

Edgar Alberto Ribeiro Pereira

**Sales of anti-smoking drugs in Portugal 2010-2020**

Faculdade de Ciências da Saúde

Universidade Fernando Pessoa

Porto, 2023



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Atesto a originalidade do trabalho,

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## Resumo

O consumo de tabaco representa anualmente em todo o mundo 8 milhões de mortes prematuras, com 1,2 milhões causadas pelo fumo passivo. A dependência de nicotina é um importante contribuinte para a utilização contínua destes produtos, que podem causar doenças como o cancro e DPOC, entre outras. Foram introduzidas farmacoterapias como terapias de substituição de nicotina (TSN), vareniclina, bupropion e outras intervenções não farmacológicas para ajudar os fumadores a deixarem de fumar.

Esta dissertação analisa as vendas de nicotina, vareniclina e bupropion em Portugal de 2010 a 2020. Além disso, foram analisados os seus mecanismos, farmacocinética, efeitos adversos, eficácia e dosagens. Os dados foram fornecidos pelo Centro de Informação do Medicamento e Produtos de Saúde e a revisão narrativa foi feita usando as bases de dados PubMed, Science Direct e Google académico incluindo referencias a partir de 2004 com ênfase nos últimos 10 anos.

Os resultados mostraram que as TSN são a farmacoterapia preferida, representando 70,47% das vendas totais para a cessação tabágica. O ano de 2012 foi o pico em termos de vendas, com 124 834 unidades vendidas. A vareniclina foi a segunda escolha para a cessação tabágica, representando 29,10% das vendas totais. Foi detetado um aumento de 48,3% nas vendas de 2016 para 2017 devido ao reembolso, disponibilizado pelo sistema nacional de saúde, que entrou em vigor em 2017. Por outro lado, o bupropion, demonstrou uma contribuição residual, representando apenas 0,43% das vendas.

Em termos de eficácia, os três medicamentos mostraram resultados positivos, com a vareniclina sendo a terapia única mais eficaz, seguido das TSN e bupropion que apresentaram resultados semelhantes. No entanto, a combinação de intervenções provou ser mais bem-sucedida na obtenção de uma cessação tabágica prolongada, reduzindo as chances de recidiva por parte dos pacientes e abandonarem o tratamento. Alguns efeitos adversos comuns associados a estes medicamentos são insónias, náuseas, dores de cabeça, tonturas, diarreia e obstipação. A vareniclina e bupropion apresentaram efeitos adversos mais graves, embora raros, como depressão, ideação suicida, efeitos cardiovasculares e outros efeitos psiquiátricos.

Em conclusão, o consumo de produtos de tabaco continua a ser um problema importante para a saúde pública, mas os dados mostram que mais pessoas procuram tratamentos para ajudá-las a deixar de fumar.

Palavras-chave: Cessação tabágica; Terapia de substituição de nicotina; Vareniclina; Bupropion

## **Abstract**

Tobacco usage worldwide represents annually 8 million premature deaths with 1,2 million being caused by second-hand smoke. Nicotine addiction is a major contributor to the continuous use of these tobacco products that can cause diseases like cancer, chronic obstructive pulmonary disease among others. Pharmacotherapies like nicotine replacement therapies (NRT), varenicline, bupropion and other nonpharmacological interventions were introduced to help smokers quitting.

This dissertation aimed to analyze the sales of nicotine, varenicline and bupropion in Portugal from 2010-2020, and to review their mechanisms, pharmacokinetics, adverse effects, efficacy, and dosages were analyzed. The sales data was provided by Centro de Informação do Medicamento e Produtos de Saúde (CIMI) and the literature review was conducted using Pubmed, Science Direct and Google Scholar as databases and references were included from 2004 onwards, focusing in the last ten years.

Results showed that NRT is the preferred pharmacotherapy representing 70.47% of total smoking cessation sales. The year of 2012 was the peak in terms of sales with 124 834 units sold. Varenicline was the second choice for smoking cessation representing 29,10% of total sales. A 48,3% increase in sales was detected from 2016 to 2017 due to the reimbursement provided by the national health care system which started in 2017. Bupropion on the other hand demonstrated a residual contribution with only 0,43% in terms of sales. In terms of efficacy, all 3 drugs showed positive results, with varenicline being the most effective single therapy and NRT and bupropion showing similar results. However, the combination of interventions proved to be more successful in achieving prolonged smoking cessation, reducing the chances of patients resuming smoking and quitting the treatment. Some common adverse effects associated with these medications are insomnia, nausea, headaches, dizziness, diarrhea, and constipation. Varenicline and bupropion also presented more severe adverse effects although rarer like depression, suicidal ideation, cardiovascular effects, and other psychiatric effects.

In conclusion, consumption of tobacco products remains a major public health issue, but the data showed that people are seeking for treatments to help them quit consuming.

**Keywords:** Smoking Cessation; Nicotine replacement therapy; Varenicline; Bupropion

*Aos meus avós, por todos os valores que me transmitiram e sigo na minha vida,*

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## Abbreviation index

<b>3HC</b>	<i>3'-hydroxycotinine</i>
<b>BID</b>	<i>Twice a day</i>
<b>CIMI</b>	Centro de Informação do Medicamento e Produtos de Saúde
<b>CL<sub>R</sub></b>	<i>Renal clearance</i>
<b>C<sub>max</sub></b>	<i>Maximum plasma concentrations</i>
<b>COPD</b>	<i>Chronic obstructive pulmonary disease</i>
<b>COVID-19</b>	<i>Coronavirus disease 2019</i>
<b>CVD</b>	<i>Cardiovascular diseases</i>
<b>CYP</b>	<i>Cytochrome P450</i>
<b>DA</b>	<i>Dopamine</i>
<b>EC<sub>50</sub></b>	<i>Half maximal response</i>
<b>EU</b>	<i>European Union</i>
<b>FDA</b>	<i>Food and Drug administration</i>
<b>GABA</b>	<i>γ-aminobutyric acid</i>
<b>hOCT2</b>	<i>Human organic cation transporter 2</i>
<b>INFARMED</b>	Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.
<b>K<sub>i</sub></b>	<i>Equilibrium binding assays</i>
<b>NA</b>	<i>Noradrenaline</i>
<b>nAChRs</b>	<i>Nicotinic cholinergic receptors</i>
<b>NE</b>	<i>Norepinephrine</i>

<b>NRT</b>	<i>Nicotine replacement therapies</i>
<b>T<sub>1/2</sub></b>	<i>Half-life time</i>
<b>T<sub>máx</sub></b>	<i>Time to peak drug concentration</i>
<b>TQD</b>	<i>Target quit date</i>
<b>UGT</b>	<i>Glucuronosyltransferase</i>
<b>UK</b>	<i>United Kingdom</i>
<b>US</b>	<i>United states</i>
<b>WHO</b>	<i>World Health Organization</i>

## **I. Introduction**

In the modern world, tobacco usage is one of the primary causes of premature death, reaching over 8 million deaths annually. Out of these, 1,2 million deaths correspond to second-hand smoke. The most common way of tobacco consumption comes in the form of cigarette smoking but other products such as smokeless products, waterpipe tobacco, cigars, bidis and kreteks, also contribute to a worse health condition (WHO, 2023).

Trough the consumption of tobacco products, a wide variety of compounds are released, mainly in the form of smoke. These compounds include nicotine, carcinogen agents such as formaldehyde and carbon monoxide, a known asphyxiant. These agents can reach the respiratory system and the bloodstream. With all the components present in the tobacco products, it's possible to associate smoking to various diseases and adverse effects, the risks associated can be translated into early morbidity and mortality because it can promote various forms of cancer like lung, pancreas, and stomach cancer. Not only that, but smoking is also responsible for promoting other diseases also associated with death, examples are stroke, COPD and aortic aneurysm (Samet, 2013).

The prevalence of smoking worldwide is reflected in a large amount of serious health problems and so, it is extremely important to find new strategies and therapies that can help smokers reach abstinence and prevent others to start smoking. One of the main problems with tobacco products is the nicotine dependance. Nicotine is known to be as addictive as other drugs such as heroin and cocaine. It causes long term dependance, even patients who suffer from serious health conditions associated with smoking, resume smoking after reaching abstinence for a set period (WHO, 2008).

Many pharmacotherapies are used in aid for smoking cessation, however nicotine replacement therapy (NRT), varenicline and bupropion are the main options used in clinical treatment (WHO, 2008).

Besides the pharmacological treatments available, there are also other interventions capable of helping patients quit smoking and prevent the number of potential future smokers, these interventions can increase the smoking cessation rate when used in conjunction the medical therapies. These interventions include individual, group and telephone counselling, self-help materials, cognitive behavioral therapy, and resident programs. There also other policies and strategies involved, these were implemented by

the World Health Organization (WHO), whose aim is to bring awareness to the tobacco epidemic, these are: promoting environments where smoking is prohibited, labels in smoke packages advertising the dangers of smoking, provide support lines to help educate patients and citizens on tobacco dependence, minimize the cost of medical treatments, increase taxes on tobacco products, and develop laws that decrease the smoking marketing (WHO, 2008).

The main objective of this dissertation was to describe and analyze the data regarding the sales of anti-smoking drugs in Continental Portugal between 2010 and 2020 with emphasis on nicotine, varenicline and bupropion. It also aimed to make a literature review of the data regarding several characteristics of these drugs such as action mechanism, pharmacokinetics, adverse effects, efficacy, and posology.

