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REVIEW

Safety and Efficacy of Nicotine Replacement Therapy in the Perioperative Period: A Narrative Review

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Abstract

Patients who smoke cigarettes are at increased risk for development of complications both during and after surgical procedures, including respiratory, cardiac, and healing-related complications. Abstinence from smoking can considerably reduce these risks. Pharmacotherapy, including nicotine replacement therapy (NRT), is an important component of efficacious tobacco use interventions. However, the use of NRT in the perioperative period is controversial. In this narrative review, we discuss the current evidence for the efficacy and safety of NRT in patients scheduled for surgical procedures, with emphasis on evidence from human studies. We performed a literature search for articles published from January 1, 1990, through May 1, 2015, in the PubMed online database using various permutations of the Medical Subject Headings terms *surgery*; *surgical procedures, operative*; *nicotine*; and *smoking cessation*. Studies were selected for inclusion according to their relevance to the preclinical and clinical evidence pertaining to how NRT affects surgical outcome and long-term rates of abstinence from tobacco. There is strong evidence that NRT enhances the efficacy of tobacco use interventions. Some preclinical studies suggest that nicotine in high doses that exceed those produced by NRT decreases the viability of skin flaps. Although the available data are limited, there is no evidence from human studies that NRT increases the risk of healing-related or cardiovascular complications. Individual clinical trials of tobacco use interventions that include NRT have revealed either no effect or a reduction in complication rates. Therefore, given the benefits of smoking abstinence to both perioperative outcomes and long-term health and the efficacy of NRT in achieving and maintaining abstinence, any policies that prohibit the use of NRT in surgical patients should be reexamined.

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Patients who smoke cigarettes are at increased risk for development of complications both during and after surgical procedures, including respiratory, cardiac, and healing-related complications.[1,2] Abstinence from smoking can considerably reduce these risks.[3-5] In addition, surgical treatment itself has been reported to increase the liklihood of quitting smoking, even if the need for surgical intervention is not directly related to a patient's smoking status.[6,7] Thus, the scheduling of elective surgical procedures presents a key opportunity to provide tobacco use interventions at this "teachable moment" for smoking cessation.[6] Nonetheless, many patients still find it difficult to abstain from cigarettes during the perioperative period, with a substantial proportion of patients reporting smoking even on the morning of their surgical procedure.[8]

Pharmacotherapy, including nicotine replacement therapy (NRT), is an important component of efficacious tobacco use interventions.[9] However, the use of NRT in the time around surgery (the perioperative period) is controversial. Nicotine has widespread pharmacological actions on multiple organ systems, and concerns have been raised that NRT may increase the risk of wound-related and cardiovascular complications. These concerns have led some surgeons in the United States to prohibit the use of NRT in the perioperative period, including in some cases the requirement of several nicotine-free weeks before operation. A recent survey of general surgeons found that only 34% agreed that NRT was safe for patients to use during surgical treatment, although 61% agreed that it was safe after the operation.[10] Such perceptions can remove a valuable tool that could help smokers facing surgical treatment quit.

The purpose of this narrative review is to discuss the current evidence for NRT's efficacy and safety in patients scheduled for surgical

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ARTICLE HIGHLIGHTS

- Patients who smoke cigarettes are at increased risk for perioperative complications, including healing-related and cardiovascular complications.
- Meta-analysis of existing studies, including studies that utilized nicotine replacement therapy (NRT) as a component of tobacco use interventions, reveals that abstinence from smoking reduces these risks.
- Nicotine replacement therapy increases the efficacy of tobacco use interventions, increasing the likelihood that patients can maintain abstinence from smoking.
- Although the available data are limited, there is no evidence from human studies that NRT increases the risk of healing-related or cardiovascular complications.
- Given the benefits of smoking abstinence to both perioperative outcomes and long-term health and the efficacy of NRT in achieving and maintaining abstinence, any policies that prohibit the use of NRT in surgical patients should be reexamined.

treatment and other invasive procedures. We performed a literature search for articles published from January 1, 1990, through May 1, 2015, in the PubMed online database using various permutations of the Medical Subject Headings terms *surgery*; *surgical procedures, operative*; *nicotine*; and *smoking cessation*. Randomized controlled trials, prospective cohort studies, laboratory-based investigations, systematic reviews, and meta-analyses were selected for inclusion according to their relevance to the various topic areas examined in this article, with particular attention to human studies.

EFFICACY OF NRT

Nicotine replacement therapy is currently available in the United States in 5 delivery methods—gum, lozenges, nasal spray, patches, and inhalers.[11] In this review, *NRT* refers to the nicotine patch (7, 14, or 21 mg of nicotine per patch, depending on baseline cigarette consumption) unless otherwise indicated. Other pharmotherapy for nicotine dependence is available, including the partial nicotinic agonist varenicline and the antidepressant bupropion (Table), but NRT is the only one available without a prescription (in gum and patch forms) and is supported by the deepest evidence base.[9] The pharmacological rationale for its efficacy is that provision of nicotine will reduce nicotine withdrawal symptoms that could otherwise occur in smokers attempting abstinence.[12] Plasma nicotine levels provided by NRT vary according to dose and delivery method but in general are lower than those maintained during active smoking when conventional dosing is employed.[11,12] The evidence for its efficacy to increase abstinence rates is robust, and national guidelines for tobacco treatment include provision of NRT as an A level, evidenced-based recommendation for all health care professionals.[9] In a wide range of populations, addition of NRT in any form to any tobacco use intervention in efficacy trials increases abstinence rates by approximately 60%,[11,13] although effectiveness trials and observational studies reveal that its population-level effectiveness to produce sustained abstinence is less.[14]

