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Nicotine delivery systems

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Over the past 20 years, medicinal nicotine has been used to aid smoking cessation, and has led to a significant increase in the number of smokers who successfully quit. This review describes currently available medicinal nicotine products, which include nicotine patch, gum, lozenge, nasal spray, inhaler and sublingual tablet, including their pharmacokinetics and recommended dosing. New developments in nicotine delivery that could further increase cessation rates include high-dose patches, rapid release gum, combined patch and acute forms, and several novel channels for nicotine delivery, such as nicotine drink, straw, lollipop and a pulmonary inhaler. New applications of existing and novel medicinal nicotine products may include relapse prevention, nicotine maintenance, temporary withdrawal management, reduced smoking and gradual quitting.

Keywords: gum, inhaler, lozenge, nasal spray, nicotine, patch, tablet, tobacco

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1. Introduction

The goal of tobacco control is to reduce the death and disease associated with tobacco use [1]. One major focus of these efforts has been to help smokers stop smoking. As smokers smoke primarily to get nicotine [2] and stopping smoking leads to the emergence of a nicotine withdrawal syndrome [3] that deters continued abstinence, an important therapeutic strategy has been to treat smokers with therapeutic doses of nicotine. In this paper, current nicotine medications (refered to as medicinal nicotine [MN]) are reviewed, and new developments in nicotine delivery systems and their clinical uses are discussed. Because this review is focused on forms of nicotine delivery rather than smoking cessation medications in general, we do not cover the use of other drugs or combinations of nicotine medications with other drugs. Combination treatments that have been studied include MN (i.e., nicotine patch) and bupropion sustained release, MN (i.e., nicotine patch) and mecamylamine, and MN (i.e., nicotine patch) and naltrexone [4].

MN has been available for abrupt smoking cessation since the late 1970s. Recently, the tobacco control community has begun to consider more varied uses of MN. Shiffman and colleagues have described several potential uses of MN to facilitate behaviour changes to reduce tobacco harm [1]. The following sections will discuss these potential uses, currently available products for each use, and what products are being developed, or could be developed, to further aid smokers.

2. Abrupt cessation

The most well-studied and well-documented pharmacological approach to help smokers quit is the therapeutic use of MN. Since the 1970s, hundreds of studies have been conducted on the safety, efficacy and mechanisms of action of this class of medications [4]. Nicotine medications enable the tobacco-dependent person to abstain from tobacco by replacing part of the nicotine formerly obtained from tobacco.

2.1 Current forms and usage

There are several MN products currently available and approved by regulatory authorities for abrupt cessation, including nicotine patch, gum, lozenge, nasal spray, inhaler and sublingual tablet. The doses and prescribed usage of these products have been summarised in **Table 1**. Usage instructions vary across countries and regulatory jurisdictions, and **Table 1** covers a sampling of these indications/jurisdictions. **Figure 1** shows the single-dose kinetics for many of the MN products discussed.

2.1.1 Patch

Nicotine patches are applied to the skin and deliver nicotine through the skin at a relatively steady rate. There are currently four patch formulations on the market that vary widely in their design, pharmacokinetics (PK) and duration of wear (i.e., 24- and 16-h wear). The diversity in patch systems has been described in reviews [5-7], differences in PK have been illustrated in a head-to-head clinical trial [8]; (see **Table 2** for PK profile data), and interindividual variability in plasma nicotine concentrations has been demonstrated [9]. All of the patch types are available in a range of dosages, and progressively lower doses are used to provide weaning over a period of several weeks or longer to enable gradual adjustment of their bodies to lower nicotine levels and ultimately to a nicotine-free state. Studies have not demonstrated that variations in this discontinuation procedure (gradual versus abrupt) differentially influences cessation. There is evidence, however, that the stepdown doses used during latter parts of the usage period provide significant symptom relief [10]. Some formulations and indications also provide for less dependent smokers to use a lower dose. The clinical significance of different patch formulations is not universally agreed.

Different patch formulations or regimens have seldom been compared. One study compared the ability of two different regimens to control craving and withdrawal symptoms during the first 2 weeks of abstinence among dependent smokers. In this study, 24-h wear of a 21-mg patch demonstrated superior control of craving and withdrawal symptoms compared with 16-h wear of a 15-mg patch [11].

Less definitive results have been observed with respect to abstinence [11,12]. For instance, in the study cited above [11], during a 2-week post-quit period, 24-h wear of a 21-mg patch yielded longer abstinence compared to 16-h wear of a 15-mg patch. In another study [12], 24-h wear of a 21-mg patch yielded similar abstinence rates to 16-h wear of a 15-mg patch. A very large study compared doses of 16-h wear patches and found that a 25-mg dose (whose blood levels are close to those of the 21-mg 24-h patch) was superior to the 15-mg dose [13].

The main advantage of the nicotine patch over acute MN formulations is that its use is uncomplicated: the patient simply places the patch on the body in the morning, rather than actively using a product throughout the day. For this reason, compliance with patch therapy tends to be higher than for other MN products [14]. The nicotine patch delivers nicotine more slowly than acute MN formulations, although nicotine plasma concentrations can get higher during the day with patch use than with acute MN use, especially if the patient does not use the acute MN product as many times during the day as recommended [5,15].

Importantly, nicotine patches do not seem to provide protection against acute craving provoked by smoking-related stimuli. Tiffany *et al.* and Waters *et al.* showed that even though nicotine patch reduced background craving compared with placebo, smokers on active patch experienced similar boosts of craving when exposed to a provocative stimulus [16,17]. Waters *et al.* also showed that wearing a nicotine patch had no effect on recovery from cue-provoked craving [17]. As cue-provoked craving appears to be a major factor in relapse [18], many authors (see Section 2.2.1.3) have suggested supplementing patch wear with acute dosing forms of MN, which are described below.

