

# Review of alternative practices to cigarette smoking and nicotine replacement therapy: how safe are they?

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## Abstract

Most adverse health effects of cigarette smoking are attributed to the products of combustion. Efforts to avoid the adverse health effects of cigarette smoking have led to the promotion of alternative products that are perceived to be less harmful. In this paper, we review the available literature for evidence of the effectiveness of the products commonly presented as alternatives to cigarette smoking, and discuss evidence-based information on whether they should be promoted as safe alternatives for long-term use or are effective as cessation aid. Water pipe smoking is becoming prevalent among young people and the electronic cigarette has been recently introduced as smoking alternative in smoke-free areas. Available limited data suggest that while smokers may perceive these alternatives as safer than cigarette smoking, they contain toxic substances and therefore are not harmless alternatives.

Data on herbal products are not easily available and where they are, evidence shows that these products are also not effective alternatives. Smokeless tobacco products vary in composition and health effects worldwide. The available literature suggests that these products may be associated with adverse health outcomes and that they cannot be promoted as 'safe' alternative tobacco products. Nicotine replacement therapy (NRT) formulations, such as chewing gums and skin patches, have been well studied and evidence suggests that all forms are effective smoking cessation aids, either used alone and in combination with other NRT or cessation medication and behavioural therapy. Primary care physicians should therefore only offer NRT to smokers who are willing to quit in combination with behavioural therapy or other cessation medications approved by the South African Medicines Control Council.

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## Introduction

The 2003 South African Demography and Health Survey (SADHS) estimated that 35% and 10% of men and women, respectively, smoked cigarettes.<sup>1</sup> Most of the adverse health effects of cigarette smoking are attributable to exposure to the products of combustion and less so to the nicotine content of cigarettes. It is well established that cessation of smoking improves health outcomes; hence, the best intervention is to cease cigarette smoking completely. However, nicotine in tobacco is very addictive, such that while most smokers want to quit and will make several attempts to quit smoking, only a few will succeed in the long term.<sup>2,3</sup>

The desire to avoid the adverse health effects of cigarette smoking has led to search and advocacy for alternative substances perceived to be less harmful than cigarette smoking. The ideal alternative to cigarette smoking should be safe to use, effectively provide nicotine, prevent the

occurrence of withdrawal symptoms and reduce the risk of harm to users and those around them. However, such ideal alternatives do not exist. Furthermore, the effectiveness and health effects of the available alternatives, other than those associated with nicotine replacement medications, are not well studied, and in some cases available evidence suggests that they may have adverse health effects. Promoting ineffective nicotine-containing alternatives carries the risk of encouraging nicotine dependence and may serve as a gateway through which new smokers are recruited. More importantly, inasmuch as these alternative products may sustain nicotine addiction among those who may have otherwise quit cigarette smoking because of health concerns or the inconvenience of not being able to smoke in public places, these alternatives may delay or prevent attempts at quitting cigarette smoking as they are often marketed for 'situational use' (i.e. where smoking is not allowed).

This article reviews available evidence regarding the effectiveness and safety of common alternative practices to cigarette smoking with the aim of providing primary care practitioners with essential information, based on which decisions could be made when caring for patients who smoke cigarettes. Health care providers' lack of knowledge about products marketed as alternative nicotine-delivery devices to cigarette smoking may lead to the provision of wrong advice, which may prevent smokers who are contemplating quitting from utilising effective therapies.

## Alternative practices to cigarette smoking

### Water pipe smoking

The water pipe is also known as the hubbly bubbly, *narghile*, *hookah*, *seesha* or *sissha*. This old recreational tobacco smoking device is commonly used in the Arab world and its origin dates back to several centuries ago in India, where it was used to smoke opium before the introduction of tobacco to the region.<sup>4,5</sup> There is renewed interest in this ancient practice both in the Arab world and the West, where it has become fashionable among young adults as a form of entertainment and leisure.<sup>6,7,8</sup> Because it promotes a sense of cultural identity and cohesiveness, this habit is socially acceptable and is not seen as dangerous.<sup>9</sup>

Using data from a repeat of the Global Youth Tobacco Survey, Warren et al<sup>10</sup> reported an increase in the prevalence of forms of tobacco use other than cigarette smoking in 34 of 100 global sites. The increase in prevalence at these sites was mostly due to water pipe smoking. Other reports suggest that up to 25% of university students in the Western

world engage in water pipe smoking and about 35% of students who smoke water pipe in a British university also smoke cigarettes.<sup>11,12</sup> Water pipe smoking can act as a 'gateway' to cigarette smoking, but whether this habit predated cigarette smoking in this group was not explored.