Nicotine replacement therapy is commonly incorporated as a component of tobacco use interventions specifically designed for surgical patients, which typically combine pharmacological and behavioral approaches. These interventions are efficacious in terms of both increasing abstinence rates and decreasing perioperative complications. The most recent systematic review of perioperative tobacco use interventions included 12 studies examining abstinence outcomes and concluded that such interventions are efficacious to promote both short- and longer-term abstinence, with efficacy increasing as intervention intensity increases.[5] Of the 12 trials included in the review, with sample sizes ranging from 46 to 286 participants, 9 included NRT as a component of their interventions. None of these studies specifically examined the efficacy of adding NRT to behavioral interventions in terms of maintaining substained perioperative abstinence, although there is no reason to believe that its efficacy would be less in the perioperative period compared with other settings.

The sole placebo-controlled trial of NRT in the perioperative period (N=121) was not intended or powered to examine its effects on postoperative abstinence.[15] Indeed, a tobacco use intervention was not delivered; rather, the purpose of the study was to examine the effect of NRT on perioperative stress and nicotine withdrawal symptoms. Nonetheless, even without a

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behavioral intervention, active NRT patches were efficacious in delaying relapse to smoking within 30 days of operation in patients undergoing outpatient (but not inpatient) surgical procedures (2.5 vs 12.5 days after discharge for placebo patch and active patch groups, respectively; P=.002), and patients were more likely to use active patches compared with placebo patches. At 30 days postoperatively, patients in both groups significantly reduced their cigarettes smoked per day from baseline, with those receiving active patches reporting a greater decrease (a mean decrease of 11±11 vs 15±7 cigarettes per day in the placebo and active groups; P=.045). No adverse events were noted, but the numbers of patients were relatively small.

One placebo-controlled trial of nonnicotine pharmacotherapy in surgical patients (N=286) found that varenicline was efficacious in increasing sustained abstinence rates, suggesting its promise as another tool to aid perioperative smoking cessation.[16] However, varenicline requires a prescription, must be started at least 1 week before a quit attempt, and was associated in this study with an increased frequency of perioperative nausea.[16]

Regarding the effects of interventions on perioperative complication rates, a recent meta-analysis found that intensive interventions (including weekly counseling beginning 4-8 weeks before operation and NRT) reduced the risk of overall postoperative complications by more than half.[5] For wound complications from all types of planned operations (2 trials, 210 participants), the risk was reduced by almost 70% (risk ratio, 0.31; 95% CI, 0.16-0.62). Although an intervention beginning 4 to 8 weeks before surgical treatment may be most beneficial, physiologic and other evidence suggests that even a brief period of preoperative abstinence may be beneficial. For example, the frequency of ST-segment depression during surgical procedures is correlated with exhaled carbon monoxide levels indicative of recent smoking.[17] There is even evidence that maintaining just postoperative abstinence may be beneficial.[18]

SAFETY OF NRT

Nicotine replacement therapy was introduced into clinical practice in the United States in the early 1990s and has an extensive record of safe use in the general population[19]; randomized controlled trials comparing NRT with placebo nicotine replacement devices have consistently reported no increase in adverse events.[13,20] One basis for concern about the safety of NRT in the perioperative period appears to be the assumption that nicotine, one of the approximately 3000 pharmacologically active substances in cigarette smoke, is at least partly responsible for the increased risks of perioperative complications caused by smoking. We are not aware of specific concerns related to NRT increasing the risk of perioperative pulmonary complications, although they have been expressed for healing-related complications and, to a lesser extent, cardiovascular complications. In this review, we concentrate on the evidence addressing these concerns, including evidence from both preclinical and clinical studies, with an emphasis on the latter.

TABLE. US Food and Drug Administration–Approved Pharmacotherapy for Smoking Cessation

Generic name	Brand name	Medication type
Bupropion	Wellbutrin	Antidepressant
Varenicline	Chantix	Nicotine partial agonist
Nicotine replacement therapy		Nicotine replacement
Gum[a]	Nicorette	
Patch[a]	Habitrol	
	NicoDerm CQ	
	Nicotrol	
	ProStep	
Lozenge	Commit	
Inhaler	Nicotrol Inhaler	
Nasal spray	Nicotrol NS	

[a]Available without prescription.

Healing-Related Effects

Wounds. Smokers are at increased risk for development of a variety of wound-related complications after surgical procedures, including surgical site infections and wound dehiscence.[1,2,21] The potential mechanisms that increase risk are numerous and complex, including decreases in tissue oxygenation caused by smoking-induced vasoconstriction, smoking-induced increases in reactive oxygen species, direct effects of smoke constituents on cellular mechanisms responsible for healing, and indirect effects mediated by smoking-related diseases such as the impaired endothelial nitric oxide release that accompanies vascular disease. An excellent

recent review by Sørensen[22] discusses these issues in depth. We briefly review the evidence that nicotine contributes to risk in smokers and whether nicotine in concentrations achieved by NRT might also pose risk.