2.1.2 Acute dosing

There are several options available to smokers that, unlike the nicotine patch, allow them to self-administer a dose of nicotine on a regular and/or an 'as-needed' basis. These include nicotine gum, lozenge, sublingual tablet, oral inhaler and nasal spray. All of these products, except the nasal spray, deliver nicotine through the oral mucosa. Compliance is an issue with each of these products because the smoker must use the product multiple times daily to achieve an adequate dose, and underdosing is the single greatest clinical challenge for successful use of these products. Smokers rarely use the amounts indicated or recommended by the labelling. The clinical benefit of these MN products can be more than doubled when smokers dose with adequate frequency [19]. Multiple analyses have demonstrated that use of more doses is associated with clinical success [19,20], yet most users use far less of these MN products than is recommended by the product labels [21]. Users also discontinue product use sooner than recommended. For instance, the vast majority of nicotine gum and patch purchase episodes lasted only 1 month, even though both are indicated for 2 – 3 months of use [22]. Adequate dosing is deterred by several factors: the effort required, concerns about the cost of the products, smokers' unfounded concerns about nicotine safety, and the sensory characteristics of the products (e.g., taste and chewing qualities). Some of the acute dosing products were designed to be relatively unappealing because of initial concern about abuse liability.

Acute-dosing products have the benefit that both the amount and timing of doses can be titrated by the user. Thus, smokers with more nicotine tolerance or greater need can get a higher nicotine dose, and smokers who are experiencing acute adverse effects can scale back their intake. Control over the timing of self-dosing is also key because it enables smokers to use MN medications as 'rescue medication' when they encounter particularly strong cravings or threats to abstinence. This form of use requires some explanation.

Table 1. Medicinal nicotine product doses and uses

Product	Doses and allocation	Dosing and schedule	Approved location
Gum*			
Nicorette® (GSKCH; Pfizer)	2 mg: < 25 cpd	Maximum dose/day: 24 pieces Weeks 1 – 6: 1 piece every 1 – 2 h Weeks 7 – 9: 1 piece every 2 – 4 h Weeks 10 – 12: 1 piece every 4 – 8 h	US, OTC‡
	4 mg: ≥ 25 cpd	Same as above	
Nicorette® (Pfizer)	2 mg: ≤ 20 cpd	Maximum dose/day: 15 pieces Weeks 1 – 12: use as needed, 1 piece at a time After 12 weeks: reduce use and conclude when only 1 – 2 pieces/day	UK, GSL§
	4 mg: > 20 cpd	Same as above	
Nicorette® (Pfizer)	2 mg: < 20 cpd	Maximum dose/day: 20 pieces Weeks 1 – 12: 8 – 12 pieces/day Weeks 13 – 14: 4 – 6 pieces/day Weeks 15 – 16: 1 – 3 pieces/day, gradually reducing to 0	Australia, P¶
	4 mg: ≥ 20 cpd or prior 2-mg use	Maximum dose/day: 10 pieces Weeks 1 – 12: 4 – 6 pieces/day Weeks 13 – 14: 2 – 3 pieces/day Weeks 15 – 16: 1 – 2 pieces/day, gradually reducing to 0	
Nicotinell® (Novartis)	2 mg: < 20 cpd	Maximum dose/day: 25 pieces Weeks 1 – 12: 1 piece as needed, averaging 8 – 12 pieces/day After 12 weeks: reduce use daily until nicotine free	EU, GSL
	4 mg: > 20 cpd	Maximum dose/day: 15 pieces Dosing schedule same as above	
NiQuitin® (GSK)	2 mg: TTFC > 30 min	Weeks 1 – 12: 1 piece as needed, chewing between 8 – 12 pieces/day After 12 weeks: gradually reduce use to 1 – 2 pieces/day until nicotine free	UK, GSL
	4 mg: TTFC ≤ 30 min	Same as above	
Lozenge			
Commit™, NiQuitin®, Nicabate™ (GSKCH)	2 mg: TTFC > 30 min	Weeks 1 – 6: 1 lozenge every 1 – 2 h Weeks 7 – 9: 1 lozenge every 2 – 4 h Weeks 10 – 12: 1 lozenge every 4 – 8 h	US, OTC; UK, France, GSL
	4 mg: TTFC ≤ 30 min	Same as above	
Nicotinell®	1 mg	Weeks 1 – 12: 1 lozenge every 1 – 2 h After 12 weeks: reduce use daily until nicotine free	
***Patch**#*			
Habitrol® (Novartis)	7 mg 14 mg: ≤ 10 cpd 21 mg: > 10 cpd	> 10 cpd dosing schedule Weeks 1 – 4: 21 mg/day Weeks 5 – 6: 14 mg/day Weeks 7 – 8: 7 mg/day	US, OTC; UK GSL

*Generic gums (e.g., Perrigo, Watson) are available and follow the label of the 'innovator' product. ‡No prescription necessary. §Sold in retail outlets without a pharmacist. ¶No doctor's prescription necessary, but must be approved by a pharmacist. #Generic patches (e.g., Perrigo [former ProStep]) exist and follow the label of the 'innovator' product. **Prescription only.

cpd: Cigarettes per day; GSK: GlaxoSmithKline; GSKCH: GlaxoSmithKline Consumer Healthcare; GSL: General sales list; OTC: Over the counter; P: Pharmacy; Rx: Prescription only; TTFC: Time-to-first cigarette.

Table 1. Medicinal nicotine product doses and uses (continued)

Product	Doses and allocation	Dosing and schedule	Approved location
		≤ 10 cpd dosing schedule Weeks 1 – 6: 14 mg/day Weeks 7 – 8: 7 mg/day	
NicoDerm CQ®, NiQuitin CQ®, Nicabate® (GSKCH)	7 mg/day 14 mg/day: ≤ 10 cpd 21 mg/day: > 10 cpd	> 10 cpd dosing schedule Weeks 1 – 6: 21 mg/day Weeks 7 – 8: 14 mg/day Weeks 9 – 10: 7 mg/day	US, OTC; UK, Australia GSL
		≤ 10 cpd dosing schedule Weeks 1 – 6: 14 mg/day Weeks 7 – 8: 7 mg/day	
Nicotrol® 16-h patch (Pfizer)	5 mg 10 mg 15 mg: > 10 cpd	Weeks 1 – 6: 15 mg patch/day Weeks 7 – 8: 10 mg patch/day Weeks 9 – 10: 5 mg patch/day	US, OTC
Inhalator			
Nicotrol® Inhaler (Pfizer)		≤ 12 weeks (initial treatment): 6 – 16 cartridges/day	US, Rx**
Nicorette® Inhaler (Pfizer)		First 3 – 12 weeks: ≥ 6, but no more than12 cartridges/day Next 6 – 12 weeks: either stop altogether or gradually reduce the number of cartridges/day	CA, OTC
Sublingual tablet			
Nicorette® Microtab (Pfizer)	2 mg: 1 tablet every h < 20 cpd 2 mg: 2 tablets every h ≥ 20 cpd	Maximum doses/day: 40 tablets Minimum treatment duration: 12 weeks After 12 weeks: gradually reduce the number of tablets/day	UK, GSL
Nasal spray			
Nicotrol® (Pfizer)		Minimum doses/day: 8 sprays Recommended doses/h: 1 – 2 sprays Maximum doses/h: 5 sprays Maximum doses/day: 40 sprays Maximum duration of treatment: 12 weeks	US, Rx
Nicorette® (Pfizer)		Maximum dose/nostril/h: 2 sprays Maximum dose/day (24 h): 64 sprays Weeks 1 – 8: spray as needed, without exceeding maximum daily dose Weeks 9 – 10: reduce use by 50% Weeks 11 – 12: reduce use to none	UK, P

