Perioperative Smoking and Alcohol Cessation

8

Gabriele Baldini

Smoking Cessation

The proportion of adults who are smoking in the developed world is decreasing (one out of five adults smoke) [1]. According to the US Centers for Disease Control and Prevention (CDC), the proportion of adults smoking cigarettes in the United States decreased from 23.3% (46.5 million) in 2000 to 15.5% (37.8 millions) in 2016 [2].

Frequently, preoperative interventions aim at optimizing a patient's comorbidities, while minimal efforts are made to modify lifestyle habits that also have been shown to increase postoperative morbidity. Despite it is well proven that smoking cessation is highly feasible, readily available, and a cost-effective intervention, interventions to help surgical patients quit smoking before surgery are rarely provided as routine surgical care.

Interestingly, perioperative physicians systematically inquire about lifestyle habits such as smoking, but this information is primarily used to stratify perioperative risks rather than triggering behavioral and lifestyle changes.

Current evidence demonstrates that preoperative smoking is associated with increased morbidity and mortality [3]. Considering that smoking is a potentially modifiable preoperative risk factor, interventions that aim at helping patients quit smoking before surgery should be more frequently adopted. Perioperative physicians and caregivers should take advantage of the perioperative period and encourage and support patients to achieve short- and long-term smoking cessation.

G. Baldini (✉)
Department of Anesthesia, Montreal General Hospital, McGill University, Montreal, QC, Canada
e-mail: gabriele.baldini@mcgill.ca

Why, When, Who, and How?

Smoking: Perioperative Pathophysiologic Changes

Airway and Respiratory System Smoking has been shown to induce inflammatory changes and impair the respiratory immune function. These effects are particularly important in patients receiving general anesthesia during which some of the physiologic mechanisms protecting the respiratory system—such as bronchial mucus transport, macrophage function, and microbicidal cellular activity—are negatively affected by smoking [4].

Smoking causes an alteration of the airway epithelial function and mucus production (increased volume and composition) and decreases mucociliary clearance [4, 5]. Clinically, these pathophysiologic changes can determine an increased irritability of the airway that is associated with intraoperative cough, laryngospasm, and breath holding [4]. With time, hyperplasia of muscle fibers and fibrosis caused by smoking determine a more rapid decline in forced expiratory volume in 1 second compared to non-smokers [4].

Cardiovascular System It is well recognized that smoking is a risk factor for atherosclerosis, coronary artery disease, heart failure, and peripheral vascular diseases. This is mainly due to nicotine, but also to many other constituents of cigarette smoke. Nicotine directly and indirectly, by stimulating the sympathetic system, increases myocardial work by increasing heart rate, blood pressure, and contractility. Smoking causes coronary vasoconstriction in patients with coronary artery disease, and it induces a hypercoagulable and chronic inflammatory state [4].

Carbon monoxide (CO) released by smoking tobacco decreases the amount of oxygen bound to the hemoglobin and decreases oxygen release to tissue. These effects predispose to angina and ventricular arrhythmia. Moreover, CO and cyanide, also released in cigarette smoke, impair mito-

O. Ljungqvist et al. (eds.), *Enhanced Recovery After Surgery*, https://doi.org/10.1007/978-3-030-33443-7_8

chondrial respiration by inhibiting enzymes such as the cytochrome c oxidase.

Considering that the half-lives of nicotine and carboxyhemoglobin are very short (1 and 4 hours, respectively), it is plausible to expect that cardiovascular benefits could be observed even for a brief period of smoking cessation. This is supported by evidence demonstrating that carbon monoxide levels correlate with ischemic electrocardiographic signs in anesthetized surgical patients. Improvement of smoking-related diseases, such as atherosclerosis, coronary disease, and peripheral vascular disease, may occur more slowly [4].

Wound and Bone Healing Many studies have reported that smokers have a higher risk to develop postoperative wound healing complications, such as dehiscence and infection. Decreased tissue oxygenation caused by nicotine-induced vasoconstriction and by carboxyhemoglobin, together with many other risk factors, contributes to development of these complications. However, experimental studies using high-nicotine concentrations (far above the levels measured in active smokers) have also suggested that smoking impairs the tissue and immune response to injury, thus compromising wound healing. Paradoxically, topical application of nicotine to wounds has shown to promote angiogenesis and accelerate healing [6]. These findings suggest that other substances than nicotine produced by cigarette smoke might also affect wound healing. The effect of nicotine on wound healing probably depends on many other factors, such as dose, route of administration, acute vs. chronic exposure, and modulation of neuro-inflammatory mechanisms involved in the response to tissue injury [4]. Moreover, impaired nitric oxide release—frequently present in patients with microvascular diseases such as smokers—might further delay wound healing [4].

Similarly, smoking has been shown to impair bone healing and increase the risk of non-union especially after major spine surgery. These risks are higher if smoking is continued in the postoperative period. Several mechanisms have been proposed [4]. Experimental studies have shown that nicotine at relatively high dose negatively affects bone healing by inhibiting several cellular pathways. In particular inhibition of tumor necrosis factor-alpha (TNF-α) secretion through the activation of the cholinergic anti-inflammatory pathway seems to play a major role [7].

Nervous System Function Nicotine binds to the ion channel nicotine acetylcholine receptors (nAChRs) widespread in the central and peripheral nervous system. Nicotine acetylcholine receptors are also located in the autonomic ganglia, the adrenal glands, and at neuromuscular junctions. Several subtypes of nAChRs have been identified, depending on their subtype units. Nicotine acts mostly as a receptor agonist, but when it binds certain nAChR subunits, it antagonizes the effect of acetylcholine. Because of the ubiquity of nAChRs, activation of these receptors produces different effects, depending on the anatomical location and type of subunits activated. In the central nervous system (CNS), activation of nAChRs modulates the release of several neurotransmitters that influence several CNS functions. As a result, the effect of nicotine on the CNS function is not completely understood and is complex in nature. Nicotine can produce psychotropic effects, such as reward and pleasure, by activating the dopaminergic system, but it can also cause unpleasant effects, such as anxiety and agitation, especially in nicotine-naïve patients.

Experimental and clinical studies also demonstrate that nicotine affects nociception, but the effects are complex and inconsistent. Animal studies show that systemic nicotine produces a mild analgesic effect when it stimulates nAChRs located in the CNS, while it increases pain perception when it stimulates nAChRs of peripheral nerves. Clinically, most of the studies have demonstrated that smoking increases pain threshold and tolerance, but other studies performed in smokers undergoing coronary artery bypass graft, oral surgery, and pelvic surgery have shown an increase of postoperative opioid requirements [4]. Although baseline and postoperative pain thresholds might be lower in smokers than in non-smokers, postoperative increase of pain score does not differ [8]. Evidence that nicotine affects perioperative pain perception comes also from the reported effects of abstinence and nicotine replacement therapy on pain thresholds in nonsurgical and surgical patients. Nicotine replacement therapy (NRT) has shown to modify pain thresholds differently, depending on patients' gender. In fact, although NRT has shown to increase the pain threshold in both smoking and nonsmoking individuals, this effect was observed only in men [9]. Moreover, intranasal nicotine injected in nonsmoking patients undergoing gynecological surgery has demonstrated to decrease pain intensity and opioid consumption in the first 24 hours after surgery [10]. However, a following randomized controlled trial (RCT) in patients undergoing gynecological surgery and receiving a 3-day NRT patch (1 hour before surgery and 2 days after surgery) did not confirm these results [11]. Epidemiological studies have reported that smoking is a risk factor for chronic pain [12].

Experimental trials also demonstrate that anesthetic agents inhibit nAChRs located in the CNS, but it remains uncertain whether smoking status affects anesthetic requirements [4].

Long-term exposure to nicotine can cause tolerance as a result of nAChR desensitization and plastic changes in the central nervous system. These changes are also responsible for somatic and affective nicotine withdrawal symptoms. Because of these long-lasting CNS effects, these symptoms can manifest within a few hours from abstinence and last for several weeks [4, 13] (Fig. 8.1).