## **II. Methodology**

The data regarding the sales of the medicines nicotine, varenicline and bupropion, in Continental Portugal between 2010 and 2020, was provided by the portuguese medicines agency: Centro de Informação do Medicamento e Produtos de Saúde (CIMI) of Autoridade Nacional do Medicamento e Produtos de Saúde, I. P. (INFARMED). The data was processed and organized in tables for each medicine by yearly and monthly sales and finally organized by total sales. Graphics were organized by yearly sales.

Regarding the literature review, the data was gathered from various articles from scientific databases like PubMed, Science Direct and Google Scholar, using the keywords: “Smoking Cessation”, “Nicotine replacement therapy”, “Varenicline”, “Bupropion”, “Adverse effects” and “Mechanism of action”. The articles chosen for this review were written in English and Portuguese and published from 2004 onwards, priority was given to the most recent articles, but some older articles were needed to help explain a few concepts. The choice of the articles was primarily made by reading their respective titles and abstracts. Secondly the articles of interest were picked and fully analyzed excluding duplicated articles and articles unrelated to the dissertation concerns. Finally, 37 articles from year 2004 to year 2023 were included in his thesis.

### **III. Development**

#### **3.1. Nicotine consumption in the world and Portugal**

Regarding nicotine consumption across the world, the European Commission conducted a survey with the objective to understand the behavior of Europeans towards tobacco and other nicotine products (European Commission, 2021).

Concerning traditional tobacco products, 21% of Portuguese participants were smokers, 15% were former smokers and 64% never smoked. In the case of the European Union (EU) plus the United Kingdom (UK), 23% were smokers, and 22% of people were former smokers. Furthermore, it was also demonstrated that in Portugal and in the EU, men displayed higher prevalence of smoking with 27% and 26% respectively when compared to women which was 21% in the EU and 16% in Portugal. Also, the age interval with most prevalent smokers were between 25 and 39 years old in both Portugal and the EU (European Commission, 2021).

The survey also showed that Boxed cigarettes were the most consumed traditional tobacco products with 85% of Portuguese participants choosing this product. In the case of the EU, 69% chose the boxed cigarettes but there was an increase in the hand-rolled cigarettes choice, displaying that 22% of people preferred the latter. Finally, the overall consumption of nicotine products was also studied, with 20% of Portuguese participants being daily consumers meanwhile in the EU that rate was 23% (European Commission, 2021).

Secondhand smoke exposure was shown to be more prevalent in places with outdoor spaces. In the case of Portugal, 78% of respondents were exposed to secondhand smoke in the outdoor space of eating and drinking establishments, 65% were exposed in outdoor events and 17% were exposed in spaces dedicated to children. On the other hand, 10% and 13% of Portuguese participants were exposed to smoke in eating and other social places where smoking is not common. In the case of bars and other drinking spaces, 35% of the participants were exposed to secondhand smoke, which was higher when compared to the 28% found in the EU (European Commission, 2021).

### **3.2 Non-pharmacological interventions**

To achieve smoking cessation, it is necessary to think in a multi component approach that has 2 fundamental principles: pharmacological therapy, and interventions that educate the patient on motivation to quit smoking, behavior analysis, triggering stimuli and auto efficacy. The rate of long-term abstinence is achieved with strong base interventions and with the pharmacological treatments, with chances of smoking cessation doubling when these principles are applied together (Mota, 2015).

With this objective in mind, the WHO developed a policy package denominated as Mpower. This package aims to provide tools so that the tobacco epidemic can be controlled (WHO, 2008).

One of the interventions involves protecting people from second-hand smoke which affects non-smokers but also smokers with the intention to quit. To achieve this, it's necessary to ensure legislation that makes smoking indoor not allowed (WHO, 2008).

Secondly, to facilitate smoking cessation and prevent relapses, counseling from health professionals help achieve this with higher success rates. The transmission of objective, easy to understand advice associated with specific matters that interest the patient, for example pregnancy improve the success of this strategy. Other way to provide counselling can be trough telephone quit lines. To improve effectiveness of this method, follow-up calls must be made to better monitor the situation of the patient (WHO, 2008).

Education is also important since it can influence decision making regarding smoking. This education may be done through the media by spreading information about the risks of smoking, and by warning signs or labels on tobacco products but also targeted to groups with lower knowledge. Other ways to spread information comes in the form of counter-advertising and media coverage of campaigns about anti-smoking activities (WHO, 2008).

Lastly, other solutions that may help to control the smoking rates are the implementation of legislation that bans promotion and advertisement of tobacco products. In addition, the increase of taxes to tobacco products, proved to be one of the most optimal ways to decrease smoking prevalence by reducing the affordability of tobacco products (WHO, 2008).

### **3.3 Pharmacological therapies**

Studies developed, revealed the efficacy of various smoking cessation drugs. These studies analyzed what drugs can increase long-term abstinence success, but also concluded about their safety for the patient (Mota, 2015).

With these characteristics, 3 major first line treatments were recognized, these being NRT, varenicline and bupropion (Mota, 2015).

In terms of efficacy, it was demonstrated that NRT increases chances of patients quit smoking when compared to placebo, NRT showed similar results to bupropion with none of the therapies having increased benefits when compared with each other. On the other hand, Varenicline demonstrated to be more effective in smoking cessation in comparison to NRT formulations such as transdermal patches and gums. All treatments involving nicotine were similarly effective with exception of nicotine gums that presented worse results by comparison. Combination therapy however, showed higher levels of efficacy in comparison to single NRT treatment and bupropion, and as able to reach the levels of efficacy of varenicline (Cahill *et al.*, 2013).

There are other drugs such as clonidine and nortriptyline that also showed some efficacy as smoking cessation drugs, however they also have significant adverse effects and as such are treated as a second line choices (Mota, 2015).

Smoking cessation drugs can also be used to reduce craving symptoms in persons which don't want to quit smoking but are temporarily unable to smoke. Examples of this could be interned patients (Mota, 2015).

#### **3.3.1 Nicotine replacement therapy (NRT)**

##### **i. Action mechanism**

To understand the basis of nicotine replacement therapy, it's necessary to understand the mechanisms of nicotine and how it creates dependance. Nicotine is responsible for the tobacco dependence, the addiction effect is compared to the addiction effect of heroin and cocaine and as a result, smokers keep smoking despite all the risk associated the tobacco. Nicotine is a drug with psycho-active characteristics, it induces craving for the many tobacco products and creates abstinence symptoms (Behrakis *et al.*, 2020).

The smoke inhaled by the smoker contains the nicotine that is transported to the lungs where it is absorbed into the bloodstream, after that it reaches the brain and connects to the nicotinic cholinergic receptors (nAChRs). The nAChRs have a lot of diversity having  $\alpha$ -2 through  $\alpha$ -10 subunits and  $\beta$ -2 through  $\beta$ -4 subunits, allowing multiple possible combinations. The most common nAChRs are the  $\alpha$ 4 $\beta$ 2 subtype,  $\alpha$ 4 subunit is responsible for nicotine sensitivity while the  $\beta$ 2 subunit for the liberation of dopamine and produces behavioral effects. There are however other subunits with other function, for example the  $\alpha$ 3 $\beta$ 4 subtype mediates the cardiovascular effects by nicotine consumption while the  $\alpha$ 7 subtypes facilitate fast synaptic channeling (Benowitz, 2008).

The pre-synaptic nAChRs modulate the liberation of neurotransmitters and consequently the activation of the receptors occurs. Not only dopamine but other neurotransmitters are also released, examples are noradrenaline, acetylcholine, serotonin, endorphins,  $\gamma$ -aminobutyric acid (GABA) and glutamate. These neurotransmitters mediate different effects induced by the consumption of nicotine. GABA and endorphins reduce anxiety and tension, serotonin modulates mood, glutamate enhances memory, dopamine induces a pleasure sensation and acetylcholine improves cognitive function (Benowitz, 2008). The reward obtained for nicotine administration comes from dopamine release in various brain areas, with the nucleus accumbens being of very significance of this mechanism. When smoking, nicotine reduces the withdrawal symptoms that are caused by the absence of nicotine when not smoking, but it also stimulates psychoactive effects (Benowitz, 2008). Consequently, physical dependence is developed because the nicotine receptors are desensitized but increase in numbers, this means that with time, more nicotine will need to be consumed to produce the same effects on the smoker (Behrakis *et al.*, 2020).

The objective with NRT is to reduce the increase in nicotinic receptors produced by smoking and therefore reduce dependence, and to reduce the craving and symptoms by stimulating the receptors. Reduction of withdrawal effects is reached with low levels in circulation. Another mechanism, with importance to fast deliver systems such as nasal spray is positive reinforcement for some effects such as stress relieve. This mechanism is regulated by fast absorption, and concentration levels of nicotine present in the arterial bloodstream. Lozenges, inhalers, and nicotine gums benefit less from this mechanism but allow the patient to control the dose of nicotine administered when the patient feels the need to smoke. NRT also reduces the positive effects from smoking, this happens because NRT desensitizes the nAChRs (Benowitz, 2008).

## ii. Pharmacokinetics

Nicotine is one of the main molecules present in tobacco products, there are however another similar molecule that are also present in many products, examples of this are anatabine, anabasine and normicotine, which by measuring of its plasma concentrations, can help determine if a person was exposed to nicotine through consumption of a tobacco product or by NRT (Anderson and Chan, 2016).