Modern narghiles (see Figure 1) have four components: a large glass bottle similar to a decanter that is partly filled with water, a length of metal tubing that is fixed to the neck of the bottle, a small clay container on which damp tobacco is tightly packed and a flexible

leather or rubber pipe that is attached to an aperture in the side of the bottle with a carved tip through which smoke can be drawn.<sup>4</sup> In water pipe smoking, heated pieces of charcoal are placed on packed tobacco and the smoke generated is drawn through water, creating the characteristic bubbling sound.

The health effects of the hubbly bubbly have not been well studied, but there is a perception that as smoke is drawn through water, the filtration process removes dangerous particles in the smoke.<sup>13</sup> In line with this thought, a study reported that, despite knowing the dangers of water pipe smoking, more than 90% of water pipe smokers think that it is less addictive than cigarette smoking.<sup>5</sup> Similarly, university students interviewed in Birmingham, England, and Toronto, Canada on their beliefs on water pipe smoking reported that they did not think deeply about the health risks associated with it and reasoned that if no warning was apparent, it was probably safe.<sup>12</sup> This risky behaviour was reinforced by the fruity flavours of the preparations and the belief that water filters the dangerous elements during narghile smoking. There was therefore little incentive (if any) to quit since this form of tobacco smoking was perceived to be safe and not addictive.<sup>12,14</sup>

During water pipe smoking, a large number of particles are emitted, and given that water pipes can be smoked for several hours at a time (providing long-time exposure to tobacco smoke), the health risks associated with smoking a hubbly bubbly may not be any different from those of heavy cigarette smoking.<sup>13</sup> Analysis of the smoke from the water pipe shows that it contains significant levels of nicotine, tar, heavy metals and other toxicants.<sup>15,16</sup> Nicotine and cotinine (an alkaloid found in tobacco and a metabolite of nicotine) levels have also been reported to be as high as 250% and 120% of those found in cigarettes, respectively, following a session of water pipe smoking.<sup>5</sup> These observations are confirmed in another study,<sup>17</sup> that reported that relative to cigarette smoking, water pipe smoking was associated with a higher carbon monoxide output (CO increases of 23.9 ppm vs 2.7 ppm and COHb level of 3.9% vs 1.3%;  $p < 0.001$ ), similar blood nicotine levels and more smoke exposure. Similar results were found in a South African study in which higher levels of baseline COHb were reported among water pipe users than cigarette smokers (481.7% vs 39.9%;  $p < 0.001$ ).<sup>18</sup> Chemical analysis for aldehydes in water pipe smoke reveals that one smoking session produces many times the number of aldehydes found in cigarettes and raises concerns that narghile smoking may lead to the same respiratory diseases associated with cigarette smoking.<sup>19</sup> Despite these health risks, most water pipe smokers by virtue of the perception of harmlessness are not interested in quitting.<sup>9</sup>



Figure 1: Water pipe (hubbly bubbly)  
(Courtesy Google Images)

The risk of transmitting infections such as herpes simplex, because of shared mouthpieces, and exposure of friends and families to second-hand smoke have clinical and public health implications.<sup>14</sup> The perception of harmlessness may have informed the behaviour of pregnant women sampled in Beirut, among whom up to 25% smoke water pipes during pregnancy.<sup>15</sup> This raises serious health concerns, given the established link between adverse obstetric outcomes and exposure to the combusive products of tobacco, such as increased risk of spontaneous abortion.

Available evidence indicates that water pipe smoking may be as toxic as cigarette smoking and may predispose smokers to similar adverse health outcomes.<sup>19</sup> Furthermore, the large volume of side-stream smoke from water pipe smoking may expose non-smokers to higher levels of toxins than in cigarette smoking. It is logical at this point in time to regard water pipe smoking as a harmful behaviour until further studies prove otherwise.