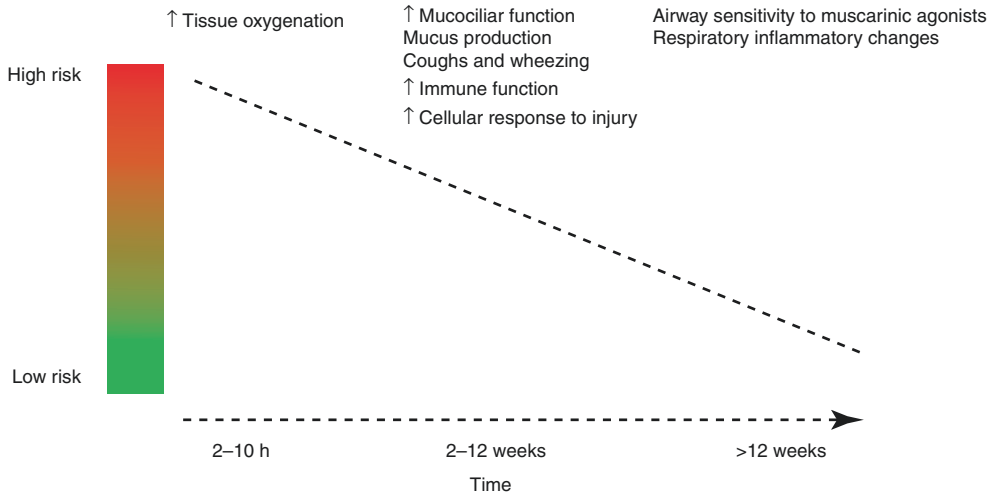


Fig. 8.1 Clinical risk and time required to recover physiologic functions and improve smoke-related symptoms following smoking cessation and preoperative risk. (↑ = improvement. Adapted from [13])

Smoking and Smoking Cessation With and Without Perioperative Interventions: Impact on Clinical Outcomes

Overall Complications and Mortality Smoking is associated with higher postoperative mortality and morbidity [3, 14]. The effect of smoking on postoperative outcomes seems procedure specific, with higher morbidity, reoperation, and readmission rates after cardiovascular and oncologic surgery [15]. This risk is higher in both active smokers and in ex-smokers (the risk in active smokers is higher than in ex-smokers) compared to patients who never smoked [14, 16–18]. It also increases proportionally to the number of pack-years smoked [3, 17]. Overall, preoperative smoking cessation interventions reduce postoperative complications by 60% [19]. A meta-analysis including 21 RCTs and 15 observational trials demonstrated that each additional week of smoking cessation further decreases by 19% the risk of developing complications and that the magnitude of this effect was greater after 4 weeks of smoking abstinence [20].

Cardiovascular Complications Whether or not preoperative smoking is an independent risk factor for major cardiovascular complications still remains controversial. This might explain why many cardiovascular score systems used to predict perioperative cardiovascular risk—except the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) calculator—do not include smoking status. However, data from the ACS NSQIP demonstrate that in 82,304 active smokers undergoing major noncardiac surgery, and propensity matched with 82,304 patients who never smoked, the risk of cardiac arrest, myocardial infarction, and stroke was higher (odds ratio [OR] 1.57, 95% confidence interval [CI], 1.10– 2.25; OR 1.73, 95% CI 1.18–2.53; OR 1.80, 95% CI 1.11–2.92, respectively) [3]. A similar cohort study from the same registry also confirmed that arterial cardiovascular complications were more frequent in active smokers than ex-smokers who quit at least 1 year before the date of surgery [14]. RCTs demonstrating that preoperative smoking cessation reduces cardiovascular morbidity are lacking. One RCT conducted in surgical patients undergoing orthopedic surgery reported that cardiovascular complications were reduced in patients receiving preoperative smoking cessation, but this difference was not significant [21].

Respiratory Complications Several studies have reported that smoking is a risk factor for postoperative pulmonary complications (PPCs). In particular it increases the risk of respiratory failure, unplanned intensive care unit, pneumonia, laryngospasm and bronchospasm, desaturation in post-anesthesia care unit (PACU), and increased need for postoperative respiratory therapy [17]. Smoking status is considered the most preventable preoperative risk factor for reducing PPCs. Some prospective studies, aiming at evaluating the independent predictors of PPC, did not identify preoperative smoking as an independent risk factor for PPCs, suggesting that low-risk smoking patients might not be at increased risk [22].

It must be also considered that it is difficult to establish if the observed increased respiratory morbidity is due to tobacco smoke itself or to the severity of the respiratory disease caused by smoking. However, children without respiratory disease undergoing surgery under general anesthesia and who have been exposed to environmental tobacco smoke also have a higher risk of developing PPCs [23, 24], suggesting that smoke per se can increase the risk of developing PPCs.

Reversibility of the respiratory effects of chronic smoke exposure mainly depends on whether patients have developed a chronic obstructive lung disease. Several observational studies demonstrate that preoperative smoking

cessation for more than 4–12 weeks is associated with a reduction in PPCs [25]. In the past, few underpowered studies demonstrated that in patients undergoing cardiac surgery, the risk of developing PPCs is higher if patients abstained from smoking less than 8 weeks before surgery compared to patients who continue to smoke up to 24 hours before surgery. However, these findings have never been reproduced, and current evidence demonstrates that preoperative smoking cessation is always beneficial, and its effects are more pronounce with longer period of abstinence [4, 20, 26, 27]. The UK National Institute for Health and Care Excellence (NICE) smoking cessation guidelines unrestrictedly promotes preoperative smoking cessation [27]. A recent observational trial conducted in patients undergoing curative lung cancer resection demonstrated that patients actively smoking at the moment of surgery had higher PPCs (22% vs. 2%; $p = 0.004$), higher frequency of intensive care admission (14% vs. 0%; $p = 0.001$), and a longer median hospital stay (6 vs. 5 days; $p = 0.001$). PPCs were not significantly different in patients who quit smoking 6 or more weeks before surgery compared to patients who quit less than 6 weeks. Also, patients who never smoked seemed to have better long-term survival after surgery [28]. Information about smoking cessation interventions (if any) were not reported. Although preoperative smoking cessation interventions aiming at reducing PPCs in high-risk patients have been not specifically studied, rehabilitation programs following major lung resections have shown to facilitate smoking cessation and, although not statistically significant, reduce PPCs (after adjusting for chronic obstructive pulmonary disease [COPD] and smoking); having the intervention tended to reduce the risk of developing a PPC (OR = 0.40, 95% CI 0.13–1.01; $p = 0.07$) [29].

Wound and Bone Healing Sørensen et al. demonstrated that, by pooling 140 cohort studies including 479, 150 surgical patients, smoking increases the risk of wound healing complications. In particular the risk of tissue and wound necrosis (adjusted OR [OR_{ad}] 3.60, 95% CI 2.62–4.93), healing delay and dehiscence (OR_{ad} 2.07, 95% CI 1.53 = to 2.81), surgical site infections (OR_{ad} 1.79, 95% CI 1.57–2.04), wound complications (OR_{ad} 2.27, 95% CI 1.82–2.84), hernia (OR_{ad} 2.07, 95% CI 1.23–3.47), and lack of healing (fistula and bone healing) (OR_{ad} 2.44, 95% CI 1.66–3.58) was higher in smokers compared to non-smokers [18]. Moreover, the risk of wound healing complication was higher in former smokers than in patients who never smoked (OR_{ad} 1.31, 95% CI 1.10–1.56), but lower in former smokers than in patients who never quit (OR_{ad} 0.28, 95% CI 0.12–0.72) [18]. These results were in agreement with the results reported by previously published meta-analysis [20]. Reversing the negative effects of nicotine and carboxyhemoglobin on wound healing could take a few hours, while to reverse the nicotine effects on the tissue and immune response to injury might take longer (months). Sørensen et al.'s meta-analysis also evaluated the impact of smoking cessation interventions on postoperative wound healing complications. The analysis included 4 RCTs including 416 patients undergoing abdominal and orthopedic surgery and utilizing different smoking cessation interventions ranging from low, intermediate, to high intensity. Pooled analysis demonstrated that despite surgical site infections being significantly reduced in patients who received smoking cessation (OR 0.40, 95% CI 0.20–0.83), wound healing complications were not (OR 0.48, 95% CI 0.19–1.25) [18]. Interestingly, among the four trials included the only study that utilized a prolonged and intense smoking cessation intervention (6–8 weeks before surgery of individual counseling, NRT, and weekly follow-up, and continued postoperatively for 10 days), which showed reduction of both wound healing complications and surgical site infections after hip and knee arthroplasty [21]. This study also reported higher preoperative smoking cessation rates (complete abstinence) in the intervention group compared to the control group (60% vs. 6%, respectively) [21]. Similar results were also reported by other meta-analyses [30].

