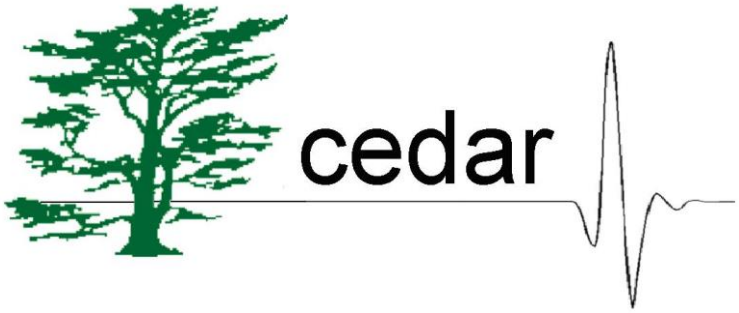

NICE public health guidance on tobacco harm reduction

Safety, risk and pharmacokinetics profiles of tobacco harm reduction technologies

Report

November 2021: NICE guidelines PH45 (June 2013) PH48 (November 2013) have been updated and replaced by NG209.
The recommendations labelled [2013] or [2013, amended 2021] in the updated guideline were based on these evidence reviews.
See www.nice.org.uk/guidance/NG209 for all the current recommendations and evidence reviews.

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1 Glossary

Abstinence
Complete cessation from smoking (indefinitely or for a period of time).

Adverse event
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. In this review we report the adverse events in studies of tobacco harm reduction (see also **serious adverse event**)

Area under the Curve (AUC)
In pharmacokinetics, the area under the curve of drug concentration in blood when plotted graphically against time. AUC is a measure of drug **bioavailability**.

Bioavailability
A pharmacokinetic parameter which describes the amount of a drug that reaches the circulation after a dose of the drug is given to the body (see **area under the curve**).

Carcinogen
A substance that can cause cancer, by damaging the nuclear material in the body's cells. Cigarette smoke contains numerous carcinogens.

C_{max}
The maximum blood concentration of a drug reached following administration of the drug.

C-reactive protein (CRP)
A protein found in the blood. The levels of CRP rise in response to inflammation.

e-cigarette
Also known as an electronic cigarette, an e-cigarette is a device marketed as an alternative to smoking cigarettes. An e-cigarette consists of a mouthpiece, reservoir of nicotine-containing fluid, atomiser and battery. The e-cigarette works by creating a nicotine vapour (not smoke) and the user puffs in a similar manner to smoking a cigarette. The action is often described by users as 'vaping'. Use of e-cigarettes in the UK is not unlawful in areas where cigarette smoking is prohibited.

Fagerstrom Test for Nicotine Dependence (FTND)
This is a standard instrument for assessing the intensity of physical addiction to nicotine. The higher the patients Fagerström score, the more intense the patient's physical dependence on nicotine.

Nicotine
A highly addictive drug that is present in tobacco. Nicotine is present in tobacco smoke and is also available in medicinal products and non medicinal products. Nicotine travels via the bloodstream and stimulates the brain. Most regular smokers are addicted to nicotine.

Nicotine containing products
In the broadest sense this means any product that contains nicotine. However in this report, nicotine containing products refers specifically to any product that contains nicotine and which is marketed with a claim that it can assist in giving up smoking, or reducing a person's level of smoking. This review excludes nicotine containing products that contain tobacco.

Nicotine replacement therapy
Licensed medicines that contain pharmaceutical nicotine. These are available from General Practitioners and over the counter in Pharmacies. Medicine formats include nicotine patches (applied to the skin), chewing gum, oral lozenges, oral spray, nasal spray, sublingual tablets (applied under the tongue) and inhalator.

Pharmacokinetics
The study of the absorption, distribution and excretion of a drug that is taken in to the body. Pharmacokinetic models typically estimate the levels of a drug in different parts of the body over time.

Potential reduced exposure products (PREPs)
These products are modified tobacco products that are intended to cause less harm than smoking conventional cigarettes. PREPs include low tar cigarettes, cigarettes with reduced levels of tobacco toxicants (including nitrosamines), tobacco products that are heated rather than burned. All tobacco containing products, including PREPs, are excluded from this review.

Serious adverse event
Any adverse event that results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability or incapacity. In this review we report the adverse events in studies of tobacco harm reduction.

Smoking cessation programmes
Measures to help people stop smoking completely and for the rest of their lives. Smoking cessation is known to be the best option for a smoker to prevent ill health and early death. Tobacco harm reduction (see below) is a pragmatic option and can only be of value for smokers in whom smoking cessation is not possible

Snus
A form of oral moist tobacco popular in Sweden and acclaimed for a role in tobacco harm reduction

$t_{1/2}$
The half life of a drug i.e. the time it takes for the quantity of a drug in blood to reduce by half from its current level (beginning with C_{max}).

T_{max}
The time it takes for the blood concentration of a drug to reach its maximum level (C_{max}) following administration of the drug.

Tobacco
A product processed from the leaves of the tobacco plant (nicotiana) and available in numerous

forms, including cigarettes. Tobacco products are excluded from this review, although data from smokers of cigarettes is used as a baseline for tobacco harm reduction.

Tobacco harm reduction
Measures to reduce the illnesses and deaths caused by smoking tobacco among people who smoke and those around them. People who smoke can do this by stopping smoking altogether, cutting down prior to quitting, smoking less and abstaining from smoking temporarily.

2 List of abbreviations

1-HOP	1-hydroxypyrene
AUC	Area Under the Curve
BBC	British Broadcasting Corporation
BME	Black and minority ethnic (groups)
CHM	Commission on Human Medicines
Cmax	maximum concentration (of a drug in the body after dosing)
CO	Carbon monoxide
COPD	Chronic Obstructive Pulmonary Disease
CPHE	Centre for Public Health Excellence
CPD	Cigarettes Per Day
CRP	C-reactive protein
EU	European Union
FDA	Food and Drug Administration
FTND	Fagerstrom Test for Nicotine Dependence
SCN	(plasma) Thiocyanate
MHRA	Medicines and Healthcare products Regulatory Agency
NCPs	Nicotine Containing Products
NICE	National Institute of Health and Clinical Excellence
NNAL	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol
NRT	Nicotine Replacement Therapy
NS	Not Significant
PREPs	Potential Reduced Exposure Products
SPC	Summary of Product Characteristics
t1/2	Half-life
tcpO2	Transcutaneous oxygen
Tmax	The time it takes for the blood concentration of a drug to reach its maximum level (C_{max}) following administration
US	United States
Vd	Volume of distribution
WBC	White Blood Cells

3 Summary

3.1 Aims

The aims of this review are:

- to summarise evidence on the safety, or risks, of tobacco harm reduction strategies, both in people who continue to smoke and in smokers who quit but continue to use NRT products indefinitely
- to summarise the pharmacokinetic factors which influence the safety, or risks, of tobacco harm reduction strategies when used as above, principally NRT products.

