Psychopharmacology of Smoking Cessation Medications: Focus on Patients with Mental Health Disorders

João Mauricio Castaldelli-Maia\textsuperscript{1,2}, Victoria Camargos de Oliveira\textsuperscript{3}, Flávia Mariana Irber\textsuperscript{3}, Israel K. Blaas\textsuperscript{4}, Bernard Angerville\textsuperscript{5}, Anderson Sousa Martins-da-Silva\textsuperscript{2}, Gislaine Koch Gimenes\textsuperscript{4}, Marcela Waisman Campos\textsuperscript{6}, Julio Torales\textsuperscript{7}, Antonio Ventriglio\textsuperscript{8}, Carine Guillois\textsuperscript{1}, Houria El Ouazzani\textsuperscript{1}, Léna Gazaix\textsuperscript{1}, Pascal Favré\textsuperscript{9}, Alain Dervaux\textsuperscript{10}, Gisèle Apter\textsuperscript{1,8,9}.

1- Cellule de Recherche Clinique, Groupe Hospitalier du Havre, Le Havre, France
2 – Department of Psychiatry, Medical School, University of São Paulo, Brazil
3 – Hospital Municipal Prof. Dr. Alípio Corrêa Neto, Brazil
4 – Perdizes Institute (IPer), Clinics Hospital (HCFMUSP), Medical School, University of São Paulo, Brazil
5 – Établissement Public de Santé Barthélémy Durand, Étampes, France
6 – Department of Cognitive Neurology, Neuropsychiatry, and Neuropsychology, FLENI, Argentina
7 – Department of Psychiatry, National University of Asuncion, Paraguay
8 – Department of Clinical and Experimental Medicine, University of Foggia, Italy
9 – Etablissement Santé de Ville-Evrard, Neuilly-sur-Marne, France
10 – Université Paris-Saclay, Le Kremlin-Bicêtre, France.
11 – Société de l’Information Psychiatrique, France
12 – University of Rouen Normandy, France
Abstract (<= 200 words)

The adverse effects of smoking cessation in individuals with mental health disorders have been a point of concern, and progress in the development of treatment has been slow. The primary first-line treatments for smoking cessation are Nicotine Replacement Therapy, Bupropion, Varenicline, and behavioral support. Nortriptyline and Clonidine are second-line treatments used when the first-line treatments are not effective or are contraindicated. Smoking cessation medications have been shown to be effective in reducing nicotine cravings and withdrawal symptoms and promoting smoking cessation among patients living with mental disorders. However, these medications may have implications for patients’ mental health and need to be monitored closely. The efficacy and side effects of these medications may vary depending on the patient's psychiatric condition, medication regimen, substance use, or medical comorbidities. Understanding the pharmacokinetics, pharmacodynamics, therapeutic effects, adverse effects, and pharmacological interactions of smoking cessation drugs is crucial for treating individuals with mental health disorders. Careful consideration of the risks and benefits of using smoking cessation medications is necessary, and treatment plans must be tailored to individual patients' needs. Monitoring symptoms and medication regimens is essential to ensure optimal treatment outcomes and avoid potential adverse events.

Key-words: Smoking, mental health, psychopharmacology, interactions, cessation
1. Introduction

Smoking is the primary preventable cause of death [1]. According to data from the World Health Organization report on the Global Tobacco epidemic, smoking is a risk factor for six of the eight leading causes of death in the world [2]. There are five million annual deaths from smoking-related diseases, a number that could reach eight million if there is no reduction in the current prevalence of smoking [2]. Among patients living with mental disorders, this problem is even greater, being as much as two to four times higher than that found in the general population [3]. Smoking rates are exceptionally high among these individuals and contribute to the high rates of morbidity and mortality [4,5]. This may be one important reason for patients with severe mental disorders die 25 years before the general population [6-8]. Numerous psychological, social, and biological factors may explain the high rates of smoking, including, for example, the lack of smoking cessation intervention in mental health treatment programs [9]. Progress in the development of treatments has been slow, in part because smokers living with mental disorders were excluded from most smoking cessation trials [10]. Moreover, smoking also complicates the treatment of mental disorders by reducing blood levels of some medications [5,10] and significantly impairing cognitive function [8,11].

First-line smoking cessation options for the general population include Nicotine Replacement Therapy (NRT - transdermal patches, chewing gum, and other forms), bupropion, varenicline, as well as behavioral support [12]. Nortriptyline and clonidine are second-line treatments used when first-line treatments are not available, are contraindicated, fail, or by the preference of the patient [13]. Practice guidelines recommend that mental health care providers advise smokers living with mental disorders to use evidence-based approved cessation medications when trying to quit [14-24]. In a systematic review that assessed the majority of therapeutic interventions for smoking cessation, combined pharmacotherapy and/or behavioral support interventions increased smoking cessation success compared to a minimal intervention or usual care [25]. In general, psychiatric diagnoses increase the risk of developing moderate-to-
severe neuropsychiatric side effects during a quit attempt [14-24]. However, a recent Cochrane systematic review gathering 102 studies provided evidence that mental health does not worsen as a result of quitting smoking and that smoking cessation is associated with improvements in anxiety and depression, also in people living with mental disorders [26]. A recent randomized controlled trial found that smoking cessation decreased depressive symptoms by 32.9% and also increased resilience by 37.5% [27]. These results are supported by several other reviews [10,28-31]. Fortunately, studies have shown that tobacco treatment in mental health settings can be efficacious [32-35] but, in general, achieves lower success rates than interventions in the general population. Retention rates are better when subjects are stable and undergoing psychiatric treatment [36,37]. Thus, there is a need to understand better the nuances of each pharmacotherapy smoking cessation treatment for people with mental disorders.