Perioperative Smoking Cessation Interventions: Short- and Long-Term Smoking Cessation Rates

Perioperative nicotine abstinence should be considered a "teachable moment" (i.e., an event that motivates individuals to adopt healthy behaviors that reduce risk [31]) to help patients achieve short- and long-term smoking cessation. Despite being challenging, perioperative smoking cessation was achieved in a significant proportion of surgical patients [19]. In an RCT of 168 patients undergoing non-cardiac surgery, Lee et al. demonstrated that preoperative smoking cessation following an intense cessation program (initiated at least 3 weeks before surgery and including brief counseling by the preadmission nurse, smoking cessation brochures, referral to a telephone quitline, and a free 6-week supply of transdermal nicotine replacement) was achieved in a higher proportion of patients receiving the intervention, compared to patients who did not (14.3% vs. 3%, relative risk [RR] 4.0, 95% CI 1.2–13.7) [32]. Thirty-day smoking cessation rates were also better (28.6% vs 11% RR 2.6, 95% CI 1.2–5.5) [32]. A long-term follow-up of the same trial [32] demonstrated also that long-term smoking cessation at 1 year can be achieved in approximately 25% of surgical patients (RR 3.0, 95% CI 1.2–7.8; $p = 0.018$) [33]. Low-nicotine baseline dependency and randomization to the intervention (smoking cessation) were found to be both successful independent predictors of long-term abstinence. Results did not change if data were adjusted for nicotine dependency [33]. Combined strategies are more successful than single interventions.

Moreover, the success of perioperative smoking cessation depends on the intensity and duration of the intervention. Detailed discussion will follow.

When and Whose Responsibility?

Clinical data suggest that in the perioperative period, nicotine abstinence contributes to reduced postoperative morbidity. Smoking cessation always should be advised before surgery, independently of the timing of the intervention [27]. Although the optimal duration to reverse the adverse effects of smoking and improve postoperative outcomes is currently unclear, longer periods of intense preoperative smoking cessation interventions (3–4 weeks or longer) are associated with better perioperative outcomes, especially less pulmonary, wound healing, and infectious complications [17, 19, 20].

These data highlight the importance of promoting smoking cessation as early as possible in the preoperative period course—ideally at the time of surgical referral or scheduling. Caregivers involved in the perioperative care of patients (surgeons, anesthesiologists, internists, general practitioners [GPs], and nurses) should all recommend smoking cessation before surgery, at every opportunity. Specialized nurses in smoking cessation are also a useful resource, especially in the context of a preoperative clinic. Although the preoperative clinic visit represents an ideal moment to initiate smoking cessation interventions, patients are often seen only few days/weeks before surgery, thereby limiting the utilization of valuable smoking cessation resources. Alternatively, general practitioners who are already aware of the patient's medical history and of the effectiveness of smoking cessation in the general population might play an important role in facilitating smoking cessation in prevision of surgery. GPs have the opportunity to better exploit the preoperative period to promote the importance of preoperative nicotine abstinence and initiate smoking cessation interventions at the time of diagnosis, way before surgical referral [34].

However, several barriers such as perception of lack of effect; lack of clinical time, skills, and professional training; reluctance to raise this issue due to patient sensitivity about smoking; perceived lack of patient motivation; and inability to use effective strategies prevent this practice, especially in the perioperative period [34]. When preoperative smoking cessation is not possible, postoperative nicotine abstinence has also proven benefits to achieve smoking cessation and improve postoperative outcomes [4].

How?

Generally, quitting smoking is difficult and rarely successful even in nonsurgical patients and individuals [35]. From a surgical patient's perspective, the preoperative period is not the easiest and ideal moment to quit smoking. A simple preoperative recommendation could work in some very motivated patients, but it will not be successful in the majority. The awareness of being diagnosed with a certain disease and the wait for the upcoming surgery can generate anxiety and paradoxically increase the number of cigarettes smoked, especially a few days or hours before the operation. This highlights the importance of utilizing specialized resources and personnel to successfully help patients to quit smoking before surgery [36]. The framework of 5As method could provide a systematic approach to identify, assist, and follow up smokers waiting for surgery [37] (Table 8.1).

Table 8.1 The "5 A's" that are the major steps to smoking intervention

1. Ask	Identify and document tobacco use status for every patient at every visit
2. Advise	In a clear, strong, and personalized manner, urge every tobacco user to quit
3. Assess	Is the tobacco user willing to make a quit attempt at this time?
4. Assist	For the patient willing to make a quit attempt, use counseling and pharmacotherapy to help him or her quit
5. Arrange	Schedule follow-up contact, in person or by telephone, preferably within the first week after the quit date

Reprinted from Five Major Steps to Intervention (The "5 A's"). Content last reviewed December 2012. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.html

Monitoring smoking cessation attempts is important, and it can be easily done by using relatively inexpensive, handheld, expired-air CO monitors. CO concentrations above 10% warn for immediate attention.

Perioperative smoking cessation interventions can be divided into counseling or pharmacotherapy.

Counseling

In the perioperative period, a variety of methods can be used to discuss the importance of smoking cessation and to facilitate the achievement of this objective. Counseling should first advise the patient to quit smoking in preparation for surgery, then assist the patient in devising a personalized quit plan, provide practical problem-solving skills, help the patient to obtain social support (e.g., from a spouse), and provide supplemental educational materials (e.g., brochures). These interventions can be delivered by a variety of providers with equal effectiveness. The effectiveness of counseling is independent from gender, ethnicity, age, and different social backgrounds [38]. Advising patients to quit smoking before surgery is the first step. In nonsurgical individuals, a simple advisory has a marginal but important effect on smoking cessations, as it increases quit rates by only 1–3% [39]. Patients with low literacy might find it difficult to understand the importance of smoking cessation. Even a simple and brief (<3 minutes) discussion with the patient about the importance of smoking cessation is useful,

and it increases quit rates [38]. This message also should be delivered and reinforced by clinical nurses working with surgeons or in the preoperative clinic. A dose-response relationship exists between the duration and intensity of the intervention and efficacy. Increasing the amount of behavioral support increases smoking cessation rates by 10–25% [40]. Efficacy also increases by combining different counseling formats [38]. These include in-person individual (face-to-face) or group counseling or telephone counseling. Free Web-based and text messaging cessation support or mobile apps are also available. Telephone counseling can be proactive (the counselor initiates one or more calls to support patients trying to quit smoking or avoid relapse) or reactive (the patient calls a specific service, telephone quitline, hotline, or helplines) [38].

Telephone quitlines are widely available, nationally and regionally. They can be accessed from the community, before and after surgery, without requiring a significant increase in resources. Their efficacy is well proven, and preliminary data show benefits even in patients with severe mental illness in whom smoking cessation is more challenging [41]. Callback counseling enhances the effectiveness of telephone quitlines. Higher quit rates have been observed in patients who received proactive counseling (most of the studies demonstrating benefits included at least two phone calls) compared to patients receiving reactive counseling [42].

Utilization of these community-based interventions might be particularly valuable in surgical patients, as they could eventually unburden GPs and perioperative physicians who frequently work with limited time and resources. Early referral is pivotal to maximize the effect of smoking cessation on postoperative outcomes.

Pharmacotherapy

Several pharmacological agents can be used depending on the timing of the intervention, patient's comorbidities, smoke history (pack-years), patient psychological characteristics, and preference. First-line pharmacologic therapies include NRT, varenicline, and bupropion (Fig. 8.2).

Nicotine Replacement Therapy (NRT) A cigarette contains 10–15 mg nicotine and delivers on average 1 mg nicotine to the smoker [43]. The peak plasma nicotine concentration during smoking is 10–50 ng/mL with about 5% being protein-bound. The half-life averages 2 hours. Genetic variability in nicotine metabolism explains the higher concentrations of nicotine metabolites in black smokers than in white smokers [43]. Plasma nicotine concentra-