*Generic gums (e.g., Perrigo, Watson) are available and follow the label of the 'innovator' product. ‡No prescription necessary. §Sold in retail outlets without a pharmacist. ¶No doctor's prescription necessary, but must be approved by a pharmacist. #Generic patches (e.g., Perrigo [former ProStep]) exist and follow the label of the 'innovator' product. **Prescription only.

cpd: Cigarettes per day; GSK: GlaxoSmithKline; GSKCH: GlaxoSmithKline Consumer Healthcare; GSL: General sales list; OTC: Over the counter; P: Pharmacy; Rx: Prescription only; TTFC: Time-to-first cigarette.

Table 2. Pharmacokinetic profiles of three nicotine patches studied from 0 to 24 h.

Parameter	Pharmacia-Upjohn 15 mg (16 h)	Novartis 21 mg (24 h)	Alza 21 mg (24 h)
AUC_{0-24} (ng/ml h)	166 (54)	290* (108)	328*,‡ (144)
C_{max} (ng/ml)	11.9 (3.8)	17.6* (6.4)	21.9*,‡ (8.9)
C_{min} (ng/ml)	1.5 (1)	13* (5.8)	11.8* (5.7)
T_{max} (h)	6.5 (2.7)	10* (3.7)	3.8*,‡ (2.7)

Values shown are baseline adjusted means excluding outliers and (standard error). Adapted from Fant *et al.* [8].

*Significantly different from Pharmacia-Upjohn ($p < 0.05$). ‡Significantly different from Novartis ($p < 0.05$).

AUC: Area under the curve; C_{max}: Maximum concentration; C_{min}: Minimum concentration; T_{max}: Maximum time.

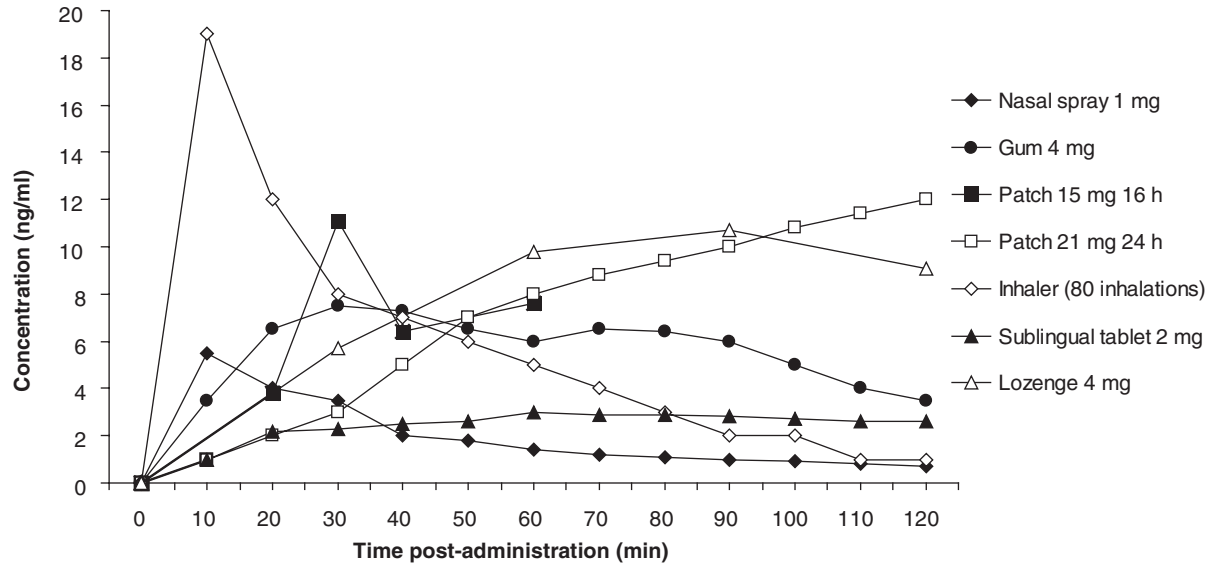

Figure 1. Venous blood concentrations in nanograms of nicotine per millimeter of blood as a function of time for various nicotine delivery systems. Data on nasal spray are from Schneider *et al.* [92]; data on gum are from Benowitz *et al.* [93]; data on patch are from Benowitz [15]; data on sublingual tablet are from Molander *et al.* [97]; data on lozenge are from Choi *et al.* [37]; data on inhaler are from Schneider *et al.* [96] and are based on 80 puffs in 20 min, a dosing regimen not typical of clinical use.

Abstinence from tobacco causes some tonic disruptions of function, including rises in overall levels of craving. This background level of craving is punctuated, however, by acute episodes of more intense craving [23]. These episodes of 'breakthrough craving' are typically provoked by situational stimuli, such as seeing someone smoke or experiencing emotional upset [24]. These acute craving episodes are particularly problematic and are associated with a very high risk of relapse [25]. Thus, an important application of acute MN products is for use as rescue medications to quickly reduce craving when such episodes threaten abstinence. The utility of this mode of use has been part of the rationale for acute dosing from the outset, and is now beginning to be empirically validated, as noted below.