3.2 Methods

The methods are a literature review and pharmacokinetic model. A literature search was run on 18 electronic databases and also relevant websites, which identified 5860 potentially relevant studies. Of these 81 papers were included as sources of evidence, with extracted data shown in evidence tables in appendices 4-9.

3.3 Evidence summary: question 1

What specific risks have been associated with the technologies within the scope of the review? What adverse events or serious adverse events have been identified and how frequently do they occur?

Evidence statement 1a Primary studies

Evidence from ten randomised controlled trials strongly suggests that adverse events are common when NRT is used for smoking harm reduction, but these tend to be mild or moderate and are rarely severe (Batra *et al.* 2005 [+]; Bolliger *et al.* 2000 [++];Carpenter *et al.* 2003 [+]; Carpenter *et al.* 2004 [++]; Etter *et al.* 2002 [++]; Haustein *et al.* 2004 [+]; Joseph *et al.* 2008 [+]; Kralikova *et al.* 2009 [+]; Rennard *et al.* 2006 [++]; Wennike *et al.* 2003) [+]. No authors have attributed serious adverse events to NRT when used as part of smoking harm reduction. NRT is generally well tolerated when used in this setting. Frequently reported adverse events depend on the route of administration but include throat irritation, coughing, nausea, vertigo / dizziness, vomiting or palpitations. There is no evidence of increased cardiac events in patients with existing cardiac disease treated with NRT for 18 months (Joseph *et al.* 2008) [+]. The duration of use of NRT in these studies varied from 1 month to 18 months. Follow up did not extend beyond 24 months, so the randomised trials do not provide safety data for longer term use.

Evuidence statement 1b Meta-analysis

Evidence from a meta-analysis (Moore 2011) [++] of 2767 participants drawn from several of the randomised trials cited above plus two unpublished sources corroborates the findings shown above. The unpublished trials used NRT for 9 months and 12 months. The results suggest that there is no difference between NRT (used for between 6 and 18 months) and placebo in terms of mortality, serious adverse events or discontinuation of therapy due to adverse events, but that nausea occurs more frequently with active NRT (OR 1.69, 95% CI 1.21-2.36). Use of the meta-analysis has two caveats:

- the meta-analysis re-iterates a substantial body of the same data from randomised trials cited above (Batra *et al.* 2005 [+]; Bolliger *et al.* 2000 [++]; Etter *et al.* 2002 [++]; Haustein *et al.* 2004 [+]; Rennard *et al.* 2006 [++]; Wennike *et al.* 2003) [+].
- there was substantial heterogeneity of results in the meta-analysis of serious adverse events.

3.3.1 Evidence statement 1c Cardiovascular risk markers

Evidence from five randomised trials (Batra *et al.* 2005 [+]; Bolliger *et al.* 2000 [++]; Joseph *et al.* 2008 [+]; Kralikova *et al.* 2009 [+]; Rennard *et al.* 2006) [++] and one non-randomised, controlled study (Haustein *et al.* 2004) [+] suggests that there are no substantial changes in risk markers for cardiac disease in people treated with NRT as part of smoking harm reduction. This evidence is cited from a Cochrane review of the randomised trials (Stead & Lancaster 2007) [+]. Risk markers studied included white blood cell count, fibrinogen, CRP, lipids, F2-isoprostanes, NNAL, 1-HOP. One study (Bolliger *et al.* 2000) [++] found favourable changes in both NRT and placebo groups. No study reported increases in risk markers for cardiovascular disease arising from NRT. Follow up did not extend beyond 24 months.

3.3.2 Evidence statement 1d Nicotine, psychological outcomes and serotonin

There is established evidence that smokers have poorer psychological outcomes than non-smokers, as summarised by McNally (2009) [+]. Evidence is lacking on whether long term exposure to NRT lowers serotonin levels. A limited amount of data from a subgroup analysis of depressed human subjects suggests that smoking correlates with reduced serotonin levels (Malone 2003) [+]. A study of human brain tissue found a similar association (Benwell et al. 1990) [+]. One study in rats found that nicotine exposure over a 40 day period correlates with reduced serotonin (Benwell and Balfour, 1979) [+].

3.4 Evidence summary: question 2

Question 2: What data are available to support the safety of long term use of the technologies?

Evidence statement 2a Safety of long-term use

There are no studies available of the safety of NRT used in SHR in the long term (maximum duration of NRT use is 5 years). The strongest evidence available for the long term safety of NRT with concurrent smoking comes from a large subgroup of patients studied the five year Lung Health Study of NRT in smoking cessation, where a large patient group continued to smoke and continued to use NRT (Murray *et al.* 1996) [+] (Murray *et al.* 2009) [+]. . The results of this multicentre randomized controlled trial suggest that long term use of NRT is not associated with an increased incidence of harm, including cardiovascular events or cancer, with the latest analysis of outcome at 12.5 years from study outset.

Evidence statement 2b Cardiac disease

Six studies evaluated the safety of NRT in patients with cardiac disease (Mahmarian *et al.* 1997) [+] (Paciullo *et al.* 2009) [-] (Leja *et al.* 2007) [+] (Tzivoni *et al.* 1998) [+] (Joseph *et al.* 2008) [+] (Joseph *et al.* 1996) [+] and did not find any increased incidence of cardiovascular events or any other adverse events.