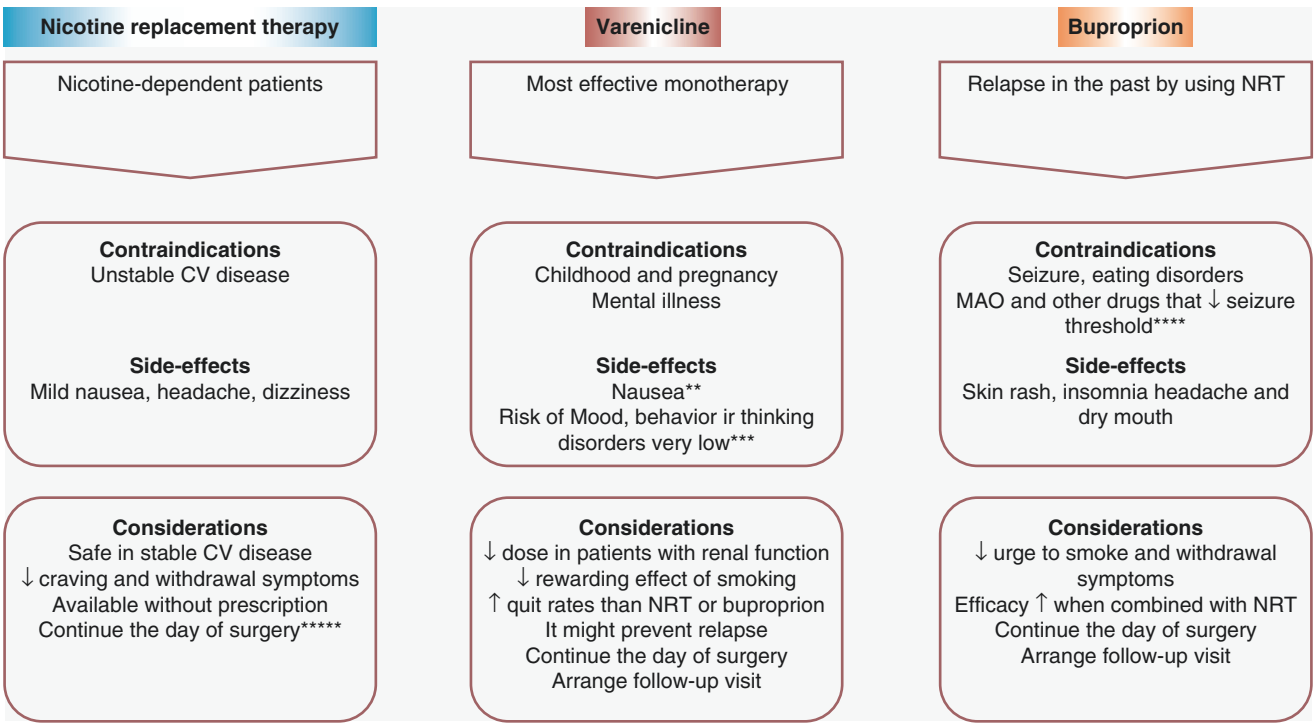


Fig. 8.2 First-line pharmacologic therapies include nicotine replacement therapy, varenicline, and bupropion. CV, cardiovascular; MAO, monoamine oxidase inhibitors; NRT, nicotine replacement therapy. (** Decrease by up-titrating the dose; *** lower than expected; benefits of stop smoking outweigh the risk of varenicline; **** oral hypoglycemic agent, antidepressant; ***** discontinue in patients requiring a vascular graft. ↓ decrease; ↑ increase. Adapted from [44])

tions measured in patients receiving any form of NRT are lower than those observed in active smokers, even when patients do not completely quit [4].

A variety of studies conducted in the nonsurgical general population have well established the effectiveness of NRT. NRT can be delivered with nicotine patches (long-acting effect) and/or though nicotine gum, inhalator, mouth spray, lozenge, sublingual microtablet, and nasal spray (rapid- and short-acting effect) [43, 44]. In the general population, all forms of NRT are effective in increasing smoking cessation rates by 50–70%, independently from the setting, duration of the therapy, and the additional support offered to the individual [45]. In surgical patients, the majority of studies demonstrating an increase in smoking cessation rates used NRT [19]. Moreover, the impact of smoking cessation interventions including NRT on postoperative complications seems to depend on the intensity and duration of the intervention [18–20, 30]. NRT initial dose depends on the number of cigarettes smoked per day (Fig. 8.3 McGill smoking cessation protocol), and NRT products can be used while patients are still smoking. The dose is gradually tapered, and NRT is recommended until 2–3 months after smoking cessation.

Combining a NRT patch with a rapid delivery form is particularly useful in nicotine-dependent patients (smoking within 30 minutes of waking in the morning or smoking more than 10 cigarettes a day [44]) to control withdrawal and craving symptoms [44]. Moreover, combining different NRT formulations (short- and long-acting NRT) is more effective (smoking cessation) than a single NRT intervention [45]. There is also evidence that NRT patch initiated for 2 weeks before quitting smoking is more effective than starting NRT on quit day [44, 45]. Combining different NRT products does not significantly increase nicotine plasma concentrations that are anyway lower than those achieved in patients smoking one pack per day [44, 45].

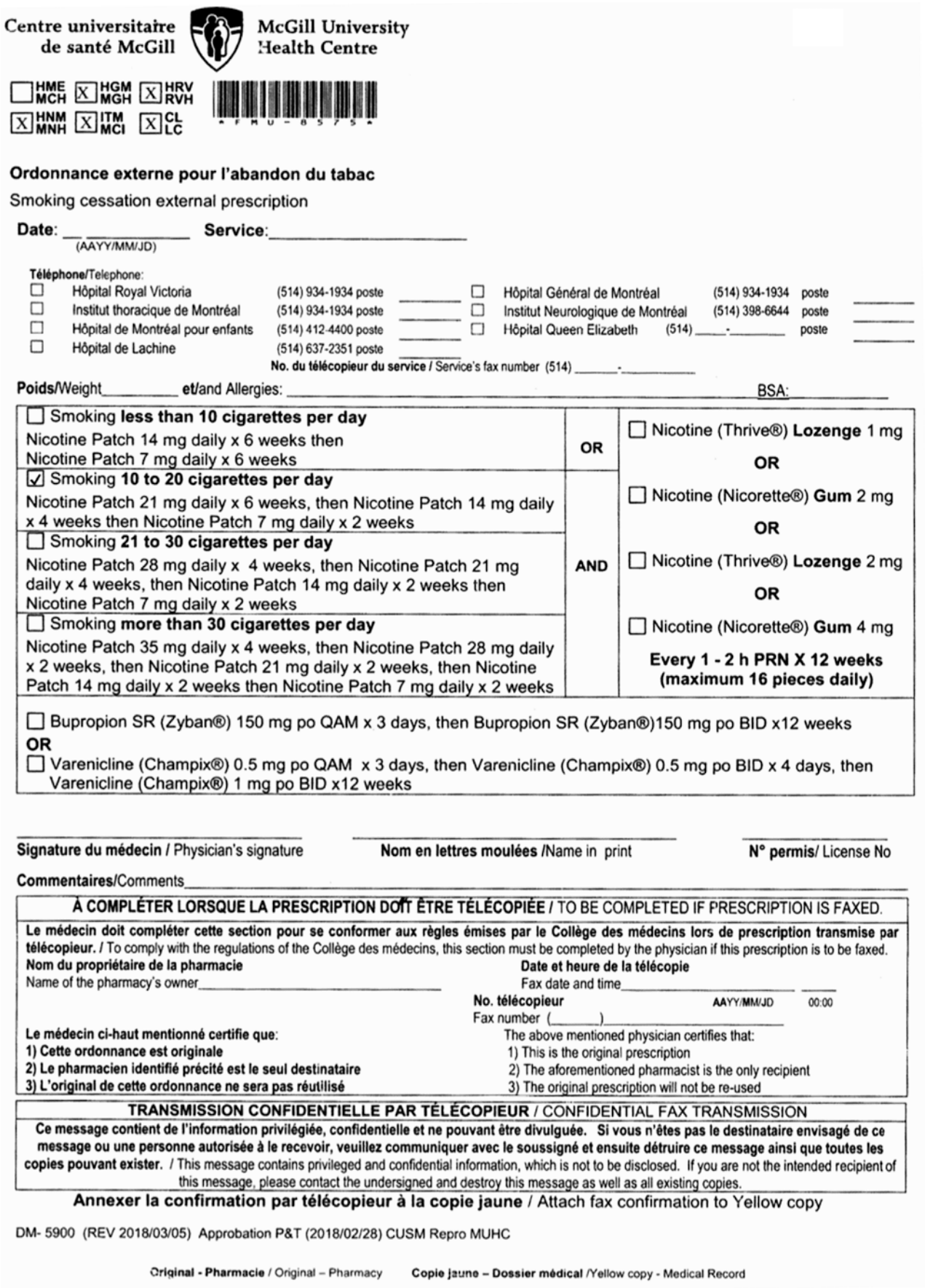
NRT side effects are mild and generally improve over time. They include gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), headache, and dizziness and depend on the delivery method [43]. An NRT patch can cause skin irritation and disturbed sleep, while an oral formulation can cause sore mouth, heartburn, or hiccups [43, 44]. In the presence of side effects, the NRT dose can be titrated down or changed to another formulation or medication. NRT dependence is rare [43].

