

# Pathophysiology of anxiety related to nicotine use

## Fisiopatologia da ansiedade relacionada ao uso de nicotina

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### ABSTRACT

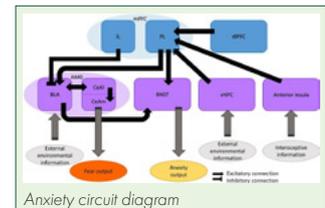
**Introduction:** Although the rate of tobacco use has decreased in recent years, tobacco-related diseases remain the leading cause of preventable death. Smoking can worsen or trigger symptoms of anxiety during withdrawal. Nicotine dependence is highly comorbid with neuropsychiatric and mood disorders.

**Objective:** To report the effects of nicotine on the central nervous system, its relationship with anxiety, and confrontation methods. **Method:** A narrative review of nicotine and anxiety was conducted in the PubMed, Google Scholar, Scielo, and Capes Periódicos databases, using the descriptors "anxiety due to lack of nicotine," "nicotine," and "anxiety." Twenty-two articles published between 2000 and 2024 were included.

**Result:** Nicotine binds to nicotinic acetylcholine receptors, releasing dopamine and causing dependence. Furthermore, prolonged exposure dysregulates the hypothalamic-pituitary-adrenal system, resulting in cortisol hypersecretion and altered stress response. With continued use, neuronal changes can occur that make nicotine anxiogenic, due to the wide range of nicotinic receptors and their varying sensitivities.

**Conclusion:** Treatment should include both an approach to nicotine dependence and management of anxiety symptoms. Nicotine modulates neurotransmitters essential for mood and anxiety, and withdrawal makes users dependent.

**KEYWORDS:** Nicotine. Anxiety. Tobacco. Addiction.



### Central Message

Nicotine directly affects the central nervous system by modulating neurotransmitters involved in anxiety and mood. Although the substance can provide momentary relief from anxiety, its use and especially abstinence favors the appearance of anxious symptoms, making smoking cessation even more difficult. Therefore, smoking cessation treatment should address both chemical dependence and associated neuropsychiatric disorders, combining pharmacological and behavioral therapies to increase the chances of success in quitting tobacco use and minimize mental health impacts.

### Perspective

Considering not only chemical dependence, but also the impacts of nicotine on neuropsychiatric disorders such as anxiety, is very relevant for clinical practice aimed at the treatment of smoking. Understanding the neurobiological mechanisms involved can aid in the development of more effective strategies, such as the use of specific pharmacological therapies and targeted behavioral interventions. Thus, integrating anxiety management into smoking cessation treatment can enhance therapeutic results.

### RESUMO

**Introdução:** Embora a taxa de usuários de tabaco tenha reduzido nos últimos anos, as doenças relacionadas ao seu uso ainda são a principal causa de morte evitável. O tabagismo pode agravar ou desencadear sintomas de ansiedade na abstinência. Sua dependência apresenta alta comorbidade com distúrbios neuropsiquiátricos e transtornos de humor.

**Objetivo:** Relatar os efeitos da nicotina no sistema nervoso central, sua relação com a ansiedade e métodos de enfrentamento.

**Método:** Realizou-se revisão narrativa sobre a nicotina e a ansiedade nas bases PubMed, Google Acadêmico, Scielo e Capes Periódicos, usando os descritores "anxiety due to lack of nicotine", "nicotine" e "anxiety". Foram incluídos 19 artigos publicados entre 2000 e 2024.

**Resultado:** A nicotina liga-se a receptores nicotínicos de acetilcolina, liberando dopamina e causando dependência. Além disso, a exposição prolongada desregula o sistema hipotálamo-hipófise-adrenal, resultando em hipersecreção de cortisol e alteração na resposta ao estresse. Com a manutenção do uso, podem ocorrer mudanças neuronais que tornam a nicotina ansiogênica, devido à grande gama de receptores nicotínicos e suas diferentes sensibilidades.

**Conclusão:** O tratamento deve incluir tanto a abordagem para a dependência de nicotina quanto a gestão dos sintomas de ansiedade. A nicotina modula neurotransmissores essenciais para o humor e ansiedade e sua abstinência, torna os usuários dependentes.

