# Smoking Cessation Pharmacotherapy and Obstructive Sleep Apnea

Subjects: Respiratory System | Cardiac & Cardiovascular Systems

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Tobacco smoking has been a recognized risk factor for cardiovascular diseases (CVD). Smoking is a chronic relapsing disease and pharmacotherapy is a main component of smoking cessation. Obstructive sleep apnea (OSA) and smoking both increase the risk of CVD and are associated with significant morbidity and mortality. There are few existing data examining how pharmacological treatment, such as nicotine replacement therapy (NRT), bupropion, and varenicline, affect smokers suffering with OSA and especially their cardiovascular effects.

Keywords: obstructive sleep apnea ; smoking cessation ; CVD ; pharmacotherapy ; nicotine replacement therapy ; varenicline ; bupropion ; clonidine ; nortriptyline ; cytisine

## 1. Introduction

Smoking is considered a chronic relapsing disease [1] and should be treated with different therapeutic interventions aimed at different aspects of nicotine addiction (physical, behavioral, psychological, and cognitive). The combination of behavioral support, education, and pharmacological treatment is the key to successful smoking cessation [2]. Clear but brief advice (3–5 min) provided by any healthcare professional significantly increases the motivation of a smoker to quit and increases abstinence rates [3].

Pharmacological treatment is an important component of smoking cessation interventions. First-line smoking cessation medications should be the first choice of clinicians as they have been approved by the European Medicines Agency (EMA) and are considered to be safe and effective in treating tobacco dependence. Nicotine replacement therapy (NRT), varenicline, and bupropion are the first-line therapies for smoking cessation [2]. Second-line medications include nortriptyline, clonidine, and cytisine that are not approved for smoking cessation in all European countries. They may be administered when first-line medications cannot be used [2]. Prolonging the duration of pharmacological treatment and a combination of different medications have been used in order to increase treatment efficacy [2][4][5].

Withdrawal symptoms are considered a main component in relapse and should be treated with the optimization of pharmacotherapy and the appropriate psychological support with counseling. Cravings and withdrawal symptoms should be evaluated at each follow-up visit of the smoker during the quitting process. During smoking cessation, sleep disturbances are frequent withdrawal symptoms and contribute to daytime symptoms such as irritability, memory loss, or concentration difficulties. Sleep problems and daytime somnolence negatively affect the ability of abstinent smokers to cope with everyday functioning, making relapse easier [6][7]. Patients suffering from OSA may have daytime somnolence due to sleep deprivation from the respiratory events. This may make their smoking cessation attempts more difficult. For that there is a need for the personalized evaluation of each smoker with the appropriate therapies according to their different needs during cessation. On the other hand, the different smoking cessation medications may affect sleep and sleep breathing events, especially in patients with OSA [6][8].

## 2. First-Line Medications

### 2.1. Nicotine Replacement Therapy (NRT)

NRTs have been used for many decades for smoking cessation with significant efficacy in order to provide the nicotine of cigarettes without the damaging effects of smoke [9][10]. On the other hand, there are few and controversial studies on NRTs' capacity to improve sleep disorders due to tobacco withdrawal [11][12]. There is evidence from self-reported questionnaires of abstinent smokers that NRTs increase sleep disruptions. On the other hand, in studies using objective

data with sleep recordings, NRTs were not found to improve the subjective symptoms of sleep disturbances during cessation, whereas the objective signs were improved [13].

The effect of NRTs on the sleep architecture of non-smokers and former smokers is similar. In non-smokers, the application of a transdermal nicotine patch resulted in increased sleep stage 2, in rapid eye movement (REM) sleep reduction, and in REM sleep rebound during the nights that followed the discontinuation of the patch. In addition, no significant effects in sleep latency, sleep continuity, and total sleep time (TST) were found [14]. Furthermore, in smokers undergoing smoking cessation, the transdermal nicotine patch of 24 h duration appeared more effective than that of 16 h in sleep quality improvement by lowering microarousals and by increasing slow wave sleep (SWS) [15]. Both patches resulted in prolonged sleep latency and shorter TST, whereas only the 24 h patch improved NREM sleep, SWS, and arousals [15]. Studies using subjective sleep variables found that more sleep difficulties were reported in those who used nicotine patches, but the effect of the concomitant use of patches and smoking contributing to higher nicotine levels was not always evaluated [16].

As both withdrawal symptoms and nicotine administration may affect sleep, it is troublesome to discriminate between them. Withdrawal effects of nicotine addiction should not be underestimated as there are studies that found that sleep disorders continued with the use of nicotine patches, whereas in the placebo group they were even more frequent [6][16][17]. Additionally, side effects such as sleep disturbances are related to the duration of nicotine abstinence and the severity of nicotine dependence [16]. The reduction in plasma nicotine levels during the night may induce withdrawal symptoms, and especially heavy smokers may wake in order to smoke. This implies high nicotine dependence and increased risk of failure or relapse [11]. However, we should take into consideration that the heterogeneity of the methodology of the different studies, i.e., the different time and dose of NRTs, the additional use of conventional cigarettes, and the use of subjective or objective measures of sleep, limit the generalization of these results.

There is evidence that nicotine has stimulant properties on the activity of the genioglossus muscle and on the ventilatory drive [18]. Further, there are studies with conflicting results evaluating the effect of nicotine for OSA treatment [8][17][19][20][21][22]. Nicotine gum (14 mg) use in OSA patients with different smoking histories resulted in the reduction in respiratory events (obstructive and mixed apneas) early at night during the first 2 h when the dilating properties of nicotine on the upper airway were efficient. However, this effect was not maintained as nicotine has a short half-life (2–4 h). For that, the respiratory events increased until the end of the night as upper airway resistance also increased. Further, sleep architecture, central apnea events, and end-tidal $CO_2$ during wakefulness were not affected [20]. On the other hand, other studies where nicotine was administered by transdermal patches [21] or by tooth patches [22] did not find any significant alterations in respiratory events. In non-smoking OSA patients that received a transdermal nicotine patch (11 mg) for 12 h, versus a placebo, no positive effects on snoring or respiratory events [21] were found. However, a negative correlation between the mean duration of apneas and hypopneas and serum nicotine concentration was observed [21]. Sleep efficiency and TST were also reduced with the nicotine patch [21]. In addition, in another study where nicotine tooth patches in doses of 2 and 4 mg in OSA patients were used, no improvement of either the apnea hypopnea index (AHI) or sleep stages was found [22].