2.1.2.1 Gum

The first MN that was made available to consumers was the transmucosally delivered nicotine polacrilex ('nicotine gum'). The gum is available in two doses: 2- and 4-mg, delivering ~ 1 and 2 mg, respectively [26]. Two product variants (e.g., Nicorette®, GlaxoSmithKline Consumer Healthcare; Nicotinell®, Novartis) and their dose and prescribed usage have been presented in **Table 1**. In highly dependent smokers, the 4-mg dose is clearly superior to the 2-mg gum [27,28]. In many countries, nicotine gum is available without a prescription, which has made the product much more widely available to consumers [5,21,29]. Mint- and fruit-flavoured gums have been marketed in an effort to increase compliance with use instructions among patients who found the original ('peppery') flavour to be unpalatable. More palatable forms are becoming available on the market, such as a flavoured coated gum that is sweeter and easier to chew.

Of the nicotine in gum ~ 50% is absorbed [26]. As smokers take in ~ 1 mg of nicotine per cigarette [30], a smoker using 2-mg gum would have to use as many gums as cigarettes in order to exactly parallel their baseline nicotine intake. A smoker using 4-mg gum would need to use a number of gums equal to half their smoking rate. Typical use does not approach these levels [31], therefore, most gum chewers do not match the daily nicotine levels achieved through the smoking of a cigarette. Furthermore, because of the relatively slow absorption of nicotine from gum compared with smoke inhalation, individual doses do not produce the extremely high arterial levels of nicotine produced by smoke inhalation [32]. Acidic beverages have been shown to interfere with buccal absorption of nicotine [33]; therefore, patients should avoid acidic beverages (e.g., soda, coffee and beer) for 15 min before and during chewing gum.

Shiffman *et al.* demonstrated that nicotine gum could reduce acute craving following exposure to a provocative stimulus [34]. Some initial reductions in craving are likely due to the behavioural effects of chewing gum [35]. However, after ~ 15 – 20 min of chewing, the nicotine itself begins to impact craving, and active gum significantly reduces craving compared with inactive gum. This suggests that smokers may be able to effectively use nicotine gum as a rescue medication when faced with acute threats to abstinence.

2.1.2.2 Lozenge

A 1-mg lozenge has been available in some European countries for some time; however, no efficacy data are available, and the efficacy of this low dose is in question. A newer nicotine lozenge, available in 2- and 4-mg formulations, has been approved in the US, Europe and Australia [19]. Like nicotine

Table 3. Multi-dose kinetics* of medicinal nicotine products.

Medicinal nicotine product	C_{max} (ng/ml)	T_{max} (mean h)	Dosing regimen
Nasal spray 1 mg (Pfizer) [202]	9	10.2	1 mg/h for 10 h
Gum 4 mg (GSKCH) [36]	32.2	13.5	4 mg/h (13 doses)
Patch 15 mg 16 h (Pfizer) [94]	13	8	15 mg/day dose
Patch 21 mg 24 h (GSKCH) [95]	23	4	21 mg/day dose
Inhaler (20 inhalations; Pfizer) [203]	40.4	10.3	80 inhalations over 20 min/h for 10 h
Sublingual tablet 2 mg (Pfizer) [97]	13.2	11.3‡	2 mg/h for 11 h (12 doses)
Lozenge 4 mg (GSK) [98]	34.9	13.6	4 mg every 60 min (13 doses)

*In multiple dosing studies, acute-use products are typically administered at the maximum frequency consistent with labelling, resulting in aggressive dosing that far exceeds what is typically seen in clinical use, making these values unrealistic projections of actual use PK parameters. ‡ Median T_{max}.
Cmax: Maximum concentration; GSK: GlaxoSmithKline; GSKCH: GlaxoSmithKline Consumer Healthcare; PK: Pharmacokinetic; Tmax: Maximum time.

gum, nicotine from the lozenge is absorbed slowly through the buccal mucosa and delivered into the systemic circulation. One advantage of the lozenge compared with gum is that chewing is not required. In addition, the amount of nicotine absorbed per lozenge appears to be somewhat higher than that delivered by gum. Single dose studies demonstrated 8 – 10% higher maximum concetration (C_{max}) values and 25 – 27% higher area under the curve ($AUC_{0-\infty}$) values from lozenges compared with gums at both 2- and 4-mg dose levels, which is probably due to the residual nicotine retained in the gum [36].

The indication for the lozenge allocates smokers to the 2- or 4-mg dose based on how soon after waking the first cigarette of the day is smoked, as described in **Table 1**. Time-to-first cigarette is considered a simple but powerful index of nicotine dependence [37] and thus a potentially useful way of determining each smoker's nicotine 'need'. This method results in the majority of US smokers being directed to the 4-mg dose. Prescribed lozenge use has been outlined in **Table 1**.

Analyses of data from the pivotal trial of the nicotine lozenge showed that it was effective even in smokers who had previously failed on another MN product [38] and that it was effective for both very heavy [39] and very light smokers [40]. Analyses also showed that smokers who used more lozenges were more likely to succeed in quitting [19].

2.1.2.3 Sublingual tablet

A small nicotine tablet has been developed and is currently being marketed in many European countries but is not yet available in the US. The product is designed to be held under the tongue, where the nicotine is absorbed sublingually over ~ 30 min. The product that is currently available contains 2 mg of nicotine, of which 1 mg is absorbed via the buccal mucosa. The sublingual tablet demands less activity from the user than gum and lozenge.

The levels of nicotine obtained by use of the 2-mg tablet and 2-mg nicotine gum are similar [41]. Multi-dose PK parameters of the 2-mg tablet have been presented in **Table 3**. Chewing and immediately swallowing the tablet decreased nicotine bioavailability in terms of rate and extent of delivery [41]. When the mouth was alkaline (after chewing antacid tablets) absorption was somewhat higher, and significantly more rapid than in a control condition and when the mouth was acidic (after drinking orange juice) [41]. Efficacy rates appear consistent with nicotine gum and lozenge, as do rates of adverse events, although they do differ somewhat qualitatively, as described below [42].

2.1.2.4 Inhaler

The nicotine vapour inhaler consists of a mouthpiece and a plastic cartridge containing nicotine. When the inhaler is 'puffed', nicotine is drawn through the mouthpiece into the mouth of the smoker. Each inhaler cartridge contains 10 mg of nicotine, of which 4 mg can be delivered and 2 mg are absorbed [43]. The product is not a true inhaler in that nicotine is not delivered to the bronchi or lungs but rather deposited and absorbed in the mouth, much like nicotine gum [44]. The majority of nicotine is delivered into the oral cavity (36%) and in the oesophagus and stomach (36%), with very little nicotine reaching the lung (4%) [44].