The absorption of nicotine is made in many ways such as inhalation, buccal and transdermal absorption. The absorption of nicotine through smoking is done by inhalation of the smoke which contains nicotine and by transport of nicotine by particles that lead to the lower tract of the respiratory system. The bioavailability of nicotine consumed by smoking ranges between 80 and 90%, these values can be explained by how the airways are impacted by the particles containing nicotine that are surrounded by fluid and, how efficiently nicotine goes from particles to smoke. Studies revealed that transdermal availability ranges between 68 and 100% while nicotine gum displayed 51-78% of bioavailability. Despite these numbers, it was confirmed that by smoking, nicotine reaches maximum plasma concentrations ( $C_{max}$ ) in 5 minutes meaning that nicotine produces its pharmacological effects fast (Anderson and Chan, 2016).

Nicotine is extensively metabolized in the liver, more specifically by CYP enzymes with CYP2A6 being the principal enzyme involved, CYP2B6 and CYP2E1 have a lesser participation on nicotine metabolism. The major metabolic path of nicotine is the conversion of nicotine in cotinine, there are however, other metabolites that are formed, although in lower proportions, during metabolism such as, nornicotine, 4-(3-pyridyl)-4-hydroxybutanoic acid and nicotine-N-oxide, other metabolic route consists in the conjugation of nicotine. After the conversion of nicotine into cotinine, great part of cotinine suffers glucuronidation reactions performed by 2 enzymes these being UGT1A4, UGT1A9 (glucuronosyltransferase). Another possible metabolism route is CYP2A6 converting cotinine into 3'-hydroxycotinine (3HC). Following this reaction 3HC is glucuronidated into O-glucuronide and 3HC-N-glucuronide by UGT2B10 and UGT2B17 (Anderson and Chan, 2016).

The metabolism of nicotine is also influenced by polymorphisms that change enzyme's ability to metabolize. Studies described the behavior of CYP2A6 on Caucasians, Latinos, Asians, and African Americans, revealing that the latter two metabolize nicotine slower in comparison to the first 2 groups. Even though nicotine dependence sits on many factors, data suggests that faster metabolism of nicotine leads to greater dependency (Anderson and Chan, 2016).

One way of knowing if the patient is adhering to the smoking cessation treatment is to check for metabolite concentrations in urine, such as cotinine and 3HC because nicotine metabolites appear in urine in major amounts (Anderson and Chan, 2016).

### iii. Adverse effects

Understanding nicotine's adverse effects is very valuable and important because it is the most prescribed smoking cessation drug, the adverse effects can be devised by the pharmacology of nicotine and by the administration method (Hays and Ebbert, 2010).

NRT is approved for use by nearly all guidelines for smoking cessation treatment, this means that NRT has been extensively studied and it's considered a safe choice for the treatment of tobacco dependence, NRT are also available for purchase without the need of prescription in various countries. Despite being considered safe, NRT display some common general adverse effects such as insomnia, abnormal dreams, nausea, headaches, dizziness, palpitations, diarrhea, and constipation. Symptoms like headaches and dizziness were revealed by studies to occur in same proportion in groups administered with placebo and NRT, insomnia however was more prevalent in groups treated with NRT, but another study, with participation of 3500 individuals, demonstrated that there was no difference in the manifestation of these symptoms by placebo and NRT- treated groups with an occurrence rate of 5 to 6%. Statistics in the US showed that, out of 21 000 patients using NRT, 4,3% and 1% using other type of NRT such as lozenge experienced insomnia. Symptoms like abnormal dreams were also declared but, there is no clarity if it is induced by NRT or if it is a consequence to nicotine withdrawal (Hays and Ebbert, 2010).

Nausea and vomits are the most common gastrointestinal effects provoked by NRT, a study involving the administration of a 2/4 mg nicotine lozenge were compared to placebo

in 1800 active smokers. Data showed that that placebo treated groups had a 4.8% incidence of nausea meanwhile, lozenge treated groups displayed higher rates with 4 mg lozenge having a 15,1% incidence rate and 2 mg groups had 12,2% additionally, another study mentioned that 12-13% of the participants experienced nausea when treated with a nicotine nasal spray (Hays and Ebbert, 2010).

Nicotine can also induce cardiovascular effects, these include vasoconstriction and increased blood pressure, these effects cause major concerns because smoking increases the risk of cardiovascular diseases (CVD). Symptoms like palpitations and cardiac awareness are the most reported ones with incidence rates between 0 and 24% with nasal spray having the higher rates (7-24%) than slower delivery methods like nicotine patch who has 2-3% rate. These results suggest that faster delivery methods have higher chance of inducing cardiovascular symptoms. Studies showed no relation between administration of NRT and serious cardiovascular effects like arrhythmia and heart attack however, even though NRT is considered safe for patients with controlled CVD, caution is required in cases of unstable CVD (Hays and Ebbert, 2010).

Other adverse effects induced by NRT depend on the delivery system. NRT delivered orally provokes symptoms like sore throat/mouth and cough, other symptoms such as aphthous stomatitis have also been associated with NRT oral systems but a recent study reported a 40% incidence rate of aphthous ulcers however, there was no relation established between the symptom and the type of NRT used or other types of therapies, the data suggests that smoking abstinence might be the cause of aphthous stomatitis. Cough however is rarely associated with oral NRT systems such as nicotine gums and lozenges but, has been reported to cause cough with rates ranging from 5,6 to 40% if nicotine is inhaled, suggesting that nicotine can cause inflammation (Hays and Ebbert, 2010).

As previously mentioned, intranasal NRT is the fastest delivery system and is also associated with various adverse effects like, nausea, cardiac awareness, and irritation in the nasal airway. Studies involving administration of nicotine nasal spray for smoking cessation revealed that the incidence rate of nasal irritation, sore throat and coughing were 76-98%,61-95% and 40-82% respectively. Further examination revealed no injury to the nasal mucosa and that the symptoms occurred mildly of moderately in early phases of the

treatment but were over the course of the treatment. Patients with respiratory diseases such as asthma can use intranasal NRT for smoking cessation (Hays and Ebbert, 2010).

Transdermal patches are a sustained delivery system and as such share the common adverse effects that nicotine provokes however, it can also provoke skin irritation or rash with an incidence between 10 and 25%. The symptoms are often mild but, in some cases, the reaction can lead to blistering and edema, redness and itch can be resolved by removing the patch or by applying topical lotions. Cases of severe allergies are rare but require the use of alternative NRT, same applies if other symptoms persist (Hays and Ebbert, 2010).

In consequence of the adverse effects already described, nicotine replacement therapies mustn't be prescribed to patients with active gastroduodenal ulcer, recent heart attack history (less than 4 weeks), non-controlled hypertension and severe arrhythmia. Also smoking cessation therapies for pregnant women must be done without NRT even though the risks associated to smoking during pregnancy are superior to the risks of taking NRT during pregnancy. In patients with controlled cardiovascular diseases, NRT is considered a safe method to quit smoking, with studies demonstrating that there is no increased chance of patients with previous history of CVD suffering heart attack or stroke. In Portugal, NRT is prescribed without the need for a medical prescription because it is considered a safe therapy. However, INFARMED provides more careful instructions in relation to the use of NRT in patients with CVD advising the individuals to seek medical counselling before taking NRT (Mota, 2015).

#### iv. Interactions

As previously explained, nicotine metabolism involves the action of CYP enzymes, particularly CYP2A6, as such the co administration of NRT with other drugs may influence the action of CYP2A6 therefore impacting the metabolism. Examples of this are selegiline, methoxsalen and tranylcypromine, these drugs slow the metabolic process of nicotine acting as inhibitors of the CYP2A6 enzyme, however their use in the clinical practice is uncommon. Another documented association is opioid abuse and smoking, studies performed aimed to reflect on potential interactions between methadone and nicotine, the trial was performed by administrating nicotine via smoking on day 1 to 40

patients also consuming methadone, in the following 2 days NRT patients received randomly placebo or NRT. The measurement of nicotine metabolites and methadone didn't detect changes in plasmatic concentrations of methadone, but nicotine plasma levels were increased when nicotine was accessed through smoking, other interaction observed was the potentializing of methadone effects by nicotine obtained by smoking. Methadone also affected the withdrawal levels of nicotine by reducing them. This study showed that it is possible that methadone and nicotine may change the pharmacodynamics. Tests involving carbamazepine, phenobarbital, rifampicin, phenytoin and dexamethasone inferred that these drugs could increase the activity of CYP2A6. Furthermore, hormones such as estrogen also increase the metabolic activity of CYP2A6, this mechanism suggests that women can have higher clearance speed of nicotine when compared to men, particularly when taking combined contraceptives (Anderson and Chan, 2016).

#### v. Efficacy and posology

While using NRT as a smoking cessation therapy it is necessary to consider possible contraindications, to this extent changes can be made to the therapy, like changing posology, to accommodate to the patient's needs. In the case of transdermal patches, 16-hour patches are used during the day and removed before bedtime, this type of transdermal patch is used in patients inclined to experience insomnia. Patients with tendency to manifest withdrawal symptoms during the nighttime or in the morning are prescribed with 24-hour patches. In terms of efficacy there is no evidence suggesting one type of patch to have higher efficacy than the other and there is no need for weaning. The posology for the 24-hour and 16-hour patches are 21mg and 15 mg respectively. The efficacy of the transdermal patch can be affected by hot weather which increases sweating, thereupon coverage of the transdermal patch is necessary to keep it attached to the skin (Mota, 2015).

