in the corresponding chamber (striped compartment with mint odor index), for one hour.

Days: D5, D7, D9 and D11 are the days of administration of distilled water with the same doses of drug, then each batch was placed in the other chamber (aspirin compartment with odor index cinnamon), also for one hour after gavage.

-Etablissement doses

For codeine paracetamol: we chose an average dose of 400mg/kg orally

(gavage), in order to compare results with those of pregabalin.

-Parameters

To assess the ability of codeine paracetamol to induce dependence, as evidenced by the relatively long time spent in the black-and-white striped compartment with the smell of mint.

- **The post-test (preference test)**

On the twelfth day, each rat is placed in the starter box and given free access to both chambers for 10 minutes.

The preference of the rats in the two chambers was recorded using a camera (post-conditioning test) and the time spent is also calculated.

The time spent in the drug compartment is compared with that spent in the neutral compartment for each batch, and a statistical analysis is then used.

III.RESULTS

III.1 Pregabalin

III.1.1 Pre-test

The pre-test is the test which allows the rat to explore the compartments of the device (the habituation phase). It takes place over 3 days and the following results were obtained.

Day 1

The average time spent by rats in compartment 1 on day 1 of the pre-test was 4.61 minutes, with a standard deviation of 1.71 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 3.88 minutes, with a standard deviation of 1.84 minutes.

the difference between the time spent in the two compartments is statistically insignificant, with a p-value of 0.32.

Day 2

Time spent by rats in compartment 1 on day 2 of the pre-test averaged 4.35 minutes, with a standard deviation of 1.72 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 3.84 minutes, with a standard deviation of 1.74 minutes.

the difference between the time spent in the two compartments is statistically insignificant, with a p-value of 0.47.

Day 3

Time spent by rats in compartment 1 on day 3 of the pre-test averaged 4.71 minutes, with a standard deviation of 1.49 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 3.77 minutes, with a standard deviation of 1.54 minutes.

the difference between the time spent in the two compartments is statistically insignificant, with a p-value of 0.15.

III.1.2 Post-test

The time spent by rats in compartment 1 during the post-test day averaged 8.81 minutes, with a standard deviation of 0.98 minutes.

Time spent in compartment 2 on the same day averaged 0.65 minutes, with a standard deviation of 0.74 minutes.

the difference between the time spent in the two compartments is statistically significant, with a p-value of 0.00.

III.2 Tramadol

III.2.1 Pre-testing

Day 1

The time spent by rats in compartment 1 during day 1 of the pre-test averaged 3.57 minutes, with a standard deviation of 0.94 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 3.83 minutes, with a standard deviation of 0.89 minutes.

the difference between the time spent in the two compartments is statistically insignificant, with a p-value of 0.45.

Day 2

The time spent by rats in compartment 1 on day 2 of the pre-test averaged 4.27 minutes, with a standard deviation of 1.33 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 3.80 minutes, with a standard deviation of 0.99 minutes.

the difference between the time spent in the two compartments is statistically insignificant, with a p-value of 0.33.

Day 3

The time spent by rats in compartment 1 on day 3 of the pre-test averaged 4.55 minutes, with a standard deviation of 1.39 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 3.50 minutes, with a standard deviation of 0.94 minutes.

the difference between the time spent in the two compartments is statistically insignificant, with a p-value of 0.05.

III.2.2 Posttest

The time spent by rats in compartment 1 during the post-test day averaged 2.26 minutes, with a standard deviation of 1.28 minutes.

Time spent in compartment 2 on the same post-test day averaged 6.79 minutes, with a standard deviation of 1.19 minutes.

the difference between the time spent in the two compartments is statistically significant, with a p-value of 0.00.

III.3 Codeine

III.3.1 Pre-testing

Day 1

The time spent by rats in compartment 1 on day 1 of the pre-test averaged 5.08 minutes, with a standard deviation of 2.38 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 2.93 minutes, with a standard deviation of 1.84 minutes.

the difference between the time spent in the two compartments is statistically significant, with a p-value of 0.03.

Day 2

The time spent by rats in compartment 1 on day 2 of the pre-test averaged 4.91 minutes, with a standard deviation of 1.02 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 3.58 minutes, with a standard deviation of 0.97 minutes.

the difference between the time spent in the two compartments is statistically significant, with a p-value of 0.00.

Day 3

The time spent by rats in compartment 1 on day 3 of the pre-test averaged 5.14 minutes, with a standard deviation of 0.79 minutes.

Time spent in compartment 2 on the same day of the pre-test averaged 2.96 minutes, with a standard deviation of 1.13 minutes.

the difference between the time spent in the two compartments is statistically significant, with a p-value of 0.00.

III .3.2 Posttest

The time spent by rats in compartment 1 during the post-test day averaged 5.64 minutes, with a standard deviation of 2.26 minutes.

Time spent in compartment 2 on the same day of the posttest averaged 2.77 minutes, with a standard deviation of 2.17 minutes.

the difference between the time spent in the two compartments is statistically significant, with a p-value of 0.00.