Nicotine delivery is related to the number and depth of inhalations. Labelling states that 80 deep puffs of the inhaler delivers 4 mg of nicotine; fewer or shallower puffs will deliver smaller amounts of nicotine. Further details on prescribed dosing appear in **Table 1**. Moreover, the amount of nicotine absorbed from the inhaler is temperature dependent, with higher temperatures delivering larger amounts of nicotine and lower temperatures delivering smaller amounts [45]. Thus, physicians should warn patients that using the product in very cold temperatures may not allow them to receive adequate amounts of nicotine; patients should keep the inhaler warm.

The vapour inhaler was designed to satisfy behavioural aspects of smoking, namely, the hand-to-mouth ritual. For some smokers, this may be a useful adjunct. Importantly, this mechanism has not been directly tested; indeed, for some smokers, this mechanism may act as a smoking cue that could undermine cessation.

2.1.2.5 Nasal spray

Nicotine nasal spay is marketed as a pharmacy-only medication in the UK, and is available only by prescription in the

US. The nasal spray was designed to deliver doses of nicotine to the smoker more rapidly than other MN products. The device is a multi-dose bottle with a pump that delivers 0.5 mg of nicotine per 50-µl squirt. Each dose consists of two squirts, one to each nostril. More detailed dosing information has been provided in **Table 1**.

Nicotine from the nasal spray is absorbed into the blood more rapidly than from gum [46]. Venous plasma concentrations after a single 1-mg dose range between 5 and 12 ng/ml. Multi-dose PK parameters are presented in **Table 3**. Venous plasma concentrations are considerably lower than tobacco product concentrations and fall within the range of the lower dose nicotine treatments (e.g., 2- versus 4-mg gum). According to labelling, the dose of nasal spray should be individualised for each patient based on the patient's level of nicotine dependence and the occurrence of symptoms of nicotine excess. Further labelling instructions have been provided in **Table 1**.

Nasal spray delivers nicotine relatively quickly (median arterial maximum time [T_{max}] = 5 min [47]). This rapid delivery may account for its greater subjective effects relative to other MN acute dosing forms. Being the MN form with the most rapid delivery, nasal spray is expected to deliver acute craving relief. A study by Hurt *et al.* suggests that a 1-mg dose of nicotine nasal spray can relieve spontaneous nicotine withdrawal symptoms, including craving, more rapidly than a single dose of 4-mg nicotine gum [48]. However, as the study did not include a provocative craving cue, the results are not definitive for efficacy against provoked craving.

There were initially concerns regarding the potential abuse liability of nicotine nasal spray. Despite these concerns, there appears to be little abuse liability associated with the formulation. In a small laboratory study, Schuh *et al.* found little evidence of 'liking' produced by the nasal spray, and only modest elevations on a measure of good drug effects [49]. Furthermore, the nasal spray engendered unpleasant effects of burning throat and nose, watery eyes, runny nose, coughing and sneezing, which may be expected to limit abuse liability.

2.1.3 Summary

Meta-analyses have revealed that, relative to placebo, all of the MN products discussed previously (nicotine patch, gum, lozenge, nasal spray, inhaler and sublingual tablet) are significantly more effective than placebo at producing smoking abstinence [50]. Moreover, although relative efficacy of MN products has seldom been assessed directly, the respective odds ratios for the gum, patch, nasal spray, inhaled nicotine and nicotine sublingual tablet/lozenge all fell within a range of 1.7 to 2.1 [50]. Both meta-analyses and direct comparative studies have concluded that, despite varying plasma nicotine concentrations (**Figure 1**), gum, patch, nasal spray and vapour inhaler appear to be equally efficacious [14,50-52].

Although these products are not indicated for long-term nicotine maintenance, some users report engaging in persistent use. It is estimated that ~ 6% of smokers who use the gum will use it for 6 months or more; this drops to 1% by 24 months [22]. Persistent use is lower for patch (0.05% for 6 months or more), perhaps because it does not lend itself to intermittent, situational use, and lacks immediate effects or links to behaviour. Most persistent users report that they are using the MN products to maintain abstinence from smoking [22]; authors have suggested that some smokers may need very long-term treatment with MN to avoid relapse to smoking [53]. A study of long-term gum use (5 years) showed no evidence of any harmful effects [54].

Generally, MN side effects are mild and topical, and are a function of the route and site of administration (e.g., firmness of gum, adhesiveness of patch; nasal and throat irritation associated with nasal spray use; hiccups, heartburn, or nausea associated with lozenge use). For example, some of the more commonly experienced side effects of nicotine gum use are jaw fatigue, and jaw and mouth soreness [55]. For the nicotine patch, local skin irritations are the most commonly reported side effect [55]. For nicotine nasal spray, the most common side effects are nasal and throat irritation [55]. For the vapour inhaler, burning sensations in the throat, as well as sneezing, coughing and hiccupping, are the most commonly reported side effects [55]. And for the lozenge, the most common side effects are mouth or throat irritation, hiccups, heartburn or stomach problems, such as nausea, particularly if the lozenge is chewed or swallowed [56].

As with other domains of pharmacotherapy, there is a looming revolution looking at individual differences in kinetics or drug response, whether by identifiable phenotype (e.g., gender, ethnicity) or by genotype (e.g.,cytochrome P450 2A6, which moderates the metabolism of nicotine [57], or dopamine D2 receptor, which affects dopamine receptors [58]). However, in the current state of scientific and clinical knowledge, the relevance of these relationships is somewhat speculative, especially with regards to their clinical implications. There are no tests demonstrating a clinical benefit of tailoring therapy based on such parameters, so this remains an area for future development rather than current practice.

In summary, a variety of MN medications have been demonstrated to be safe and effective in smoking cessation. Current medications have similar efficacy profiles, and it is generally recommended that choice of a particular form be guided by patient preference [14,50].

2.2 New developments

There are several new developments in nicotine delivery. These consist of improving the delivery from existing or slightly modified forms currently being used, and completely new formulations.