The present review aimed to summarize the pharmacokinetics, pharmacodynamics, therapeutic effects, side effects, and drug interactions of the first- and second-line smoking cessation medications, with a focus on patients living with mental disorders.

2. NRT

2.1. Pharmacokinetics and Pharmacodynamics

There are several presentations of NRT: gum, transdermal patch, nasal spray, inhaler, and sublingual lozenges [38]. Among the NRT options, the nasal spray is the one with the fastest-release formulation. Nicotine patches continue to deliver the nicotine release gradually, producing sustained effects throughout the day [39]. NRT releases smaller amounts of nicotine into the bloodstream than a tobacco cigarette. Thus, it is much safer to take into account the nicotine levels and also the absence of various toxic products that are present in cigarettes [39]. NRT works by binding to nicotinic cholinergic receptors, stimulating the release of dopamine, norepinephrine, serotonin, GABA, glutamate, endorphins, and adrenaline in the body, causing various effects such as
increased blood pressure, heart rate, and blood vessel contraction [39,40]. The alpha4beta2 subtype is probably the main receptor that acts on nicotine dependence and is abundant in the central nervous system [39]. The mesolimbic area, striatum, and prefrontal cortex are the most activated areas after dopamine release [39,41]. Nicotine is metabolized by the liver, mainly by cytochrome P2A6 (CYP2A6), but studies have identified activities, to a lesser extent, of CYP2B6 and CYP2E1 [42,43]. The predominant metabolite of nicotine is cotinine, which is further metabolized to hydroxy cotinine [42,43]. The half-life of nicotine is around 2 hours, and that of cotinine is approximately 16 hours, and they are metalized by the glucuronidation process [42,43].

2.2. Therapeutic Effects

NRT aims to partially replace the nicotine from cigarettes to reduce craving and nicotine withdrawal symptoms. NRT increases the rate of quitting by 50–70%, regardless of the setting [44,45]. NRT stimulates neural nicotinic acetylcholine receptors (NAChrs) in the brain’s ventral tegmental area, resulting in dopamine release in the nucleus accumbens. It leads to a reduction in nicotine withdrawal symptoms [46,47]. It does not eliminate all of the symptoms because all available nicotine delivery systems rely on systemic venous absorption, unable to achieve the rapid and high levels of arterial nicotine when cigarette smoke is inhaled [48]. Nicotine replacement also provides a coping mechanism, making tobacco products less rewarding [46]. The effect of nicotine from cigarettes is reduced, and when a person relapses smoking while on NRT, the cigarette is less satisfying, and the patient is less likely to resume the cigarette. Another benefit of the therapy is positive reinforcement, particularly for the arousal and stress-relieving effects [39].

The choice of the form of NRT prescription should be based on factors such as patient preference, word-of-mouth, advertising, price, route of administration, and perceived adverse effects [44,49]. Certain behavioral aspects of smoking should be considered. For example, ritual cigarette handling may be substituted by handling a nicotine inhaler. Chewing gum or sucking on a lozenge may reduce anxiety or thoughts about smoking.
There are a few pharmacological interventions for smoking cessation currently, but NRT is the most used worldwide. There are several types of nicotine replacement products. All of them have different levels of efficacy and variable rates of nicotine absorption. It is generally recommended to start when the patient stops smoking to avoid higher-than-usual nicotine concentrations [50].

The nicotine gum was the first easily accessible NRT product. The tablets come in the form of 2 and 4 mg dosages. Some studies have shown that 2 mg of chew gum has lower withdrawal success rates than 4 mg. The dosage is reduced daily after a few weeks or months of usage. It must be prescribed for at least 6–12 weeks, with a maximum of 6 months. There is also the rapid-release gum that has faster absorption and rapidly relief nicotine craving symptoms [51]. The nicotine lozenges can be used to replace the nicotine gum in patients who are unable to chew them for a longer period. They are available in 1, 2, and 4 mg formulations [52]. It is placed sublingually for 30 min, which releases nicotine into the systemic circulation [53].

A Nicotine patch is a transdermal patch that slowly releases nicotine. It is available in 5, 10, and 15 mg doses patches that can be worn over 16 h; and 7, 14, and 21 mg doses patches can be worn over 24 h [54]. Plasma concentration of nicotine gets higher during the day with nicotine patch usage than with any other NRT. Other forms of nicotine replacement therapy are the Nicotine inhaler, the Nicotine nasal spray, and the Nicotine sub-lingual tablet [51]. People with severe withdrawal symptoms can receive combined therapy. It consists of the transdermal nicotine dose of 7, 14, and 21 mg with a dosage of any other NRT. The most common are nicotine gum or a nasal spray [55].

2.3. Side Effects

The side effects of NRT should be compared with the side effects of smoking, which makes the nicotine replacement itself much safer than smoking [56, 58-61]. The most common side effects of nicotine replacement are nausea, vomiting, indigestion and
gastrointestinal disturbances, insomnia and sleep apnea, headaches, oral ulcers, skin irritation, heart palpitation/ chest pain, and coughing [51]. However, NRT has a good overall adverse event profile, with a low rate of discontinuation due to adverse events (i.e., 3.3% in a recent meta-analysis involving 177,390 individuals) [62]. It was observed that one of the most prevalent reasons for poor adherence to NRT is its effectiveness. When the craving and withdrawal symptoms are managed during the treatment, patients can wrongly assume that the treatment is no longer necessary [63]. This can be handled by providing scientific information to the patients before and during the treatment [64].