**Cardiovascular Effects of NRTs**

Nicotine's action on the α4β2 nicotinic acetylcholinergic receptor (nAChR) enhances its reinforcing and addictive effects and on α3β4 nAChR mediates sympathetic neural stimulation. Due to this effect blood pressure, heart rate, and myocardial work increase. In addition, this may result in the constriction of coronary arteries and reduction in the myocardial blood supply. These effects may increase myocardial ischemia risk and the possibility of arrhythmias. It seems that smokers develop a degree of tolerance to these cardiovascular effects of nicotine. NRTs provide less plasma concentration of nicotine compared with cigarette smoking [23]. Several clinical studies have evaluated the cardiovascular effects of NRT, showing different results. Some studies found a significant increase in heart rate and systolic blood pressure following the use of NRTs [24][25][26][27] while others did not find any effects [28][29][30][31][32].

It has also been reported that nicotine patches (21 mg/24 h) increased the heart rate and blood pressure of non-smokers and normotensive smokers, but not of smokers with hypertension [30]. This could be explained by the fact that heavy smokers might develop tolerance to the effects of nicotine, resulting in no hemodynamic effects. In addition, a study assessing high cardiovascular risk patients did not show an association between nicotine patch use and first myocardial infarction [33]. Furthermore, a meta-analysis showed no increase in the risk of cardiovascular side effects such as hypertension, palpitations, arrhythmias, myocardial infarction, or stroke in patients using NRT versus those treated with a placebo [34], suggesting that NRTs are safe for smoking cessation.

Due to the aforementioned concerns on the cardiovascular safety of NRTs, some large clinical trials aimed to evaluate their safety, especially for patients with CVD [35][36][37]. These studies did not find increased cardiovascular risk in the group of patients using NRTs for smoking cessation. Cardiac arrest, myocardial infarction, death, and hospitalization due to arrhythmias, angina, or heart failure did not differ between the group using placebo and that using NRTs, although smoking cessation was more successfully achieved in the NRT group [38][39].

## 2.2. Bupropion

Bupropion SR is a first-line medication for smoking cessation and the first non-nicotine therapy. Since 1989, it has been used as an anti-depressant and it has been observed that patients experienced smoking cessation unintentionally. For that, bupropion was evaluated for smoking cessation [40]. Bupropion is a weak norepinephrine–dopamine reuptake inhibitor but without significant antagonism at histaminic or muscarinic receptors. While it is not a classic stimulant, it may increase dopamine and norepinephrine resulting in non-specific stimulation [40][41][42]. Its main mechanism of action is by blocking the neuronal release of dopamine and noradrenaline and possibly by inhibiting anti-cholinergic nicotine receptors [41]. Bupropion's efficacy for smoking cessation is independent from its anti-depressant action, as it has been proven effective also in non-depressive smokers. Bupropion reduces the severity of withdrawal symptoms such as depression and increased appetite and it has been found to almost double the abstinence ratio by reducing the severity of withdrawal syndrome in both sexes [42]. Bupropion is recommended for smoking cessation especially in smokers concerned about post-abstinence weight gain and for preventing smoking relapses. With the exception of one study [43] in smokers with chronic obstructive pulmonary disease (COPD), that expressed the hypothesis that bupropion could alter the ventilator response to hypoxia and hypercapnia, no other study has found similar effects [44].

As bupropion has been on the market for many years as an anti-depressant, its adverse effects have been well documented [44]. The most common adverse effects include headaches, oral dryness, and insomnia. More specifically, the short-acting formulations of bupropion that were administered late before sleep were associated with sleep disorders due to their alerting effects [45]. In order to avoid sleep problems such as insomnia, the first bupropion tablet is recommended in the early morning, so that the second tablet is administered at least four hours before sleep, early in the afternoon. If insomnia is considered a significant problem the dose may be reduced to 150 mg/day.

Moreover, unlike other anti-depressants, the use of bupropion in patients with depression may increase REM sleep and decrease REM latency [46]. A study has found that the differences in REM latency change after the administration of bupropion reflects the different response to the medication and the different response to treatment assessed by depression rating scales. Patients that showed an increase in REM latency after bupropion use responded better in the anti-depressive treatment compared with those who showed a decrease in REM latency that did not show anti-depressive response [47]. Further, it has been found that bupropion presents a relatively low risk of inducing REM sleep behavioral disorder [48] and restless legs syndrome [49][50].

Despite the administration of bupropion for many years as an anti-depressant and later for smoking cessation, there are few data concerning its effects in OSA patients. The co-existence of insomnia and OSA (Comorbid insomnia and sleep apnea, COMISA) is a rather common condition that has been under-recognized for several years. COMISA further impairs the quality of sleep and may cause problems in the diagnosis but also treatment. [51]. It has been observed that COMISA is linked with an increased risk of all-cause mortality and also higher rates of hypertension and cardiovascular disease (CVD) [52]. Insomnia is one of the most frequent side effects of bupropion; however, researchers did not find any studies evaluating the effects of bupropion on the sleep continuity of OSA patients and more specifically those suffering from COMISA.

In addition, bupropion, unlike other anti-depressants, does not have REM suppressant effects and may increase REM [46]. Although OSA occurs during any sleep stage, the majority of respiratory events occur in REM, as during this stage of sleep there is reduced muscle tone in every muscle apart from the diaphragm. In addition, some patients present obstructive events only during REM sleep. For this reason, bupropion may affect the severity of OSA, especially in patients with predominantly REM OSA. However, this is a hypothesis as no studies are available yet.