While awake, nicotine patches and gums are usually administered every 2 hours however, the patient can use more in case of emergency or combine with other formulations such as transdermal patches in certain scenarios. Patients using oral nicotine formulations must wait 15 mins in cases of previously drinking coffee or soda drinks because the efficacy of the therapy is affected. Using the correct technique is important

because it helps improve the efficacy of the formulation and at the same time decreases adverse effects. Nicotine tablets must be slowly chewed until nicotine is released from the tablet. To help maximize absorption, chewing process must be interrupted regularly to promote contact between the nicotine tablet and the buccal mucosa, also it reduces the production of saliva which increases the chances of ingestion of the tablet and reduced absorption. The process for nicotine gums is similar, the gum must be slightly moistened and kept in contact with the mucosa to promote absorption. Nicotine gums with a dose of 1,5 mg release an equivalent amount of nicotine as 2 mg nicotine tablets (Mota, 2015).

Regarding transdermal patches, they must be placed in zones with dry skin, zones with few body hairs and without injuries, the patches must be changed and placed in different place to minimize skin reactions (Mota, 2015).

### 3.3.2 Varenicline

#### i. Action mechanism

Varenicline is known to be a partial agonist to  $\alpha 4\beta 2$  nicotinic acetylcholine receptors (nAChRs), it has high compatibility for  $\alpha 6\beta 2$ -nAChRs, involved in the mechanism related to nicotine dependence. Varenicline may act in two different ways, as an agonist, that has the capability of reducing activation of nAChRs like what nicotine released from smoking does, but also as a competitive antagonist (Tonstad *et al.*, 2020).

Studies performed on this matter revealed that varenicline had high selectivity for the  $\alpha 4\beta 2$ -nAChR but had sub abnormal affinity, reaching 0,06 nM in equilibrium binding assays ( $K_i$ ). Other subtypes reached higher values these being 240 nmol/L for  $\alpha 3/\beta 4$  subtypes, 3540 nmol/L for  $\alpha 1\beta\gamma\Omega$  and 322 nmol/L for  $\alpha 7$  subtypes. Compared to cytosine and nicotine, varenicline reached 3-fold and 16-fold more affinity towards the  $\alpha 4\beta 2$ -nAChR respectively. It also showed average affinity to serotonin 5-HT<sub>3</sub> receptors reaching 350 nmol/L. Another assay revealed that to reach half maximal response ( $EC_{50}$ ), the concentration of varenicline needed was inferior comparing to nicotine. Antagonistic activity was also showed with varenicline reducing the effect of nicotine by 34%. *In vivo*, administration of the maximum effective subcutaneous dose (1 mg/kg) of varenicline resulted in complete blockage of the nicotine. The replacement of nicotine obtained through smoking with varenicline can result in reduced urge to smoke during treatment

for smoke cessation. On the other hand, the antagonistic mechanism revolves around nicotine and varenicline competing for binding locations, the result is less nicotine bonded to the  $\alpha 6\beta 2$  and  $\alpha 4\beta 2$  nicotinic acetylcholine receptors (Tonstad *et al.*, 2020).

The antagonistic activity of varenicline leads to reduced rewards from smoking in the case of relapse, this happens because the dopamine activation induced by nicotine's activity, when inhaled from the smoke, at the  $\alpha 4\beta 2$  nAChRs is stopped due to the competitive mechanism of varenicline, meaning that occupation of  $\alpha 4\beta 2$  and  $\alpha 6\beta 2$  receptors by nicotine is reduced due to varenicline binding to the same receptors (Ebbert *et al.*, 2010; Aubin *et al.*, 2014).

## ii. Pharmacokinetics

When administrated orally, varenicline is extensively absorbed by the gastrointestinal system, reaching over 90% of systemic bioavailability. Variables such as time of day, race, sex, and administration in conjunction with food didn't affect these pharmacokinetics parameters (Jiménez-Ruiz *et al.*, 2009; Faessel *et al.*, 2010).

The time necessary reach maximum concentration in plasma ( $t_{m\acute{a}x}$ ), following single dose administration, happened between 3 or 4 hours. An *in vitro* test performed showed that varenicline presents high apparent permeability surpassing the levels of metoprolol, a positive control on cell permeation. Furthermore, other examinations indicated that varenicline is a highly dissolvable molecule and very permeable. Due to these characteristics, varenicline is considered to follow first-order kinetics (Jiménez-Ruiz *et al.*, 2009; Faessel *et al.*, 2010).

Other studies revealed that varenicline presents a  $t_{1/2}$  it being 24 hours, not only that but repeated administration led to steady-state levels being reached after 4 days (Jordan and Xi, 2018).

The distribution profile of varenicline is marked by being highly available in the bloodstream. This means that the majority of varenicline is not bounded to plasma proteins (less than 20%). Ex-vivo tests were performed in young and elderly smoker, they showed that the interval of free varenicline available for distribution was from 87,9% to 93,5% in plasma, these values weren't affected by variables such as age and renal

function. Because of this it's proven that varenicline is rapidly dispended to body and brain tissues. In the stationary state, the apparent volume available for distribution of varenicline is 415 liters for a 70Kg individual (Faessel *et al.*, 2010).

Majority of varenicline reached the urine in the unaltered state, with 92% of varenicline reaching urine, however less than 10% of varenicline appears in urine in the form of metabolites, these being N-carbamoylglucuronide and hydroxyvarenicline. In the bloodstream, varenicline also stays in its primary form. Although 91% it's not altered, there are 4 metabolic paths identified, these are varenicline N-carbamoyl glucuronidation, N-formylation, conjugation with a hexose sugar, and oxidation (Jiménez-Ruiz *et al.*, 2009; Faessel *et al.*, 2010).

Due to the nature of molecule structure and their low concentration, it is expected that these metabolites don't participate in any interactions with  $\alpha_4\beta_2$  nAChR and have no relevant pharmacological effects. Metabolic profiles were studied in smokers and non-smokers revealing no differences between them, furthermore, tests conducted *in vitro* using human hepatic microsomes, did not detect depletion of varenicline over time and did not identified metabolites produced by cytochrome P450 (CYP) enzymes (Faessel *et al.*, 2010). However, when the hepatic microsomes were in favorable environment to promote the action of UGT enzymes, varenicline N-carbamoylglucuronide conjugate was produced enzymes (Faessel *et al.*, 2010).

Patients suffering from hepatic impairment do not face any changes in the hepatic metabolism of varenicline since has previously showed, the hepatic metabolism of varenicline is minimal (Tonstad *et al.*, 2020).

Most of varenicline is eliminated though urine, its elimination half-life ( $t_{1/2}$ ) is about 24 hours and dose independent. As such, varenicline depends on the renal clearance ( $CL_R$ ) to be eliminated, and there is a linear relation between varenicline's apparent total oral clearance and  $CL_R$ . These parameters can be altered depending on the severity of renal impairment and it's expected that the increase of the renal impairment leads to reduced clearance of varenicline, consequently the levels of systemic varenicline increase followed by long half-life in plasma (Faessel *et al.*, 2010).

Tests were performed to study the relation between varenicline pharmacokinetics and renal impairment. The results revealed that there was no alteration in the stationary state

of varenicline in patients with mild renal inefficiency in comparison with individuals with no renal problems, however it was also showed that patients suffering from moderate and severe renal conditions had lower values of apparent total oral clearance and  $CL_R$  and higher values for elimination half-life ( $t_{1/2}$ ). It was proven that the major characteristic involved in possible alteration to varenicline pharmacokinetics is the renal function (Faessel *et al.*, 2010).

### iii. Adverse effects

The treatment with varenicline may lead to the development of some adverse effects, one of the most common is nausea although it is presented as being mild to moderate with tendencies to reduce over time, and as such, didn't lead to patients quitting the treatment. Besides nausea, varenicline can also induce other adverse effects such as insomnia, abnormal dreams, and headaches (Cahill *et al.*, 2012; Rigotti and Clair, 2013).

Concerning serious adverse effects, the Food and Drug administration (FDA) , noted that the administration of varenicline could induce neuropsychiatric problems, these being suicidal tendencies, with patients idealizing or committing suicide and depressed mood (Aubin *et al.*, 2014; Crooks *et al.*, 2014).

Studies were conducted to confirm this concern and there was no evidence that patients on varenicline had more neuropsychiatric symptoms in comparison with other treatments besides, smoking cessation is connected to psychiatric symptoms, which increases the difficulty in distinguishing if the symptoms are due to varenicline or the smoking cessation process. Since there is no conclusion, patients on varenicline need to be monitored for these symptoms (Aubin *et al.*, 2014; Crooks *et al.*, 2014).

In respect to cardiovascular adverse effects, varenicline does interact with nicotine subtype receptors that are responsible for modulating the hemodynamic effects, and as such is not probable that it could cause cardiovascular effects. Studies conducted revealed that the risk associated with varenicline and cardiovascular adverse effects were less than 1%, since smoking increases the risk of cardiovascular conditions, the benefit of using varenicline as a smoking cessation treatment outweighs the risk of it causing cardiovascular problems (Rigotti and Clair, 2013).