Evidence statement 2c Critically ill patients

Two retrospective case-control studies have found an increased mortality associated with nicotine replacement therapy among critically ill patients (Paciullo *et al.* 2009) [-](Lee *et al.* 2007) [-]. However the confidence intervals around the odds ratios for mortality are wide indicating significant uncertainty surrounding the size of the effects.

3.5 Evidence summary: question 3

What are the risks associated with use of NCPs which are currently unlicensed? (Questions especially relevant to the e-cigarette: What is the nature of the absorbent material? Are there other components present in the nicotine solution used in this device? Do these represent risks to the user? Are any harmful chemicals released when the nicotine solution is heated?)

Evidence statement 3a Risks associated with use of unlicensed nicotine containing products

All available evidence relates to e-cigarettes. There is no evidence on the long term safety of e-cigarettes, whether used alone or with concurrent cigarette smoking. There isn't a large volume of reliable evidence on the short term safety of e-cigarettes. One randomized crossover trial (Bullen

et al. 2010) [+] found that the rate of acute adverse events arising from e-cigarette use (occurring on the first day of use) were intermediate between placebo e-cigarette and licensed nicotine inhalator. A non randomised study also found no acute effect on heart rate from the use of two models of e-cigarette (Vansickel et al. 2010) [+].There are no firm cases of harm that are directly attributable to e-cigarette use. One news article in the British press (BBC, 2011) [-] reported a death from lipoid pneumonia where e- cigarette use was implicated by a treating clinician. The inquest to the death recorded an open verdict.

Evidence statement 3b Scale of use and regulation

Scale of use of e-cigarettes

Stakeholder statements submitted to NICE by the Electronic Cigarette Consumer Association of the United Kingdom (ECCA UK 2011) [-], suggest that there is increasing and widespread use of e-cigarettes in the UK since 2006. Evidence from a survey of established e-cigarette users in the US also suggests that use is widespread (Foulds et al. 2011) [+].

Regulatory status

E-cigarettes are not regulated as medicines and their regulation is limited to the General Product Safety Directive of the European Parliament. Personal communication with MHRA suggests that post market surveillance of e-cigarettes, as required by the directive, is problematic in practice (Medicines and Healthcare Products Regulatory Agency 2011b) [-].

British Medical Association statement on e-cigarettes

The British Medical Association (BMA) has, in March 2012, advised UK doctors not to recommend the use of e-cigarettes as aids to smoking cessation or as a lower risk option than continuing to smoke. The summary of the BMA briefing states (BMA, 2012):

- “e-cigarettes are not regulated as a tobacco product or as a medicine in the UK and there is no peer-reviewed evidence that they are a safe and effective nicotine replacement therapy
- the use of e-cigarettes may undermine smoking prevention and cessation by reinforcing the normalcy of cigarette use in public and workplaces
- health professionals should not recommend the use of e-cigarettes as smoking cessation aid or a lower risk option than continuing to smoke due to a lack of evidence of their safety and efficacy.”

Evidence statement 3c Contents of e-cigarettes

There is evidence from laboratory analyses that e-cigarettes can contain nicotine derived nitrosamine contaminants and diethylene glycol, a highly toxic substance (Westenberger 2009 [++]; Medicines and Healthcare Products Regulatory Agency 2011a) [++]. Most e-cigarettes include propylene glycol. This chemical is generally considered to be of low toxicity although there appears to be insufficient data concerning its inhalational toxicity. A physical evaluation of e-cigarettes found that e-cigarettes (including their constituent parts and instruction manuals) lack important information regarding contents, use and essential warnings (Trtchounian et al. 2011) [+]. The same study found that e-cigarettes frequently leak, presenting a hazard, and that there are currently no methods for proper disposal of e-cigarettes, including cartridges (Trtchounian et al. 2011) [+].

3.6 Evidence summary: questions 4 and 5

Do the data suggest the technologies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Do the data suggest the combination of nicotine replacement therapies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Evidence statement 4a Impact of nicotine replacement therapies and nicotine containing products on the concentration of nicotine in the blood

Evidence from controlled studies suggests that nicotine concentrations with smoking alone are typically in the range 22-30 ng/ml. When NRT use is accompanied by smoking, nicotine concentrations can rise to higher levels (Ebert et al. 1984) [+], (Fagerstrom et al. 2002) [+], (Foulds et al. 1992) [+], (Pickworth et al. 1994) [+], (Russell et al. 1976) [+], (Zevin et al. 1998) [+]. The highest value observed was 63.4ng/ml when a 44mg patch was used with ad libitum smoking (Pickworth et al. 1994) [+]. Some authors suggest that smoking behaviour self regulates to maintain a constant nicotine concentration but evidence (particularly for patches) suggests that this is imprecise.

Despite increased nicotine concentration with concomitant use, the available evidence suggests there are no increases in the incidence of side effects or significant changes in physiological parameters such as blood pressure and heart rate (Pickworth et al. 1994) [+] (Zevin et al. 1998) [+].

Evidence statement 4b Compensatory smoking

Compensatory smoking is a mechanism whereby smokers, who have reduced the number of cigarettes they smoke per day, modify their smoke intake, e.g. by puffing more frequently or more intensely, and thus titrate their nicotine intake (Hughes and Carpenter, 2005) [+]. Studies correlating reductions in expired CO with reductions in the number of cigarettes per day have demonstrated that some compensation occurs, but that the reduction in CO is significant (Hughes 2000 [-], Hughes and Carpenter, 2005 [+]). A narrative review of studies Fagerstrom & Hughes 2002 [-] suggests that for acute NRT forms (gum, lozenge, inhalator, nasal spray) a reduction in CO is accompanied by little change in plasma nicotine, suggesting close titration by subjects. In contrast the same study found for nicotine patches, plasma nicotine increased, suggesting poor titration for the transdermal route.

Studies of snuff use and low yield cigarettes also indicate that users are able to manage their intake to achieve a plasma nicotine level of typically 35-37 ng/ml (Holm et al. 1992 [+], Jarvis et al. 2001 [+], Russell et al. 1981 [+]). One study showed that users of nasal snuff can generate similar plasma nicotine levels to those generated by smoking a cigarette, in approximately equal time (10 minutes) Russell et al. 1981 [+]).