Preoperative smoking cessations provide benefits that far outweigh the cardiovascular risk of continuing smoking or of the potential risk of using NRT until surgery [3, 21, 46, 47]. The safety of NRT in patients with stable cardiovascular disease is well established [43]. This is probably due to the fact that adverse events caused by smoking are also due to other constituents present in the cigarette smoke and that peak plasma nicotine concentrations produced by cigarettes are higher than those observed during NRT [4]. Nicotine plasma concentrations of smokers receiving NRT are lower even in patients who do not completely quit smoking before surgery [4]. Moller et al. reported a nonsignificant reduction of cardiovascular complications in surgical patients receiving NRT (0% vs. 10%, $p = 0.07$). Higher heart rate has been observed post tracheal intubation in surgical patients receiving NRT patch compared to patients receiving placebo [48].

Beneficial effects of NRT also have been observed in studies evaluating wound healing [4, 49]. Some studies have also shown that NRT promotes angiogenesis, thus suggesting that NRT does not negatively affect wound healing [4]. On the contrary, the study by Moller et al. demonstrated that preoperative smoking cessation interventions including NRT were particularly beneficial in reducing wound-related complications [21]. Many orthopedic surgeons avoid NRT because of concern that it will impede bone healing. However, clinical trials demonstrating that perioperative NRT negatively affect bone healing compared with smoking tobacco is lacking [43].

Whether to discontinue NRT patches 24 hours before surgery or continue use throughout the entire perioperative period is controversial. Most of the studies demonstrating reduction in complications following preoperative smoking cessation interventions including NRT patch did not interrupt NRT before surgery [18–21, 30]. NICE guidelines suggest discontinuing NRT 24 hours before surgery, in particular for patients undergoing microvascular reconstructive procedures [27].

Varenicline Varenicline is a partial nicotine agonist that has been successfully used to alleviate craving and withdrawal symptoms and to reduce the rewarding effect of smoking [43, 44, 50]. The results of a network meta-analysis found that varenicline is the most effective pharmacological intervention to achieve abstinence (assessed at 6 months or after initiation of the intervention) when compared to NRT alone (OR 1.57; 95% credible interval [CredI] 1.29–1.91) or bupropion (OR 1.59; 95% 95% CredI 1.29–1.96), but not when it was compared to combined NRT interventions (OR 1.06; 95% CredI 0.75–1.48) [51]. Pharmacologic superiority of varenicline as monotherapy to achieve smoking abstinence (assessed at 9–12 weeks after initiation), compared to NRT or bupropion, was also confirmed in a large multicenter RCT [52]. Varenicline is also more effective than NRT and bupropion to achieve short-term smoking cessation, defined as 4 weeks post target quit date [53]. Treatment should be initiated with 0.5 mg per os once a day for 3 days and progressively increased over time (Fig. 8.3). Dosage should be reduced in patients with reduced renal function [44].The most common side effect of varenicline is nausea (mild to moderate) in 30% of users. However, it rarely causes discontinuation, observed only in 3% of the patients [44]. Nausea can be reduced by up-titration of the dose and by consuming the drug with food [44].



Centre universitaire de santé McGill — McGill University Health Centre

☐ HME MCH ☒ HGM MGH ☒ HRV RVH
☒ HNM MNH ☒ ITM MCI ☒ CL LC

* F M U - 8 5 7 5 *

Ordonnance externe pour l'abandon du tabac

Smoking cessation external prescription

Date: __ _____ (AAYY/MM/JD) **Service**:_____

Téléphone/Telephone:

☐	Hôpital Royal Victoria	(514) 934-1934 poste _____	☐	Hôpital Général de Montréal	(514) 934-1934 poste _____
☐	Institut thoracique de Montréal	(514) 934-1934 poste _____	☐	Institut Neurologique de Montréal	(514) 398-6644 poste _____
☐	Hôpital de Montréal pour enfants	(514) 412-4400 poste _____	☐	Hôpital Queen Elizabeth	(514) ___-_____ poste _____
☐	Hôpital de Lachine	(514) 637-2351 poste _____			

No. du télécopieur du service / Service's fax number (514) _____-_____

Poids/Weight_____ **et**/and Allergies: _____ BSA: _____

☐ Smoking **less than 10 cigarettes per day** Nicotine Patch 14 mg daily x 6 weeks then Nicotine Patch 7 mg daily x 6 weeks	**OR**	☐ Nicotine (Thrive®) **Lozenge** 1 mg **OR** ☐ Nicotine (Nicorette®) **Gum** 2 mg **OR** ☐ Nicotine (Thrive®) **Lozenge** 2 mg **OR** ☐ Nicotine (Nicorette®) **Gum** 4 mg **Every 1 - 2 h PRN X 12 weeks (maximum 16 pieces daily)**
☑ Smoking **10 to 20 cigarettes per day** Nicotine Patch 21 mg daily x 6 weeks, then Nicotine Patch 14 mg daily x 4 weeks then Nicotine Patch 7 mg daily x 2 weeks	**AND**	
☐ Smoking **21 to 30 cigarettes per day** Nicotine Patch 28 mg daily x 4 weeks, then Nicotine Patch 21 mg daily x 4 weeks, then Nicotine Patch 14 mg daily x 2 weeks then Nicotine Patch 7 mg daily x 2 weeks		
☐ Smoking **more than 30 cigarettes per day** Nicotine Patch 35 mg daily x 4 weeks, then Nicotine Patch 28 mg daily x 2 weeks, then Nicotine Patch 21 mg daily x 2 weeks, then Nicotine Patch 14 mg daily x 2 weeks then Nicotine Patch 7 mg daily x 2 weeks		

☐ Bupropion SR (Zyban®) 150 mg po QAM x 3 days, then Bupropion SR (Zyban®)150 mg po BID x12 weeks
OR
☐ Varenicline (Champix®) 0.5 mg po QAM x 3 days, then Varenicline (Champix®) 0.5 mg po BID x 4 days, then Varenicline (Champix®) 1 mg po BID x12 weeks

Signature du médecin / Physician's signature **Nom en lettres moulées** /Name in print **N° permis**/ License No

Commentaires/Comments_____

À COMPLÉTER LORSQUE LA PRESCRIPTION DOIT ÊTRE TÉLÉCOPIÉE / TO BE COMPLETED IF PRESCRIPTION IS FAXED.

Le médecin doit compléter cette section pour se conformer aux règles émises par le Collège des médecins lors de prescription transmise par télécopieur. / To comply with the regulations of the Collège des médecins, this section must be completed by the physician if this prescription is to be faxed.

Nom du propriétaire de la pharmacie
Name of the pharmacy's owner_____

Date et heure de la télécopie
Fax date and time_____ ____
No. télécopieur AAYY/MM/JD 00:00
Fax number (_____)_____

Le médecin ci-haut mentionné certifie que:
1) Cette ordonnance est originale
2) Le pharmacien identifié précité est le seul destinataire
3) L'original de cette ordonnance ne sera pas réutilisé

The above mentioned physician certifies that:
1) This is the original prescription
2) The aforementioned pharmacist is the only recipient
3) The original prescription will not be re-used

TRANSMISSION CONFIDENTIELLE PAR TÉLÉCOPIEUR / CONFIDENTIAL FAX TRANSMISSION

Ce message contient de l'information privilégiée, confidentielle et ne pouvant être divulguée. Si vous n'êtes pas le destinataire envisagé de ce message ou une personne autorisée à le recevoir, veuillez communiquer avec le soussigné et ensuite détruire ce message ainsi que toutes les copies pouvant exister. / This message contains privileged and confidential information, which is not to be disclosed. If you are not the intended recipient of this message, please contact the undersigned and destroy this message as well as all existing copies.

Annexer la confirmation par télécopieur à la copie jaune / Attach fax confirmation to Yellow copy

DM- 5900 (REV 2018/03/05) Approbation P&T (2018/02/28) CUSM Repro MUHC

Original - Pharmacie / Original – Pharmacy **Copie jaune – Dossier médical** /Yellow copy - Medical Record

Fig. 8.3 McGill smoking cessation protocol. (developed by Dr. Sean Gilman, director of the McGill Smoking cessation program, and his team; with permission)

Sleep disorders such as insomnia or abnormal dreams are also common. Post-marketing reports have described depression, agitation, changes in behavior, and suicidal ideation with the use of varenicline. However, the results of a meta-analysis including 17 RCTs did not confirm these findings in patients with and without mental illness [54]. Moreover, the results of a recent large multicenter RCT further validate the safety of varenicline [52]. Current evidence does not indicate cardiovascular toxicity [43].

Two RCTs evaluating the perioperative efficacy of varenicline in patients undergoing noncardiac surgery demonstrated that varenicline is effective in achieving long-term smoking cessation, when compared to placebo [55] or to brief nonpharmacological smoking cessation interventions [55, 56]. However, it did not impact postoperative outcomes [19].