2.4. Drug Interactions

Smoking cigarettes cause blood levels reduction of many psychotropic drugs. It induces the enzyme CYP1A2 [65,66] and increases enzyme activity by up to 70% in heavy smokers [67,68]. It is important to be aware that the plasma levels of some drugs used to treat psychiatric disorders can rise significantly a few days after reducing the consumption of cigarettes or smoking cessation. After about one week, a new steady state is reached [67]. NRT does not affect medication levels once this effect happens due to the polycyclic aromatic hydrocarbons in smoke, not nicotine [65]. Some studies analyzed the clinically relevant smoking and psychotropic drug interactions. Tsuda et al. [69] and found that Clozapine and Olanzapine serum levels rise after smoking cessation, and the dose should be reduced by 50% and 30%, respectively. Zevin et al. [66] and Desai et al. [70] studies show that Haloperidol, Chlorpromazine, and Fluphenazine serum levels may rise, but the clinical significance is unclear. Fluvoxamine plasma levels may increase, and it may need a dose reduction [66]. Duloxetine [71], Mirtazapine [72], and Imipramine [70] serum levels may also rise, and the side effects of Imipramine must be monitored. Benzodiazepines can possibly cause increased sedation due to loss of CNS (central nervous system) stimulation by nicotine. The doses may need to be reduced [66]. Caffeine levels rise, and it is recommended to reduce consumption by half within a week [66]. Finally, it can increase alcohol levels, causing cognitive impairment, intoxication, and sedation. The alcohol intake should be reduced [66].
3. Varenicline

3.1. Pharmacokinetics and Pharmacodynamics

Varenicline is a partial agonist of the nicotine receptor. It binds more specifically to the α4β2 receptor (acetylcholine receptor) in the mesolimbic region, decreasing the release of dopamine and consequently reducing the reinforcing and rewarding effects in people who continue to smoke, as well as alleviating withdrawal symptoms and the urge to smoke [73-79]. Varenicline also binds to the serotonin (5-HT3) receptor, and this binding may be involved in reducing withdrawal symptoms [80]. Varenicline is completely absorbed by the gastrointestinal tract, having its systemic availability greater than 90%. Its bioavailability is not affected by food. It has a fast distribution throughout the body’s tissues, good penetration into the central nervous system, and can be administered at any time of the day [81,82]. The peak plasma concentration of Varenicline occurs between 3 and 4 hours after oral administration [83], and its maximum tolerated dose is 2 mg/day, being excreted almost exclusively for the kidneys [81]. It has an elimination half-life of approximately 24 hours and a steady state of around four days [81,84]. There are two metabolites found in urine: hydroxyquinoxaline and N-carbamoylglucuronide. However, they are not considered active metabolites, as they have very low concentrations when compared to Varenicline itself [85]. It is recommended to start with a dosage of 0.5 mg once a day for three days, followed by 0.5 mg twice a day for four days, and after that, starting a dosage of 1 mg twice a day for 12 weeks in patients who are motivated to quit smoking [83].

3.2. Therapeutic Effects

Varenicline was approved in 2006 as a prescription-only drug for smoking cessation by the FDA (Food and Drug Administration) and by the European Medicines Evaluation Agency. In July 2007, it was approved by the NICE (National Institute for Health and Care Excellence) for prescribing by the United Kingdom National Health Service (NHS) [86].
Varenicline acts in smoking cessation by preventing withdrawal symptoms and maintaining moderate levels of dopamine in the brain at the same time. It activates the α4β2 receptor and decreases craving and withdrawal symptoms while reducing the reward system by preventing nicotine binding [87,88]. Varenicline also has positive effects on cognition and processing of smoking-related cues, which are major triggers for new relapse episodes [89]. It increases the blood-oxygen-level-dependent signal in the anterior cingulate cortex and dorsolateral prefrontal cortex and improves response time activation in regions involved in attention, learning, and memory, including the insula, putamen, thalamus, and cingulate cortex in heavily dependent smokers [90,91]. Impulsivity and mesocorticolimbic dysfunction were also restored after varenicline treatment in abstinent smokers [92]. The 2019 systematic review and meta-analysis conducted by Oon-Arom et al. [83] provided evidence that varenicline, being a medication with high acceptability and tolerability, may be an option for patients with alcoholism who want to decrease alcohol consumption or those who cannot tolerate other medication by decreasing alcohol consumption over a period of time.

### 3.3. Side Effects

The most common side effect of Varenicline use is nausea, which is largely related to the administrated dose. It occurs in approximately 30% of patients taking 1 mg two times a day [89,83,94]. Insomnia is the second most prevalent adverse effect, reported in 14–37.2% of patients [94]. Abnormal dreams, sleep disturbances, headaches, and dizziness can also occur but are less common. They are usually time-limited and mild to moderate in severity [95,96]. It is very important to inform Patients that the adverse effects are usually resolved after one week of treatment and could be avoided by taking the medication on a full stomach [87,97]. The FDA placed a box warning for ‘serious neuropsychiatric events’ on Varenicline in 2009. These events included depressed mood, suicidal ideation and behavior, completed suicide, mood changes, psychosis, agitation, aggression, and hostility, in smokers with and without previous psychiatric conditions [89,98]. In 2015, FDA added a warning that Varenicline may change the way people react to alcohol. Some patients experienced reduced alcohol tolerance, increased drunkenness, aggression, unusual behavior, and memory lapse [89,99] after
consuming alcohol while taking Varenicline, as well as a potentially increased risk of seizures [100]. In 2016, a joint FDA advisory committee voted to remove all the warnings based on the results of a very large randomized clinical trial conducted by Pfizer [100]. The incidence of serious neuropsychiatric adverse events, such as suicidal behavior, was low and not statistically different among the treatment groups (i.e., varenicline, bupropion, nicotine patch, and placebo) in both psychiatric and non-psychiatric patients [100].