#### iv. Interactions

Since smoking increases the risk of cardiovascular problems, it's common that varenicline is prescribed alongside with cardiovascular drugs. Some of the medicines used for cardiovascular conditions have strict therapeutic windows, suffer metabolism by CYP enzymes and get removed by renal transporters. Examples of these drugs are warfarin and digoxin, which have interactions that can increase toxicity or reduce their effects due to subnormal plasma concentrations. Studies conducted revealed that varenicline didn't change pharmacokinetics parameters nor did it alter the pharmacodynamics of warfarin. *In vitro* tests further showed that the enzymes responsible for warfarin metabolism weren't influenced by (Faessel *et al.*, 2010).

Varenicline also didn't affect digoxin's pharmacokinetics, however  $CL_R$  was increased by a minimum amount when both drugs were administered. Also, exams performed on Caco-2-cells corroborated that varenicline doesn't interact with P-glycoprotein-mediated efflux of digoxin (Faessel *et al.*, 2010).

Varenicline interacts with renally excreted cationic drugs, example of this is cimetidine. Cimetidine is a natural inhibitor of human organic cation transporter 2 (hOCT2) and has been used in many *in vivo* studies to examine various drug interactions between drugs that are eliminated renally. Co-administration of varenicline and cimetidine resulted in increased levels of systemic varenicline however, the results were not clinically impactful. Studies were also performed with metformin, the most reactive substrate of the hOCT2. No meaningful alterations in pharmacokinetics were spotted, with further *in vitro* tests demonstrating that there are no interactions between the 2 drugs (Faessel *et al.*, 2010).

Varenicline showed no interactions with bupropion and nicotine replacement therapies (NRT) in respects to the steady-state pharmacokinetics. Nonetheless, association of varenicline with cotinine, a nicotine metabolite, aggravated the occurrence of adverse effects such as nausea, vomits, fatigue, dizziness, dyspepsia, and headaches (Faessel *et al.*, 2010).

#### v. Posology and efficacy

Varenicline is sold as film-coated oral tablets, with 2 different doses available, 0.5 mg and 1 mg. The advisable time to start treatment is 1 week prior to the day the patient decides as target quit date (TQD), however, studies have revealed that varenicline was also efficient with flexible quit dates. It's also recommended to take varenicline after eating with a full glass of water to reduce possible adverse effects such as nausea. Recommended treatment schemes for adult are 0,5 mg once a day on first 3 days followed by 0,5 mg twice a day (BID) on the next 4 days and finally 1 mg of varenicline BID from day 8 until the end of treatment, this being 12 weeks. In cases of successful attempts patients can extended treatment for another 12 weeks to improve chances on long term abstinence (Garrison and Dugan, 2009; Rennard *et al.*, 2012).

In comparison with other smoking cessation drugs, studies revealed varenicline to be the most effective treatment, with it outperforming every form of single NRT and bupropion. Even so combined NRT was as effective as varenicline (Cahill *et al.*, 2013).

In combination with other smoking cessation drugs, varenicline when co-used with NRT, improved smoking cessation rates at 12 weeks and 6 months when compared to varenicline alone and when combined with bupropion, varenicline showed notably increased long term abstinence at 12 and 26 weeks (Ebbert *et al.*, 2014; Koegelenberg *et al.*, 2014).

### 3.3.3 Bupropion

#### i. Action mechanism

Initially, bupropion was used as an antidepressant, its mechanism of action was different from other antidepressants, but it is still not fully understood. However, it is studied that bupropion works by inhibiting dopamine (DA) and noradrenaline (NA) intake to striatal and hypothalamic neurons respectively. Also depending on the dose administered, bupropion can also improve vesicular dopamine re-absorption by inducing vesicular monoamine transporter-2 protein activity (Crooks *et al.*, 2014; Costa *et al.*, 2019).

Sustained release of bupropion might help as a smoke cessation treatment because it blocks the reuptake of dopamine in the mesolimbic dopamine system, responsible for

modulating rewards obtained from nicotine use. Not only that but bupropion also inhibits various nicotinic acetylcholine receptors. Studies revealed that bupropion and S,S-hydroxybupropion showed inhibiting activity towards  $\alpha3\beta4$  and  $\alpha4\beta2$  nicotinic subtype receptors respectively, bupropion also demonstrated to be although feeble, an inhibitor of  $\alpha7$  subtypes. Hydroxybupropion, a bupropion metabolite, acted as a stronger nAChR inhibitor by comparison, including  $\alpha4\beta2$  and  $\alpha3\beta4$ . Neither bupropion nor its metabolites demonstrated any competitive activity (Costa *et al.*, 2019).

## ii. Pharmacokinetics

Bupropion is dispensed orally, cases of incorrect use of bupropion were also found these being, nasal insufflation and intravenous administration, both considered in abusive environments. Bupropion absorption is fast and isn't affected by food. The time needed for bupropion reach maximum plasma concentration ( $T_{max}$ ), ranges from 1.3 hours to 1.9 hours. As there isn't an intravenous preparation, it's not possible to determine the absolute oral availability of bupropion. Still studies conducted on instantaneous and prolonged preparations of bupropion, revealed that bioavailability on sustained preparations to be 68%, this could be because absorption rates are lower or because it suffers more metabolism. Furthermore, bupropion suffers substantial first-pass metabolism which reduces its bioavailability, with tests suggesting that the bioavailability values range from 5% to 20%. In the case of sustained release formulations, these demonstrate longer absorption values (Costa *et al.*, 2019).

Metabolites are produced in the liver such as Hydroxybupropion and threohydrobupropion. These metabolites are present in higher amounts in comparison with bupropion but erythrohydrobupropion, another bupropion metabolite appears in similar ratios to the main compound (Costa *et al.*, 2019).

These metabolites need between 5 to 8 days to obtain steady state concentrations in plasma. The relation between  $C_{max}$  and  $T_{max}$  can be explained by comparing the various formulation available. The fastest release formulation will have the higher maximum plasma concentration; however, it will take longer to reach the maximum concentration in serum. This relation is also applied to slower release forms (Costa *et al.*, 2019).

Bupropion has a lipophilic nature and small size which translates in a large apparent distribution value reaching close to 19L/kg in its stationary state. Not only that, bupropion and hydroxybupropion exhibit high percentages of connection to plasma proteins, these values are 84% and 77% respectively while, threohydrobupropion exhibited 42%, which was non-relevant from a clinical point of view (Costa, *et al.*, 2019).

Referring to bupropion metabolism, it happens to a great extent in the hepatic microsomes enzymes, with particular importance to the CYP2B6 isoform. As a result, 3 major metabolites are produced: hydroxybupropion, threo-bupropion and erythro-bupropion (Khan *et al.*, 2016).

Many metabolic paths have been identified with some reactions occurring during phase 1 of hepatic metabolism and others occurring during phase 2. In the case of hydroxybupropion, this metabolite is obtained by hydroxylation reactions, there is however a variation of this reaction called aromatic hydroxylation leading to an alternate metabolite denominated 4'-hydroxy-bupropion (Costa *et al.*, 2019).

Bupropion can also be metabolized through reduction reactions, leading to the appearance of erythro and threo groups and producing the other metabolites, threohydrobupropion and erythrohydrobupropion. These compounds can also be a part of aromatic and aliphatic hydroxylation reactions (Costa *et al.*, 2019).

Other reactions include hydration, side-chain cleavage and sulfate and glucuronide conjugation (Costa *et al.*, 2019).

The metabolites previously described are clinically relevant due to their pharmacological activity. In the case of hydroxybupropion, the enantiomer (2S,3S)-hydroxybupropion demonstrates the same or higher activity when compared to bupropion in blocking the behavioral effects of nicotine (Damaj *et al.*, 2010).

This blockage is associated with the potency displayed by the action of (2S,3S)-hydroxybupropion in the DA, NE transporters and more importantly the antagonism of  $\alpha 4\beta 2$ -nAChR (Damaj *et al.*, 2004). Also, studies suggested that oral administration of hydroxybupropion leads to improved pharmacokinetics parameters such as half-life of elimination and plasma concentrations (Costa *et al.*, 2019).

Since bupropion is vastly metabolized, a vast majority of it is excreted in urine and feces as a metabolite. Also, most of the bupropion is excreted in urine, with studies conducted supporting that 88% of bupropion and metabolized compounds are present in urine and only 23% appear in feces. Another important aspect is the terminal half-life of elimination, with bupropion needing between 6 and 7 days to be eliminated from the organism (Khan *et al.*, 2016; Costa *et al.*, 2019).

Moreover, bupropion can also be eliminated through breast milk and its clearance is influenced by the renal function of the organism and therefore, patients with renal insufficiency decrease the clearance of bupropion (Khan *et al.*, 2016; Costa *et al.*, 2019).

### iii. Adverse effects

The use of bupropion as an antidepressant and as aid in smoke cessation, can cause several adverse effects, the most common ones are insomnia and xerostomia. These adverse effects can be neutralized by lowering the dose administered and in the case of insomnia bupropion should be taken a few hours before bed. Other common adverse effects are nausea, diarrhea, anxiety, and headaches. Studies showed that headaches and nausea were present equally in placebo groups and in treatment groups (Hays *et al.*, 2010; Costa *et al.*, 2019).

Also, it was shown that due to the adverse effects, patients quit the treatment with bupropion for smoking cessation, with it reaching a percentage of 12% (Hays and Ebbert, 2010; Costa *et al.*, 2019).

Another study revealed that 20% patients treated with bupropion for smoking cessation, switched the treatment for NRT because of the adverse effects produced by bupropion (Hughes *et al.*, 2014).