### Electronic cigarette or e-cigarette

This is a battery-powered device that vaporises nicotine, flavouring and other chemical substances into inhalable vapour (see Figure 2), with a nicotine delivery capability that is much less than that of cigarette smoking.<sup>20</sup> The device was recently introduced by manufacturers from China and marketed as cessation aid and safe alternative to cigarette smoking in smoke-free areas. The poor nicotine delivery capability raises doubts about the suitability of the e-cigarette as an effective substitute for cigarette smoking. Since most of the adverse health effects of cigarette smoking are attributable to combusive products during smoking, the manufacturers of the e-cigarette claim that the vapour inhaled from it does not contain such harmful substances.<sup>20</sup> In May 2009, the Division of Pharmaceutical Analysis of the United States Food and Drug Administration (FDA) tested the contents of e-cigarette cartridges by two vendors (Njoy e-cigarette and Smoking Everywhere Electronic Cigarette, with Nicotrol Inhaler 10 mg used as control for some test methods).<sup>21</sup> Trace amounts (detectable but not measurable) of diethylene glycol (also found in cigarette smoke) were found in one of the 18 cartridges

tested. In addition, tobacco-specific nitrosamines (TSNAs) were detected in some of the cartridges tested that used tobacco flavouring. Further concerns were raised over inconsistent amounts of nicotine delivered when drawing on the device.<sup>21</sup> These initial FDA findings suggest that the e-cigarette exposes users to toxins and carcinogens similar to those associated with cigarette smoking.

In the past the tobacco industry negatively influenced smokers' motivation for cessation by introducing modified cigarettes (low tar or 'lights', mentholated, filtered, etc.), which prevented or delayed attempts to quit smoking.<sup>22</sup> The activities of the industry may not be different regarding the e-cigarette. The recent court ruling that the FDA does not have the authority to regulate the e-cigarette in the US as a drug or delivery system may be yet another effort by the industry to avoid scientific scrutiny and allow this product to be marketed without prior rigorous clinical trials.<sup>23</sup> While the e-cigarette may have the potential to be an NRT device, exposure to toxic substances and the absence of adequate scientific scrutiny have caused the WHO study group (WHO, 2009)<sup>20</sup> to recommend that electronic nicotine delivery devices, including the e-cigarette, not be promoted as a safe alternative to cigarette smoking.

### Herbal cigarettes and other nicotine source products

Many smokers report they will use herbal products, with or without tobacco, as an alternative treatment, motivated by a general interest in 'natural' products, the perceived lack of efficacy and side effects of conventional tobacco dependence treatment medications and the high costs of currently available smoking cessation aids.<sup>24</sup> Many naturally occurring herbal and non-herbal products have been suggested as smoking alternatives that aid in cessation, but their efficacy has not been verified in clinical trials. Where data exist, as in the case of lobeline, a Cochrane review found no evidence of the efficacy of these alternatives.<sup>25</sup> Other non-herbal products that contain nicotine and flavourings have been marketed as cessation aids and alternatives to cigarette smoking in Europe, the USA and Asia.<sup>26</sup> Despite the claims of effectiveness, there is no documented evidence of efficacy for most of them. In light

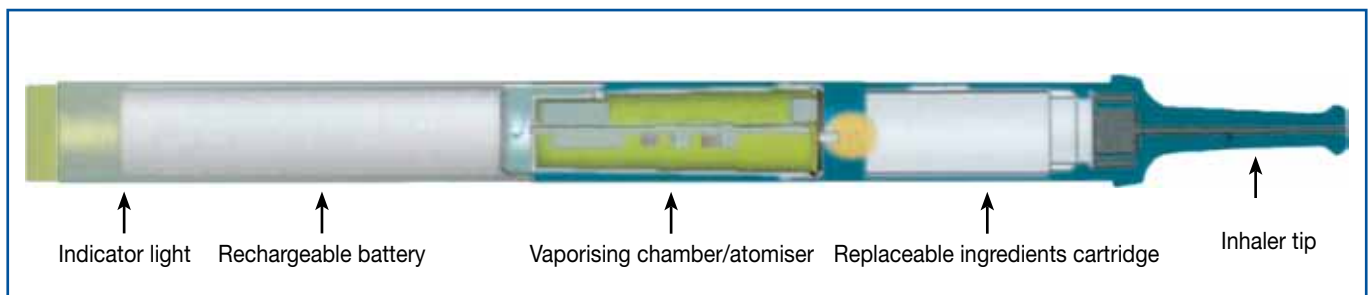


Figure 2: Electronic or e-cigarette

(Courtesy: WHO Report on the scientific basis of tobacco product regulation: third report of a WHO study group. WHO2009;955:5)<sup>20</sup>

of the lack of documented efficacy, these products cannot be promoted as effective alternatives to cigarette smoking. They may divert the focus of smokers, wishing to quit, from approved methods such as NRT and delay attempts to quit.