3.4. Drug Interaction

Varenicline neither inhibits nor induces the activity of cytochrome P450 enzymes and does not have any clinically meaningful pharmacokinetic drug-drug interaction [87,97]. However, nicotine withdrawal may influence drug metabolism resulting in alterations in the pharmacokinetics and pharmacodynamics of medications such as theophylline, tacrine, warfarin, and oral contraceptives. Dosage adjustments may be necessary for these medications [101]. The contraindications, absolute or relative, to Varenicline prescription, are hypersensitivity to the active substance or any of the substances used in the medication, pregnancy, breastfeeding, and patients under the age of 18 years old [87]. The use of Varenicline with other smoking cessation agents was the main theme of several studies. In a randomized, placebo-controlled crossover study, the chronic administration of Varenicline resulted in no clinically relevant effect on bupropion steady-state pharmacokinetics. Similarly, when administered with transdermal nicotine, it also did not alter the steady-state pharmacokinetics of nicotine or its major metabolite cotinine, but the combined use of both medications increased the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue [102,103].

4. Bupropion

4.1. Pharmacokinetics and Pharmacodynamics
Bupropion is a drug that inhibits the reuptake of dopamine and norepinephrine [104-106]. It belongs to the aminoketone class and may be known by its generic name, amfebutamone [107]. It is a medication used as a first line in the treatment of tobacco smoking [104]. Bupropion, after oral administration, is absorbed throughout the gastrointestinal tract [107,108], with less absorption near the colon, and it is not influenced by the presence of food in the tract [107]. It is metabolized by liver enzymes, mainly by cytochrome P2B6 (CYP2B6), which will convert Bupropion into three metabolites: hydroxybupropion, threohydrobupropion, and erythrohydrobupropion [104,107,108]. Bupropion is a racemate and has two enantiomers: R-(-)-bupropion and S-(+)-bupropion, with S-(+)-bupropion being the most active [107]. Sager et al. [109] identified the activities of the enzyme CYP2C19, acting on the activity and toxicity of Bupropion. Faucette et al. [110] carried out in vitro studies analyzing the isoenzymes related to Bupropion’s metabolism and concluded that CYP2B6 is the main enzyme related to the formation of hydroxybupropion and that CYP2C19, CYP3A4, CYP1A1, and CYP2E1 play a secondary role.

The half-life of Bupropion depends on its presentation (IR, SL, and XR) [104,107], but the approximate value is between 1.5 and 5 hours, with its mean half-life being 3.5 hours and its elimination half-life terminal approximately 18 hours [104,108]. Bupropion and its metabolites, after 5-8 days, reach their steady state [107], and the dosage of 150 mg to 300 mg needs 6-7 days to be completely eliminated from the body [104]. The maximum recommended dose is 450 mg/day. Doses greater than 450 mg/day are not recommended due to the high risk of seizures [107]. Bupropion is mostly excreted in the urine (88%), and a small amount is excreted in the feces (10%) and can also be excreted in breast milk [111]. Bupropion crosses the blood-brain barrier and the placenta. Therefore, it is contraindicated in pregnant women [112]. The exact mechanism of action of Bupropion for the treatment of smoking is not fully known [107], but the effects on smoking cessation are the inhibition of dopamine and norepinephrine reuptake and the blockade of the nicotinic receptors of acetylcholine [106,113]. Bupropion also acts by inhibiting the α4β2 nicotine receptor and also affects an allosteric blockade of 5-hydroxytryptamine (5-HT) receptors [107].
4.2. Therapeutic Effects

The onset of action of bupropion is two weeks, and its full efficacy is attained at four weeks of treatment. When compared to SSRIs, bupropion had similar depression remission rates with an approximate time to relapse of 44 weeks [114]. Taking into consideration that bupropion has a predominant effect on norepinephrine and dopamine and has a no sedating side effect profile, it appeared to be particularly suited to treat lethargic depression, producing greater improvement in sleepiness and fatigue scores, derived from the HAM-D [115]. Bupropion has demonstrated effectiveness in the prevention of seasonal affective disorder [116]. Bupropion has also been approved for smoking cessation and may have a combined role in treating depression and nicotine cravings [114]. The mechanism of action of bupropion in the process of cessation seems to be maintaining central levels of dopamine, and the effectiveness has been identified to be independent of symptoms of depression [113,117]. Bupropion has shown significantly higher activity in attention/concentration (attention deficit disorder) than placebo [115,118]. The dosage of 150-300mg/day of bupropion has demonstrated efficacy in the treatment of neuropathic pain in a single-center double-blind, placebo-controlled study [115].

The stimulant properties of bupropion have shown to be beneficial in the treatment of various fatigue syndromes. Some small-uncontrolled studies suggested that it has reduced cancer-related fatigue [119,120]. **Bupropion appears to produce weight loss.** Results from a multi-center 8-week randomized, double-blinded-controlled trial of patients with depression demonstrated a dose-dependent weight reduction with bupropion SR [121]. Recent studies suggest in both women and men with SSRI-induced sexual dysfunction, the adjunctive treatment with bupropion can improve sexual function [122-124] in any of the domains: desire, arousal, and orgasm [115].

4.3. Side Effects
The most commonly associated adverse reactions with the use of bupropion include irritability [125], agitation, dry mouth, insomnia, headaches, migraines, nausea, vomiting, constipation, and tremor. Some of the additional adverse reactions include the worsening of suicidal thoughts and behaviors that are most pronounced in adolescents and young adults, and the activation of mania or hypomania with or without psychosis was also noted mainly in patients with bipolar I disorder [126]. It is a known fact that bupropion is associated with an increased risk of seizures in its initial use as an antidepressant, most commonly if used in higher doses and an intermediate release form. The patients with a higher risk of seizure are the ones with a history of head injury, alcohol withdrawal, or anorexia [125,127]. Of the patients that took extra doses of bupropion, more than 10% had some significant adverse effects. Seizures were reported twice as often as expected with correct dosing. Taking extra doses of bupropion also appeared to increase the risk of agitation, dizziness, tremor, nausea and/or vomiting, drowsiness, seizures, and hallucination [128]. The Ebbert et al. [129] study reported that those being treated with bupropion for smoking cessation experienced a significantly higher incidence of insomnia, anxiety, and irritability compared with those who received NRT.