Evidence statement 4c Nicotine absorption routes from NRT and e-cigarettes

The routes of absorption of medicinal nicotine are buccal (lozenge, gum, microtab, inhalator), dermal (patches) and nasal mucosa (nasal spray). Notably nicotine is mainly absorbed from the inhalator via the oral mucosa, with minimal absorption via the lungs. The degree of absorption of nicotine from electronic cigarettes is uncertain and published studies suggest the delivery of nicotine by these devices is via buccal absorption. (Russell *et al.* 1987) [-], (Vansickel & Eissenberg, 2012 [-] (see also Section 3.7.2, below).

Evidence statement 4d Nicotine in arterial and venous blood

Following administration of nicotine by any route, nicotine has a different concentration profile over time in arterial blood compared to venous blood Henningfield et al, 1993 [+]. Few studies report arterial nicotine concentrations because venous blood samples are easier to collect.The arterial concentration relative to venous concentration (expressed as a ratio of the two concentrations) indicates the potential for distribution to the brain via the arterial circulation (Gourlay & Benowitz, 1997) [+].

Nicotine in cigarette smoke is rapidly absorbed in the lungs and quickly reaches the brain via the left side of the heart and the arterial circulation. One experimental study (Rose et al, 2010) [+] found that brain nicotine accumulation from cigarette smoking begins approximately 7 seconds after nicotine is first detected in the oral cavity and that maximum brain accumulation occurs at 290 seconds in dependent smokers and 210 seconds in non dependent smokers. The same study suggests that during typical smoking patterns, there are no spikes in brain nicotine concentrations, although there are puff-associated oscillations in the rate of nicotine accumulation which could affect nicotine receptor function (Rose et al, 2010) [+]. The authors concluded that dependent smokers accumulate nicotine more slowly than non-dependent smokers, due to reduced nicotine washout from the lungs (Rose et al, 2010) [+].

Another experimental study (Gourlay and Benowitz, 1997) [+] found that during cigarette smoking, median ratios between the arterial and venous plasma concentration of nicotine at the time of arterial Cmax were 4.6 (nasal spray), 2.3 (smoking) and 1.6 (intravenous).

3.7 Evidence summary: question 6

Are kinetic data available which allow comparison of the relative bioavailability of different technologies i.e. maximum (peak) concentration (Cmax), time to peak concentration (Tmax) and half life (t ½)?

3.7.1 Pharmacokinetic model

Cedar commissioned Professor Glyn Taylor as an independent expert to construct a pharmacokinetic model using data from published pharmacokinetic studies. The pharmacokinetic model is a stand alone report for consideration by the PDG and is attached as Appendix 1.

3.7.2 Narrative summaries of pharmacokinetic data for each nicotine administration route

Cedar has written concise, summary statements on the pharmacokinetic data for different nicotine administration routes, shown below. More in-depth discussion is provided in Section 6.5.

Evidence statement 5 Pharmacokinetic data for each nicotine administration route

Cigarettes

Evidence from pharmacokinetic studies indicates that ten minutes of cigarette smoking can generate an arterial blood C_{max} of 38-40 ng/ml nicotine in T_{max} 8 minutes and a venous blood C_{max} of 17-19 ng/ml in a T_{max} of 10-12 minutes.

Snus

Absorption of nicotine from snus is primarily through the oral mucosa and can produce a venous blood C_{max} of 14ng/ml in a T_{max} of 30-37 minutes.

NRT lozenge / tablet

These products dissolve in the mouth (and are not intended to be swallowed) and absorption of nicotine is primarily through the oral mucosa. A single dose of between 1-6mg nicotine taken as a dissolvable lozenge / tablet can generate a C_{max} of 3-6 ng/ml in T_{max} of approximately 48 minutes. Multiple doses do not appear to result in a C_{max} higher than 30ng/ml.

NRT gum

NRT gum is chewed in the mouth. Absorption of nicotine is primarily through the oral mucosa. When 8mg nicotine or less is administered as gum, a C_{max} of 10 ng/ml is reached in T_{max} of 38 min. Larger, sequential doses totalling 24-48mg result in a C_{max} of approximately 22 ng/ml and do not appear to exceed 30ng/ml.

NRT nasal spray

The absorption route for nasal spray is primarily through the nasal mucosa. A dose of 0.5-2.5 mg nicotine given via nasal spray over 5 minutes or less can result in C_{max} of 10 ng/ml in T_{max} of 11 min (range 5-23 min). Nasal spray would therefore appear to offer relatively rapid absorption of nicotine, compared to the other NRT routes.

NRT inhalator

The pharmacokinetic data on the NRT inhalator appear to support buccal absorption as the primary nicotine absorption route. 20 minutes of use appears to generate a variable C_{max} of mean 23 ng/ml (range 2-34) in T_{max} of 27 min (range 20-32 min).

NRT patch

The absorption route for nicotine patches is transdermal. Patches appear to offer slow, but sustained absorption of nicotine. Doses of 15-40mg given over 16-24 hours can result in a C_{max} of 19 ng/ml (range 14-26 ng/ml) in T_{max} of 9 hours.

e-cigarettes

e-cigarettes are not licensed medicines in the UK and little is known about the extent to which they deliver nicotine to the circulation. A small volume of available data suggest that a 16mg dose given over 5 minutes can result in a C_{max} of 1.3 ng/ml in T_{max} of 20 min.

3.8 Evidence summary: question 7

Do the data support the safety of an approach where smokers receive doses of medicinal nicotine (potentially by different routes) while continuing to smoke. Is there a greater risk of adverse effects?

On reviewing the available evidence we concluded that there is no useful distinction between studies that answer this question and those that answer question 1. We agreed with NICE technical staff to present all relevant data under question 1.

3.9 Evidence summary: question 8

There are marked differences in smoking rates among socioeconomic groups, Black and Minority ethnic (BME) groups, age (lifestage) and people with mental illness. Do the data suggest there may be inequalities among these groups with respect to the risk, safety and pharmacokinetics of smoking harm reduction technologies?