2.2.1 Improving delivery using current forms

2.2.1.1 High-dose patches

In typical use, none of the current MN formulations achieves nicotine levels like those seen during typical smoking, leading

to the idea that higher doses are needed. An early patch efficacy study demonstrated a dose–response curve for the nicotine patch, with increased efficacy for a 24-h 21-mg dose over a 14-mg dose [59]. Similarly, Tonnessen *et al.* demonstrated a modest benefit of increasing the dose of 16-h patches from 15 to 25 mg [13]. The tolerability of doses as high as 63 mg has been demonstrated [60]. Several high-dose patch regimens have been evaluated, typically in heavy smokers, who are presumed to most need higher dosing [15]. Results have been mixed. Jorenby *et al.* found a substantial increase in efficacy for 44- versus 22-mg patches but only under conditions of minimal contact [61]. However, Hughes *et al.* found no incremental benefit of increasing dose from 21 to 42 mg [62]. Taken together, these results suggest that transdermal nicotine doses of ≤ 44 mg provide, at best, modest improvements in treatment outcomes for highly dependent individuals.

2.2.1.2 Rapid-release gum

The authors have noted that an advantage of acute dosing forms is their potential as rescue medications when smokers face threats to abstinence. While a study of nicotine gum demonstrated the principle [63], it also suggested that the effect was relatively slow: nicotine effects were evident within 15 – 20 min, whereas acute cravings could lead to relapse in 10 min or less [25]. This suggests the need for faster delivery and faster onset of craving relief. A rapid-release gum has been formulated to provide biphasic nicotine delivery, starting with accelerated delivery to promote rapid craving relief and then levelling off to avoid overdosing [301,302]. This is accomplished through a combination of rapid initial release and buffering to increase pH to facilitate rapid absorption through the oral mucosa [301,302]. In a proof-of-principle study, Niaura *et al.* compared this rapid-release gum with the current gum formulation for rapid craving relief following a provocative stimulus [63]. The rapid-release gum achieved faster and more complete craving relief, differentiating itself from current nicotine gum within the first 3 min of use. The use of such a product to provide rapid craving relief when a rescue medication is needed could forestall relapse and thus enhance clinical efficacy. This new technology for rapid nicotine delivery via the transmucosal route merits further study in cessation efficacy trials.

2.2.1.3 Combined patch and acute forms

A strategy for further improving the efficacy of MN is to combine one medication that allows for passive nicotine delivery (e.g., transdermal patch) with another medication that permits acute *ad libitum* nicotine delivery (e.g., gum, nasal spray, inhaler). The rationale for combining MN medications is that smokers may need both a slow delivery system to achieve a constant concentration of nicotine to relieve cravings and tobacco withdrawal symptoms, as well as a faster acting preparation to function as rescue medication for immediate relief of breakthrough cravings [64]. Thus, combining the nicotine patch, which may prevent the appearance of severe withdrawal, with acute dosing forms, which can provide relief in trigger-to-smoke contexts, may provide an excellent treatment option over either therapy alone.

Clinical trials suggest incremental efficacy of patch plus gum [50,65-67] or nasal spray [50,68], compared with either product alone. Studies suggest that combinations with other acute dosing forms may also provide a clinical benefit, as would be expected [68]. The fact that adding an acute dosing form to patch regimens yields substantial incremental benefit, whereas adding another patch (above) yields less benefit, suggests that the mechanism is not simply an increase in nicotine dose but the combination of steady-state dosing and acute dosing to provide for use as a rescue medication.

Despite the possibility of increased efficacy and demonstrated safety, present MN labelling warns against combination use. Without the removal of such warnings, these strategies will be largely limited to smoking cessation specialists and clinics. The complexity of obtaining approval for combination medications, combined with the difficulty of marketing combination products, has slowed attempts by manufacturers to gain regulatory approval for combination therapies [64].

2.2.2 Novel delivery forms

2.2.2.1 Nicotine drink

Recent research has examined the feasibility of adding drops of nicotine solution into beverages to obtain nicotine. Westman *et al.* found that peak serum nicotine concentrations after consumption of 5, 10 and 15 mg of nicotine were 9, 16 and 24 ng/ml, respectively [69]. Peak concentrations were reached ~ 1 h after consumption. The advantage of such a delivery system would be the potential for increased palatability and compliance among smokers, and the potential to titrate dosing (i.e., more heavily dependent smokers could add more drops of nicotine solution). One study with 25 healthy volunteers found the product to be well-tolerated, and suggested that the blood nicotine levels achieved may be useful as an aid to cessation [70]. Although there may be concern about the potential for nicotine-induced toxicity due to individual differences in first-pass metabolism, there is no evidence of toxic effects based on tolerability, side effect and safety data collected during the study [70]. No clinical efficacy data have been published.

2.2.2.2 Straw

The nicotine straw is a single-use plastic straw containing small beads of nicotine. When the smoker drinks a beverage through the straw, the nicotine beads are swallowed. The nicotine is then gastrically absorbed. The product is designed to be used 10 – 12 times a day.

In a small safety and PK study [71], 24 smokers administered with single doses of 0, 4, 8 or 12 mg achieved C_{max} of 6.4, 20.1 and 20.3 ng/ml, respectively. The T_{max} ranged from 1.3 (4 mg) to 1.9 h (12 mg), which probably makes this dosing route too slow for use as a rescue medication. No serious adverse events were reported and adverse events of only mild severity (gastrointestinal disturbance, lightheadedness) were

reported. Evaluating the kinetics and safety of the product is complicated by the potential for interactions with different beverages. No efficacy data have been published.

2.2.2.3 Lollipop

A nicotine lollipop would have the advantage of providing nicotine to the smoker while providing manual and oral stimulation and relatively fine dose titration. One such product that has been developed and tested is oral transmucosal nicotine (OT-nicotine). The product is a nicotine delivery system consisting of a nicotine lozenge mounted on a handle. In an open-label trial, OT-nicotine was compared with nicotine gum and patch [72], and appeared to hold promise for smoking cessation.

One concern regarding the nicotine lollipop is that it could have substantial abuse liability among youths, or present a significant safety concern among very small children to whom the product looks like candy.

2.2.2.4 Pulmonary nicotine delivery

There is a vast difference in the PK profiles of cigarettes and currently available nicotine medications. Even nicotine nasal spray, which produces measurable differences in venous blood nicotine levels, faster than oral MN formulations, does not approach the venous levels produced by cigarettes. Even more importantly, none of the currently available formulations produces the spikes in arterial blood, the blood levels that actually enter the brain. Henningfield *et al.* demonstrated that the arterial levels achieved by smoking are much higher than the levels seen in venous blood, and the nicotine may reach the brain even faster after smoking than after intravenous dosing [32]. The pulmonary route is an efficient method of delivering drugs to the body because of the large surface area of the pulmonary alveoli.