4.4. Drug Interaction

Bupropion is metabolized by the cytochrome P450 enzymes and, as such, may interact with other medications that are metabolized by this system [130-131]. Bupropion is metabolized to hydroxybupropion by CYP2B6, and administer inhibitors of this system, including paroxetine, sertraline, norfluoxetine, fluvoxamine, diazepam, and clonazepam, can increase levels of bupropion and its metabolites [131,132]. Inducers of CYP2B6, including carbamazepine [133], phenobarbital, ritonavir, and efavirenz, can decrease the effective doses of bupropion. As an inhibitor of the CYP2D6 enzymes, bupropion can increase levels of medications, including serotonin-norepinephrine reuptake inhibitors like venlafaxine, selective serotonin reuptake inhibitors like fluoxetine and paroxetine [134], tricyclic antidepressants like desipramine [135] and antipsychotics [108]. Bupropion increases dopaminergic activity. It has the potential to interact with other dopaminergic agents due to the additive dopamine agonist effects.
of the medications [108,114,132-136]. In patients that are on levodopa and amantadine, bupropion has been shown to result in central nervous system toxicity [114]. Because bupropion lowers the seizure threshold, it must be cautiously used with other medications that also lower the threshold [137], like antipsychotics and other antidepressants [108,138,139]. When alcohol or medications such as benzodiazepines are discontinued abruptly, the use of bupropion should be carefully evaluated due to the increased risk for seizure during withdrawal states [139]. Bupropion should not be administered with or within 14 days after discontinuation of monoamine oxidase inhibitors [131-133].

5. Nortriptyline

5.1. Pharmacokinetics and Pharmacodynamics

Nortriptyline is the pharmacologically active metabolite of the amitriptyline, a tricyclic antidepressant (TCA) with sedative effects [140], after the N-Demethylation by the cytochrome P450 (CYP) 2C19 enzyme [141]. Nortriptyline is hydroxylated by CYP2D6 into less active or inactive hydroxy metabolites, including 10-hydroxy-amitriptyline and 10-hydroxy-nortriptyline [142-144]. The parent drugs are less active and have approximately half the potency of their hydroxylated metabolites [145], which are further glucuronidated and excreted in the urine in the form of water-soluble substrates [146]. Nortriptyline plasma concentration variability has been associated with polymorphisms in CYP2D6 and CYP2C19 [142,143,147-149]. The nortriptyline mechanism of action is not completely understood. However, it is believed to block the reuptake of norepinephrine, serotonin, or dopamine, enhancing the activity of the neurotransmitters [150]. It has a lower serotoninergic effect but higher noradrenergic activity than amitriptyline [143]. In addition to that, nortriptyline inhibits the activity of histamine, 5-hydroxytryptamine, and acetylcholine. It also increases the pressor effect of norepinephrine but hinders the pressor response of phenethyamine, desensitizes adenyl cyclase, down-regulates beta-adrenergic receptors, and down-regulates serotonin receptors [151]. High plasma concentrations of nortriptyline are associated
with a high risk of anticholinergic side effects due to the binding of TCAs to cholinergic receptors [152]. The hydroxymetabolites of amitriptyline and nortriptyline have less affinity for the muscarinic acetylcholine receptor than their parent drugs (hydroxy nortriptyline has only one-eighteenth the affinity of nortriptyline [145]), generating much fewer side effects [146,153].

### 5.2. Therapeutic Effects

Nortriptyline is a tricyclic antidepressant that can inhibit the reuptake of serotonin, dopamine, and noradrenaline [154]. Traditionally, it has therapeutic actions for the treatment of major depressive disorder, nocturnal enuresis, and migraine [155-157]. The most common reason for using antidepressants for smoking cessation is that nicotine withdrawal increases depression, depression increases relapse, and depression can be prevented by antidepressants. Several studies concluded that nortriptyline is effective in the treatment of smoking [158,159]. Effective both in the treatment of depression caused by withdrawal and in the efficacy, mainly, noradrenergic drugs that replace the noradrenergic actions of nicotine [160]. Nortriptyline's database is not as extensive as that of some NRTs and/or bupropion. However, there is enough data in favor of its effectiveness. Bupropion, according to studies, has a numerically higher dropout rate than nortriptyline; however, it is not significantly different. The odds ratio for nortriptyline is similar to that for NRTs. The advantages of nortriptyline are that, unlike bupropion and SSRIs, there is therapeutic monitoring of blood levels that can be used to ensure adequate medication exposure and avoid adverse effects. Another possible advantage is that, in most countries, nortriptyline is available generically and is, therefore, less expensive [161]. Still, it is debatable whether nortriptyline should be a first-line treatment for smoking cessation, as its usefulness is limited by its potential side effects, including dry mouth, constipation, nausea, sedation and headaches, risk of arrhythmia. In hospitalized patients with cardiovascular disease and lethality in overdose, due to this, the use of nortriptyline is an option in the second line of therapy in the treatment of smoking [159].
5.3. Side Effects