Evidence statements 6

3.9.1 Evidence summary: Socioeconomic groups

Few data were found which investigate the safety of nicotine with respect to socioeconomic groups although it is widely accepted that smoking prevalence is far higher among people from manual as opposed to non manual socio-economic groups. One community-based randomised controlled trial studied NRT in young smokers who were socioeconomically deprived. 98 subjects were recruited and randomised to nicotine patch or placebo patch. The authors suggest NRT appears to be safe in this group (on the basis of few reported side effects). However it is worth noting that the adherence to therapy was very low (only eight subjects (3 with active treatment and 5 with placebo) completed the full six week treatment course) and 63 subjects did not attend any follow up (Roddy *et al.* 2006) [+].

3.9.2 Evidence summary: Black and Minority Ethnic groups

No data were found which specifically study the relative safety of NRT among different BME groups although there is evidence from studies of genetics to suggest there are differences in nicotine metabolism among different BME groups.

Genetic studies

Much of this evidence concerns the well studied genetic polymorphism in the hepatic detoxifying system (Cytochrome P450 family of enzymes). Variant alleles resulting in reduced enzyme activity are more commonly found among Asian populations (Chinese, Japanese and Korean) compared

with Caucasian. Two open label clinical trials have found significantly increased plasma nicotine concentrations among slow metabolisers receiving NRT patches (Malaiyandi *et al.* 2006 [+]; Schnoll *et al.* 2009) [+]. Where NRT nasal spray was used, slow metabolisers used significantly fewer doses but maintained a similar plasma nicotine concentration (Schnoll *et al.* 2009) [+]. This trial of 568 smokers did not find any association between the measures of metabolic rate (3-HC/cotinine ratio) and patch related side effects although the 3-HC/cotinine ratio was considered a significant predictor of quit rates.

A review article concludes that the genetics of nicotine dependence may involve contributions of hundreds of genes, interacting with each other and with the environment (Bierut 2009). These genes may include nicotine receptors, metabolic pathways and dopaminergic pathways.

Implications for treatment

These studies show that the influence of CYP 2A6 genotype on nicotine metabolism may affect usage of NRT, the nicotine concentrations obtained during use and the efficacy of treatment (for cessation). Authors have suggested there may be some value in assessing pretreatment nicotine metabolism rate when considering the use of NRT since slow metabolisers are considered better candidates for this form of treatment. Alternative therapies (such as bupropion) may be more beneficial for faster metabolisers (Schnoll et al. 2009) [+]. The 3-HT/Cot ratio (ratio of 3-hydroxycotinine to cotinine) is regarded as a useful marker of the rate of nicotine metabolism and CYP 2A6 activity generally (Dempsey et al. 2004).

Glucuronidation

There may be differences among ethnic groups in the metabolism of nicotine by the process of glucuronidation. This detoxifying process adds glucuronide to substrates such as nicotine and cotinine to make them more water soluble and more readily excreted. The evidence of one open label clinical trial suggests glucuronidation is significantly lower among African Americans compared to European Americans (Berg *et al.* 2010) [+].

3.9.3 Evidence summary: Age (lifestage)

Adolescence

Four separate clinical trials dealt with safety of NRT in the adolescent group. Two of these involved NRT patch monotherapy, one involved patch or gum in combination with cognitive behavioural therapy and one involved the NRT nasal spray. One trial was a double-blind randomized controlled trial, one was a randomized, open label trial and two were non-randomized, open labelled studies.

A double-blind, randomized trial of the safety and efficacy of nicotine patch and gum in a sample of 120 adolescents (13 to 17 year olds) treated for 12 weeks found that a total of 745 adverse events were documented throughout the trial. Incidence of sore throat (gum), hiccups (gum), shoulder/arm pain (patch), pruritis (patch and gum) and erythema (patch) were significantly greater with NRT than with placebo. There was a mean reduction in self reported smoking (CPD) for all three groups (gum, patch and placebo) and this exceeded 80% reduction in each case. The authors suggest that the pattern of adverse events reported in this trial was similar to those reported in adult trials (Moolchan *et al.* 2005) [++]. Similar findings were reported by Smith et al (Smith *et al.* 1996) [+] and Hurt et al (Hurt *et al.* 2000) [+] in non randomised open label trials of patch therapy in 22 and 101 adolescents respectively.

The evidence from one randomized, open label trial suggests there may be safety concerns regarding the use of NRT nasal spray among adolescents (Rubinstein et al, 2008) [++]. This study randomly assigned 23 subjects to the nicotine nasal spray and 17 to control group. 38.9% of individuals using the spray were of the opinion that there were lots of side effects. The most common adverse effect was nasal irritation (34.8%), followed by complaints about taste and smell (13%). The authors suggest that the symptoms may explain a low rate of use and that such poor adherence may explain the low overall quit rates observed (Rubinstein *et al.* 2008) [++].

Older people

One pharmacokinetic study was found which suggests the clearance of nicotine is significantly decreased by approximately 25% in elderly subjects (65 to 76 years) compared with younger adults (22 to 43 years). The maximal nicotine concentration was higher in the elderly subjects (16.8 ± 7.8 ng/ml vs 10.4 ± 3.5 ng/ml) following an intravenous infusion of 0.028 mg/kg of nicotine over 10 minutes. The maximal heart rate increase was significantly ($p = 0.0062$) lower in elderly subjects than younger adults (15 ± 6 bpm vs 21 ± 8 bpm) and there were no differences in the systolic and diastolic blood pressure responses between the two groups. There were no differences in the adverse events experienced by the subjects, either in terms of the type of event or severity (Molander *et al.* 2001) [+].

3.9.4 Evidence summary: Individuals with psychiatric illness

Safety of NRT use in people with psychiatric illness

One study was found which explores the safety of NRT in individuals with mental illness. Stapleton et al (2008) [-] evaluated a consecutive series of 412 smokers receiving smoking cessation

treatment, 111 (27%) of whom reported that they were being treated for a mental illness. Subjects could choose NRT (whichever licensed preparation they preferred) or varenicline. The study was powered to detect a difference in the primary outcome measure (abstinence) but also measured tobacco withdrawal symptoms and adverse drug reactions as secondary outcomes. In terms of efficacy, cessation rates were greater with varenicline than NRT. The authors report the incidence of adverse events for NRT and varenicline groups but did not analyse the frequency of adverse events in the NRT treated subjects with and without mental illness (Stapleton *et al.* 2008) [-].