Preclinical Experimental Studies. Consistent with clinical observations, studies in animal models of surgical wounds have reported that smoke exposure increases the risk of surgical flaps becaming nonviable,[23-26] although apparently this does not hold true for free flaps requiring vascular anastomosis.[27] Several studies have investigated the specific role of nicotine in increasing risk. Prolonged (>4 weeks) administration of nicotine in doses that produce blood nicotine levels that either considerably exceed or are at the upper limit of those achieved by human smokers impaired the survival of experimental skin flaps.[28,29] These effects could be reversed by nicotine abstinence. Lower nicotine doses, which produce nicotine levels more consistent with those produced by clinical NRT, had no effects.[29,30] As an example of the complexities of interpreting experimental data regarding the effects of nicotine on wound healing, several preclinical studies found that the application of topical nicotine in low doses actually accelerated the healing of experimental wounds.[31-35] Many of the cells involved in the healing process, including inflammatory cells, expressed nicotine receptors and could be modulated by relatively high doses of nicotine in vitro,[22] but the potential physiologic role of such modulation is unknown.

Our literature search revealed no animal studies exploring how smoking or nicotine may affect the risk of surgical site infections. We were also unable to identify any animal studies that performed the relevant comparison of animals exposed to cigarette smoking with animals exposed to levels of nicotine commensurate with those achieved by NRT.

Clinical Experimental Studies. Several human studies have documented that smoking a cigarette causes a temporary reduction in tissue blood flow and oxygenation, which could impair surgical wound healing.[22,36-38] However, smoking a cigarette and receiving intravenous nicotine in doses producing similar plasma nicotine concentrations produced quite distinct effects on local tissue.[38] Both decreased subcutaneous blood flow, but smoking decreased tissue oxygenation and subcutaneous blood flow in humans whereas nicotine infusion increased both. Smoking, but not nicotine, also affected tissue metabolism as reflected by glucose and lactate levels. These results are consistent with findings that cutaneous microvascular perfusion is lower in smokers than in nonsmokers but that smoking cessation aided by a nicotine patch normalizes perfusion[39] and another study that found that decreases in digital blood flow were greater following smoking than with a nicotine patch.[40] Thus, to the extent that smoking-induced changes in tissue blood flow and oxygenation contribute to clinical complications, substitution of NRT for smoking should reduce risk.

There is also evidence that nicotine, either delivered via cigarettes or NRT, may actually enhance the axon reflex responses important in the initial tissue response to injury. Warner et al[41] examined the effects of either smoking a cigarette or nicotine nasal spray on the initial vasodilator responses to local healing, which are mediated by axon reflexes. They found that both methods of nicotine administration enhanced these responses, suggesting that nicotine facilitates the release of vasodilator peptides from small afferents and could thus enhance the initial response to injury.

An important series of studies by Sørensen et al[33,38,42-45] directly examined how NRT affects the healing of experimental wound models in humans. In general, these studies (fully reviewed elsewhere[22]) involved dermal punch biopsy wounds created in both nonsmoking and smoking volunteers who were otherwise healthy, with some of the latter randomized to abstain from smoking with either placebo or active nicotine patches. The wounds were excised to examine wound inflammation and proliferative responses. In general, inflammatory and proliferative responses were impaired in smokers compared with nonsmokers, associated with evidence of increased oxidative stress in smokers. Abstinence from smoking improved inflammatory cell function and host defense mechanisms, although abstinence did not affect smoking-induced changes in wound proliferation and remodeling, such as reductions in collagen synthesis and deposition. In abstinent smokers, when groups receiving active and placebo

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patches were compared, abstinence-induced reversal of some parameters of inflammation was somewhat less in those receiving active patches, but other measures of fibroblast function and collagen synthesis were actually increased. The active patch did not affect angiogenesis, wound contraction, or epidermal regeneration.

In the study of most direct clinical relevance from this group,[43] 48 smokers and 30 persons who had never smoked volunteered to participate. Smokers were randomized to continue smoking, abstain using an active nicotine patch, or abstain using a placebo patch; the latter 2 groups were blinded to treatment assignment. Incisional wounds lateral to the sacrum were made after 1 week of continued smoking and at 4, 8, and 12 weeks after randomization. Both wound infection and wound dehiscence were more likely in smokers compared with nonsmokers. Abstinence from smoking reduced the rate of wound infections (from 22% to 1% [$P<.05$], similar to the rate in those who had never smoked [2%]) but not the rate of dehiscence. Wound infection rates in the abstinent smokers were not different between those receiving active and placebo patches, ie, use of NRT did not alter the dramatic benefit of abstinence on the rate of wound infections (Figure 1).[43]