Nortriptyline has anticholinergic and adrenergic action that contribute to several side effects [162,163]. A meta-analysis by Howes et al. [164] analyzed the side effects of Nortriptyline compared to placebo and reported that more than 80% of patients had xerostomia [165], and more than 50% had perspiration, constipation [165], drowsiness, and dizziness. Patients who received the placebo also had these symptoms but in a smaller percentage. Fatigue and drowsiness are also possible side effects, according to Hashemi et al. [154]. Palpitation may be one of the symptoms present in patients who are taking Nortriptyline, as reported in a randomized controlled trial carried out by Aveyard et al. [166]. Costa et al. [167] carried out a prospective, randomized, double-blind study comparing Nortriptyline with a placebo and demonstrated that Nortriptyline has lower rates of side effects when compared to other tricyclic antidepressants and that it is well tolerated by the elderly. Within the class of tricyclic antidepressants, Nortriptyline is the medication that has the smaller effect on increasing appetite and, consequently, weight gain [153]. Nortriptyline should be used with caution in patients at risk of self-extermination due to the risk of serious intoxication if a suicide attempt is made [154]. A patient diagnosed with bipolar affective disorder limits the use of Nortriptyline due to the risk of a manic episode [154]. In a study carried out with pregnant women with postpartum depression, is reported that after using Nortriptyline, one of the patients developed an episode of mania [168]. Piaktov et al. [169] carried out a study reporting the development of psychotic symptoms in two patients who used Nortriptyline. Reynolds et al. [170] carried out a double-blind, randomized study evaluating the use of Nortriptyline for the treatment of depression in 41 elderly people, and one of them had psychotic symptoms.

5.4. Drug Interactions

Cytochrome P450 enzymes influence nortriptyline metabolism [171]. More specifically, nortriptyline is metabolized by CYP2D6 into active metabolites, E-10-hydroxy (OH-) nortriptyline and Z-10-hydroxy (OH-) nortriptyline [172]. Other drugs metabolized by
CYP2D may interact with the action of Nortriptyline [172]. Solai et al. [172] carried out a study evaluating the change in serum levels of Nortriptyline with the introduction of 5 mg of Paroxetine and concluded that after administration of Paroxetine, serum levels of Nortriptyline, which were previously within the therapeutic range, decreased to below the therapeutic range. Laine et al. [173] evaluated the treatment of patients who are fast nortriptyline metabolizers, concluding that Paroxetine at 20-40mg per day can be an effective tool in normalizing the metabolic state of patients that metabolize CYP2D6 very quickly. Berm et al. [174] carried out an analysis of a clinical trial, evaluating the drug interaction between nortriptyline and venlafaxine, both metabolized by CYP2D6, and no phenoconversion changes were found in the metabolism of patients using these medications. Hefner et al. [175] performed a case report of a patient using nortriptyline concomitantly with Melprelone medication, a medication used for some sleep disorders and for psychomotor agitation, both metabolized by CYP2D6. He reported a 50% increase in nortriptyline concentration, with important side effects. Many antidepressants and neuroleptics are metabolized by CYP2D6, which requires caution in choosing two or more medications. Haloperidol, perphenazine, risperidone, and zuclopenthixol are examples of neuroleptics metabolized by this enzyme, as well as the antidepressants nortriptyline, fluvoxamine, mirtazapine and venlafaxine [176].

6. Clonidine

6.1. Pharmacodynamics and Pharmacokinetics

Clonidine is an imidazole derivative, which acts as an α-2-adrenergic receptor agonist. It inhibits cerebral noradrenergic transmission and has an alpha-antagonist effect on the posterior hypothalamus and spinal cord, which can cause sedation and a decrease in blood pressure and heart rate [177-184]. It may also act on the endogenous opioid system [184]. Clonidine can be administered orally or transdermally, with the oral dosage ranging from 0.15 to 0.45 per day and the transdermal dosage ranging from 0.1 to 0.3 mg per day, and it is necessary to take into account the patient's weight and tolerance when determining the chosen dosage [181,185,186]. Oral administration of
Clonidine is well absorbed from the gastrointestinal tract and can be divided into two to four daily doses, being adjusted according to withdrawal symptoms and side effects [182]. It has an oral bioavailability of 70-80%, and after administration, it has a peak plasma concentration of 1-3 hours [184,187]. It has a half-life that can vary from 5-20 hours, approximately 50% of the absorbed substance is metabolized in the liver, and the remainder is excreted in the urine [184]. Transdermal administration can be performed at a dosage of 0.1mg/day, 0.2mg/day, or 0.3mg/day, changing the patch every seven days [183]. It is recommended that treatment with Clonidine be started 48-72 hours before smoking cessation, but it is not contraindicated to start the use of this medication in patients who have already stopped using tobacco [181]. In addition, as Clonidine is more effective in withdrawal, the recommended treatment is three to four weeks, which is the estimated time for the duration of tobacco withdrawal symptoms [181]. When discontinuation of Clonidine is initiated, it should be withdrawn in gradual doses to avoid withdrawal symptoms from Clonidine itself [181].