A true pulmonary inhaler, unlike the currently available nicotine inhaler (which actually delivers nicotine into the mouth for buccal absorption), would deliver nicotine to the lung in a manner more comparable to cigarette smoking [73]. This mode of delivery would be expected to reduce background cravings and withdrawal symptoms, and allow for rapid relief of acute cravings. In theory because the delivery of nicotine directly to the lung would more effectively mimic the effects of cigarette smoking at a physiological level, the smoker could more readily eliminate the need for tobacco and, subsequently, taper the nicotine level over time to alleviate dependence on nicotine altogether.

Technical challenges are not insignificant, as the nicotine molecules need to be appropriately condensed onto particles of ~ 1 micron median diameter to enable inhalation into the pulmonary alveoli, and the nicotine particles must be designed so as to prevent the production of unacceptably harsh sensory effects. A significant barrier to the development of a pulmonary inhaler is the potential for abuse and the regulatory implications that would follow from a system that delivers pulmonary nicotine, much as a cigarette does. Specifically, if the medication meets criteria for a controlled substance, its marketing could be severely restricted along the lines of morphine-like analgesics. Such marketing restrictions can be expected to limit commercial development of such a product because of the uncertain market for a tobacco cessation product that is regulated as a controlled substance. This issue may require resolution by WHO if the organisation deems it important so encourage the development of MN products that deliver nicotine to the lung or by other means that increase its abuse liability.

3. Gradual quitting

A procedure established in the 1970s, gradual quitting, is a smoking cessation approach whereby cigarette consumption decreases gradually over a period of time, eventually culminating in abstinence prior to a quit date [74,75]. Many smokers prefer to quit gradually, rather than all at once. However, the emergence of craving and withdrawal may be a major barrier to this approach for many smokers because reducing the number of cigarettes smoked per day would presumably produce lower nicotine levels than during regular smoking. Furthermore, a reduction in the number of cigarettes smoked often leads to compensation. That is, a smoker will often smoke more intensely (i.e., take deeper puffs, take more puffs per cigarette, reduce the interpuff interval) when the number of cigarettes per day is reduced to obtain the levels of nicotine obtained before the reduction [76].

Medicinal nicotine could be used to facilitate gradual quitting by 'replacing' some of the nicotine normally consumed by smoking. This would reduce craving and withdrawal caused by smoking reduction. It presumably would also reduce the amount of compensation, as demonstrated in a study that reported that use of nicotine gum decreased the inhalation of tobacco smoke during *ad libitum* smoking [77].

In a study of motivated quitters [78], the use of active gum was associated with increased rates of both reduction and cessation. These studies suggest that MN may be an effective aid for smoking cessation by gradual reduction.

4. Relapse prevention

It has been suggested that MN could be used to the reduce rates of relapse after smoking cessation. Relapse prevention using MN could take place immediately after the 'normal' treatment period, or to prevent progression to relapse after an initial lapse. There is substantial continuing lapse risk after the typical MN treatment period of 3 months (US) or 6 months (Europe). Some smokers may need prolonged use of pharmacotherapy to manage craving and prevent relapse.

The long-term use of MN may help to prevent relapse. However, more research is needed to further clarify questions regarding the ideal duration of therapy. Additional challenges include identifying smokers who need such treatment and promoting adequate compliance over a long period.

With regard to preventing progression to relapse after an initial lapse, data provide compelling evidence that after even a

single limited re-exposure to smoking ('lapse'), the probability of complete relapse is very high [79-81]. If MN could impede this progression, it may have significant clinical benefit. Current labelling seems to imply that users should stop MN if they start smoking, which would curtail any benefit. Shiffman and Scharf [82] showed that continued treatment with high-dose patch had a substantial and significant effect in lowering the risk of progression to relapse. Use of MN after a lapse to prevent progression may be an effective relapse-prevention strategy.

5. Nicotine maintenance

The goal of smoking cessation treatments with MN is to get smokers off tobacco and subsequently to withdraw them from nicotine as well. However, some smokers may have developed such a strong need for nicotine that it may be too difficult for them to withdraw completely. In those instances, it has been suggested that some smokers could benefit by continuing to use MN for longer periods of time, even indefinitely, to prevent relapse to smoking [1,83]. There are no studies that have directly examined long-term nicotine maintenance. This strategy is currently used in methadone maintenance programmes for heroin-dependent patients, where individuals may be maintained on daily doses of methadone for years. Like methadone, nicotine is not entirely without risk; however, the risk of nicotine, without the myriad of toxins found in tobacco smoke, is clearly much safer than resumption of smoking.

Although current MN formulations can be applied to long-term maintenance (e.g., gum), it is possible that formulations optimised for cessation may not be ideal for maintenance. For example, maintenance regimens would presumably need to be maintained for years, rather than the weeks or months typical of current cessation indications. To be suitable for this indication, a product may need to be more palatable than current cessation products, some of which were designed to discourage long-term use. Side effects that are considered minor in cessation medications (e.g., minor skin rashes from patches) may become intolerable when use extends into years. The delivery profile most suitable to a maintenance indication remains to be established. It is possible that a rapid-delivery vehicle that provides immediate effects would be most suitable. A delivery system that supported nicotine dependence may be tolerable or even desirable for this indication. In any case, it is probable that new delivery technology will need to be developed and tested to optimise application of MN to this new indication.

6. Temporary withdrawal management

MN products are currently used to help people stop smoking, partly by treating the craving and withdrawal symptoms associated with quitting. However, many smokers suffer from craving and withdrawal symptoms in the course of 'normal' smoking, particularly when clean-indoor-air regulations prohibit smoking; for example, in the workplace, or on transportation vehicles. It has been suggested that MN may be used to relieve symptoms in those instances. The aim would not necessarily be to change smoking behaviour but merely to ameliorate 'pain'. An indication for relief from symptoms during temporary abstinence has been approved in several jurisdictions, including Austria, France, Norway, Portugal, New Zealand, Brazil, Colombia and Venezuela. One concern with this application of MN is whether reducing the suffering imposed by smoking restrictions may reduce the incentive for smokers to quit. Alternatively, and more optimistically, giving smokers experience with the ability of MN to help control their symptoms may encourage more smokers to try quitting (as has been observed with the use of MN for smoking reduction). This question has yet to be addressed empirically.