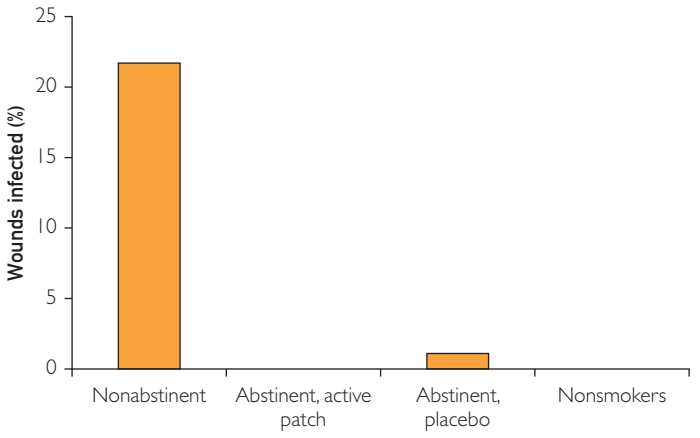

FIGURE 1. Effect of smoking abstinence on wound infection rates. In a study of 48 smokers and 30 persons who had never smoked, smokers were randomized to (1) continued smoking (n=16), (2) smoking abstinence with active nicotine patch (n=16), or (3) smoking abstinence with placebo patch (n=16). Sutured incisional wounds were created over a 12-week period and monitored for 2 weeks for the development of wound infection. Abstinence from smoking dramatically decreased the wound infection rate to that of those who had never smoked, with or without active nicotine replacement. Thus, nicotine did not change the beneficial effect of abstinence. Data from *Ann Surg*.[43]

Other Clinical Studies. As previously discussed, 9 of 12 studies in the most recent systematic review examining the efficacy of perioperative tobacco use interventions employed NRT as a part of the intervention,[5] although information regarding the actual utilization of NRT is lacking, as well as important details such as whether NRT was continued through the perioperative period. Nonetheless, the reductions in complications noted in these studies (including wound-related complications) have been documented in the context of NRT use.[5] Even in the studies that did not find a reduction in complications, no evidence of increased risk was reported.

A definitive study specifically focused on the safety of perioperative NRT would face several challenges, including (1) the likely need for a large sample size (several thousand participants) given the (fortunately) small absolute risk of wound-related complications for most procedures and (2) the confounding effect that those randomized to receive placebo NRT would be less likely to maintain abstinence and thus be at greater risk because of their continued smoking. In addition, urinary levels of cotinine, a nicotine metabolite commonly employed in studies to confirm abstinence from smoking, are difficult to interpret in the context of continued NRT use. This consideration also applies to the ability of surgeons to verify that their patients are abstinent from smoking using urinary cotinine measurement, which may provide motivation for surgeons to avoid the use of NRT before surgical procedures. However, measurement of other metabolites specific to other smoke constituents, such as anabasine, can be employed to distinguish between continued smoking and NRT use.

Bones. Smokers are at increased risk for the nonunion of spinal fusions,[46-50] hip fracture secondary to accelerated osteoporosis,[51] and delayed healing and nonunion of fractures.[52-57] Potential mechanisms for these findings include, as in the case of wound healing, effects on tissue oxygenation, oxidative stress, and direct effects of smoke constituents on osteoblasts and other cellular components important to bone healing.

Preclinical Experimental Studies. Consistent with clinical observations, various animal models

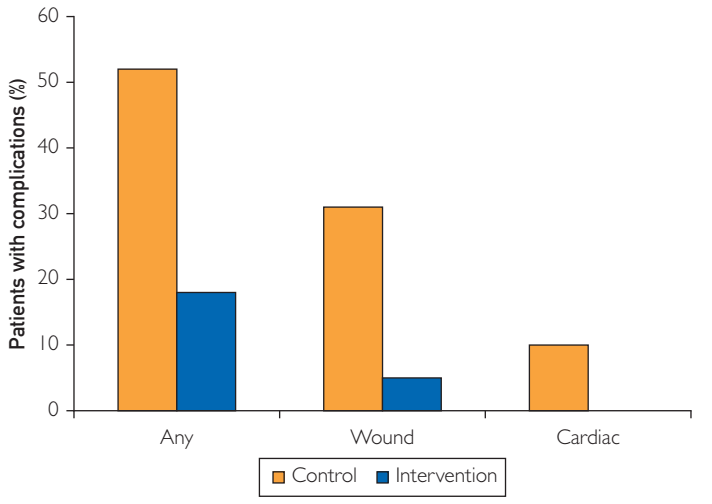

FIGURE 2. Effect of smoking abstinence on postoperative complications. In a study of 120 smokers undergoing total joint replacement, patients were randomized to tobacco intervention (counseling and nicotine replacement therapy) vs control (no intervention) 6 to 8 weeks before operation. Complication rates for the intervention and control groups are shown for any complication, wound-related complications, and cardiac complications within 4 weeks of operation. The relative risk reduction for wound complications was 83%, with a number needed to treat of 4. Data from *Lancet*.[78]

of fracture healing or fusion have found that the long-term administration of nicotine or tobacco smoke extract impairs bone healing and measures of bone metabolism in some,[58-70] but not all,[71-73] models. However, as noted by Skott et al,[74] many of these models employ nicotine administration methods that produce nicotine levels considerably in excess of those achieved in smokers. In vitro studies suggest that nicotine in lower concentrations may actually increase osteoblast proliferation and bone metabolism.[75,76] Also, studies comparing the effects of nicotine alone with tobacco smoke extract, which contains other pharmacologically active constituents, have reported adverse effects of extracts, but not nicotine alone, on various parameters.[71,74,77] There are no preclinical studies of the effects of nicotine in concentrations commensurate with those achieved by NRT.