Bupropion Bupropion is an antidepressant, and it could be administered in patients with nicotine addiction and depressed mood. It decreases the urge to smoke and symptoms of withdrawal. Its effectiveness improves when used together with NRT. Dosing of bupropion is 150 mg per os daily for 3 days followed by 150 mg per os twice daily for up to 12 weeks, and it is usually started 1–2 weeks before a patient starts to quit [4]. It is contraindicated in patients with seizure, with eating disorders, or taking monoamine oxidase. Caution should be used in patients who take medications that reduce the seizure threshold such as hypoglycemic agents and antidepressants [44].

The risk of neuropsychiatric and cardiovascular toxicity in individuals using bupropion is not higher than those receiving placebo [51]. One small RCT of surgical patients treated with bupropion as monotherapy to achieve preoperative smoking cessation demonstrated that bupropion is useful to reduce the number of cigarettes smoked before surgery, reduce end-expired CO, increase arterial oxygen saturation on pulse oximetry before surgery, and increase smoking cessation rates at 3 weeks but not 6 weeks, after surgery [57].

Other Pharmacological Agents and Methods A variety of other pharmacological agents and methods have been used to achieve smoking cessation, but their efficacy is not proven in surgical patients. In particular, the efficacy of electronic cigarettes to achieve smoking cessation is marginal compared to smokers receiving placebo, and it is not superior to results reported with approved pharmacological agents [58]. However, they do not produce carcinogens and toxins as conventional cigarettes. Perioperative studies investigating the ability of electronic cigarettes to achieve smoking cessation are lacking. Due to the lack of safety data in surgical patients, electronic cigarettes cannot be recommended as a strategy to achieve preoperative smoking cessation, and patients already using electronic cigarettes should be encouraged to substitute nicotine assumption with NRT products before surgery [58, 59].

Duration and Intensity of Preoperative Smoking Cessation Interventions, Smoking Cessation Rates, and Complications

The best strategy to support preoperative tobacco abstinence is unknown, and individualized interventions are more likely to be effective. In the general population, a combination of counseling with pharmacotherapy increases smoking cessation rates (RR 1.82, 95% CI 1.66–2.00) [42, 44, 60]. These data are also confirmed in surgical patients. Overall, preoperative prolonged (4 weeks or longer) and intense (pharmacological therapy combined with preoperative counseling) interventions are very effective to increase preoperative and long-term smoking cessation rates, compared to patients not receiving any interventions (RR 10.76, 95% CI 5.55–25.46 and RR 2.96, 95% CI 1.57–5.55, respectively) [19, 59]. Brief preoperative smoking interventions (without follow-up) also increase preoperative and long-term smoking cessation rates but not to the same extent (RR 1.30, 95% CI 1.14–1.46, and RR 2.29, 95% CI 1.14–1.61, respectively), compared to patients not receiving any interventions [19, 59]. In contrast, postoperative complications are reduced only by preoperative intense smoking cessation interventions, by almost 60% (RR 0.42, 95% CI 0.27–0.65) [19, 59].

Finally, it might be possible that preoperative smoking cessation interventions are more beneficial in certain surgical populations than others, as the impact of smoking on postoperative outcomes seems to be procedure specific [15]. Current benefits have been mainly proven in patients undergoing orthopedic and abdominal procedures, while studies evaluating the efficacy of preoperative smoking cessation interventions in patients undergoing thoracic or cardiac surgery (high prevalence of smoking and high risk of pulmonary complications) are lacking.

Withdrawal Syndrome

Neurobiology of nicotine withdrawal syndrome is complex, as nicotine modulates the release of several neurotransmitters [61]. Withdrawal syndrome symptoms are rare postoperatively and are more frequent when the abstinence period is forced rather during the stressful perioperative period [4]. Thus, routine NRT is not indicated in every smoker undergoing surgery [4]. However, it can significantly help to reduce the number of cigarettes smoked per day once patients are discharged from the hospital [4].

Alcohol Cessation

It is well recognized that alcohol abuse is a risk factor for several chronic diseases and that hazardous drinking increases the risk of postoperative morbidity. Although withdrawal from alcohol partially reverses organic dysfunction in

nonsurgical patients, perioperative alcohol cessation strategies have been infrequently studied and rarely offered as routine surgical care.

Alcohol abuse disorders in surgical patients (defined by the consumption of at least five drinks per day and identified by a self-reported alcohol intake questionnaire) have been reported ranging from 7% to 49%, depending on gender and diagnosis [62]. Alcohol dependency is found in one out of ten hospitalized surgical patients, in 25% of trauma patients, and up to 50% in patients with certain cancers [63]. Moreover, alcohol use disorders are underestimated when assessed in the preoperative setting, especially in women and younger patients [64]. The use of preoperative screening tools, such as the CAGE ("cut down," "annoyance," "guilt," and "eye-opener") and AUDIT (Alcohol Use Disorders Identification Test) questionnaires, together with the use of certain laboratory testing, can be useful to better identify surgical patients with alcohol dependency [63]. A recent Cochrane meta-analysis including surgical patients undergoing elective and emergency surgery defined "risky drinking" patients with an alcohol consumption equivalent to more than 3 alcoholic units (AU)/day or 21 AU/week (with 1 AU containing 12 grams of ethanol) with or without symptoms of alcohol abuse or dependency. This corresponds to the amount of alcohol associated with increased postoperative complication rates in most clinical studies [65]. Higher cutoff (alcohol intake of more 60 g of ethanol per day, five drinks or 1.5 l of beer), associated with at least double the complication and mortality rates, also has been used [63].

Alcohol Abuse and Cessation in the Perioperative Period: Pathophysiologic Changes and Impact on Clinical Outcomes

High-moderate quality of evidence suggests that alcohol overconsumption is associated with increased morbidity, in particular infections, cardiopulmonary complications, bleeding and delirium, withdrawal syndrome, and prolonged intensive care unit stay [63, 66]. This is probably due to alcohol-induced organ dysfunction and to the stronger surgical stress response observed in alcohol-abusing patients undergoing surgery. In fact, the magnitude of the stress response to surgery in patients who continue drinking alcohol until surgery is greater than those who quit 4 weeks before surgery. As a consequence, preexisting subclinical organ dysfunctions possibly present in these patients could be further aggravated [13, 67, 68]. Interestingly, in alcohol-abusing surgical patients undergoing gastrointestinal surgery, treatment with low-dose continuous infusion of intravenous morphine (15 mcg/h) reduced postoperative plasma cortisol and preserved cellular immune function. This intervention was also associated with lower pneumonia rates and shorter intensive care unit stay [69].

Alcohol affects the cell-mediated immune response, in particular the delayed-type hypersensitivity (DTH). Studies demonstrate that DTH is already impaired in alcohol-abusing surgical patients [62, 69] and that DTH is associated with higher risk of surgical site infections [62]. A small RCT found that in alcohol-abusing patients, 4 weeks of alcohol abstinence before colorectal surgery improves DTH preoperatively, and this is associated with less postoperative complications than patients who continued drinking until surgery (31% vs. 74%; $p = 0.02$, respectively) [67]. However, in this study infectious complications were not reduced. A recent meta-analysis including 13 observational studies and 5 RCTs confirmed that surgical patients consuming a total of 50 ml spirits 40%, or 150 ml wine 13%, or 500 ml 4% beer or alcopop (a ready-mixed drink containing alcohol) of alcohol per day have a higher risk of developing postoperative surgical site infections [65]. Preoperative abstinence of 4 weeks reduces such risk [13, 70] (Fig. 8.4).