### Cardiovascular Effects of Bupropion

The most important side effects of bupropion include the dose-related risk of seizures and hypertension reported even without the pre-existence of hypertension [40][41][42][43]. Precautions for these effects are included in the package label. Older studies did not find clinically important effects of bupropion on heart rate, blood pressure, conduction complications, or a higher risk of an AV block [53][54]. The use of bupropion SR for smoking cessation in patients with CVD has been also examined [55][56][57][58]. No significant effects on blood pressure were found at 12 weeks between bupropion and placebo

and the adverse cardiovascular events were similar in both groups. However, the cardiovascular events were greater in the bupropion group after 12 months of observation, even though in the early post hoc analysis no significant differences were found between the cardiovascular events in patients who completed 30 days and 12 weeks of therapy [55]. Another study that evaluated the effect of bupropion in smokers hospitalized for acute coronary syndrome ended early due to a lack of efficacy, but did not find significant cardiovascular risk differences, even after one year of follow up [56]. Other studies that evaluated the cardiovascular effects of bupropion in the outpatient setting [57][58] did not find significant increase in blood pressure or heart rate, even in patients suffering from CVD. However, CVD patients that received bupropion reported more frequent adverse events such as palpitation and angina [57] and a small difference in heart rate occurred in those that received higher dose of bupropion SR (400 mg) [58].

## 2.3. Varenicline

Varenicline is a first-line medication for smoking cessation and is one of the most effective ones as it has been found that it significantly increases smoking abstinence rates [59]. It binds with high selectivity and affinity with alpha4beta2 nAChRs (α4β2nAChRs). It also stimulates dopamine release [60]. Varenicline acts as a partial agonist reducing withdrawal symptoms, but also as an antagonist reducing the rewarding effects of smoking and facilitating smoking cessation.

The most common side effects of varenicline include nausea, headaches, insomnia, and abnormal dreams. There is evidence that smokers that are treated with varenicline often report sleep disorders that decrease over time [6]. For example, insomnia symptoms peak during the first week of use and progressively decline after 2–12 weeks [61]. On the other hand, sleep disorders are a commonly reported symptom during smoking cessation and are considered a withdrawal symptom [6][17][62]. Furthermore, abnormal dreams and nightmares are also frequently reported as varenicline's side effects [63][64]. Frequent awakenings and abnormal dreams but without significant alterations in sleep measures were reported in a study that evaluated sleep diaries after varenicline use [64]. Due to the stimulation of dopamine release from varenicline, amelioration of restless leg syndrome has been reported during smoking cessation attempts [65]. Rarely, in some cases, somnambulism and REM sleep disorders have been reported [63][65]. In the study of Savage et al. [63] that reviewed the original reports from WHO Global Individual Case Safety Reports Database, 27 reports were found about the adverse effects of varenicline. These included ten reports of aggressive activity during sleep and seven of other sleep-related harmful or potentially harmful activities (violent dreaming, nightmares, and other REM sleep behavior disorders, as well as NREM parasomnias such as somnambulism).

The data on the effect of varenicline on patients with OSA that smoke are rather limited. A study showed that in smokers suffering from OSA, varenicline administration resulted in prolongation of sleep latency, of N2 and N3 sleep stage latency, in an increased arousal index, and in the reduction in AHI, especially during REM sleep [66]. The main concern was the fact that it is difficult to differentiate between the adverse effects of varenicline or withdrawal symptoms per se. Unfortunately, due to the presence of N-nitroso-varenicline above the acceptable intake limits, varenicline has been recalled from European market over the last 2 years, limiting studies to further explore its effects on sleep and sleep-disordered breathing [67].

### Cardiovascular Effects of Varenicline

As varenicline binds selectively to α4β2nAChRs, its cardiovascular effects via the α3β4 nAChRs should be rather limited [68]. However, it has been found that varenicline binds to α7 homomeric nAChR, that may affect endothelial function and/or angiogenesis, contributing to cardiovascular adverse effects [69][70]. Early clinical trials including smokers with CVD did not find significantly higher rates of CV events as myocardial infarction and stroke compared to the placebo [71]. However, the US Food and Drug Administration (FDA) in 2011 mandated strengthened product warnings on the possible increased CV event risk in smokers with CVD [72]. In order to assess the neuropsychiatric adverse effects of bupropion and varenicline, the FDA and the EMA requested that their manufacturers conduct a randomized clinical trial (RCT) to evaluate their safety. The Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) was extended in order to also evaluate possible cardiovascular events during and after smoking cessation treatment [73][74]. EAGLES was a large phase IV 24-week randomized double-blind, triple-dummy, placebo- and active-controlled trial in smokers with and without psychiatric disease and assessed the safety and efficacy of three first-line smoking cessation treatments: varenicline, bupropion with a tapering regimen with NRTs (control). This study concluded that there was no evidence of increased risk of serious cardiovascular adverse events with the use of smoking cessation pharmacotherapies [73][74].

In the meantime, several studies have reached mixed conclusions regarding varenicline's safety [75][76][77][78][79][80]. An observational study reported a 34% increased risk of CVD hospitalizations and emergency department visits during varenicline use compared with controls, concluding that varenicline was associated with increased risk of cardiovascular but not neuropsychiatric events [80]. However, this study design was criticized for bias due to the inappropriate use of a

self-controlled risk, due to reverse causality and measurement errors [81]. On the other hand, other studies on patients with acute coronary syndromes using varenicline did not report increased cardiovascular events but increased smoking abstinence compared with placebo [79][82]. In addition, more recent studies in a real-life setting have also reported minimal risk of cardiovascular side effects of first-line smoking cessation medication on cardiovascular events, heart rate, and blood pressure, further supporting their safety for patients with CVD [74][83][84].

# 3. Second-Line Medications

## 3.1. Nortriptyline

Nortriptyline is a tricyclic anti-depressant that has been used as a second-line medication for smoking cessation [2][42][44]. The main indication of nortriptyline is as an antidepressant, but it has also been administered for chronic pain, i.e., orofacial pain, postherpetic neuralgia, and diabetic neuropathy (off-label). Nausea, headaches, constipation, dry mouth, sedation, and arrhythmia risk in patients suffering from CVD are its main side effects. Due to the potential side effects, the use of nortriptyline for smoking cessation is rather limited.