Clinical Studies. To our knowledge, there are no clinical experimental studies on the effects of nicotine or smoking on bone metabolism or other properties in humans. Of the 12 clinical trials examining the efficacy of tobacco use interventions in surgical patients, 5 specifically included orthopedic surgical patients (1 exclusively[78] [Figure 2]), and 4 of the 5 utilized NRT as a part of the intervention.[5] Impaired bone healing was not observed in the treatment groups of these studies, although the number of patients studied was insufficient to draw conclusions (numbers of participants ranged from 117 to 210). The study of perhaps the greatest direct relevance is that of Nåsell et al,[18] who randomized 105 smokers requiring operative repair of acute fractures who had smoked up to the time of fracture to a postoperative 6-week tobacco use intervention that utilized NRT or no intervention. The intervention significantly reduced the rate of complications (38% and 20% in control and intervention groups, respectively; $P=.048$), and no complications related to bone healing were observed, although again the numbers were relatively small and the rate of NRT utilization was not reported.

Cardiovascular Effects

Cigarette smoking causes cardiovascular disease, which itself increases perioperative risk of adverse outcomes such as myocardial infarction and cerebrovascular accidents. In addition, status as a current smoker confers additional risk of these complications.[79] In the general population, cardiovascular risk is either unchanged or reduced by NRT.[80] This reduced or unchanged level of risk is mediated in part by a reduction in smoking but may also be due to the vasoactive properties of nicotine itself. Interestingly, nicotine may play a role in salvaging ischemic or infarcted tissue in mice after myocardial infarction,[31] which may contribute to the "healthy smoker" paradox[81] in which survival after myocardial infarction is increased in smokers compared with nonsmokers. In humans, the use of NRT in patients with myocardial perfusion defects on nuclear imaging actually reduces exercise-induced myocardial ischemia, even if patients continue smoking.[82]

There is almost no information available regarding specifically how NRT might affect perioperative cardiovascular risk. One study found that heart rates immediately after endotracheal intubation were higher in patients who received an active vs a placebo nicotine patch,[83] but this higher heart rate did not lead to clinical complications.

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DISCUSSION

Summary of Evidence

The evidence reviewed herein may be summarized as follows:

- Patients who smoke cigarettes are at an increased risk for perioperative complications, including healing-related and cardiovascular complications. Meta-analysis of existing studies, including studies that utilized NRT as a component of tobacco use interventions, reveals that abstinence from smoking reduces these risks. Both smoking-related diseases and the multiple pharmacological compounds in cigarette smoke, including nicotine, may contribute to this risk.
- Nicotine replacement therapy increases the efficacy of tobacco use interventions, increasing the likelihood that patients can maintain abstinence from smoking.
- Some, but not all, preclinical studies have found that the long-term administration of relatively large doses of nicotine can reduce the viability of surgical flaps and interfere with the healing of bone in some models. To date, no preclinical studies have examined the effects of nicotine in doses commensurate with those provided by clinical NRT, and no studies have examined the effects of nicotine on surgical site infections, the most common clinical healing-related perioperative complication.
- Although available data are limited, there is no evidence from human studies that NRT increases the risk of healing-related or cardiovascular complications. Clinical trials of tobacco use interventions that include NRT have found either no effect or a reduction in complications.

Study Limitations

The most important limitation of this review is that data are lacking in several relevant areas. Although a definitive placebo-controlled randomized clinical trial examining NRT safety is unlikely to be performed, topics of interest for further studies include (1) models of experimental wounds and flaps in animals, comparing the effects of continued exposure to cigarette smoke with abstinence achieved with and without nicotine in doses comparable to those used with NRT, (2) studies employing animal models of wound infections, (3) animal and human studies of the effects of nicotine on bone metabolism utilizing doses commensurate with those used with NRT, (4) better delineation of the duration of preoperative smoking abstinence necessary to reduce perioperative risk in patients, and (5) further exploration of the efficacy of nonnicotine pharmacotherapy such as bupropion in the perioperative period.

CONCLUSION

As with any other drug, the risks of NRT must be balanced against its potential benefits. Tobacco use interventions that include NRT can reduce the risk of perioperative complications, and by increasing abstinence rates, NRT could thus contribute to this benefit. Although more clinical studies would be welcome (and likely challenging to perform), there is currently no evidence from human studies that NRT is harmful to surgical patients, and data from extant preclinical studies is either reassuring or of questionable relevance to the clinical use of NRT. Even if nicotine itself does increase risk, it would be far preferable to expose patients to the relatively low levels of nicotine produced by NRT compared with the higher levels of nicotine, as well as the carbon monoxide and numerous other poisons in cigarette smoke, produced by smoking, because in the absence of efficacious interventions, most will continue to smoke. Given the benefits of smoking abstinence to both perioperative outcomes and long-term health and the efficacy of NRT in achieving and maintaining abstinence, any policies that prohibit the use of NRT in surgical patients should be reexamined.

Abbreviations and Acronyms: **NRT** = nicotine replacement therapy

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REFERENCES

1. Grønkjær M, Eliasen M, Skov-Ettrup LS, et al. Preoperative smoking status and postoperative complications: a systematic review and meta-analysis. *Ann Surg*. 2014;259(1):52-71.
2. Turan A, Mascha EJ, Roberman D, et al. Smoking and perioperative outcomes. *Anesthesiology*. 2011;114(4):837-846.
3. Hawn MT, Houston TK, Campagna EJ, et al. The attributable risk of smoking on surgical complications. *Ann Surg*. 2011;254(6):914-920.
4. Warner DO. Perioperative abstinence from cigarettes: physiologic and clinical consequences. *Anesthesiology*. 2006;104(2):356-367.