Asymptomatic preoperative cardiac dysfunction has also been reported in alcohol-abusing patients scheduled for surgery [66]. In a small prospective non-RCT, asymptomatic surgical patients scheduled for colorectal surgery

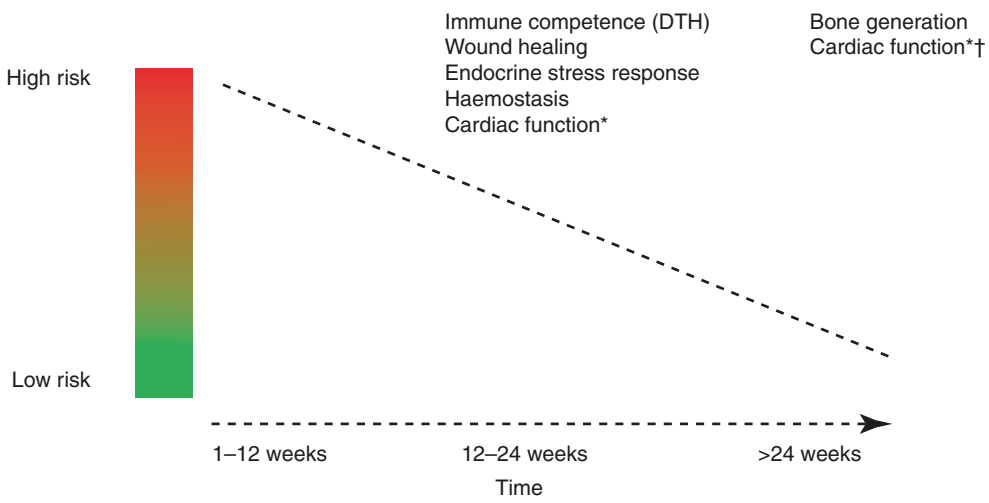


Fig. 8.4 Clinical risk and time required to recover physiologic functions and improve alcohol-related symptoms following preoperative alcohol cessation. (∗ Without symptoms; † with severe failure. Adapted from [13])

and who were drinking at least 60 g of alcohol per day had lower preoperative left ventricle ejection fraction (although within a normal range) than appropriately matched surgical patients who were consuming below 25 g of alcohol daily. The former patients also had a higher incidence of postoperative arrhythmia [66]. Four-week preoperative alcohol abstinence has also shown to reduce postoperative myocardial ischemia [67].

Hemostasis is also influenced by alcohol, as demonstrated by prolonged bleeding time observed in alcohol-abusing surgical patients [66–68]. However, chronic alcohol exposure also negatively affects coagulation and fibrinolysis, and this might further predispose to perioperative bleeding [66].

The results of the latest Cochrane systematic review evaluating the efficacy of perioperative alcohol interventions demonstrated that perioperative alcohol cessation is feasible, safe, and effective. This systematic review and meta-analysis included three small RCTs: one of patients undergoing colorectal surgery and two of patients undergoing orthopedic surgery. The intervention was initiated and terminated preoperatively in two trials and postoperatively for 6 weeks in one trial. All trials included intense interventions, including pharmacological strategies, patient education, and relapse prophylaxis. The pool analysis demonstrated that preoperative alcohol cessation decreases postoperative complications (RR 0.62, 95% CI 0.40–0.96). All three studies aimed at achieving alcohol cessation in the perioperative period. Overall, patients receiving perioperative alcohol cessation interventions were approximately eight times more likely to successfully achieve abstinence (RR 8.22, 95% CI 1.67–40.44; $p = 0.01$) and to reduce alcohol consumption. There was no effect on length of hospital stay and mortality [65].

Perioperative Alcohol Cessation Strategies

Counseling

In the primary care setting, brief interventions, ranging from 1 to 30 minutes, have shown to decrease alcohol by 38 g per week, especially in men (mean difference, 95% CI −54 to −23) [71]. These include motivational, ambivalence-accepting, and non-confronting conversations, in person or computer-based [63]. Perioperative counseling should discuss the risks of continuing alcohol consumption before surgery, discuss the importance of preoperative alcohol cessation, record baseline alcohol intake, ideally schedule weekly meetings during which alcohol consumption is recorded, and provide information on how to manage immediate withdrawal symptoms [13]. About 80% of patients who have been informed about the higher risk of complications are highly motivated in reducing alcohol intake but also seek hospital support [13]. Telephone helplines are also available. Consulting a psychiatrist or substance abuse specialist might be useful to plan a perioperative detoxification program [63].

Pharmacotherapy

Benzodiazepines are mainly prescribed to manage alcohol withdrawal symptoms. Alpha-2 agonists and neuroleptic agents also have been utilized in hospitalized patients [63]. Withdrawal symptoms are frequent, they can be life-threatening, and they can manifest even before a patient is completely sober. After surgery, early recognition is essential as higher mortality rates have been reported in patients who have mistreated alcohol [72]. Medications to support alcohol abstinence such as disulfiram (e.g., 800 mg per os taken during controlled supervision twice per week, until the week before surgery [67]) and/or B vitamins could be prescribed based on patient's preferences. Disulfiram should not be administered when contraindicated and unless blood or air alcohol concentrations have been proven to be zero [13]. Its safety has been demonstrated, and it does not affect craving or withdrawal symptoms [13].

Conclusions and Main Findings

- Smoking and alcohol overconsumption induce several organ dysfunctions that predispose to postoperative complications.
- Longer periods of preoperative smoking cessation abstinence are associated with better outcomes.
- Caregivers involved in the perioperative care of patients (surgeons, anesthesiologists, internists, GPs, and nurses) should all recommend smoking and alcohol cessation before surgery, at every opportunity, and provide assistance when possible.
- Prolonged (4 weeks or longer) and intense (combined counseling and pharmacotherapy) preoperative smoking cessation programs significantly increase preoperative and long-term smoking cessation rates and reduce postoperative complications, in particular PPCs, infections, and wound healing complications (high-moderate quality of evidence).
- Prolonged and intense perioperative alcohol cessation programs increase alcohol cessation rates and decreased complications (low quality of evidence based only on three small RCTs).
- Preoperative smoking and alcohol cessation interventions are infrequent in clinical practice.
- Smoking and alcohol cessation should be initiated as early as possible in the preoperative period course, ideally at the time of surgical referral or scheduling.
- Lack of training, skills, time, and resources is the main factor limiting clinical implementation.