### Smokeless tobacco

Smokeless tobacco (SLT) is non-smoked tobacco, used (intranasally or intraorally) mainly as snuff (dry, moist and fine cut) or as chewed tobacco leaves (loose leaf, plug and twist).<sup>27</sup> The constituents of SLT vary according to the region of the world, producing varying adverse health effects in different areas. The 2003 SADHS estimated that 12% of women and 3% of men respectively were users of SLT,<sup>1</sup> while a study published in 2005 estimated the prevalence of SLT use among rural black women to be 28.1%.<sup>28</sup> Traditional, homemade SLT is commonly used in the rural areas of South Africa, prepared with different local additives.<sup>29</sup> Industrially made SLT is also used, mostly in the urban areas. The nicotine delivery capacity of SLT products in South Africa has been shown to be high and varied from low values consistent with that of snus (a form of SLT used in Sweden) to very high levels, as found in toombak in Sudan.<sup>30</sup>

SLT users find it difficult to quit,<sup>30</sup> and reports project that about 60% of people who start using snus to quit cigarette smoking will become chronic users.<sup>31</sup> This addictive property of nicotine in SLT, coupled with the development of withdrawal symptoms during cessation, underscores why NRT has been advocated as cessation aids for SLT users, just as for cigarette smokers.<sup>32</sup> The consideration of SLT as an alternative to cigarette smoking is based on the premise that switching to SLT reduces the health risks of smokers, effectively replaces nicotine and does not act as a gateway to smoking.<sup>33</sup> Snus has long been promoted as a harm-reduction substance, and reports suggest that this has resulted in significant reduction in the prevalence of cigarette smoking in countries such as Sweden and Norway with less risk for adverse health outcomes.<sup>34</sup> Similarly, SLT has been reportedly used for cessation purposes in the USA and this report found that about 1/3 of current SLT users in the survey were ex-smokers with up to 7% of ex-smokers having used SLT to quit cigarette smoking.<sup>35</sup> Additionally, SLT users were three times more likely to report being ex-smokers in this survey. Two other intervention trials in the USA and Denmark also suggest that switching to SLT may be efficacious only on a short-term basis (six months) when combined with group support.<sup>36</sup> In these trials, there was no evidence to support the long-term effectiveness of SLT as cessation aid. Data regarding its effectiveness as an alternative and cessation aid are not available from other regions.

The association of increased alcohol consumption with SLT use and vice versa has been documented among young

adolescents in Sweden (OR = 16.7; CI: 12.9–21.7).<sup>36</sup> In South Africa, a similar association was found in dual users of cigarettes and SLT, who were more likely to be binge drinkers, among other undesirable behaviours (OR = 3.7; CI: 2.1–6.6).<sup>37</sup> Though not a causal link, this association raises a public health concern in South Africa where alcohol use is already a public health challenge.

Several other adverse health outcomes have been linked to SLT use and these risks tend to be lower than those associated with cigarette smoking.<sup>38</sup> These risks vary and depend on the type of SLT in a specific region of the world. As an example of the effects of the regional differences in SLT, although SLT was associated with higher blood pressure, hypertension was not significantly associated with snuff use in a study of black South African women.<sup>39</sup> SLT use in India was, however, found to be significantly associated with diastolic hypertension.<sup>40</sup> Apart from increased risks for cancer, poor pregnancy outcomes, nicotine dependence and periodontal diseases, SLT use may predispose people to increased risks for chronic bronchitis and tuberculosis infections.<sup>41</sup> Despite these findings in Africa and Asia, studies conducted especially in Europe among male snus users have found lower risks for hypertension and oral cancer. The conflicting findings make it difficult to extrapolate results from one region of the world to the other, where differences in SLT constituents and additives exist. Furthermore, these modern products have been on the market for too short a time for there to be any convincing epidemiological support for a lower cancer risk among their users as compared to users of traditional SLT products.