Other patients although more rarely, suffered allergic reactions to bupropion, these allergies can manifest symptoms such as angioedema, dyspnea, and pruritus which need medical attention (Hughes *et al.*, 2014).

Bupropion also produces serious adverse effects, studies revealed that bupropion can cause seizures with a rate of incidence between 0,1% and 0,4%. The risk of seizures when

taking bupropion was superior in patients susceptible to seizures and as such patients with seizure disorder, brain abnormality and other conditions that improve the chance of seizures shouldn't use bupropion as a smoking cessation treatment (Hays and Ebbert, 2010).

A lot of studies were conducted to study the potential risk of bupropion causing psychiatric events, these include behavioral changes, depression, and suicidal ideation. Some studies revealed that there was no connection between bupropion use and serious psychiatric events. However, it is advised to monitor closely possible depressive symptoms that can be caused by bupropion (Hughes *et al.*, 2014; Mota, 2015).

Despite this, an US data analysis compared the psychiatric symptoms cause by 3 smoking cessation drugs: Bupropion, NRT, and varenicline. Results showed that bupropion had increased risk of suicide tendencies and depressive behavior when compared to NRT, but varenicline proved to have even higher risk than bupropion to cause these adverse effects (Hughes *et al.*, 2014; Mota, 2015).

Finally, bupropion cannot be administered in patients who suffered from heart attack with less than 4 weeks, non-controlled hypertension, bipolar disorder, or any condition that could increase the likelihood of seizures, these also include anorexia, nervous bulimia, diabetes and co administration with drugs that lower the seizure threshold. Bupropion also has relevancy in pregnancy because it is associated higher rate of abortions (Hughes *et al.*, 2014; Mota, 2015).

#### iv. Interactions

During clinical practice, several interactions have been reported involving bupropion and other drugs that can change bupropion and other drugs pharmacokinetic parameters (Foley *et al.*, 2006).

Interaction between desipramine and bupropion were evaluated and revealed that bupropion and its metabolites were responsible for lower clearance values, higher  $C_{max}$  and  $t_{1/2}$  values (Foley *et al.*, 2006).

Other drugs such as fluoxetine and venlafaxine also had interactions with bupropion, with venlafaxine having higher plasma concentration when co-administered with bupropion. In another case study, the metabolic conversion of dextromethorphan in dextropran in individuals with extensive metabolic capability when co administered with bupropion, was investigated. Results showed that bupropion reduced the metabolic activity of CYP2D6 and consequently the levels of dextropran were lower in these subjects (Foley *et al.*, 2006).

Other adverse effects might occur when taking bupropion and other drugs that are metabolized by CYP2D6, due to bupropion's activity as an inhibitor for CYP2D6 (Hughes *et al.*, 2014).

On the other hand, many drugs also influence bupropion activity, example of this is carbamazepine. Carbamazepine promotes the activity of CYP enzymes and as such reduces plasmatic concentrations ( $C_{max}$ ) of bupropion however, the  $C_{max}$  of bupropion metabolites such as hydroxybupropion were higher (Foley *et al.*, 2006).

Studies involving valproate, indicated that there was a 56% increase of  $C_{max}$  of hydroxybupropion without altering the levels of bupropion, also the AUC values were increased by 94%. These values suggest that the inhibitory effects of valproate reduce the metabolism of bupropion and its metabolites (Foley *et al.*, 2006).

The use of bupropion as aid in smoking cessation and as an antidepressant is dependent on its most active metabolite hydroxybupropion. Interactions between bupropion and drugs that decrease levels of hydroxybupropion lead to lower efficacy, on the contrary, drugs that increase concentrations of hydroxybupropion can promote toxicity and therefore corrections of dose might be needed (Foley *et al.*, 2006).

#### v. Posology and efficacy

Bupropion is administered orally as sustained release pills. The posology consists of 150 mg once a day in the first 3 days and at day 4 patients take 150 mg (BID). To do an attempt at quitting smoking, patients must wait 2 weeks or a week minimum after starting to take bupropion since the time needed for bupropion to reach stationary state concentration levels is between 5 and 8 days. The treatment has a duration of at least 8

weeks but can be ceased at any time because there's no need for weaning (Aubin *et al.*, 2014; Mota, 2015).

A meta-analysis review compared the efficacy of bupropion in comparison with other smoking cessation drugs, revealing that bupropion improved the chances of patients reaching abstinence when compared to NRT but when compared to varenicline, smoking cessation rates were more favorable towards varenicline (Hughes *et al.*, 2014). Also, trials have shown that bupropion when combined with some form of NRT, didn't demonstrate more efficacy than NRT alone (Cahill *et al.*, 2013).

### **3.4 Sales of smoking cessation medicines in Portugal 2010-2020**

It is important to note that the data that will be presented corresponds to the number of packages of smoking cessation medicines (Nicotine, Varenicline and Bupropion) sold in the pharmacies in Continental Portugal from January 1<sup>st</sup>, 2010, through December 31, 2020, and was organized by yearly units and monthly units sold. Units sold in the region of Azores and Madeira were not included in this analysis. Also, this analysis does not include medicines available in a hospital environment and lastly regarding bupropion, only one medicine has been approved in Portugal and it's prescribed both as an antidepressant and anti-smoking medicine.

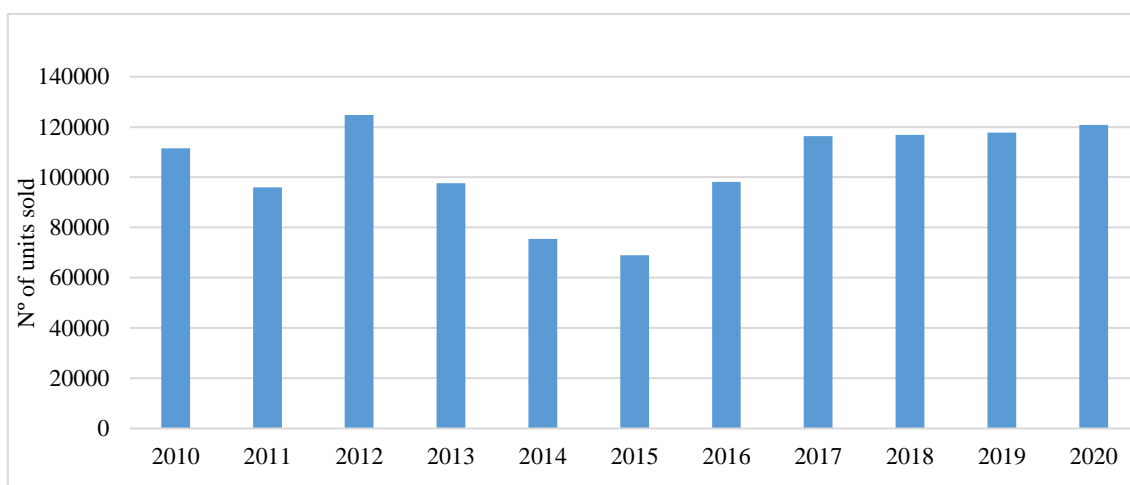
#### **3.4.1 Description of Nicotine sales**

As demonstrated by Table 1 and Graph 1, regarding the yearly sales of nicotine medicines, 2012 was the year with the highest number of sales for nicotine with 124 834 units sold, contributing with 10,91% of total sales in the ten-year period analyzed.

In contrast, 2014 and 2015 were the years with the lowest number of sales reaching 75 428 and 68 956 units sold respectively. Another important information regards the year of 2020 which registered the second highest value of units sold reaching 120 888, the equivalent of 10,56% of total sales.

**Table 1.** Absolute (N) and relative frequency (%) of yearly nicotine medicine sales in Continental Portugal (2010-2020).

Units sold	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
N	111574	96006	124834	97656	75428	68956	98194	116407	116855	117784	120888	1144582
%	9,75	8,39	10,91	8,53	6,59	6,02	8,58	10,17	10,21	10,29	10,56	100



**Graph 1.** Absolute frequency of yearly nicotine medicine sales in Continental Portugal (2010-2020).

The monthly sales of nicotine medicines were also studied and as shown in Table 2, it was noted that in every year, excluding 2015, the month with most units sold was January. January 2016 registered 17 370 units sold being not only the highest value in terms of sales of nicotine medicines, but also the highest value for sales across the board.

On the other hand, it's possible to note that there was a decrease in terms of sales in 2015, registering the worst results, with February registering 4918 sales, this value was the lowest in the year but also the lowest value in general. January revealed to be the most productive month across the board in terms of sales however in 2015 the most productive month was October, with 7285 units sold meanwhile, only 5998 units were sold in January 2015.