References

1. Lumb AB. Pre-operative respiratory optimisation: an expert review. Anaesthesia. 2019;74(Suppl 1):43–8.
2. Jamal A, Phillips E, Gentzke AS, Homa DM, Babb SD, King BA, et al. Current cigarette smoking among adults – United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(2):53–9.
3. Turan A, Mascha EJ, Roberman D, Turner PL, You J, Kurz A, et al. Smoking and perioperative outcomes. Anesthesiology. 2011;114(4):837–46.
4. Warner DO. Perioperative abstinence from cigarettes: physiologic and clinical consequences. Anesthesiology. 2006;104(2):356–67.
5. Erskine RJ, Murphy PJ, Langton JA. Sensitivity of upper airway reflexes in cigarette smokers: effect of abstinence. Br J Anaesth. 1994;73(3):298–302.
6. Cooke JP, Bitterman H. Nicotine and angiogenesis: a new paradigm for tobacco-related diseases. Ann Med. 2004;36(1):33–40.
7. Chen Y, Guo Q, Pan X, Qin L, Zhang P. Smoking and impaired bone healing: will activation of cholinergic anti-inflammatory pathway be the bridge? Int Orthop. 2011;35(9):1267–70.
8. Warner DO, Patten CA, Ames SC, Offord K, Schroeder D. Smoking behavior and perceived stress in cigarette smokers undergoing elective surgery. Anesthesiology. 2004;100(5):1125–37.
9. Jamner LD, Girdler SS, Shapiro D, Jarvik ME. Pain inhibition, nicotine, and gender. Exp Clin Psychopharmacol. 1998;6(1):96–106.
10. Flood P, Daniel D. Intranasal nicotine for postoperative pain treatment. Anesthesiology. 2004;101(6):1417–21.
11. Turan A, White PF, Koyuncu O, Karamanliodlu B, Kaya G, Apfel CC. Transdermal nicotine patch failed to improve postoperative pain management. Anesth Analg. 2008;107(3):1011–7.
12. Shi Y, Weingarten TN, Mantilla CB, Hooten WM, Warner DO. Smoking and pain: pathophysiology and clinical implications. Anesthesiology. 2010;113(4):977–92.
13. Tønnesen H, Nielsen PR, Lauritzen JB, Møller AM. Smoking and alcohol intervention before surgery: evidence for best practice. Br J Anaesth. 2009;102(3):297–306.
14. Musallam KM, Rosendaal FR, Zaatari G, Soweid A, Hoballah JJ, Sfeir PM, et al. Smoking and the risk of mortality and vascular and respiratory events in patients undergoing major surgery. JAMA Surg. 2013;148(8):755–62.
15. Schmid M, Sood A, Campbell L, Kapoor V, Dalela D, Klett DE, et al. Impact of smoking on perioperative outcomes after major surgery. Am J Surg. 2015;210(2):221–9.e6.
16. Hawn MT, Houston TK, Campagna EJ, Graham LA, Singh J, Bishop M, et al. The attributable risk of smoking on surgical complications. Ann Surg. 2011;254(6):914–20.
17. Miskovic A, Lumb AB. Postoperative pulmonary complications. Br J Anaesth. 2017;118(3):317–34.
18. Sørensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Arch Surg. 2012;147(4):373–83.
19. Thomsen T, Villebro N, Moller AM. Interventions for preoperative smoking cessation. Cochrane Database Syst Rev. 2014;3:CD002294.
20. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO. Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. Am J Med. 2011;124(2):144–54 e8.
21. Moller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet. 2002;359(9301):114–7.
22. Mazo V, Sabate S, Canet J, Gallart L, de Abreu MG, Belda J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. Anesthesiology. 2014;121(2):219–31.
23. Lyons B, Frizelle H, Kirby F, Casey W. The effect of passive smoking on the incidence of airway complications in children undergoing general anaesthesia. Anaesthesia. 1996;51(4):324–6.
24. Skolnick ET, Vomvolakis MA, Buck KA, Mannino SF, Sun LS. Exposure to environmental tobacco smoke and the risk of adverse respiratory events in children receiving general anesthesia. Anesthesiology. 1998;88(5):1144–53.
25. Wong J, Lam DP, Abrishami A, Chan MT, Chung F. Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. Can J Anaesth. 2012;59(3):268–79.
26. Myers K, Hajek P, Hinds C, McRobbie H. Stopping smoking shortly before surgery and postoperative complications: a systematic review and meta-analysis. Arch Intern Med. 2011;171(11):983–9.
27. Smoking: acute, maternity and mental health services. Public health guideline [PH48], published date: November 2013; https://www.nice.org.uk/guidance/ph48.
28. Lugg ST, Tikka T, Agostini PJ, Kerr A, Adams K, Kalkat MS, et al. Smoking and timing of cessation on postoperative pulmonary complications after curative-intent lung cancer surgery. J Cardiothorac Surg. 2017;12(1):52.
29. Bradley A, Marshall A, Stonehewer L, Reaper L, Parker K, Bevan-Smith E, et al. Pulmonary rehabilitation programme for patients undergoing curative lung cancer surgery. Eur J Cardiothorac Surg. 2013;44(4):e266–71.
30. Thomsen T, Tønnesen H, Moller AM. Effect of preoperative smoking cessation interventions on postoperative complications and smoking cessation. Br J Surg. 2009;96(5):451–61.
31. McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: the case of smoking cessation. Health Educ Res. 2003;18(2):156–70.
32. Lee SM, Landry J, Jones PM, Buhrmann O, Morley-Forster P. The effectiveness of a perioperative smoking cessation program: a randomized clinical trial. Anesth Analg. 2013;117(3):605–13.
33. Lee SM, Landry J, Jones PM, Buhrmann O, Morley-Forster P. Long-term quit rates after a perioperative smoking cessation randomized controlled trial. Anesth Analg. 2015;120(3):582–7.
34. Zwar NA, Richmond RL. Role of the general practitioner in smoking cessation. Drug Alcohol Rev. 2006;25(1):21–6.
35. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. A clinical practice guideline for treating tobacco use and dependence: a US public health service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. JAMA. 2000;283(24):3244–54.
36. Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. Anesthesiology. 2010;112(1):102–7.
37. Agency for Healthcare Research and Quality, US Department of Health and Human Services. Five major steps to intervention (The "5 A's"). 2012. Accessed 1 Apr 2019. Available from: http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.html.
38. Warner DO. Helping surgical patients quit smoking: why, when, and how. Anesth Analg. 2005;101(2):481–7, table of contents.
39. Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. Cochrane Database Syst Rev. 2013;31(5):CD000165.
40. Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev. 2015;12(10):CD009670.
41. Baker AL, Turner A, Beck A, Berry K, Haddock G, Kelly PJ, et al. Telephone-delivered psychosocial interventions targeting key health priorities in adults with a psychotic disorder: systematic review. Psychol Med. 2018;48(16):2637–57.
42. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2012 reviews. Addiction. 2013;108(10):1711–21.
43. Uptodate-Pharmacotherapy for smoking cessation in adults. [cited April 1, 2019]. Available from: https://www.upto-

date.com/contents/pharmacotherapy-for-smoking-cessation-in-adults?search=Preoperative%20smokers&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4#H2271656238.
44. Zwar NA, Mendelsohn CP, Richmond RL. Supporting smoking cessation. BMJ. 2014;348:f7535.
45. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2012;11:CD000146.
46. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: implications for electronic cigarette use. Trends Cardiovasc Med. 2016;26(6):515–23.
47. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol. 1997;29(7):1422–31.
48. Puura A. Transdermal nicotine increases heart rate after endotracheal intubation. Methods Find Exp Clin Pharmacol. 2003;25(5):383–5.
49. Sørensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. Ann Surg. 2003;238(1):1–5.
50. Hays JT, Ebbert JO. Varenicline for tobacco dependence. N Engl J Med. 2008;359(19):2018–24.
51. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;31(5):CD009329.
52. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. 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(10037):2507–20.
53. Mills EJ, Wu P, Spurden D, Ebbert JO, Wilson K. Efficacy of pharmacotherapies for short-term smoking abstinance: a systematic review and meta-analysis. Harm Reduct J. 2009;6:25.
54. Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. Am J Psychiatry. 2013;170(12):1460–7.
55. Wong J, Abrishami A, Yang Y, Zaki A, Friedman Z, Selby P, et al. A perioperative smoking cessation intervention with varenicline: a double-blind, randomized, placebo-controlled trial. Anesthesiology. 2012;117(4):755–64.
56. Wong J, Abrishami A, Riazi S, Siddiqui N, You-Ten E, Korman J, et al. A perioperative smoking cessation intervention with varenicline, counseling, and fax referral to a telephone quitline versus a brief intervention: a randomized controlled trial. Anesth Analg. 2017;125(2):571–9.
57. Myles PS, Leslie K, Angliss M, Mezzavia P, Lee L. Effectiveness of bupropion as an aid to stopping smoking before elective surgery: a randomised controlled trial. Anaesthesia. 2004;59(11):1053–8.
58. Steliga MA. Smoking cessation in clinical practice: how to get patients to stop. Semin Thorac Cardiovasc Surg. 2018;30(1):87–91.
59. Pierre S, Rivera C, Le Maitre B, Ruppert AM, Bouaziz H, Wirth N, et al. Guidelines on smoking management during the perioperative period. Anaesth Crit Care Pain Med. 2017;36(3):195–200.
60. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev. 2012;10:CD008286.
61. Kenny PJ, Markou A. Neurobiology of the nicotine withdrawal syndrome. Pharmacol Biochem Behav. 2001;70(4):531–49.
62. Tønnesen H. Alcohol abuse and postoperative morbidity. Dan Med Bull. 2003;50(2):139–60.
63. Kork F, Neumann T, Spies C. Perioperative management of patients with alcohol, tobacco and drug dependency. Curr Opin Anaesthesiol. 2010;23(3):384–90.
64. Kip MJ, Neumann T, Jugel C, Kleinwaechter R, Weiss-Gerlach E, Guill MM, et al. New strategies to detect alcohol use disorders in the preoperative assessment clinic of a German university hospital. Anesthesiology. 2008;109(2):171–9.
65. Egholm JW, Pedersen B, Moller AM, Adami J, Juhl CB, Tønnesen H. Perioperative alcohol cessation intervention for postoperative complications. Cochrane Database Syst Rev. 2018;11:CD008343.
66. Tønnesen H, Kehlet H. Preoperative alcoholism and postoperative morbidity. Br J Surg. 1999;86(7):869–74.
67. Tønnesen H, Rosenberg J, Nielsen HJ, Rasmussen V, Hauge C, Pedersen IK, et al. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomised controlled trial. BMJ. 1999;318(7194):1311–6.
68. Tønnesen H, Petersen KR, Hojgaard L, Stokholm KH, Nielsen HJ, Knigge U, et al. Postoperative morbidity among symptom-free alcohol misusers. Lancet. 1992;340(8815):334–7.
69. Spies C, Eggers V, Szabo G, Lau A, von Dossow V, Schoenfeld H, et al. Intervention at the level of the neuroendocrine-immune axis and postoperative pneumonia rate in long-term alcoholics. Am J Respir Crit Care Med. 2006;174(4):408–14.
70. Shabanzadeh DM, Sørensen LT. Alcohol consumption increases post-operative infection but not mortality: a systematic review and meta-analysis. Surg Infect. 2015;16(6):657–68.
71. Kaner EF, Dickinson HO, Beyer F, Pienaar E, Schlesinger C, Campbell F, et al. The effectiveness of brief alcohol interventions in primary care settings: a systematic review. Drug Alcohol Rev. 2009;28(3):301–23.
72. Spies CD, Rommelspacher H. Alcohol withdrawal in the surgical patient: prevention and treatment. Anesth Analg. 1999;88(4):946–54.