**PALAVRAS-CHAVE:** Nicotina. Ansiedade. Tabaco. Vício.

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Conflict of interest: None | Funding: None | Received: 10/08/2025 | Accepted: 27/10/2025 | Publication date: 28/11/2025 | Correspondence: [izabelacray@gmail.com](mailto:izabelacray@gmail.com) | Associate Editor: Thelma Larocca Skare

How to cite:

da Costa IBC, Vasconcellos LM, Baena ML, Piluski PD, Defavari J, de Moura IW. Fisiopatologia da ansiedade relacionada ao uso de nicotina. BioSCIENCE. 2025;83(S2):e00006

## INTRODUCTION

**W**hile global tobacco addiction rates have steadily declined in recent years with the fall from 1.362 billion people using one or more tobacco products in 2020 to 1.245 billion in 2024, tobacco-related diseases remain the leading global cause of preventable mortality. According to the WHO, smoking is responsible for 63% of deaths related to chronic non-communicable diseases, 85% of deaths from chronic lung disease, 30% of deaths from various types of cancer (lung, mouth, larynx, pharynx, esophagus and others), 25% of deaths from coronary heart disease and 25% of deaths from cerebrovascular diseases.<sup>2</sup> And in addition to the well-known physical diseases caused by the habit of smoking, such as cardiovascular and pulmonary problems, smoking can also cause mental disorders, such as anxiety.<sup>3</sup>

Nicotine, the main substance present in tobacco that causes dependence, is a psychostimulant that, from the first puff, reaches the central nervous system, acting on the reward system, causing the release of the neurotransmitter dopamine, generating a sensation of momentary pleasure that has little durability, causing the individual to repeat the act of smoking and then enter the addiction.<sup>4</sup> Furthermore, it is well established that nicotine can modulate several neurotransmitter systems involved in the regulation of mood and anxiety, including dopamine, GABA, glutamate, serotonin (5-HT), and acetylcholine. And, also, nicotine dependence shows exceptionally high comorbidity with variety of neuropsychiatric disorders, including schizophrenia, mood and anxiety disorders.<sup>5</sup>

Anxiety disorder is related to the neurophysiological mechanisms of nicotine in active smokers, but anxiety is also one of the main symptoms of withdrawal syndrome, which occurs in those smokers who are trying to quit smoking.<sup>6</sup>

Despite the decrease in the number of smokers in the world population, smoking cessation treatment has not achieved the desired therapeutic success rates. In this context, there are smokers with a greater degree of difficulty in quitting the habit and others with a lower degree. Many of them quit smoking spontaneously, while others are unable to quit even with the use of medication. The latter are generally the most dependent, have a higher smoking history and have several failed attempts to quit.<sup>7</sup>

The objective of this review was to report the effects of nicotine on the central nervous system and its relationship with neuropsychiatric disorders, with emphasis on anxiety, seeking to understand the neurobiological mechanisms involved in nicotine dependence, the impacts of the substance during its use and abstinence, in addition to discussing therapeutic approaches to minimize anxiety symptoms and optimize smoking cessation treatment.

## METHOD

Narrative review carried out from the search for information contained in selected and credited

scientific articles. The search was initiated in the Pubmed, Scielo, Google Scholar and Capes Periódicos databases, through descriptors related to the theme, which were identified through DeCS using the following terms: "Anxiety", "Nicotine", "Withdrawal", "Addiction", "Central Nervous System" with AND or OR search, considering title and/or abstract. A total of 31 articles were found and read in full, of which 19 were published in the last 20 years (2004/2024), in English and Portuguese, which were more related to the theme and the proposed objective.

## DISCUSSION

### Nicotine and its effect on the body

Nicotine is part of the organic group of closed-chain amines, and for this reason it is liquid at room temperature. It can be acidic or alkaline. The first cannot penetrate the mucous membranes of the mouth, reaching the alveoli, where it becomes alkaline and is diffused in the blood by the action of the lungs. The second is easily absorbed in the oral mucous membranes, diffusing directly into the blood.

This substance is a psychoactive agent found in some plants, such as tobacco leaves, and in some fungi. It is known to have a bitter taste and high toxicity, in addition to inducing neoangiogenesis, responsible for cell proliferation.<sup>8</sup>

In the form of cigarettes, nicotine is the biggest cause of dependence on smokers, because, when burned, it reaches the brain in about 9 seconds, binding to nicotinic acetylcholine receptors, which facilitate the release of neurotransmitters, such as dopamine, acting on the feeling of well-being and acting as a physiological stimulant (increases blood pressure and respiratory and heart rates).<sup>8</sup>

In addition to the action on the brain, which is permanent, this substance affects the tissues and lungs, causing yellowing of the dentition, premature aging, reduced respiratory and circulatory capacity.