There are few studies evaluating the effects of nortriptyline on sleep and they are even more limited for patients with OSA. A study on elderly patients that were suffering from major depression found that nortriptyline decreased sleep apnea as it decreased REM sleep and increased phasic REM activity but did not have any effect on periodic limb movements during sleep [85].

### Cardiovascular Effects of Nortriptyline

Clinical trials have shown that the use of nortriptyline increased heart rate and reduced heart rate variability, cardiac conduction, and cardio-respiratory coupling [86][87][88]. An animal study indicated that nortriptyline may affect QT prolongation [89]. On the contrary, subsequent studies evaluating elderly depressed patients [90] or non-depressed patients [91] supported its safety in patients with impaired cardiac function. Additionally, a cohort study evaluating anti-depressant medication did not find significant association with cardiovascular events or all-cause mortality risk [92].

## 3.2. Clonidine

Clonidine is a second-line treatment for smoking cessation. It is an a2-adrenergic agonist that is indicated as an anti-hypertension treatment [93]. Its other off-label uses include drug withdrawal, certain pain conditions, flushing due to menopause, attention deficit hyperactivity disorder, and restless leg syndrome [90][94]. Clonidine is not approved worldwide as a medication for smoking cessation [94]. Clonidine's most common adverse effects include postural hypotension, drowsiness, dry mouth, and fatigue and these side effects limit its use for smoking cessation.

The effects of clonidine on sleep and specifically on OSA have not been widely investigated. In a study including eight men suffering from OSA, clonidine hydrochloride was administered for ten days; this resulted in the reduction in respiratory events, as REM sleep was suppressed and REM sleep latency increased. However, during non-REM sleep, no changes were reported [95].

### Cardiovascular Effects of Clonidine

Clonidine's hemodynamic effects are mediated by both the heart and peripheral vascular system. Clonidine decreases heart rate and stroke volume, especially early in therapy, and reduces peripheral resistance, an effect that seems to persist even after the initial treatment period. Clonidine has a coronary vasodilating effect, proven beneficial for patients with coronary artery disease. Severe bradycardia is uncommon, even though clonidine reduces the heart rate. However, it should be used with caution in patients with AV conduction disease [96].

## 3.3. Cytisine

Cytisine is nicotine receptor partial agonist that is used for smoking cessation and as a second-line medication in certain countries, especially in eastern European countries since 1960. It is an alkaloid that may be found in a number of plants. During the last years, the interest in the use cytisine for smoking cessation has increased due to its low cost [97]. Cytisine has similar characteristics to varenicline, as a partial agonist of alpha4beta2 nAChRs, preventing the binding of nicotine on these receptors and reducing cravings and symptoms of withdrawal [98][99]. The most common side effects of cytisine include nervousness, depression, vomiting, nausea, and sleep disorders [98]. Varenicline was more effective for smoking cessation compared with cytisine [100]. On the other hand, when cytisine was compared with NRTs, it was found to have superior effectiveness [99]. However, no studies on the possible effects of cytisine on patients with OSA were found.

**Cardiovascular Effects of Cytisine**

In one of the larger studies on cytisine [101], patients with a previous CVD such as severe atherosclerotic disease and those who have undergone percutaneous coronary interventions were excluded. In a recent study that evaluated the use of cytisine in patients with coronary artery disease 30 days after percutaneous coronary interventions found that it is a rather safe and promising treatment with no increase in cardiovascular complications. However, the compliance was rather low. Due to its low cost, cytisine may be beneficial for smoking cessation in patients with coronary artery disease. However further research is needed to confirm its efficacy and safety [102].

## References


1. Steinberg, M.B.; Schmelzer, A.C.; Richardson, D.L.; Foulds, J. The case for treating tobacco dependence as a chronic disease. Ann. Intern. Med. 2008, 148, 554–556.
2. Available online: https://ensp.network/ensp-tdt-guidelines/ (accessed on 20 June 2023).
3. Aveyard, P.; Begh, R.; Parsons, A.; West, R. Brief opportunistic smoking cessation interventions: A systematic review and meta-analysisto compare advice to quit and offer of assistance. Addiction 2012, 107, 1066–1073.
4. Smith, S.S.; McCarthy, D.E.; Japuntich, S.J.; Christiansen, B.; Piper, M.E.; Jorenby, D.E.; Fraser, D.L.; Fiore, M.C.; Baker, T.B.; Jackson, T.C. Comparative effectiveness of 5 smoking cessation pharmacotherapy in primary care clinics. Arch. Intern Med. 2009, 169, 2148–2155.
5. Cahill, K.; Stevens, S.; Perera, R.; Lancaster, T. Pharmacological interventions for smoking cessation: An overview and network meta-analysis. Cochrane Database Syst. Rev. 2013, CD009329.
6. Patterson, F.; Grandner, M.; Malone, S.K.; Rizzo, A.; Davey, A.; Edwards, D.G. Sleep as a Target for Optimized Response to Smoking Cessation Treatment. Nicotine Tob. Res. 2017, 21, 139–148.
7. Colrain, I.M.; Trinder, J.; Swan, G.E. The impact on smoking cessation on objective and subjective markers of sleep: Review, synthesis and recommendations. Nicotine Tob. Res. 2004, 6, 913–925.
8. Pataka, A.; Kotoulas, S.; Kalamaras, G.; Tzinas, A.; Grigoriou, I.; Kasnaki, N.; Argyropoulou, P. Does Smoking Affect OSA? What about Smoking Cessation? J. Clin. Med. 2022, 11, 5164.
9. Jorenby, D.E.; Hatsukami, D.K.; Smith, S.S.; Fiore, M.C.; Allen, S.; Jensen, J.; Baker, T.B. Characterization of tobacco withdrawal symptoms: Transdermal nicotine reduces hunger and weight gain. Psychopharmacology 1996, 128, 130–138.
10. Fredrickson, P.A.; Lee, G.M.; Wingender, L.; Hurt, R.D.; Croghan, I.T.; Lauger, G.; Offord, K.P.; Gomez-Dahl, L. High dose transdermal nicotine therapy for heavy smokers: Safety, tolerability and measurement of nicotine and cotinine levels. Psychopharmacology 1995, 122, 215–222.
11. Rieder, A.; Kunze, U.; Groman, E.; Kiefer, I.; Schoberberger, R. Nocturnal sleep-disturbing nicotine craving: A newly described symptom of extreme nicotine dependence. Acta Med. Austriaca 2001, 28, 21–22.
12. Page, F.; Coleman, G.; Conduit, R. The effect of transdermal nicotine patches on sleep and dreams. Physiol. Behav. 2006, 88, 425–432.
13. Wetter, D.W.; Fiore, M.C.; Baker, T.B.; Young, T.B. Tobacco withdrawal and nicotine replacement influence objective measures of sleep. J. Consult. Clin. Psychol. 1995, 63, 658–667.
14. Gillin, J.C.; Lardon, M.; Ruiz, C.; Golshan, S.; Salin-Pascual, R. Dose-dependent effects of transdermal nicotine on early morning awakening and rapid eye movement sleep time in non-smoking normal volunteers. J. Clin. Psychopharmacol. 1994, 14, 264–267.
15. Staner, L.; Luthringer, R.; Dupont, C.; Aubin, H.; Lagrue, G. Sleep effects of a 24-h versus a 16-h nicotine patch: A polysomnographic study during smoking cessation. Sleep Med. 2006, 7, 147–154.
16. Gourlay, S.G.; Forbes, A.; Marriner, T.; Pethica, D.; McNeil, J.J. Double blind trial of repeated treatment with nicotine patch for relapsed smokers. BMJ 1995, 311, 363–366.
17. Krishnan, V.; Dixon-Williams, S.; Thornton, J.D. Where there is smoke there is sleep apnea: Exploring the relationship between smoking and sleep apnea. Chest 2014, 146, 1673–1680.
18. Jaehne, A.; Loessl, B.; Bárkai, Z.; Riemann, D.; Hornyak, M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. Sleep Med. Rev. 2009, 13, 363–377.
19. Taveira, K.V.M.; Kuntze, M.M.; Berretta, F.; De Souza, B.D.M.; Godolfim, L.R.; Demathe, T.; Canto, G.D.L.; Porporatti, A.L. Association between obstructive sleep apnea and alcohol, caffeine and tobacco: A meta-analysis. J. Oral Rehabil.