5. Thomsen T, Villebro N, Møller AM. Interventions for preoperative smoking cessation. *Cochrane Database Syst Rev*. 2014;3:CD002294.
6. Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. *Anesthesiology*. 2010;112(1):102-107.
7. Warner DO. Helping surgical patients quit smoking: why, when, and how. *Anesth Analg*. 2005;101(2):481-487.
8. Shi Y, Ehlers S, Hinds R, Baumgartner A, Warner DO. Monitoring of exhaled carbon monoxide to promote preoperative smoking abstinence. *Health Psychol*. 2013;32(6):714-717.
9. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update; a U.S. Public Health Service report. *Am J Prev Med*. 2008;35(2):158-176.
10. Warner DO, Sarr MG, Offord KP, Dale LC. Anesthesiologists, general surgeons, and tobacco interventions in the perioperative period. *Anesth Analg*. 2004;99(6):1766-1773.
11. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2012;11:CD000146.
12. Benowitz NL. Pharmacology of nicotine: addiction and therapeutics. *Annu Rev Pharmacol Toxicol*. 1996;36:597-613.
13. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;5:CD009329.
14. Carpenter MJ, Jardin BF, Burris JL, et al. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: a review of the literature. *Drugs*. 2013;73(5):407-426.
15. Warner DO, Patten CA, Ames SC, Offord KP, Schroeder DR. Effect of nicotine replacement therapy on stress and smoking behavior in surgical patients. *Anesthesiology*. 2005;102(6):1138-1146.
16. Wong J, Abrishami A, Yang Y, et al. A perioperative smoking cessation intervention with varenicline: a double-blind, randomized, placebo-controlled trial. *Anesthesiology*. 2012;117(4):755-764.
17. Woehlck HJ, Connolly LA, Cinquegrani MP, Dunning MB III, Hoffmann RG. Acute smoking increases ST depression in humans during general anesthesia. *Anesth Analg*. 1999;89(4):856-860.
18. Nåsell H, Adami J, Samnegård E, Tønnesen H, Ponzer S. Effect of smoking cessation intervention on results of acute fracture surgery: a randomized controlled trial. *J Bone Joint Surg Am*. 2010;92(6):1335-1342.
19. Zhu SH, Lee M, Zhuang YL, Gamst A, Wolfson T. Interventions to increase smoking cessation at the population level: how much progress has been made in the last two decades? *Tob Control*. 2012;21(2):110-118.
20. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ*. 2009;338:b1024.
21. 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):373-383.
22. Sørensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg*. 2012;255(6):1069-1079.
23. Kaufman T, Eichenlaub EH, Levin M, Hurwitz DJ, Klain M. Tobacco smoking: impairment of experimental flap survival. *Ann Plast Surg*. 1984;13(6):468-472.
24. Craig S, Rees TD. The effects of smoking on experimental skin flaps in hamsters. *Plast Reconstr Surg*. 1985;75(6):842-846.
25. Lawrence WT, Murphy RC, Robson MC, Heggers JP. The detrimental effect of cigarette smoking on flap survival: an experimental study in the rat. *Br J Plast Surg*. 1984;37(2):216-219.
26. Nolan J, Jenkins RA, Kurihara K, Schultz RC. The acute effects of cigarette smoke exposure on experimental skin flaps. *Plast Reconstr Surg*. 1985;75(4):544-551.
27. Yaffe B, Cushin BJ, Strauch B. Effect of cigarette smoking on experimental microvascular anastomoses. *Microsurgery*. 1984;5(2):70-72.
28. Forrest CR, Xu N, Pang CY. Evidence for nicotine-induced skin flap ischemic necrosis in the pig. *Can J Physiol Pharmacol*. 1994;72(1):30-38.