IV. Discussion

IV.1 Pregabalin

According to the results of our study, during the pre-test and for the three days, the rats spent time in both compartments in a homogeneous manner. Application of the Student's t-test gave a p value > 0.05, which confirms that the difference between the averages of the time spent in the two compartments is zero.

This can be explained by the fact that the rats do not have a preference for one of the two compartments.

After application of pregabalin (4 days over an 8-day period), the rats responded with a preference for the compartment where pregabalin was administered. The Student's t-test gave a P value of 0, which means that this difference between the means of time spent in the two compartments is highly significant.

This result suggests that pregabalin has the potential to induce dependence.

Several articles have addressed the issue of pregabalin dependence, with its detour of use occupying health authorities around the world (Laboudi et al., 2019 ; Dahan et al., 2017 ; Roche & Blaise, 2020 ; Sastre et al., 2022 ; Lapeyre-Mestre et al., 2020).

On the other hand, the mechanism of this dependence remains poorly elucidated, a few *in vivo* studies have been carried out to investigate the power of pregabalin to induce dependence as well as the mechanisms involved, Jouanjus and his team used PPC and found that pregabalin causes a conditioned place preference but by measuring dopamine concentrations they concluded that the dopaminergic pathway is not involved in the mechanism of dependence on the latter (Jouanjus et al., 2018) another study was carried out by a team of pharmacists in Algeria using the same protocol concluded that pregabalin causes conditioned place preference, this team studied two possible sees; the dopaminergic and the glutamergic pathway, and they found that these two pathways are not involved in the addiction mechanism (Nacer et al., 2022).

Further studies are desirable to enrich the data on this subject and to find an explanation for the mechanism of pregabalin dependence.

IV.2 Tramadol

Tramadol has been used in our study in order to compare the results of pregabalin dependence with a substance sharing several points with it; starting with the fact that both molecules are medicinal substances undergoing a detour of use especially at the level of the Algerian territory, both substances are considered as poor people's drugs given the reduced price compared to other drugs such as heroin and cocaine, and finally easy accessibility to both products.

According to the results of our study, during the pre-test and on all three days, the rats spent time in both compartments in a homogeneous manner. Application of the Student's t-test gave a p value > 0.05, confirming that the difference between the mean times spent in the two compartments was zero.

This can be explained by the fact that the rats do not have a preference for one of the two compartments.

After tramadol application (4 days over an 8-day period), the rats responded with a preference for the compartment where tramadol was administered. Application of the Student's t-test gave a P value of 0, which means that this difference between the means of time spent in the two compartments is highly significant.

We can therefore conclude that tramadol is potentially addictive.

In recent years, tramadol, like pregabalin, has experienced a detour of use, reported as an alert to be taken seriously (Benner & Robinet, 2021 ; Soedje et al., 2014 ; Maurice-Szamburski, 2021 ; Roussin & Lapeyre-Mestre, 2018 ; Eberhart, 2022 ; Roussin et al., 2015)

Tramadol addiction involves the endogenous opioid system, one of the neurochemical systems that play a key role in addiction. Endogenous opioid receptors and peptides are widely present in brain structures that control reward phenomena, particularly the mesolimbic system. These opioid receptors and peptides are selectively involved in several aspects of the addictive processes induced by opiates, cannabinoids, psychostimulants, alcohol and nicotine(Maldonado, 2010).

IV.3 Codeine

Codeine was used in our study with the same objective in mind: to compare it with pregabalin, since it has a very low addictive power.

According to the results of our study, during the pre-test and for the three days, the rats spent time in the two compartments in a non-homogeneous way. Application of the Student's t-test gave a p value<0.05, confirming that the difference between the averages of the time spent in the two compartments is statistically significant.

This is explained by the fact that the rats already have a preference for one of the two compartments outside the codeine application.

After codeine application (4 days over an 8-day period), the rats responded with a preference for the compartment where the codeine had been administered. Application of the Student's t-test gave a P value of 0, which means that this difference between the means of time spent in the two compartments is highly significant.

Unfortunately, in this case, no conclusion can be drawn as to the addictive power of codeine.

This result does not rule out the fact that codeine also poses a problem of abuse and detour of use, with several cases reported in the literature(Lacroix et al., 2018)(Fabre, 2012).

V.Conclusion

In conclusion, this in-depth study of pregabalin dependence has enabled us to gain a better understanding of the effects of this substance and the risks it presents in terms of dependence. The results obtained using the conditioned place preference test confirmed that pregabalin has a significant impact on reward-seeking behavior in rats, and that it can induce dependence. Dependence on pregabalin is a complex and worrying issue that requires ongoing attention from healthcare professionals, policy-makers and society as a whole. By taking appropriate measures to inform, prevent and treat pregabalin dependence, we can help reduce the negative impacts associated with this substance and improve the health and well-being of the individuals concerned. This work will contribute to the advancement of knowledge on the effects of pregabalin on the brain, and may guide future research and interventions related to pregabalin dependence.

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