2018, 45, 890–902.

20. Gothe, B.; Strohl, K.P.; Levin, S.; Cherniack, N.S. Nicotine: A Different Approach to Treatment of Obstructive Sleep Apnea. Chest 1985, 87, 11–17.
21. Davila, D.G.; Hurt, R.D.; Offord, K.P.; Harris, C.D.; Shepard, J.W. Acute effects of transdermal nicotine on sleep architecture, snoring, and sleep-disordered breathing in nonsmokers. Am. J. Respir. Crit. Care Med. 1994, 150, 469–474.
22. Zevin, S.; Swed, E.; Cahan, C. Clinical Effects of Locally Delivered Nicotine in Obstructive Sleep Apnea Syndrome. Am. J. Ther. 2003, 10, 170–175.
23. Benowitz, N.L.; Gourlay, S.G. Cardiovascular toxicity of nicotine: Implications for nicotine replacement therapy. J. Am. Coll. Cardiol. 1997, 29, 1422–1431.
24. Mundal, H.H.; Hjemdahl, P.; Ghesdal, K. Acute effects of low dose nicotine gum on platelet function in non-smoking hypertensive and normotensive men. Eur. J. Clin. Pharmacol. 1995, 41, 411–416.
25. Fishbein, L.; O'Brien, P.; Hutson, A.; Theriaque, D.; Stacpoole, P.W.; Flotte, T. Pharmacokinetics and pharmacodynamic effects of nicotine nasal spray devices on cardiovascular and pulmonary function. J. Investig. Med. 2000, 48, 435–440.
26. Yugar-Toledo, J.C.; Ferreira-Melo, S.E.; Sabha, M.; Nogueira, E.A.; Coelho, O.R.; Colombo, J.F.M.; Irigoyen, M.C.; Moreno, H. Blood pressure circadian rhythm and endothelial function in heavy smokers: Acute effects of transdermal nicotine. J. Clin. Hypertens. 2005, 7, 721–728.
27. Najem, B.; Houssiere, A.; Pathak, A.; Janssen, C.; Lemogoum, D.; Xhaet, O.; Cuylits, N.; van de Borne, P. Acute cardiovascular and sympathetic effects of nicotine replacement therapy. Hypertension 2006, 47, 1162–1167.
28. Khoury, Z.; Comans, P.; Keren, A.; Lerer, T.; Gavish, A.; Tzivoni, D. Effects of transdermal nicotine patches on ambulatory ECK monitoring findings: A double-blind study in healthy smokers. Cardiovasc. Drugs Ther. 1996, 10, 179–184.
29. Blann, A.D.; Steele, C.; McCollum, C.N. The influence of smoking and of oral and transdermal nicotine on blood pressure, and haematology and coagulation indeces. Thromb. Haemost. 1997, 78, 1093–1096.
30. Zevin, S.; Jacob, P.; Benowitz, N.L. Dose-related cardiovascular and endocrine effects of transdermal nicotine. Clin. Pharmacol. Ther. 1998, 64, 87–95.
31. Tanus-Santos, J.E.; Toledo, J.C.Y.; Cittadino, M.; Sabha, M.; Rocha, J.C.; Moreno, H. Cardiovascular effects of transdermal nicotine in mildly hypertensive smokers. Am. J. Hypertens. 2001, 14, 610–614.
32. Benowitz, N.L.; Hansson, A.; Jacob, P. Cardiovascular effects of nasal and transdermal nicotine and cigarette smoking. Hypertension 2002, 39, 1107–1112.
33. Kimmel, S.E.; Berlin, J.A.; Miles, C.; Jaskowiak, J.; Carson, J.L.; Strom, B.L. Risk of acute first myocardial infarction and use of nicotine patches in the general population. J. Am. Coll. Cardiol. 2001, 37, 1297–1302.
34. Greenland, S.; Satterfield, M.H.; Lanes, S.F. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. Drug Safety. 1998, 18, 297–308.
35. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. Arch. Intern Med. 1994, 154, 989–995.
36. Joesph, A.M.; Norman, S.M.; Ferry, L.H.; Prochazka, A.V.; Westman, E.C.; Steele, B.G.; Sherman, S.E.; Cleveland, M.; Antonuccio, D.O.; Hartman, N.; et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N. Engl. J. Med. 1996, 335, 1792–1798.
37. Pack, Q.R.; Priya, A.; Lagu, T.C.; Pekow, P.S.; Atreya, A.; Rigotti, N.A.; Lindenauer, P.K. Short-Term Safety of Nicotine Replacement in Smokers Hospitalized with Coronary Heart Disease. J. Am. Heart Assoc. 2018, 18, e009424.
38. Meine, T.J.; Patel, M.R.; Washam, J.B.; Pappas, P.A.; Jollis, J.G. Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. Am. J. Cardiol. 2005, 95, 976–978.
39. Woold, K.J.; Zabad, M.N.; Post, J.M.; McNitt, S.; Williams, G.C.; Bisognano, J.D. Effect of nicotine replacement therapy on cardiovascular outcomes after acute coronary syndromes. Am. J. Cardiol. 2012, 110, 968–970.
40. Hays, J.T.; Hurt, R.D.; Decker, P.A.; Croghan, I.T.; Oxford, K.P.; Patten, C.A. A randomized, controlled trial of Bupropion sustained release for preventing tobacco relapse in recovering alcoholics. Nicotine Tob. Res. 2009, 11, 859–867.
41. Roddy, E. Bupropion and other nonnicotine pharmacotherapies. BMJ 2004, 328, 509–511.
42. Hughes, J.R.; Stead, L.F.; Hartmann-Boyce, J.; Cahill, K.; Lancaster, T. Antidepressants for smoking cessation. Cochrane Database Syst. Rev. 2014, CD000031.