Pharmacokinetics of NRT in people with psychiatric illness

A placebo controlled crossover trial measured nicotine concentrations following cigarette smoking and NRT nasal spray use among a group of 31 patients diagnosed with schizophrenia or schizoaffective disorder. Blood samples were taken for nicotine measurement before and after administration of cigarette or nasal spray. When subjects received two sprays of NRT to each nostril the mean nicotine plasma concentrations were 9.1 ng/ml. Administration of four sprays to each nostril resulted in a mean nicotine concentration of 22.4 ng/ml (Smith *et al.* 2002) [+].

Effects on psychiatric symptoms

A randomised, double blind, balanced crossover study of withdrawal and psychiatric symptoms in nineteen cigarette smokers with schizophrenia found that there were no significant changes in psychiatric symptoms during three days of smoking abstinence with or without nicotine replacement (Dalack *et al.* 1999) [++].

3.10 Swedish snus

Note: for further details on snus and cancer risk please refer to Appendix 10, Section 21.1, pages 275-283.

Evidence statement 7 Snus and cancer risk

The evidence suggests that there is a statistically significantly increased risk of some types of cancer (pancreatic, oesophageal and possibly squamous cell head and neck cancer) associated with using Swedish snus after taking account of the risk arising from concurrent smoking (Boffetta et al. 2008, Broadstock 2007, Lee and Hamling 2009a, SCENIHR 2008, Lewin et al. 1998 (cited by Broadstock et al. 2007)). However, these risks from snus are substantially lower than those associated with smoking. Nicotine itself is not regarded as a carcinogen.

Compared to non-smokers, smokers are at increased risk of cancers of the lung, oesophagus, oropharyx, stomach, rectum and anus (Luo et al. 2007 Lewin et al. 1998, Lagergren et al. 2000, Ye et al. 1999, Roosaar et al. 2008, Zendehdel et al. 2008, all cited by Broadstock et al. 2007).

The risk of cancers (lung, pancreatic, oral, colon, rectum and anus) in dual smoker and snus users exceeds the risk of cancer attribute to using snus alone (Luo et al. 2007, Zendehdel et al. 2008, Boffetta et al. 2005, all cited by Broadstock et al. 2007) and Nordenvall et al. 2011).

3.10.1 Evidence summary – Swedish snus and the risk of cardiovascular disease

Note: for further details on snus and cardiovascular disease risk please refer to Appendix 10, Section 21.2, pages 283-288.

Evidence statement 8 Snus and risk of myocardial infarction

The evidence suggests that use of Swedish snus is associated with greater likelihood of fatal myocardial infarction (Broadstock 2007, Boffetta and Straif 2009, SCENIHR 2008). Duration of exposure is not consistently reported but 1 study suggested that duration of exposure was 15 years (Bolinder et al. 1994 cited by Broadstock et al. 2007). The evidence suggests that lengthy exposure is not associated with a change in resting blood pressure but there is experimental evidence that nicotine may affect lipid metabolism (SCENIHR 2008).

Smokers are at substantially increased risk of myocardial infarction compared to non-smokers and also in comparison to non-smokers who use snus (Huhtasaari et al. 1999 cited by Broadstock 2007). While former smokers currently using snus had an increased risk of acute myocardial infarction than never smokers[6], the risk in current smokers who also use snus was larger (Bolinder et al. 1994 and Huhtasaari et al. 1999, both cited by Broadstock 2007).

3.10.2 Evidence summary – snus in the context of years of life lost due to tobacco

Evidence statement 9 Snus in the context of years of life lost due to tobacco SCENIHR (2008) [+] report that the precise magnitude of health gains arising from choosing less harmful alternatives to smoking are difficult to quantify. SCENIHR (2008) [+] report that data from a modelling study (Gartner et al. 2007) suggest that the health benefit experienced by a smoker who switches to snus but would not otherwise have quit smoking is substantially greater than the risk of snus (compared to non-tobacco users). SCENIHR (2008) [+] conclude that according to Gartner's model, the overall population effect of snus is likely to be beneficial.

NRT should be an intuitively safer option than Swedish snus because it does not contain the numerous potentially harmful constituents of snus e.g. nitrosamines. In terms of NRT, a safety

issue to overcome is whether through smoking with concurrent NRT, any harm is likely to result from the maximum blood concentrations of nicotine achieved and also the potentially long term exposure to nicotine. Data from Swedish studies presented in this report appear to be based on long term exposure (i.e. decades). The same studies do not accurately estimate the volume of nicotine taken over time from cigarettes and snus combined. Studies of efficacy may inform the PDG whether NRT use with concurrent smoking leads to a reduced volume of smoking expressed as cigarettes per day.

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4 Background

4.1 Smoking harm reduction

In the past, public health strategies with respect to smoking have focused on discouraging people from starting to smoke and helping smokers to quit the habit completely. There remains a group of smokers who either want to quit but feel unable to stop abruptly or otherwise are not willing or able to quit but may be prepared to reduce the amount they smoke. The healthiest course of action for all smokers is to stop smoking but harm reduction measures attempt to limit the risks by reducing exposure to the toxic chemicals found in tobacco smoke (Royal College of Physicians 2007).

Harm reduction is defined as "policies, programmes, services and actions which aim to reduce the harm to individuals, communities and society that are associated with the use of drugs". Such measures are pragmatic, recognising that the reduction of harms may be more feasible than complete elimination of drug use (UK Harm Reduction Alliance 2011).

Following the advice of the Commission on Human Medicines (CMH) in 2009 the Medicines and Healthcare products Regulatory Agency (MHRA) approved an extension to the license for the Nicorette inhaler to include an indication for harm reduction. The product can now be used for temporary abstinence or for reduction in the number of cigarettes smoked, without an intention to quit and with no limit placed on the duration of use. The CMH has agreed the principle for all currently licensed forms of NRT (Medicines and Healthcare Products Regulatory Agency 2011b).

The smoking harm reduction principle may appeal to individuals who:

- want to quit smoking but feel unable to do so 'abruptly' (that is, they want to cut down before quitting). This is also known as pre-loading
- are not willing or able to quit, but want to reduce the harm that smoking is doing to their health (or to the health of those around them)
- want to quit smoking but are not willing or able to stop using nicotine (so they will continue to use nicotine following a successful quit attempt)
- want to stop smoking temporarily, for example, while at work.