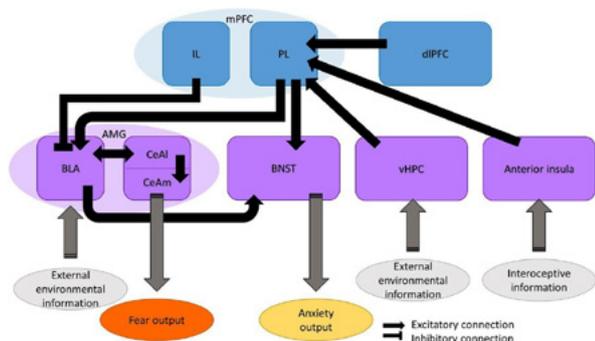
Nicotine is metabolized in the liver, by cytochrome 450, in about 15 minutes and the substance of each cigarette takes about 2 hours to decompose in the body.

### Nervous system and anxiety

Anxiety is a state of apprehension about the threat of the future, more diffuse and uncertain than that of fear. However, there is a big difference between the natural feeling of anxiety, related to daily life commitments, and the disorders that affect individuals. These are characterized by the expression of symptoms in an excessive way, such as those found in generalized anxiety disorder, panic syndrome, social phobia and OCD. The most common symptoms, for example, are shortness of breath, sweating, tremors, and rapid heart rate.

The neural circuit of anxiety works from the arrival of external environmental information to the ventral hippocampus (vHPC) and interoceptive information to the anterior insula of the brain. Subsequently, these

two areas of the brain, together with the dorsolateral prefrontal cortex (dlPFC), transmit signals to the medial prefrontal cortex (mPFC), more precisely to the infralimbic (IL) and paralimbic (PL) cortices, and will be routed to the 2 nuclei of the cerebral amygdala (AMG and BLA) and to the nucleus of the stria terminalis bed (BNST), conditioning the sensation of anxiety<sup>9</sup> (Figure).



Source: Robinson et al.<sup>9</sup>

**FIGURE** — Anxiety circuit diagram

### Anxiety caused during nicotine use

In many cases of nicotine dependence, it is possible to identify an association between smoking and symptoms of anxiety or panic attacks. Such conditions may predispose individuals to smoke cigarettes, when the diagnosis occurs prior to smoking, or they may be potentiated by nicotine withdrawal syndrome. However, anxiety symptoms often reach their peak during nicotine use.<sup>10</sup>

Smoking has adrenergic effects and consequently pulse rate, blood pressure and lactate and pyruvate levels increase. Nicotine crosses the blood-brain barrier and activates several pathways of the central nervous system, leading to the release of norepinephrine, acetylcholine, dopamine, and serotonin, effects that may be related to the development of anxiety. The presence of anxiety may alter the pharmacokinetics of nicotine and contribute to even more severe manifestations of panic syndromes.<sup>10,11</sup>

Prolonged exposure to nicotine dysregulates the hypothalamus-adrenal pituitary system, leading to cortisol hypersecretion and changes in the activity of the associated monoamine neurotransmitter system, whose function is to regulate stressful reactions, generating a predisposition to anxiety. The medial habenula, an interpeduncular nucleus (a circuit composed of neurons that project to the midbrain) has a high density of nicotinic acetylcholine receptors, which controls acute nicotine responses. Recent studies affirm a relationship between this circuit and symptoms of anxiety and fear. Levels of dependence are significantly correlated with anxious symptoms, i.e., the greater the smoking dependence, the higher the levels of anxiety.<sup>4-12</sup>

### Nicotine withdrawal syndrome

Nicotine withdrawal syndrome is a preponderant factor for the maintenance of smoking habits in young people and adults. This condition generates

a series of symptoms due to the abrupt withdrawal of the drug nicotine present in cigarettes, vapes, hookahs and several other vectors. This condition has physical and mental effects on its symptoms, with regard to the physiological effects, it is possible to mention bradycardia, gastrointestinal discomfort and increased appetite. In the psychological aspect, the consequences can be depressed mood, anxiety, irritability, dysphoria and concentration difficulties.<sup>13</sup>

### Anxiety caused by nicotine withdrawal

Nicotine withdrawal may be accompanied by an increase in anxiety, a factor that makes it difficult to stop smoking habits. Animal and clinical studies create hypotheses about the pathophysiology of correlation of this disease with the lack of this drug, the action of GABA<sub>B</sub> receptors, the use of nicotine for self-medication of pre-existing anxiety and the action of nicotinic receptors are some of them.<sup>14-17</sup>