43. GarcıaRıo, F.; Serrano, S.; Mediano, O.; Alonso, A.; Villamor, J. Safety profile of Bupropion for chronic obstructive pulmonary disease. Lancet 2001, 358, 1009–1010.

44. Fiore, M.C.; Jaen, C.R.; Baker, T.B.; Mecklenburg, R.E.; Mermelstein, R.J.; Bailey, W.C.; Mullen, P.D.; Benowitz, N.L.; Orleans, C.T.; Curry, S.C.; et al. Treating Tobacco use and dependence. In Clinical Practice Guideline 2008 Update Rockville; US Department of Health and Human Services: Rockville, MD, USA, 2008.

45. Gandotra, K.; Jaskiw, G.E.; Williams, S.G.; Fuller, M.A.; Chen, P.; Wilson, B.; ElGhoul, R.; Konicki, E.; Strohl, K.P. Development of Insomnia Associated with Different Formulations of Bupropion. Prim. Care Companion CNS Disord. 2021, 23, 22621.

46. Nofzinger, E.A.; Reynolds, C.F.; Thase, M.E.; Frank, E.; Jennings, J.R.; Fasiczka, A.L.; Sullivan, L.R.; Kupfer, D.J. REM sleep enhancement by bupropion in depressed men. Am. J. Psychiatry 1995, 152, 274–276.

47. Ott, G.E.; Rao, U.; Nuccio, I.; Lin, K.M.; Poland, R.E. Effect of bupropion-SR on REM sleep: Relationship to antidepressant response. Psychopharmacology 2002, 165, 29–36.

48. McCarter, S.J.; Howell, M.J. Importance of Rapid Eye Movement Sleep Behavior Disorder to the Primary Care Physician. Mayo Clin. Proc. 2016, 91, 1460–1466.

49. McCall, C.A.; Winkelman, J.W. Respiratory-Related Leg Movements of Sleep Are Associated with Serotonergic Antidepressants but Not Bupropion. J. Clin. Sleep Med. 2018, 14, 1569–1576.

50. Bayard, M.; Bailey, B.; Acharya, D.; Ambreen, F.; Duggal, S.; Kaur, T.; Roller, K.; Tudiver, F.; Rahman, Z.U. Bupropion and Restless Legs Syndrome: A Randomized Controlled Trial. J. Am. Board Fam. Med. 2011, 24, 422–428.

51. Sweetman, A.; Lack, L.; McEvoy, D. Refining the measurement of insomnia in patients with obstructive sleep apnea. J. Clin. Sleep Med. 2019, 15, 1717–1719.

52. Lechat, B.; Appleton, S.; Melaku, Y.A.; Hansen, K.; McEvoy, R.D.; Adams, R.; Catcheside, P.; Lack, L.; Eckert, D.J.; Sweetman, A. Comorbid insomnia and sleep apnoea is associated with all-cause mortality. Eur. Respir. J. 2022, 13, 2101958.

53. Roose, S.P.; Dalack, G.W.; Glassman, A.H.; Woodring, S.; Walsh, B.T.; Giardina, E.G. Cardiovascular effects of bupropion in depressed patients with heart disease. Am. J. Psychiatry 1991, 148, 512–516.

54. Settle, E.C.; Stahl, S.M.; Batey, S.R.; Johnston, J.A.; Ascher, J.A. Safety profile of sustained-release bupropion in depression: Results of three clinical trials. Clin Ther. 1999, 21, 454–463.

55. Rigotti, N.A.; Thorndike, A.N.; Regan, S.; McKool, K.; Pasternak, R.C.; Chang, Y.; Swartz, S.; Torres-Finnerty, N.; Emmons, K.M.; Singer, D.E. Bupropion for smokers hospitalized with acute cardiovascular disease. Am. J. Med. 2006, 119, 1080–1087.

56. Planer, D.; Lev, I.; Elitzur, Y.; Sharon, N.; Ouzan, E.; Pugatsch, T.; Chasid, M.; Rom, M.; Lotan, C. Bupropion for smoking cessation in patients with acute coronary syndrome. Arch. Intern Med. 2011, 171, 1055–1060.

57. Tonstad, S.; Farsang, C.; Klaene, G. Bupropion SR for smoking cessation in smokers with cardiovascular disease: A multicenter randomized study. Eur. Heart J. 2003, 24, 946–955.