It is not clear which product forms would be most suitable for this use. Products such as patches, which deliver nicotine slowly over a long period, may not be suitable for this application because of the length of time required to reach plasma levels of nicotine that would alleviate withdrawal symptoms. Convenient dosing would also be required of such a product. It is possible that some currently available products could be used for this indication, but new product formulations may need to be developed.

7. Reduced smoking

Nicotine provides the main motivation for tobacco use. However, tobacco-related death and disease is a consequence of exposure to toxins in tobacco smoke as a 'side effect' of nicotine seeking. The mainstays of attempts to control tobacco-related death and disease have been the prevention of uptake of smoking and cessation by current smokers. However, with the realisation that many smokers are unable or unwilling to quit, some focus has shifted to attempts to reduce the harm of smoking [84]. One proposed strategy for reducing harm is to promote reduced smoking, with the expectation that smoking less is safer [1]. Past studies [85] have shown that smokers resist reductions in nicotine intake and respond to reduced smoking by unconsciously extracting more nicotine from each cigarette; in the process by which they also expose themselves to more tar and toxins from other tobacco constituents. MN medications could potentially be used to facilitate harm reduction by helping the smoker to achieve real decreases in toxic exposure by replacing some of the nicotine normally obtained by smoking.

Fagerstrom and Hughes [86] reviewed and conducted a meta-analysis of 11 studies that provided data on blood nicotine concentrations, carbon monoxide (CO) in exhaled air and the number of cigarettes smoked during periods of concurrent use of cigarette and MN products. With simultaneous use of smoking and acute MN products (gum and inhaler) the nicotine concentrations were unchanged, whereas they increased (by 54%) with nicotine patches. With both types of MN products, the number of cigarettes smoked per day was reduced by ~ 50% and CO by 30%. Where smokers had the intention or received instructions to reduce smoking, a greater

reduction in cigarettes smoked and exhaled CO was observed. Despite substantially increased nicotine concentrations (e.g., up to three-times baseline levels [i.e., 60 versus 20 ng/ml, respectively]), there were no significant adverse reactions.

The prospect of treatments for reduction raises several significant policy concerns. One is to ensure that the smoking reductions and consequent reductions in toxin exposure are adequate in magnitude and duration to result in a real health benefit for the user. Another is to ensure that the offer of smoking reduction does not diminish progress towards smoking cessation, which may outweigh the health benefits achieved through reduction. Fortunately, several studies [87-89] have suggested that engaging smokers in reduction actually promotes interest in and progress towards cessation. For example, in a study of smokers who were not motivated to quit smoking [90], smokers who received reduction counselling and MN were as likely as smokers in a motivational treatment geared towards complete cessation to make a quit attempt within 6 months, and were more likely to have achieved smoking abstinence at 6 months; both active treatment groups were more likely to make a quit attempt and to have achieved cessation at 6 months than a no-treatment group.

Although current MN formulations can be applied to reducing smoking, it is possible that formulations meant for cessation may not be ideal for reduction. As with a long-term maintenance indication, reduction regimens would presumably need to be maintained for years, rather than the weeks or months typical of current cessation indications. The delivery profile most suitable to a reduction indication remains to be established. It is possible that a rapid-delivery vehicle that provides immediate effects would be the most suitable. A delivery system that supported nicotine dependence may be tolerable or even desirable for this indication. In any case, it is probable that new delivery technology will need to be developed and tested to optimise application of MN to this new indication.

8. Conclusions

Smoking continues to be the largest preventable cause of death and disease in the developed world, making smoking cessation one of the most important and urgent mandates in medicine. MN has been proven to help people quit smoking but the absolute success rates leave much room for improvement. Accordingly, scientists have been searching for new MN formulations that may improve efficacy or provide other incremental clinical benefits. It is likely that we will see new and improved MN formulations in the next 5 years. Equally important, new applications of existing and novel MN products will most probably be introduced to support increasingly diverse approaches to tobacco control.

9. Expert opinion

The idea of nicotine replacement has proven to be sound. Experience has shown that MN can be put into widespread use for self-treatment in the over the counter/general sales list (OTC/GSL) market without engendering problems of abuse. At the same time, experience, epidemiology and human clinical research have suggested that MN is safe, even in the OTC/GSL market. An important consideration is that MN products are meant for use by people (i.e., smokers) who are already self-administering nicotine at higher doses, and thus have proven their tolerance and toleration of the drug before ever starting on MN. By replacing the nicotine normally obtained by smoking, one can reduce the nicotine craving and withdrawal symptoms associated with tobacco abstinence. However, because of initial regulatory concern about nicotine abuse liability and safety, product development has been highly conservative in every respect, as is evident by the nature of the forms and formulations, sensory appeal, dosing amount, dosing speed and dosing regimens. Applications have likewise been very conservative, focusing narrowly on abrupt complete cessation, rigid dosing schemes, prohibition on concomitant smoking and short treatment periods. This is comparable to administering only one dose of methadone, and only for rapid detoxification, whereas this application would certainly work for some people, expanding the number of dosages and treatment regimens would clearly have greater efficacy and public health impact.

Although tobacco control efforts have been relatively successful, we still have 5 million people worldwide dying annually from smoking-related disorders [201]. Clearly more needs to be achieved in terms of treating tobacco dependence. Although MN has been proven effective, improvements in efficacy are needed. Accordingly we need and are likely to see products that are more aggressive in dosing (higher dosages and faster delivery) and more appealing (flavour, format). Higher dose products would likely benefit some highly dependent or heavier smokers. Faster delivery would be expected to benefit smokers trying to fend off relapse when exposed to smoking cues. More appealing flavours and formats will likely be useful to help smokers comply with treatment regimens. Eventually, products comparable in dose and rate of delivery and, therefore, as reinforcing as cigarette smoking, may be needed for some smokers [91].

We also need and are likely to see broader and more flexible indications and applications of MN that will:

- address the diverse ways in which smokers want or are able to quit
- provide help more flexibly and for longer
- reach out to the full range of smokers, including those who are not yet ready to quit completely but are willing to use MN to assist in making changes in their smoking

Currently available MN products could be used to facilitate these additional indications and applications; however, new forms may be better suited for certain applications than others. The broader application of MN will challenge scientists to create new forms of MN to address this spectrum of needs.

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