Therefore, to the extent that studies conducted in South Africa and in similar settings have shown adverse outcomes, SLT use cannot be regarded as a safe alternative to cigarette smoking in South Africa. In the presence of safer and well-studied NRT, it is an ethical misnomer to advocate the use of a more toxic alternative, especially in Africa and Asia where there is reasonable evidence that the local SLT products are different from snus.

### Nicotine replacement therapy

NRT products, by virtue of their small nicotine content, provide a small amount of nicotine and in so doing reduce craving and help limit the symptoms and discomfort of nicotine withdrawal. These properties of NRT facilitate the smoking cessation process, including reduction of the discomfort associated with withdrawal, increasing the odds of significant smoking reduction<sup>42,43</sup> and eventual quitting. Despite nicotine's being a vasoconstrictor, NRT has been found to be a safe cessation aid, even in pregnancy.<sup>44</sup>

NRT is the most used cessation aid,<sup>45</sup> and is commonly available in the form of nicotine gum (2 mg and 4 mg doses),

inhalers (used as 10 mg), patches (used 21–42 mg per day), lozenges (used as 9–20 per day) and nasal sprays.<sup>46</sup> All of these have been shown by different studies to significantly improve quitting rates and reduce the number of cigarettes consumed, both alone and more significantly when combined with other cessation interventions.<sup>45,47</sup> A Cochrane review indicated that all commercially available forms of NRT improved quitting rates by 50–70%, regardless of the intensity of additional support or duration of therapy (RR = 1.58; 95% CI: 1.50–1.66).<sup>48</sup> In this systematic review, the 4 mg gum was more effective than the 2 mg gum among highly dependent cigarette smokers in improving quitting rates, but larger doses did not offer additional benefits. Other meta-analyses showed that the use of NRT resulted in a six-month abstinence rate twice that of smokers on placebo (RR = 2.06; 95% CI: 1.34–3.15).<sup>49,50,51</sup> In South Africa, NRT is mainly available in the form of patches, gum and lozenges.

One piece of nicotine gum chewed slowly and intermittently 'parked' and rubbed against the cheek will release about 90% of available nicotine over one hour. Under-dosing is therefore usually a result of chewing too few pieces of gum. A nicotine patch, however, allows sustained release of nicotine over 16 to 24 hours and provides a basal amount of nicotine. Since the serum nicotine concentration achieved with the patch is less than that associated with smoking, use of the patch may lead to craving. It is therefore advisable to combine its use with other intervention modalities. When combined with other intervention modalities, subtherapeutic dosing, which predisposes the person to treatment failure, may be avoided.<sup>43</sup> When a nicotine patch was used as pretreatment before cessation in a South African study, early withdrawal symptoms were not reduced but sustained abstinence was significantly increased among the intervention group compared to the placebo group (22% vs 12%;  $p = 0.03$ ).<sup>52</sup>

The nicotine inhaler is more of a puffer than an inhaler. Absorption of nicotine is mainly through the oral cavity and this results in a slow onset of action.<sup>43</sup>

Nicotine micro-tablets and lozenges are used sublingually and orally respectively. The lozenge appears to be very effective and has been reported to result in higher abstinence rates compared to other NRTs.<sup>53</sup> This is probably because it delivers more nicotine than the other forms of NRT and should therefore be cautiously used in combination with other forms of NRT to avoid overdosing.

Nicotine mouth spray is available in a few countries, providing fast delivery of nicotine, and has been reported to be preferred over the gum and inhaler in a study conducted among South African healthy smokers who were willing to quit.<sup>52</sup> Its use was associated with more local adverse effects, which were mostly burning of the tongue/throat, nausea and hiccups.<sup>54</sup> Despite the low nicotine dosage per actuation (1 mg/actuation), the six-month abstinence

rate was not significantly different compared to the other formulations ( $p$  values > 0.05).<sup>54</sup>

NRT formulations should be used at effective doses for up to eight weeks and then tapered off. Side-effects associated with NRT include nausea, hiccups, sore jaw, abdominal upset, dizziness, sleep disturbances and rash at the site where the patch is applied.<sup>55</sup> Nicotine gum is not suitable for patients with dentures and its use in patients with peptic ulcers is also contraindicated. Care needs to be exercised with its use in patients with unstable coronary artery disease.