The harm reduction approach assumes that combustion products are responsible for most of the harm associated with smoking, that nicotine is relatively safe, and that smokers continue to smoke due to nicotine addiction. Thus if an individual's level of smoking can be reduced by replacing

nicotine obtained through smoking with 'cleaner' nicotine then the individual will have a reduced intake of harmful combustion products and a reduced risk of tobacco related harm.

4.2 Toxic effects of nicotine

Nicotine is described as highly toxic by ingestion, inhalation and skin contact. The fatal dose may be as little as 40 mg in an adult but children may be more susceptible. Acute nicotine exposure may cause severe toxicity in children; TOXBASE (the clinical toxicology database for the National Poisons Information Service) recommends medical observation for ingestion of more than 0.1 mg/kg bodyweight (TOXBASE 2011).

A typical pack-per-day smoker attains a plasma nicotine concentration of 25 to 35 ng/ml by the afternoon (Henningfield & Singleton 1994).

The effects of nicotine depend on both the dose of nicotine and the speed of absorption (Fant *et al.* 2000). For example nicotine patches deliver nicotine relatively slowly and steadily transdermally (Veaugh-Geiss *et al.* 2010) whereas other NRT forms deliver nicotine rapidly through the mucosa (Guthrie *et al.* 1999; Kotiyar *et al.* 2007). No form of NRT delivers nicotine as quickly as cigarette smoking.

Nicotine acts as a central nervous system stimulant at low doses and as a central nervous system depressant at high doses (Benowitz 2008). Smokers acquire a degree of tolerance to nicotine rapidly and with a pattern during the day; the first cigarette smoked can have a greater stimulant effect than subsequent cigarettes throughout the day (Benowitz 2008).

4.3 Nicotine and drug interactions

Nicotine is understood to have numerous drug interactions. These are summarised from Stockley's drug interactions, 8th edition (Baxter 2011) in Appendix 2 for reference.

4.4 Pharmacokinetics

'Pharmacokinetics is the quantitation of the time course of a drug and its metabolites in the body and the development of appropriate models to describe observations and predict outcomes in other situations' (Rowland & Tozer 2011).

4.4.1 Absorption

Nicotine can be absorbed by ingestion, through the oral mucosa, by inhalation or transdermally. Nicotine absorbed by ingestion is subjected to extensive hepatic metabolism ('first-pass effect') so a small percentage reaches the systemic circulation. Hence the bioavailability is low by this route.

Cigarette smoke

Cigarette smoke is a very potent aerosol, which carries pyrolised particles of tobacco deep into the lung, resulting in rapid absorption of nicotine. For the inhalation route, particle size affects deposition in the airways/lung and subsequent PK outcomes. A particle size of 5 microns is a significant threshold for penetration into the lung. Furthermore, if the particle is to deposit and the contents be absorbed via the alveoli then a size range of 1 – 3 microns is desirable (Labiris & Dolovich 2003). Development of licensed NRT aerosols for the inhalation route is technically difficult and unlike cigarette smoke there is no licensed NRT product that delivers nicotine to the alveoli to a significant degree. The nicotine from the licensed NRT inhalator is intended to be absorbed via the oral mucosa, with a user action similar to that of sucking a pipe rather than that of inhaling cigarette smoke. The Electronic Medicines Compendium lists the inhalator product as an 'inhalation cartridge for oromucosal use'.

Nicotine patches

The pharmacokinetics of transdermal NRT (patches) depends on the concentration of nicotine in the patch, the nature of the membrane, the excipients used to prepare the vehicle, the area of patch-skin contact, skin temperature and the thickness of the epidermis, which varies with anatomical location (Kalia & Guy, 2001).

4.4.2 Distribution

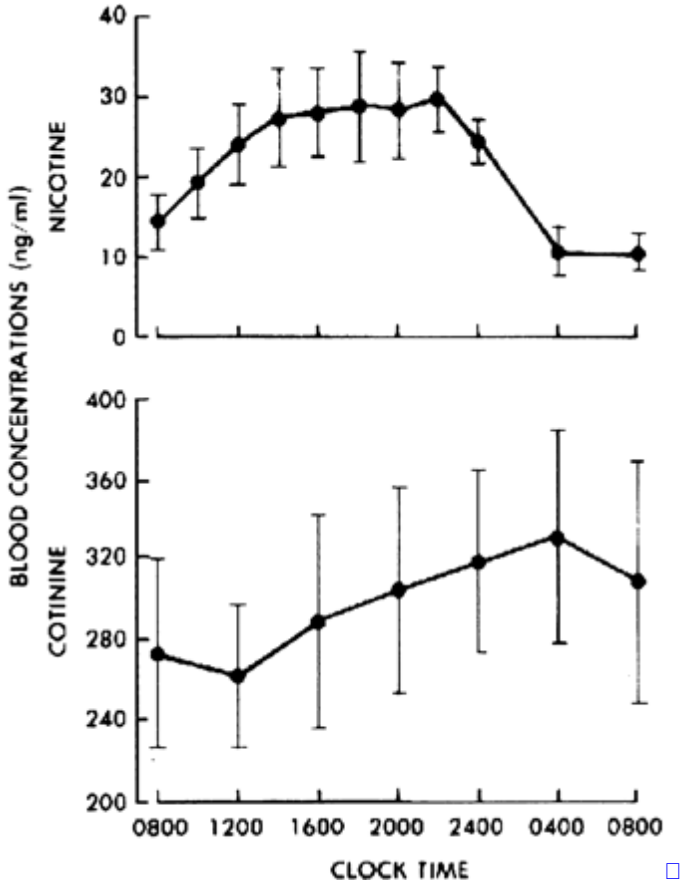
The volume of distribution of nicotine (Vd) is 2 to 3 l/kg. Rapid distribution throughout the body occurs and nicotine crosses the blood-brain barrier.

Nicotine concentrations in blood after cigarette smoking

Studies have measured blood nicotine concentrations following sustained, regular cigarette smoking throughout the day. Nicotine absorbed in the lung from cigarette smoke travels to the left side of the heart via the pulmonary vein and then to the body via the arterial circulation. Most studies report concentrations of nicotine in venous blood because it is easier to collect venous blood than arterial blood.