29. Forrest CR, Pang CY, Lindsay WK. Dose and time effects of nicotine treatment on the capillary blood flow and viability of random pattern skin flaps in the rat. *Br J Plast Surg*. 1987;40(3):295-299.
30. Falcone RE, Ruberg RL. Pharmacologic manipulation of skin flaps: lack of effect of barbiturates or nicotine. *Plast Reconstr Surg*. 1980;66(1):102-104.
31. Martin JW, Mousa SS, Shaker O, Mousa SA. The multiple faces of nicotine and its implications in tissue and wound repair. *Exp Dermatol*. 2009;18(6):497-505.
32. Ng KK, Awad N, Brook MA, Holloway AC, Sheardown H. Local delivery of nicotine does not mitigate fibrosis but may lead to angiogenesis. *J Biomater Appl*. 2011;26(3):349-358.
33. Sørensen LT, Nielsen HB, Kharazmi A, Gottrup F. Effect of smoking and abstention on oxidative burst and reactivity of neutrophils and monocytes. *Surgery*. 2004;136(5):1047-1053.
34. Jacobi J, Jang JJ, Sundram U, Dayoub H, Fajardo LF, Cooke JP. Nicotine accelerates angiogenesis and wound healing in genetically diabetic mice. *Am J Pathol*. 2002;161(1):97-104.
35. Morimoto N, Takemoto S, Kawazoe T, Suzuki S. Nicotine at a low concentration promotes wound healing. *J Surg Res*. 2008;145(2):199-204.
36. Jensen JA, Goodson WH, Hopf HW, Hunt TK. Cigarette smoking decreases tissue oxygen. *Arch Surg*. 1991;126(9):1131-1134.
37. Hopf HW, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg*. 1997;132(9):997-1004.
38. Sørensen LT, Jørgensen S, Petersen LJ, et al. Acute effects of nicotine and smoking on blood flow, tissue oxygen, and aerobe metabolism of the skin and subcutis. *J Surg Res*. 2009;152(2):224-230.
39. Fulcher SM, Koman LA, Smith BP, Holden M, Smith TL. The effect of transdermal nicotine on digital perfusion in reformed habitual smokers. *J Hand Surg Am*. 1998;23(5):792-799.
40. Netscher DT, Wigoda P, Thornby J, Yip B, Rappaport NH. The hemodynamic and hematologic effects of cigarette smoking versus a nicotine patch. *Plast Reconstr Surg*. 1995;96(3):681-688.
41. Warner DO, Joyner MJ, Charkoudian N. Nicotine increases initial blood flow responses to local heating of human nonglabrous skin. *J Physiol*. 2004;559(pt 3):975-984.
42. Sørensen LT, Jorgensen LN, Zillmer R, Vange J, Hemmingsen U, Gottrup F. Transdermal nicotine patch enhances type I collagen synthesis in abstinent smokers. *Wound Repair Regen*. 2006;14(3):247-251.
43. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. *Ann Surg*. 2003;238(1):1-5.
44. Sørensen LT, Toft B, Rygaard J, Ladelund S, Teisner B, Gottrup F. Smoking attenuates wound inflammation and proliferation while smoking cessation restores inflammation but not proliferation. *Wound Repair Regen*. 2010;18(2):186-192.
45. Sørensen LT, Toft BG, Rygaard J, et al. Effect of smoking, smoking cessation, and nicotine patch on wound dimension, vitamin C, and systemic markers of collagen metabolism. *Surgery*. 2010;148(5):982-990.
46. Glassman SD, Anagnost SC, Parker A, Burke D, Johnson JR, Dimar JR. The effect of cigarette smoking and smoking cessation on spinal fusion. *Spine (Phila Pa 1976)*. 2000;25(20):2608-2615.
47. Hadley MN, Reddy SV. Smoking and the human vertebral column: a review of the impact of cigarette use on vertebral bone metabolism and spinal fusion. *Neurosurgery*. 1997;41(1):116-124.
48. Andersen T, Christensen FB, Laursen M, Høy K, Hansen ES, Bünger C. Smoking as a predictor of negative outcome in