58. Thase, M.E.; Haight, B.R.; Johnson, M.C. A randomized, double-blind, placebo-controlled study of the effects of sustained-release bupropion on blood pressure in individuals with mild untreated hypertension. J. Clin. Psychopharmacol. 2008, 28, 302–307.

59. Tonstad, S.; Tønnesen, P.; Hajek, P.; Williams, K.E.; Billing, C.B.; Reeves, K.R.; Varenicline Phase 3 Study Group. Effect of Maintenance Therapy with Varenicline on Smoking Cessation: A Randomized Controlled Trial. JAMA 2006, 296, 64–71.

60. Coe, J.W.; Brooks, P.R.; Vetelino, M.G. An alpha4-beta2 nicotine receptor partial agonist for smoking cessation. J. Med. Chem. 2005, 48, 3474–3477.

61. Foulds, J.; Russ, C.; Yu, C.-R.; Zou, K.H.; Galaznik, A.; Franzon, M.; Berg, A.; Hughes, J.R. Effect of Varenicline on Individual Nicotine Withdrawal Symptoms: A Combined Analysis of Eight Randomized, Placebo-Controlled Trials. Nicotine Tob. Res. 2013, 15, 1849–1857.

62. Htoo, A.; Talwar, A.; Feinsilver, S.; Greenberg, H. Smoking and sleep disorders. Med. Clin. N. Am. 2004, 88, 1575–1591.

63. Savage, R.L.; Zekarias, A.; Caduff-Janosa, P. Varenicline and Abnormal Sleep Related Events. Sleep 2015, 38, 833–837.

64. Polini, F.; Principe, R.; Scarpelli, S.; Clementi, F.; De Gennaro, L. Use of varenicline in smokeless tobacco cessation influences sleep quality and dream recall frequency but not dream affect. Sleep Med. 2016, 30, 1–6.

65. Romigi, A.; Vitrani, G. Improvement of Restless Legs Syndrome by Varenicline as Antismoking Treatment. J. Clin. Sleep Med. 2013, 9, 1089–1090.

66. Pataka, A.; Frantzidis, C.; Kalamaras, G.; Gkivogkli, P.; Kotoulas, S.; Nday, C.; Chriskos, P.; Karagianni, M.; Styliadis, C.; Paraskevopoulos, E.; et al. Varenicline administration for smoking cessation may reduce apnea hypopnea index in sleep apnea patients. Sleep Med. 2021, 88, 87–89.

67. FDA Updates and Press Announcements on Nitrosamine in Varenicline (Chantix). Available online: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamine-varenicline-chantix (accessed on 5 June 2023).

68. Rollema, H.; Chambers, L.K.; Coe, J.W.; Glowa, J.; Hurst, R.S.; Lebel, L.A.; Lu, Y.; Mansbach, R.S.; Mather, R.J.; Rovetti, C.C.; et al. Pharmacological profile of the α4β2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology 2007, 52, 985–994.

69. Mihalak, K.B.; Carroll, F.I.; Luetje, C.W. Varenicline is a partial agonist at α4β2 and a full agonist at α7 neuronal nicotinic receptors. Mol. Pharmacol. 2006, 70, 801–805.

70. Lee, J.; Cooke, J.P. Nicotine and pathological angiogenesis. Life Sci. 2012, 91, 1058–1064.

71. Rigotti, N.A.; Pipe, A.L.; Benowitz, N.L.; Arteaga, C.; Garza, D.; Tonstad, S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: A randomized trial. Circulation 2010, 121, 221–229.

72. US Food and Drug Administration. FDA Drug Safety Communication: Chantix (Varenicline) May Increase the Risk of Certain Cardiovascular Adverse Events in Patients with Cardiovascular Disease. Available online: http://www.fda.gov/Drugs/DrugSafety/ucm259161.htm (accessed on 10 November 2023).

73. Anthenelli, R.M.; Benowitz, N.L.; West, R.; St Aubin, L.; McRae, T.; Lawrence, D.; Ascher, J.; Russ, C.; Krishen, A.; Evins, A.E. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomised, placebo-controlled clinical trial. Lancet 2016, 387, 2507–2520.

74. Benowitz, N.L.; Pipe, A.; West, R.; Hays, J.T.; Tonstad, S.; McRae, T.; Lawrence, D.; St Aubin, L.; Anthenelli, R.M. Cardiovascular Safety of Varenicline, Bupropion, and Nicotine Patch in Smokers: A Randomized Clinical Trial. JAMA Intern Med. 2018, 178, 622–631.

75. Prochaska, J.J.; Hilton, J.F. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: Systematic review and meta-analysis. BMJ 2012, 344, e2856.

76. Sterling, L.H.; Windle, S.B.; Filion, K.B.; Touma, L.; Eisenberg, M.J. Varenicline and adverse cardiovascular events: A systematic review and meta-analysis of randomized controlled trials. J. Am. Heart Assoc. 2016, 5, e002849.

77. Ware, J.H.; Vetrovec, G.W.; Miller, A.B.; Van Tosh, A.; Gaffney, M.; Yunis, C.; Arteaga, C.; Borer, J.S. Cardiovascular safety of varenicline: Patient-level meta-analysis of randomized, blinded, placebo-controlled trials. Am. J. Ther. 2013, 20, 235–246.

78. Kotz, D.; Viechtbauer, W.; Simpson, C.; van Schayck, O.C.; West, R.; Sheikh, A. Cardiovascular and neuropsychiatric risks of varenicline: A retrospective cohort study. Lancet Respir Med. 2015, 3, 761–768.

79. Eisenberg, M.J.; Windle, S.B.; Roy, N.; Old, W.; Grondin, F.R.; Bata, I.; Iskander, A.; Lauzon, C.; Srivastava, N.; Clarke, A.; et al. EVITA Investigators. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. Circulation 2016, 133, 21–30.

80. Gershon, A.S.; Campitelli, M.A.; Hawken, S. Cardiovascular and neuropsychiatric events following varenicline use for smoking cessation. Am. J. Respir Crit. Care Med. 2018, 197, 913–922.