Using combinations of NRTs or combining NRT with other cessation interventions also improves abstinence rates.<sup>56</sup> Smokers who have tried quitting and failed with a single NRT may therefore use a combination such as a nicotine patch supplemented with gum or lozenges, which significantly increased the likelihood of abstinence (likelihood ratio = 1.42; 95% CI: 1.14–1.76).<sup>44</sup> The combination of NRT with bupropion (a dopaminergic-adrenergic antidepressant effective for smoking cessation) also improved abstinence rates,<sup>57,58</sup> but this was not confirmed in a study of smoking alcoholics, in which, although NRT alone increased abstinence, the addition of bupropion did not improve smoking outcomes and up to 1/3 of participants had discontinued bupropion by the fourth week.<sup>58</sup> In the group that discontinued, alcohol intake was increased, possibly because of increased insomnia. In another study of combination therapies, compared to NRT alone, there was no significant difference in the six months abstinence rate when NRT was combined with nortriptyline. Although nortriptyline is effective when used alone (RR = 1.34; 95% CI: 0.97–1.86), potential side-effects limit its use as a first-line cessation aid.<sup>59</sup>

Smokers are often asked by their health care providers to use NRT on a regular basis (*ad libitum*) with the hope that this will increase the number of smokers that successfully quit. The issue of high cost could have an influence on the frequency of NRT usage in developing countries, as efforts to minimise cost could make per demand usage preferred over regular usage. It is reported that instructions given to patients to administer NRT in the form of nicotine nasal spray on a regular basis was not followed by patients.<sup>60</sup> Instead, patients used their nicotine nasal sprays frequently regardless of the instructions, and when compared to use only during craving, regular use did not improve smoking cessation rates at six months (RR = 0.69; 95% CI: 0.34–1.39).<sup>60</sup>

Genetics, including variability in genotypes of genes encoding nicotinic acetylcholine receptors, influences vulnerability to nicotine addiction, smoking patterns and the handling of NRT. Race and female genotypes have thus been reported to influence the effectiveness of nicotine

patches and other NRT.<sup>3,61</sup> While NRT was found to be more effective than a placebo among non-white heavy smokers (as compared to whites), highly dependent non-white smokers, who smoke within 30 minutes of awakening have high salivary cotinine levels and smoke mentholated cigarettes, tend to find it difficult to quit regardless of the number of cigarettes smoked per day.<sup>61</sup> This suggests that assessing the degree of nicotine addiction and the type of cigarette, smoked may be important considerations when providing cessation treatments to non-white smokers. Yudkin et al suggested that the effectiveness of nicotine patches may vary with genotypes, based on their findings that women with variant T allele of the dopamine D2 receptor (DRD232806) benefited while those with genotype CC did not. In men, there was no variation of effectiveness with genotype. This suggests that nicotine patches may work through different processes and may be subject to different genetic influences in men compared to women.<sup>62</sup>

General medical practitioners' perceptions have been reported to affect their intention to prescribe NRT. Although they perceive NRT as effective, this effectiveness was believed to be critically dependent on behavioural support<sup>63</sup> and was a predictor of their intention to prescribe NRT. This belief could serve as a barrier to NRT being prescribed in that, in the absence of behavioural support, NRT may not be prescribed. However, providing general practitioners with training and support on smoking cessation activities could help address this barrier. All types of NRT should be promoted as smoking cessation aids because they are all effective and current evidence does not support the effectiveness of one over the other. Primary care physicians should therefore actively offer NRT to smokers contemplating quitting, as merely making NRT available as an easily accessible over-the-counter preparation (not needing prescription) has not been shown to increase quitting attempts or cessation rates.<sup>64</sup>

## Conclusion

There is little or no evidence that water pipe smoking, e-cigarettes and herbal products are effective alternatives to cigarette smoking. There are serious concerns that water pipes and e-cigarettes may contain carcinogenic and harmful products of combustion, although to a smaller extent than conventional cigarettes in the case of e-cigarettes. SLT forms and their associated health effects differ according to regions of the world, and their use has been associated with several adverse health outcomes, especially in Africa and Asia. For this reason and given the availability of safer alternatives, it is an ethical misnomer to advocate the use of SLT as a safe alternative to cigarette smoking in the South African context.

NRT products are effective and safe (alone or in combination) in reducing craving and withdrawal symptoms and improving quitting rates. While these products may not reduce relapse rates, primary care physicians should offer them to smokers who are willing to quit, in combination with behavioural support or other cessation medications approved by the South African Medicines Control Council.

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