6.2. Therapeutic Effects

The Cochrane review evaluating clonidine compared to placebo in RCTs study [185] describes Clonidine as a medication sold as an antihypertensive agent that has been used as a treatment for menopausal flushing [188,189], chronic pain syndromes [190], Tourette's syndrome [191] and withdrawal from opiate or alcohol abuse [192,193]. It has also been reported the use of clonidine for smoking cessation. Some double-blind studies have reported that Clonidine therapy has reduced nicotine withdrawal symptoms such as craving, anxiety, restlessness, tension, and hunger [178, 194-197]. One study failed to find any effect [198]. When all results were analyzed in a meta-analysis, it was shown that clonidine improved smoking cessation rates compared to placebo [186]. Clonidine is considered a second-line pharmacotherapy by the U.S. clinical practice guideline for treating tobacco dependence. Its efficacy for smoking cessation is based on its ability to counteract the neurobiological features of nicotine withdrawal [199]. The therapy is most interesting for patients that will have multiple beneficial effects with its use or when there are intense withdrawal symptoms. For example, if a patient experiences severe agitation and anxiety during the period of
nicotine withdrawal, the sedative effects of clonidine may be desirable. Clonidine can also be used in the treatment of withdrawal from multiple drug abuse because it also reduces the withdrawal symptoms from drugs other than nicotine [185]. On a regular basis, the use for smoking cessation is limited due to the need for close attention to dose-dependent adverse effects [186]. Clonidine may not be the best option for patients that want to quit smoking, but it can be useful for people who do not respond well to nicotine replacement therapy or antidepressants [185]. Because its mechanism of action is different from NRT and bupropion, clonidine can be used in combination with these other treatments [200]. Clonidine has also been used as an off-label medication to treat insomnia and attention-deficit hyperactivity disorder as a conjunctive treatment [199]. The results from some clinical trials suggest that women tend to respond more favorably to Clonidine in smoking cessation than men, although no trial has randomized the study by gender to formally test this hypothesis [185].

6.3. Side Effects

Clonidine use in smoking cessation therapy is limited due to its side effects. Sedation, dizziness, postural hypotension, dry mouth, and fatigue are the most common side effects and make it a second-line therapy [200]. Some other side effects in the central nervous system are agitation, anxiety, delirium, delusional perception, hallucinations (including visual and auditory), insomnia, mental depression, nervousness, other behavioral changes, paresthesia, restlessness, sleep disorder, vivid dreams, and nightmares [201]. Clonidine dose has to be tapered down because abrupt discontinuation can cause rebound hypertension [200]. Sudden cessation has also resulted in symptoms such as nervousness, agitation, headache, tremor, and elevated catecholamine concentrations in the plasma in some cases [201]. The transdermal patch formulation can cause skin allergic reactions. These patients can switch to oral clonidine, but they may be susceptible to systemic allergic reactions as well [202]. Future studies are necessary to conclusively demonstrate that clonidine is an effective treatment and has fewer side effects than other drugs before it can be considered as a first-line therapy for smoking cessation [185, 200].
6.4. Drug Interactions

Clonidine may potentiate the effects of CNS-depressive effects of barbiturates, alcohol, and other sedating drugs [201,202]. In patients receiving clonidine at the time of taking tricyclic antidepressants, the hypotensive effect may be reduced, and an increase in clonidine dosage can be necessary. If a patient is receiving neuroleptics in general and taking clonidine, orthostatic regulation disturbances like orthostatic hypotension, dizziness, and fatigue can be induced or exacerbated [201]. High doses of intravenous clonidine in patients in some states of alcoholic delirium can cause QT-prolongation and ventricular fibrillation, increasing the arrhythmogenic potential of high doses of intravenous haloperidol used in the treatment of delirium. The concomitant use of amitriptyline and clonidine enhanced the manifestation of corneal lesions in rats [201]. The co-administration of clonidine and beta-blockers, calcium channel blockers, and digitalis must be cautious because of the risk of sinus bradycardia. Sudden cessation of clonidine treatment can cause symptoms such as agitation, headache, and tremor, as well as rebound hypertension [201-203].

7. Discussion

The purpose of this review was to synthesize the pharmacokinetics, pharmacodynamics, therapeutic effects, adverse effects, and pharmacological interactions of first- and second-line smoking cessation drugs, with an emphasis on patients suffering from mental illnesses.

The pharmacokinetics and pharmacodynamics of smoking cessation medications have important implications for psychiatric patients. NRT, Varenicline, Bupropion, Nortriptyline, and Clonidine all have different mechanisms of action that affect the release or reuptake of various neurotransmitters such as dopamine, norepinephrine, serotonin, GABA, glutamate, endorphins, adrenaline, and histamine. These
neurotransmitters are associated with a range of psychiatric disorders, including depression, anxiety, bipolar disorder, and schizophrenia. Therefore, the use of these medications in patients with psychiatric conditions may have implications for their mental health and must be monitored closely. The efficacy and side effects of these medications may vary depending on the individual patient's psychiatric condition, medication regimen, and other factors, such as substance use or medical comorbidities. It is essential to consider the potential interactions of these medications with psychiatric medications and the need for close monitoring of patients to avoid any adverse events.

The positive outcomes of using smoking cessation medications hold significant importance for individuals with psychiatric conditions. NRT, Varenicline, Bupropion, Nortriptyline, and Clonidine have been shown to be effective in reducing nicotine cravings and withdrawal symptoms and promoting smoking cessation. These medications can be particularly useful for psychiatric patients who are more likely to smoke than the general population and who may have a more difficult time quitting due to their underlying psychiatric condition. However, it is important to consider the potential impact of these medications on psychiatric symptoms, medication regimens, and comorbidities. For example, Bupropion may be effective in treating both depression and nicotine cravings, but its use may need to be monitored closely in patients with a history of seizures or eating disorders. Additionally, Varenicline has been shown to have positive effects on cognition and processing of smoking-related cues but may also exacerbate symptoms of depression or schizophrenia in some patients. Therefore, it is important to carefully consider the risks and benefits of using smoking cessation medications in psychiatric patients and to tailor treatment plans to individual patients' needs. Close monitoring of symptoms and medication regimens is essential to ensure optimal treatment outcomes and avoid potential adverse events.