81. Goulden, R.; Nguyen, Q.D.; Azoulay, L. Risk of Bias in Study of Varenicline and Cardiovascular Outcomes. Am. J. Respir Crit Care Med. 2018, 198, 690–691.

82. Windle, S.B.; Dehghani, P.; Roy, N.; Old, W.; Grondin, F.R.; Bata, I.; Iskander, A.; Lauzon, C.; Srivastava, N.; Clarke, A.; et al. EVITA Investigators. Smoking abstinence 1 year after acute coronary syndrome: Follow-up from a randomized controlled trial of varenicline in patients admitted to hospital. CMAJ 2018, 190, E347–E354.

83. Silva, A.P.; Scholz, J.; Abe, T.O.; Pinheiro, G.G.; Gaya, P.V.; Pereira, A.C.; Santos, P.C. Influence of smoking cessation drugs on blood pressure and heart rate in patients with cardiovascular disease or high risk score: Real life setting. BMC Cardiovasc. Disord. 2016, 16, 2.

84. Havard, A.; Choi, S.K.Y.; Pearson, S.A.; Chow, C.K.; Tran, D.T.; Filion, K.B. Comparison of Cardiovascular Safety for Smoking Cessation Pharmacotherapies in a Population-Based Cohort in Australia. JAMA Netw. Open 2021, 4, e2136372.

85. Buysse, D.J.; Reynolds, C.F., 3rd; Hoch, C.C.; Houck, P.R.; Kupfer, D.J.; Mazumdar, S.; Frank, E. Longitudinal effects of nortriptyline on EEG sleep and the likelihood of recurrence in elderly depressed patients. Neuropsychopharmacology 1996, 14, 243–252.
86. Roose, S.P.; Laghrissi-Thode, F.; Kennedy, J.S.; Nelson, J.C.; Bigger, J.T., Jr.; Pollock, B.G.; Gaffney, A.; Narayan, M.; Finkel, M.S.; McCafferty, J.; et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA 1998, 279, 287–291.
87. Bar, K.J.; Schuhmacher, A.; Hofels, S.; Schulz, S.; Voss, A.; Yeragani, V.K.; Maier, W.; Zobel, A. Reduced cardio-respiratory coupling after treatment with nortriptyline in contrast to S-citalopram. J. Affect. Disord. 2010, 127, 266–273.
88. Kiev, A.; Masco, H.L.; Wenger, T.L.; Johnston, J.A.; Batey, S.R.; Holloman, L.C. The cardiovascular effects of bupropion and nortriptyline in depressed outpatients. Ann. Clin. Psychiatry 1994, 6, 107–115.
89. Jeon, S.H.; Jaekal, J.; Lee, S.H.; Choi, B.H.; Kim, K.S.; Jeong, H.S.; Han, S.Y.; Kim, E.J. Effects of nortriptyline on QT prolongation: A safety pharmacology study. Hum. Exp. Toxicol. 2011, 30, 1649–1656.
90. Thayssen, P.; Bjerre, M.; Kragh-Sorensen, P.; Moller, M.; Petersen, O.L.; Kristensen, C.B.; Gram, L.F. Cardiovascular effect of imipramine and nortriptyline in elderly patients. Psychopharmacology 1981, 74, 360–364.
91. Giardina, E.G.; Johnson, L.L.; Vita, J.; Bigger, J.T.; Brem, R.F. Effect of imipramine and nortriptyline on left ventricular function and blood pressure in patients treated for arrhythmias. Am. Heart J. 1985, 109, 992–998.
92. Hamer, M.; Batty, G.D.; Seldenrijk, A.; Kivimaki, M. Antidepressant medication use and future risk of cardiovascular disease: The Scottish Health Survey. Eur. Heart J. 2011, 32, 437–442.
93. Sharma, A.; Gupta, L. Clonidine aWonder Drug. Indian J. Anesth. Analg. 2019, 6, 2057–2062.
94. Barua, R.S.; Rigotti, N.A.; Benowitz, N.L.; Cummings, K.M.; Jazayeri, M.A.; Morris, P.B.; Ratchford, E.V.; Sarna, L.; Stecker, E.C.; Wiggins, B.S. ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J. Am. Coll. Cardiol. 2018, 72, 3332–3365.
95. Issa, F.G. Effect of Clonidine in Obstructive Sleep Apnea. Am. Rev. Respir. Dis. 1992, 145, 435–439.
96. Brest, A.N. Hemodynamic and cardiac effects of clonidine. J. Cardiovasc. Pharmacol. 1980, 2, S39–S46.
97. Gotti, C.; Clementi, F. Cytisine and cytisine derivatives. More than smoking cessation aids. Pharmacol. Res. 2021, 170, 105700.
98. Etter, J.F. Cytisine for smoking cessation: A literature review and a meta-analysis. Arch. Intern Med. 2006, 166, 1553–1559.
99. Walker, N.; Howe, C.; Bullen, C.; McRobbie, H.; Glover, M.; Parag, V.; Williman, J.; Veale, R.; Nosa, V.; Barnes, J. Study protocol for a noninferiority trial of cytisine versus nicotine-replacement therapy in people motivated to quit smoking. BMC Public Health 2011, 11, 880.
100. Courtney, R.J.; McRobbie, H.; Tutka, P.; Weaver, N.A.; Petrie, D.; Mendelsohn, C.P.; Shakeshaft, A.; Talukder, S.; Macdonald, C.; Thomas, D.; et al. Effect of Cytisine vs Varenicline on Smoking Cessation: A Randomized Clinical Trial. JAMA 2021, 326, 56–64.
101. West, R.; Zatonski, W.; Cedzynsk, M.; Lewandowska, D.; Pazik, J.; Aveyard, P.; Stapleton, J. Placebo-controlled trial of cytosine for smoking cessation. N. Engl. J. Med. 2011, 365, 1193–1200.
102. Ramotowski, B.; Budaj, A. Is cytisine contraindicated in smoking patients with coronary artery disease after percutaneous coronary intervention? Kardiol Pol. 2021, 79, 813–819.