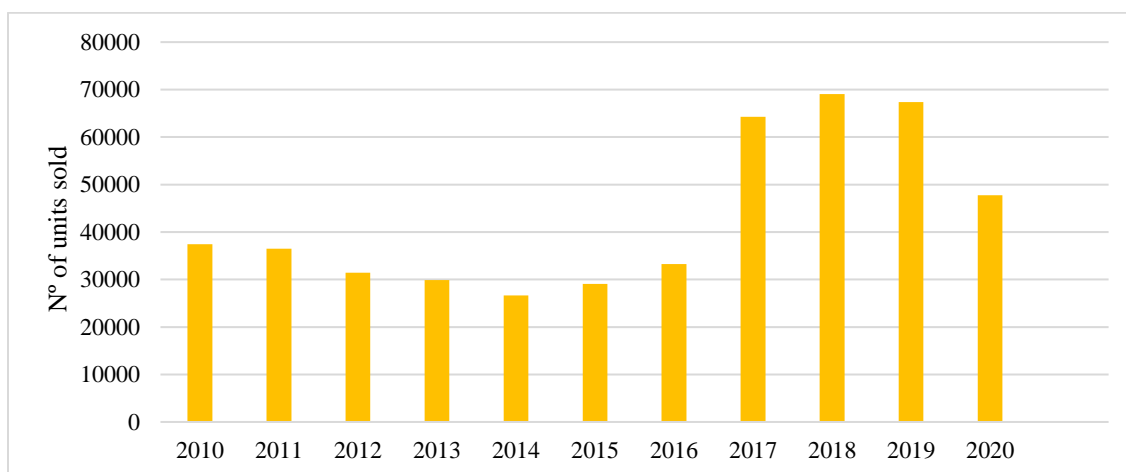
**Table 2.** Absolute frequency (N) of monthly sales of nicotine medicine in Continental Portugal (2010-2020).

Month	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
<b>January</b>	10022	10639	13481	12632	10218	5998	17370	12209	15516	13422	14735
<b>February</b>	8722	8544	13349	8888	7201	4918	10050	9723	10870	10100	11542
<b>March</b>	10017	9036	12598	8478	6225	5576	9149	10174	9593	9320	12594
<b>April</b>	8986	7810	9400	8728	5992	5250	7342	8077	9235	9303	8831
<b>May</b>	8953	8435	10954	7655	6610	5254	7974	10435	8821	9923	9289
<b>June</b>	8641	7504	8589	6511	5551	5392	7130	8269	8584	8310	9063
<b>July</b>	9272	7033	8927	7187	5725	5560	7441	8205	9714	9256	9512
<b>August</b>	9703	8266	8509	6789	5237	5554	7536	8205	8219	9207	8188
<b>September</b>	9660	7533	9525	7881	5860	6197	8307	9271	9043	10214	9887
<b>October</b>	9242	7609	12019	8860	6439	7285	8241	10490	10303	10224	9181
<b>November</b>	9489	7084	9360	7191	4969	6050	7654	10776	9024	9514	8968
<b>December</b>	8867	6513	8123	6856	5401	5922	7182	10442	7933	8991	9098

### 3.4.2 Description of Varenicline sales

**Table 3.** Absolute (N) and relative frequency (%) of yearly varenicline sales in Continental Portugal (2010-2020).

Units sold	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
N	37435	36463	31457	29906	26640	29104	33231	64286	69082	67347	47725	472676
%	7,92	7,71	6,66	6,33	5,64	6,16	7,03	13,60	14,62	14,25	10,10	100



**Graph 2.** Absolute frequency of yearly varenicline sales in Continental Portugal (2010-2020).

The Table 3 and Graph 2 refers to the yearly varenicline sales from 2010 to 2020. It's possible to infer that 2017 and 2018 were the years with most sales followed by 2019 and 2020 respectively but the greatest increase in sales was from 2016 to 2017 with a 48,3% increase. On the contrary, 2014 proved to be the year with least sales with only 26 640 units sold.

It was also analyzed the monthly sales of varenicline in the same time period to learn more about the tendencies of sales for this medicine. Table 4 discriminates the monthly sales of varenicline in Continental Portugal.

Sales of anti-smoking drugs in Portugal 2010-2020

The results showed an increase in sales from 2017 to 2020 with these being the only years to present more than 10% contribution to total varenicline sales. In this time, apart from 2017, January was the month with most sales registering 6898, 6938 and 6827 units sold for 2018, 2019 and 2020 respectively. Furthermore, January 2019 registered the highest number of varenicline sales across the board.

**Table 4.** Absolute frequency (N) of monthly sales of varenicline in Continental Portugal (2010-2020).

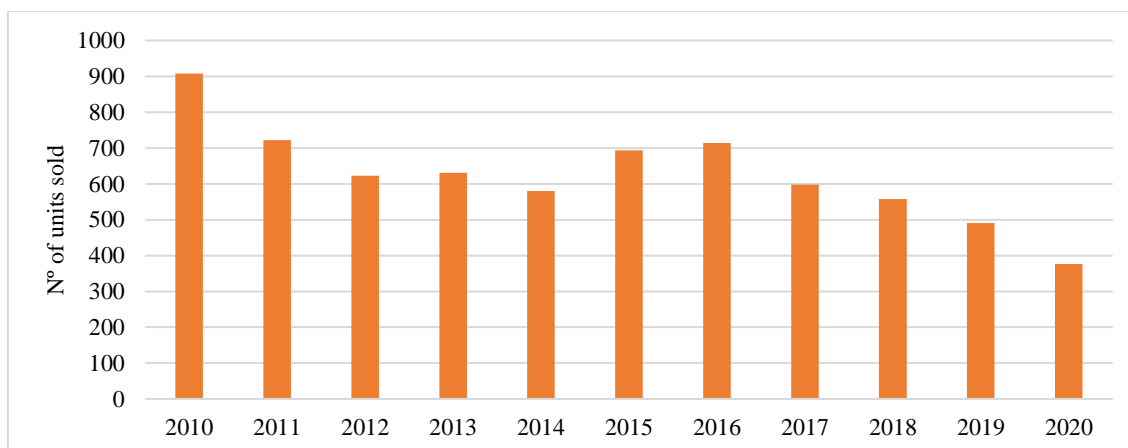
Month	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
<b>January</b>	3251	3786	3041	3431	2926	2308	3169	4824	6896	6938	6827
<b>February</b>	2887	3309	2534	2808	2344	1924	2916	4358	5784	6084	5853
<b>March</b>	3207	3830	3169	2571	2567	2251	2996	6095	5861	5688	5931
<b>April</b>	2825	3327	2319	2541	2176	2266	2516	5153	5613	5754	3199
<b>May</b>	3310	3658	2289	2569	2161	2379	2645	5703	5530	5739	2571
<b>June</b>	2952	2772	2214	2082	1974	2338	2506	5348	5572	4753	2851
<b>July</b>	3021	2683	2423	2440	2126	2581	2373	5604	5932	5606	3326
<b>August</b>	3228	2678	2362	2129	1923	2454	3060	5058	5606	5066	3339
<b>September</b>	3123	2796	2344	2284	2206	2606	3105	5111	5320	5225	3528
<b>October</b>	2950	2571	3163	2587	2365	2767	2909	6207	6185	5760	3596
<b>November</b>	3778	2677	3034	2352	1990	2597	2639	5700	5250	5228	3463
<b>December</b>	2903	2376	2565	2112	1882	2633	2397	5125	5533	5506	3241

On the other hand, December 2014 registered the lowest number of varenicline sales for that year and in general with only 1882 units sold. In the case of 2020, despite displaying a contribution of 10,10% of total varenicline sales, from April onwards it's possible to visualize a decrease of sales to half or in some cases more than half, for example May, when compared to January, February, and March 2020.

### 3.4.3 Description of Bupropion sales

**Table 5.** Absolute (N) and relative frequency (%) of yearly bupropion sales in Continental Portugal (2010-2020).

Units sold	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
N	908	722	623	631	580	693	714	598	558	491	376	6894
%	13,17	10,47	9,04	9,15	8,41	10,05	10,36	8,67	8,09	7,12	5,45	100



**Graph 3.** Absolute frequency of yearly bupropion medicine sales in Continental Portugal (2010-2020).

The Table 5 and Graph 3, demonstrate the yearly sales of bupropion used as an anti-smoking medicine. The results show that 6894 units were sold in total with 2010 being the most profitable year with 908 sales (representing 13,17% of the 10-year sales). On the

other hand, 2020 stands out since it registered the lowest value in sales with only 376 units sold, the equivalent of 5,45% of total bupropion sales. It should also be noted that, across the board the values of bupropion sales were very low compared to the other anti-smoking medicines. For instance, comparing the sales of the best year for bupropion (2010) with the worst year of nicotine medicines (2015), it's possible to see that nicotine medicines sold more 98,68% units.

**Table 6.** Absolute frequency (N) of monthly sales of bupropion in Continental Portugal (2010-2020).

Month	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
<b>January</b>	88	56	53	66	52	49	72	76	63	20	52
<b>February</b>	71	59	51	46	42	48	76	43	47	40	41
<b>March</b>	73	60	56	34	56	43	53	57	41	45	62
<b>April</b>	50	72	58	46	36	46	66	36	51	45	48
<b>May</b>	74	68	60	55	43	43	48	46	42	50	40
<b>June</b>	62	43	27	56	69	73	53	50	49	32	28
<b>July</b>	75	67	44	61	53	107	52	50	60	40	44
<b>August</b>	84	58	57	50	42	79	84	58	58	40	7
<b>September</b>	89	72	63	52	47	69	60	51	42	45	13
<b>October</b>	51	51	70	53	63	47	36	46	45	44	8
<b>November</b>	79	56	35	62	37	44	56	54	41	37	6
<b>December</b>	112	60	49	50	40	45	58	31	19	53	27

The analysis of the monthly sales of bupropion, indicated a more heterogeneous perspective. The months with most and least sales vary from year to year. Table 6 demonstrates the monthly sales of bupropion from 2010 to 2020. It's possible to verify that December 2010, was the month with most sales in that year and in general with 112 units sold with the runner-up being July 2015 with 107 units. It's also important to note that in 2011 the months with most sales were both April and September, reaching 72 sales. In the case of 2015, both March and May displayed the lowest number of sales for that year with 43 units sold and 2017 and 2018 displayed the same behavior having January as the most profitable month (76 and 63 units sold respectively) and, December as the least profitable month (31 and 19 units sold, respectively). Finally, 2020 displays the lowest sales in general with November displaying only 6 units sold.