The side effects of smoking cessation medications have important implications for psychiatric patients. Common side effects of nicotine replacement therapy, Varenicline, Bupropion, Nortriptyline, and Clonidine include gastrointestinal disturbances, insomnia, headaches, dry mouth, and dizziness. These side effects can potentially exacerbate psychiatric symptoms such as anxiety or depression, disrupt sleep patterns, or interfere
with medication adherence. Additionally, some of the less common side effects of these medications, such as abnormal dreams or hallucinations, may be particularly concerning for patients with certain psychiatric disorders. Therefore, careful consideration of the potential risks and benefits of smoking cessation medications is necessary when prescribing these medications to psychiatric patients. In some cases, it may be necessary to adjust medication regimens or closely monitor symptoms in order to avoid potential adverse events. It is also important to educate patients about potential side effects and encourage open communication about any concerns or issues that may arise during treatment. Overall, a balanced approach to smoking cessation medication use in psychiatric patients is necessary to achieve optimal treatment outcomes while minimizing potential risks and side effects.

NRT and varenicline neither inhibit nor induce the activity of cytochrome P450 enzymes and do not have any clinically meaningful pharmacokinetic drug-drug interaction. The levels of bupropion may be influenced by inhibitors and inducers of CYP2B6, including several psychiatric medications. As an inhibitor of the CYP2D6 enzymes, bupropion can increase levels of various psychiatric medications, including nortriptyline. Bupropion also increases dopaminergic activity, potentially interacting with other dopaminergic agents due to the additive dopamine agonist effects of the medications. Clonidine may potentiate the depressive effects of neuropsychiatric medications. In addition, its effects may be reduced by tricyclic antidepressants.

Psychiatric patients who require smoking cessation medications may also be taking other medications, and drug-drug interactions between these medications can have significant implications. Nicotine replacement therapy (NRT) does not affect medication levels, but other medications such as bupropion and nortriptyline are metabolized by CYP2B6 and CYP2D6 enzymes, respectively, and can interact with inhibitors and inducers of these enzymes. Bupropion can increase dopamine agonist effects and levels of medications, while nortriptyline can interact with the action of other medications, such as bupropion. Clonidine, on the other hand, can potentiate the effects of CNS-depressant medications and may cause orthostatic regulation disturbances when co-administered with neuroleptics, beta-blockers, calcium channel blockers, and digitalis. Healthcare
providers must be cautious when prescribing smoking cessation medications to psychiatric patients and consider potential drug-drug interactions to ensure patient safety and the efficacy of treatment.

The particularities of smoking cessation medications have important implications for psychiatric patients. Nicotine replacement therapy (NRT) and varenicline may produce sleep changes, but they have good efficacy in treating nicotine withdrawal psychological symptoms and do not have relevant drug interactions. Bupropion may have a combined role in treating depression and nicotine cravings, but it cannot be used in individuals with anorexia nervosa or when discontinuing tranquilizers and alcohol due to the increased risk of seizures. Moreover, it may be affected by medications that act on CYP2B6 and may affect those metabolized by CYP2D6. Nortriptyline has therapeutic actions for the treatment of major depressive disorder, anxiety disorders, nocturnal enuresis, and migraine. It can be particularly useful for smokers with depressive symptoms. However, several antidepressants can substantially inhibit CYP2D6 and may reduce nortriptyline levels. Clonidine reduces craving, anxiety, restlessness, tension, and hunger during smoking cessation and may be useful in patients with chronic pain syndromes, Tourette's syndrome, and withdrawal from opiate or alcohol abuse. However, it may induce or exacerbate orthostatic hypotension, dizziness, and fatigue in patients taking neuroleptics. Therefore, healthcare professionals must consider the particularities of each medication and their potential interactions with psychiatric medications to provide the best possible smoking cessation treatment for their patients.

8. Conclusion

Smoking cessation medications have been shown to be effective in reducing nicotine cravings and withdrawal symptoms and promoting smoking cessation in patients with mental illnesses. However, careful consideration of potential drug interactions and side effects is necessary when prescribing these medications to this population. The use of NRT, varenicline, bupropion, nortriptyline, and clonidine may impact the release or
reuptake of various neurotransmitters, which are associated with psychiatric disorders. Hence, the potential impact on psychiatric symptoms, medication regimens, and comorbidities must be considered. Adverse effects such as gastrointestinal disturbances, insomnia, headaches, dry mouth, and dizziness can exacerbate psychiatric symptoms, disrupt sleep patterns, or interfere with medication adherence. Therefore, a balanced approach that considers individual patient needs is necessary to achieve optimal treatment outcomes while minimizing potential risks and side effects. Healthcare providers must be cautious when prescribing smoking cessation medications to psychiatric patients and consider potential drug-drug interactions to ensure patient safety and the efficacy of treatment.

9. References


64. Ferguson SG, Gitchell JG, Shiffman S, Sembower MA, Rohay JM, Allen J. Providing accurate safety information may increase a smoker’s willingness to use nicotine replacement therapy as part of a quit attempt. Addict Behav. 2011;36:713–6.


122. Maneeton N, Maneeton B, Eurviriyanukul K, Srisurapanont M. Efficacy, tolerability, and acceptability of bupropion for major depressive disorder: a meta-analysis of


142. Dean L. Amitriptyline Therapy and CYP2D6 and CYP2C19 Genotype. Medical Genetics Summaries. Bethesda, MD: National Center for Biotechnology Information; 2012


204. Catapres transdermal therapeutic system [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; 2006.
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<tr>
<th>Table 1. Smoking Cessation Medications: Pharmacokinetics and Pharmacodynamics, Therapeutic Effects, Side Effects, Drug Interactions, and Particularities for Patients living with mental disorders.</th>
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<tbody>
<tr>
<td>Nicotine Replacement Treatment (NRT)</td>
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<tr>
<td><strong>Pharmacokinetics and Pharmacodynamics</strong></td>
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<tr>
<td><strong>Therapeutic Effects</strong></td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
</tr>
<tr>
<td><strong>Particularities for Patients living with mental disorders</strong></td>
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</tr>
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