### Nicotine as self-medication for pre-existing anxiety

There is a wide range of patients who use tobacco in this way. Nicotine, as an escape valve for existing anxiety, would bring a feeling of calm, reducing the symptoms of the disease. Data show that the smoking rate in the American population increased from 22% to 54.6% comparing those not affected and those affected by anxiety disorder. However, with the maintenance of smoking habits, making it chronic, there may be changes in the neuronal mechanisms that transform the hitherto anxiolytic drug into anxiogenic one within the body, which is due to the wide range of nicotinic receptors and their great expression, since some neurotransmitters released by them are more sensitive to nicotine withdrawal than others. In this way, the drug would initially combat those symptoms and start to increase them in moments of abstinence. In addition, patients with psychological disorders already present are more likely to have withdrawal symptoms, which makes the cessation process more complex, leading many patients to even give up. Making the comparison between healthy people and those with anxiety disorders, the propensity rate to quit smoking drops by almost half, from 42.5% to 23.2/32%. Some studies also show that withdrawal symptoms, especially psychological, are greater in patients with these disorders when pre-existing; however, the physiological relationship is not clearly described in the literature.<sup>5-17</sup>

### Action of nicotinic receptors on anxiety during withdrawal

Nicotinic acetylcholine receptors play a certain role in the response to stress, anxiety and depression, with the use of nicotine these responses can be exacerbated, causing cases of anxiety disorder. Nicotinic receptors are formed by subunits, being the most affected by nicotine 4 and 2. This drug will encourage the release of several neurotransmitters such as dopamine, GABA, glutamate, acetylcholine,

norepinephrine and serotonin. However, this action depends on which nicotinic receptor is being activated, since they can be stimulators, modulators, and inhibitors, causing the different effects of nicotine on the nervous system. It is possible that nicotine does not have an anxiolytic role in itself, it only generates relief for the anxiety caused by withdrawal, which would justify the paradox that exists in the action of the drug, since in the physiological action the cigarette would have a sympathetic excitement effect and in the physiological part the users would be more relaxed and calm. Thus, if the emotional part is justified by the relief of the withdrawal situation, the physiology of cigarettes would make sense. However, this would be a reason for anxiety to increase for a period of time with smoking cessation due to the expectation of relief from the feeling of abstinence. 17

### Ways to reverse or alleviate anxiety symptoms and forms of treatment for nicotine-dependent patients

After the smoking cessation process, many individuals find it difficult to reverse the symptoms of anxiety arising from nicotine addiction. Therefore, it is important that they are aware of some ways to alleviate such anxious symptoms and some forms of treatment for nicotine dependence.<sup>10</sup>

Sudden cessation of smoking in patients with anxiety may exacerbate symptoms of panic attacks or generate withdrawal symptoms, similar to panic attacks. It is possible that pharmacological treatment of this disorder decreases nicotine withdrawal symptoms in smokers. Therefore, in addition to nicotine withdrawal treatments, it is necessary to control anxiety symptoms. The probable mechanism that associates smoking with anxiety is noradrenergic. Clonidine, an  $\alpha$ -adrenergic agonist with some anti-panic properties, may improve tobacco withdrawal symptoms. In addition, pharmacological interventions are necessary when symptoms are severe and disabling. Selective serotonin reuptake inhibitors can be effective for relieving anxiety symptoms and are considered the medication of choice due to their side effect profile, greater safety, easy administration, and when there is comorbidity with mood disorder.<sup>10-18</sup>

Regarding the treatment of nicotine addiction, dialogue with the patient is the first step towards quitting smoking. It should be evaluated whether or not the patient is dependent on nicotine, how much he smokes, if he is willing to quit smoking, if he has associated diseases and what are the forms of treatment most accessible to him. Then, it proceeds to pharmacotherapy, which is indicated for nicotine-dependent people. It is divided into first-line drugs (bupropion and nicotine replacement therapy) and second-line drugs (clonidine and nortriptyline). Another form of treatment involves alternative methods such as acupuncture, cognitive behavioral therapy, and self-help groups.<sup>19</sup>

## CONCLUSION

The literature review showed that nicotine exerts profound effects on the central nervous system, modulating neurotransmitters critical for mood and anxiety, such as GABA. Not only does this substance have addictive effects, that make tobacco addictive, but it is also associated with increased anxiety symptoms, both during continuous use and withdrawal, due to the paradox that exists in its physiology. These findings reinforce the need for integrated therapeutic approaches that simultaneously treat nicotine dependence and anxiety disorders, using both pharmacological interventions and alternative therapies, to increase the chances of smoking cessation and promote sustainable recovery.

#### Authors' contributions

Izabela Berezina Cray da Costa - Conceptualization  
Luana Mattos Vasconcelos - Formal analysis  
Mariana Latronico Baena - Methodology  
Pietra Delgado Piluski - Writing (original draft)  
Jaciele Defavari - Writing (proofreading and editing)  
Irlena Wisniewska de Moura - Supervision

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