lumbar spinal fusion. *Spine (Phila Pa 1976)*. 2001;26(23):2623-2628.
49. Deguchi M, Rapoff AJ, Zdeblick TA. Posterolateral fusion for isthmic spondylolisthesis in adults: analysis of fusion rate and clinical results. *J Spinal Disord*. 1998;11(6):459-464.
50. Mooney V, McDermott KL, Song J. Effects of smoking and maturation on long-term maintenance of lumbar spinal fusion success. *J Spinal Disord*. 1999;12(5):380-385.
51. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. *BMJ*. 1997;315(7112):841-846.
52. W-Dahl A, Toksvig-Larsen S. Cigarette smoking delays bone healing: a prospective study of 200 patients operated on by the hemicallotasis technique. *Acta Orthop Scand*. 2004;75(3):347-351.
53. Schmitz MA, Finnegan M, Natarajan R, Champine J. Effect of smoking on tibial shaft fracture healing. *Clin Orthop Relat Res*. 1999;365:184-200.
54. Abidi NA, Dhawan S, Gruen GS, Vogt MT, Conti SF. Wound-healing risk factors after open reduction and internal fixation of calcaneal fractures. *Foot Ankle Int*. 1998;19(12):856-861.
55. Kwiatkowski TC, Hanley EN Jr, Ramp WK. Cigarette smoking and its orthopedic consequences. *Am J Orthop (Belle Mead NJ)*. 1996;25(9):590-597.
56. Kyrö A, Usenius JP, Aarnio M, Kunnamo I, Avikainen V. Are smokers a risk group for delayed healing of tibial shaft fractures? *Ann Chir Gynaecol*. 1993;82(4):254-262.
57. Scolaro JA, Schenker ML, Yannascoli S, Baldwin K, Mehta S, Ahn J. Cigarette smoking increases complications following fracture: a systematic review. *J Bone Joint Surg Am*. 2014;96(8):674-681.
58. Fung YK, Iwaniec U, Cullen DM, Akhter MP, Haven MC, Timmins P. Long-term effects of nicotine on bone and calciotropic hormones in adult female rats. *Pharmacol Toxicol*. 1999;85(4):181-187.
59. Broulik PD, Jaráb J. The effect of chronic nicotine administration on bone mineral content in mice. *Horm Metab Res*. 1993;25(4):219-221.
60. Yuhara S, Kasagi S, Inoue A, Otsuka E, Hirose S, Hagiwara H. Effects of nicotine on cultured cells suggest that it can influence the formation and resorption of bone. *Eur J Pharmacol*. 1999;383(3):387-393.
61. Daftari TK, Whitesides TE Jr, Heller JG, Goodrich AC, McCarey BE, Hutton WC. Nicotine on the revascularization of bone graft: an experimental study in rabbits. *Spine (Phila Pa 1976)*. 1994;19(8):904-911.
62. Riebel GD, Boden SD, Whitesides TE, Hutton WC. The effect of nicotine on incorporation of cancellous bone graft in an animal model. *Spine (Phila Pa 1976)*. 1995;20(20):2198-2202.
63. Feitelson JB, Rowell PP, Roberts CS, Fleming JT. Two week nicotine treatment selectively increases bone vascular constriction in response to norepinephrine. *J Orthop Res*. 2003;21(3):497-502.
64. Galatz LM, Silva MJ, Rothermich SY, Zaegel MA, Havlioglu N, Thomopoulos S. Nicotine delays tendon-to-bone healing in a rat shoulder model. *J Bone Joint Surg Am*. 2006;88(9):2027-2034.
65. Silcox DH III, Boden SD, Schimandle JH, Johnson P, Whitesides TE, Hutton WC. Reversing the inhibitory effect of nicotine on spinal fusion using an osteoinductive protein extract. *Spine (Phila Pa 1976)*. 1998;23(3):291-296.
66. Silcox DH III, Daftari T, Boden SD, Schimandle JH, Hutton WC, Whitesides TE Jr. The effect of nicotine on spinal fusion. *Spine (Phila Pa 1976)*. 1995;20(14):1549-1553.
67. Wing KJ, Fisher CG, O'Connell JX, Wing PC. Stopping nicotine exposure before surgery: the effect on spinal fusion in a rabbit model. *Spine (Phila Pa 1976)*. 2000;25(1):30-34.
68. Raikin SM, Landsman JC, Alexander VA, Froimson MI, Plaxton NA. Effect of nicotine on the rate and strength of long bone fracture healing. *Clin Orthop Relat Res*. 1998;353:231-237.
69. Theiss SM, Boden SD, Hair G, Titus L, Morone MA, Ugbo J. The effect of nicotine on gene expression during spine fusion. *Spine (Phila Pa 1976)*. 2000;25(20):2588-2594.
70. Broulik PD, Rosenkrancová J, Růzicka P, Sedlácek R, Kurcová I. The effect of chronic nicotine administration on bone mineral content and bone strength in normal and castrated male rats. *Horm Metab Res*. 2007;39(1):20-24.
71. Hastrup SG, Chen X, Bechtold JE, et al. Effect of nicotine and tobacco administration method on the mechanical properties of healing bone following closed fracture. *J Orthop Res*. 2010;28(9):1235-1239.
72. Balatsouka D, Gotfredsen K, Lindh CH, Berglundh T. The impact of nicotine on osseointegration: an experimental study in the femur and tibia of rabbits. *Clin Oral Implants Res*. 2005;16(4):389-395.
73. Balatsouka D, Gotfredsen K, Sørensen L, Lindh CH, Berglundh T. Effect of systemic administration of nicotine on healing in osseous defects: an experimental study in rabbits; part II. *Clin Oral Implants Res*. 2006;17(5):488-494.
74. Skott M, Andreassen TT, Ulrich-Vinther M, et al. Tobacco extract but not nicotine impairs the mechanical strength of fracture healing in rats. *J Orthop Res*. 2006;24(7):1472-1479.
75. Rothem DE, Rothem L, Dahan A, Eliakim R, Soudry M. Nicotinic modulation of gene expression in osteoblast cells, MG-63. *Bone*. 2011;48(4):903-909.
76. Rothem DE, Rothem L, Soudry M, Dahan A, Eliakim R. Nicotine modulates bone metabolism-associated gene expression in osteoblast cells. *J Bone Miner Metab*. 2009;27(5):555-561.
77. Gullihorn L, Karpman R, Lippiello L. Differential effects of nicotine and smoke condensate on bone cell metabolic activity. *J Orthop Trauma*. 2005;19(1):17-22.
78. Møller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet*. 2002;359(9301):114-117.
79. Musallam KM, Rosendaal FR, Zaatari G, et al. Smoking and the risk of mortality and vascular and respiratory events in patients undergoing major surgery. *JAMA Surg*. 2013;148(8):755-762.
80. Benowitz NL, Zevin S, Jacob P III. Sources of variability in nicotine and cotinine levels with use of nicotine nasal spray, transdermal nicotine, and cigarette smoking. *Br J Clin Pharmacol*. 1997;43(3):259-267.
81. Ruiz-Bailén M, de Hoyos EA, Reina-Toral A, Torres-Ruiz JM, Alvarez-Bueno M, Gómez Jiménez FJ. Paradoxical effect of smoking in the Spanish population with acute myocardial infarction or unstable angina: results of the ARIAM Register. *Chest*. 2004;125(3):831-840.
82. Mahmarian JJ, Moyé LA, Nasser GA, et al. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. *J Am Coll Cardiol*. 1997;30(1):125-130.
83. Puura A. Transdermal nicotine increases heart rate after endotracheal intubation. *Methods Find Exp Clin Pharmacol*. 2003;25(5):383-385.