#### 3.4.4 Comparison of total sales

The Table 7 indicates the global sales of Nicotine, Varenicline and Bupropion and their contribution to the total sales of anti-smoking drugs in Continental Portugal (2010-2020).

**Table 7.** Absolute (N) and relative frequencies (%) of total sales of Nicotine, varenicline and bupropion in Continental Portugal (2010-2020).

Units sold	Nicotine	Bupropion	Varenicline	Total
N	1144582	6894	472676	1624152
%	70,47	0,43	29,10	100

As shown in the table above, nicotine composed more than two thirds of the total anti-smoking drug sales with 70,47%. On the contrary, Bupropion sales were minimal not even reaching 1% of total sales indicating that its use as an anti-smoking drug is limited. In the case of varenicline it contributed to 29,10 % of total sales.

### 3.4.5 Discussion

The focus of this project was to study the sales of Nicotine, Varenicline and Bupropion in Continental Portugal from 2010 to 2020. The year of 2020 was marked by the COVID-19 pandemic and as such it had a major influence in the results obtained during this year. It's also important to note that these results don't reflect if the patients effectively initiated or completed the treatment, nor does it infer about the success rate of the treatments.

Regarding nicotine, the results showed that NRT was the preferred therapy for patients to attempt quit smoking, representing 70,47% sales followed by varenicline with 29.10% and Bupropion with 0.43%. A reason that may explain this result is the fact that, nicotine is a more accessible drug in comparison with varenicline and bupropion, because it doesn't require a prescription from a physician and its available in every pharmacy. Also, other establishments like parapharmacies and supermarkets are allowed to sale these over-the-counter drugs.

A representative study made in England comparing the prevalence of smoking cessation therapies before and during the pandemic reached the same conclusion indicating that out of these 3 medications, NRT was the most used therapy to quit smoking. This might be due to the accessibility of this medicine which was even more relevant during the pandemic period since pharmacies remained opened and NRT was possible to obtain without a prescription. Varenicline placed second place in terms of usage followed by bupropion due to the need of a medical prescription, which in certain cases could force the patient to change treatments and look for other alternatives like NRT, which were even more visible during the pandemic period (Jackson *et al.*, 2022).

It was also noted that except for January 2015, January scored the highest number of sales for nicotine, this might indicate that there is a seasonal pattern regarding the sales. A reason for this seasonal variation can be related to new year resolutions to quit smoking resulting in an increase in sales.

A study made in Canada showed similar conclusions, indicating that the demand for smoking cessation therapies increased during February and March and that the demand for smoking cessation therapies during summer was lower possibly due to the holidays (Veldhuizen *et al.*, 2021).

Despite the Covid pandemic, 2020 scored the second highest number in nicotine sales with a growth of 2.6% in comparison with the previous year (2019). January, February, and March scored the highest sales with 14 725, 11 542 and 12 594 units sold respectively followed by a decrease in sales in the next months. This result can mean that patients were stockpiling due to concerns regarding the Covid restrictions which decreased access to these medications, due primarily to quarantine period and the closure of certain stores that sell these medications.

A similar result was observed in a study in the United States, which indicated that sales of nicotine products in the first quarter of 2020 peaked, particularly lozenges. These results once again may indicate a case of stockpiling. Also, the study noted a decrease in sales from Quarter 2 onwards regarding nicotine products (Trigger *et al.*, 2023).

Bupropion displays a very different sales behavior when compared to nicotine or varenicline, as its sales represent only 0.43% of total sales. The first possible explanation for the difference in sales may be the fact that bupropion is an antidepressant and as such requires a prescription to be dispensed. Another possibility is that the prices for these medications can be high and as such, some individuals may not be able to pay or in other cases be discouraged to proceed with the treatment leading to them not buying the medication. Another concern about bupropion is the potential adverse effects that, as previously discussed, are more serious and therefore might not be the first choice for physicians to prescribe patients. Not only that, but the manifestation of these effects may discourage patients to initiate or complete the treatment.

In England, bupropion was the lowest medication in terms of usage with 0.5% rate in the pre-pandemic period and 0.4% in the pandemic period. Between 2015 and 2021, Bupropion also showed the lowest quit rate of all cessation methods displaying only 11.1% of quit rate (Jackson *et al.*, 2022). These levels of sales are comparable to the ones found in Portugal.

In the year of 2017, the sales of bupropion decreased about 16.2%. This result contrasts with the results observed for varenicline, as varenicline registered in 2017 a growth of 48.3% in sales.

One possible explanation for this difference in sales can be the fact that varenicline started to be reimbursed in 37% from 2017 onwards, as a measure made by the Portuguese

government to help patients afford smoking cessation medication. This measure was not applied to bupropion (SNS, 2017).

Bupropion registered in 2020 the lowest sales with only 376 units sold. Adding to the reasons stated above, the COVID-19 pandemic could negatively impact the sales of bupropion.

These results seem to be consistent with what was observed in Italy, reporting that during the quarantine period, restricted access to prescriptions and health facilities are contributors to the decrease in sales (Farina *et al.*, 2021).

As previously stated, the reimbursement of varenicline was made effective starting January 2017. The results obtained concerning varenicline showed a major increase in sales from 2016 to 2017 representing a 48,3% increase.

In 2018, a 6.9% increase in sales was observed in comparison with 2017, this resulted in 2018 being the most profitable year for varenicline sales. These results can be attributed to the reimbursement approved by the government which helped make varenicline a more affordable and accessible medicine.

On the other hand, 2020 scored a 29,1% decrease in sales when compared to 2019. These changes can be attributed to the COVID-19 pandemic due to restrictions since varenicline is also only accessible with a prescription and is only sold in pharmacies like bupropion (Carmo, 2021).

A study evaluated the safety and efficacy of nicotine, varenicline and bupropion, on individuals with and without psychiatric disorders, concluded that neither bupropion nor varenicline significantly increased the chances of manifestation of moderate or grave adverse effects. The study also concluded that varenicline was the most efficient alternative to quit smoking when compared to the other choices (Anthenelli *et al.*, 2016).

The role of the pharmacist is of extreme importance since it's the healthcare professional more accessible to the citizens, and as such has the duty of educating and counselling people on the dangers of smoking, motivate and give advice to those attempting to quit and finally guide patients through the treatments so that it can be completed successfully.

A study conducted in Canada indicated that the implementation of intensive and abbreviated smoking cessation programs by pharmacists and other clinicians improves the success rate of smoking abstinence after 6 months by 36% and 22% respectively opposed to the 7% abstinence in general population after 6 months (Phillips *et al.*, 2022).

Furthermore, patients who came back for 3 or more visits, showed a 50% and 33% improved chance of quitting for intensive and abbreviated smoking cessation programs respectively which further cements the importance of the pharmacist role in the education and encouragement of the patients to complete the treatment and also the importance of further investment in these programs and therapies (Phillips *et al.*, 2022).

The investment in the education of pharmacists towards smoking cessation services and programs are of extreme significance since, as shown in some countries like Poland and Malaysia, the knowledge about these issues is also moderate which negatively impacts the smoking cessation counselling by pharmacists. On the other hand, countries like Australia and US, shown a superior level of knowledge about smoking cessation services due to implementation of programs designed to educate and improve confidence of pharmacists when assisting patients in reaching smoking abstinence (Sakka *et al.*, 2022).

#### **IV. Conclusion**

The consumption of tobacco products remains a major concern towards public health worldwide since it facilitates and improves the likelihood of developing many diseases otherwise preventable. The study using the data provided by CIMI presented in this dissertation, revealed that people are aware of the dangers and consequences of smoking and therefore interested in looking for medication to help them quitting smoking.

All 3 medications are backed by clinical trials showing positive results. However, it was also showed that using a combination of interventions improved the success rate of smoking cessation for longer periods of time and prevented setbacks and interruptions in the treatment. NRT was the preferred therapy for patients to attempt quit smoking, representing the vast majority of sales followed by varenicline with 30% of total sales. Bupropion represented less than 1% of total sales ruling for a very minor role in terms of therapy for smoking cessation.

The nicotine monthly sales showed January as the most profitable month across the board suggesting seasonality. This pattern indicates more willingness to quit smoking by the patients in the beginning of the year when compared to the end of the year. The reduction of varenicline price in 2017 supported by the Portuguese health care system led to an increased search for this medication as an alternative to NRT which resulted in a 43% increase in sales from 2016, indicating that financial stability and accessibility are major factor when deciding to start treatment. The low sales of bupropion can be attributed to the adverse effects it produces, less financial accessibility, and not being the first choice by physicians due to the lower success quit rates. The COVID-19 pandemic also influenced the sales, reducing varenicline and bupropion sales as they require prescription. On the other hand, NRT saw an increase in sales during the pandemic due to the concerns of patients on the restrictions which led probably to stockpiling the medication.

Finally, the role of clinicians in particular pharmacists, is imperative when leading with the tobacco epidemic. Counselling, education, and dedicated programs proven to be very beneficial to increase smoking cessation success rates. On the other hand, more investment is needed to increase the pharmacist's knowledge and confidence when advising on possible smoking cessation therapies and on smoking cessation programs to help patients achieve longer abstinence periods.

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