The figure below is reproduced from Benowitz et al. 1983 and shows the profile of blood nicotine and cotinine in eight smokers over 24 hours of unrestricted smoking (mean +/- SEM).

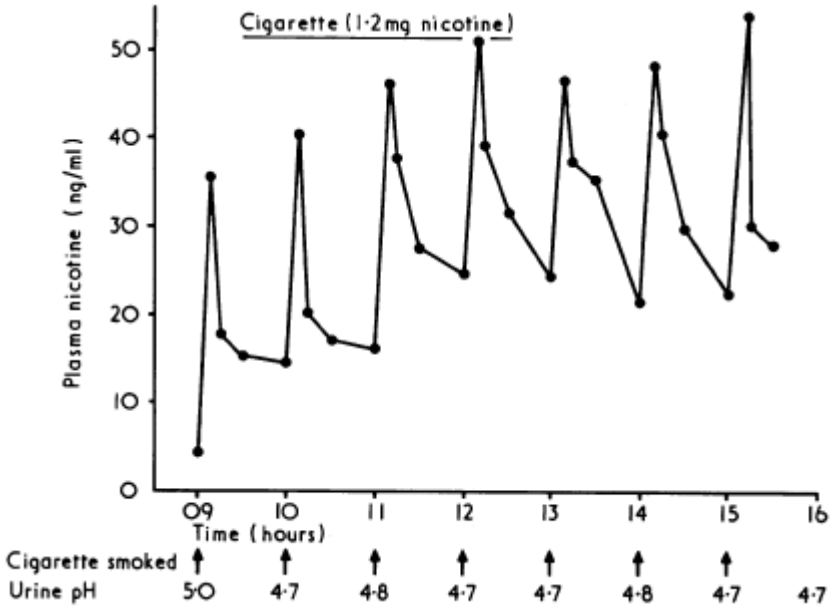
Time profile of blood nicotine and cotinine during unrestricted smoking. Data are shown as mean (±SE) in eight subjects, from Benowitz et al (1983). Reproduced with copyright license number 2863590302624, license date Mar 07 2012



The figure shows that nicotine rises through the morning, reaching a plateau concentration of just under 30ng/ml before tailing off during sleeping hours.

Results from another study (Russell et al. 1976) of a single smoker smoking a cigarette each hour are shown below.

Plasma nicotine while a subject smokes one cigarette per hour for seven hours (Russell et al. 1976). Reproduced with copyright license number 2863601269998, license date Mar 07, 2012



The figure, based on four blood samples per hour, shows the spikes in blood nicotine concentrations in an individual as plasma nicotine levels rapidly rise and fall. The general trend over the seven hour period mirrors that seen over a similar period in Benowitz et al. 1983, above.

As an individual smokes a cigarette in a series of puffs, the amount of nicotine absorbed per puff increases because in the earlier puffs vaporised nicotine condenses as it moves away from the tip, thus concentrating further along the cigarette. By the time the last puff is taken the amount of nicotine inhaled will have increased (Xie et al, 2006).

4.4.3 Metabolism

Nicotine is metabolised extensively in the liver by cytochrome P450 enzymes. A major metabolite is cotinine.

4.4.4 Excretion

The half life of nicotine is approximately 2 hours and the half life of its metabolite cotinine is approximately 16 hours (Benowitz 2008).

4.4.5 Rate of delivery

The abuse liability and potential toxicity of any drug or drug delivery system is partly related to the bioavailability of the drug and its rate of delivery. One major issue when comparing nicotine delivery systems is the rate of initial nicotine uptake and the plasma nicotine concentrations developed (Henningfield & Keenan 1993). Most NRT products deliver nicotine more slowly than smoking and the increase in blood levels is more gradual.

The table below shows the bioavailability of different nicotine technologies (from Hukkanen et al, 2005). Bioavailability is the fraction of the administered dose which reaches the systemic circulation.

Technology	**Biovailability (%)**
NRT gum 2 mg	78
NRT lozenge 4 mg	79
NRT transdermal patch 21 mg	68 - 100
NRT nasal spray 1mg	60-80
NRT inhalator	51-56
NRT sublingual tablet 2mg	65
Cigarette	80 – 90

Bioequivalence and bioavailibility

Bioequivalence is defined by Birkett (2003) as follows:

"Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards."

Consequently if the same dosage form is administered by two different routes, even though the PK values may be the same it can only be claimed that there is similar bioavailability and not that they are bioequivalent (European Medicines Agency, 1999).

4.5 Description of nicotine containing products that fall within the guideline scope

The following technologies are within the scope of this review:

- licensed nicotine containing medicines, including

- nicotine chewing gum: contain nicotine polacrilex (nicotine is bound to an ion exchange resin to maximise delivery of nicotine for absorption by the buccal mucosa)
- nicotine transdermal patches: an adhesive patch placed on the skin which delivers a dose of nicotine through the skin and into the bloodstream. Release 10, 15 or 25 mg of nicotine over a 16 hour period
- nicotine inhalers: a device which vaporises nicotine from a cartridge loaded within the device. The user puffs on the device and vaporised nicotine is absorbed via the buccal mucosa. The puffing action is similar to that of smoking a pipe, rather than a cigarette
- nicotine microtabs: a sublingual NRT formulation (dissolves under the tongue, releasing nicotine to be absorbed by the buccal mucosa
- nicotine nasal spray: each 50 µl delivers 0.5 mg of nicotine which is rapidly absorbed by the nasal membranes
- nicotine lozenges: contain nicotine hydrogen tartrate. Nicotine released is absorbed by the buccal mucosa

- non licensed nicotine containing products (e.g. e-cigarettes).

4.6 Regulated pharmaceutical products

NRT may be administered as monotherapy (where only one type of product is used) or combination therapy (where more than one product is used concurrently). This latter approach may be beneficial particularly where nicotine replacement with a patch is combined with an ad lib form (gum, lozenge, sublingual tablet, inhalator or nasal spray). The patch releases nicotine steadily but the ad lib NRT is thought to help smokers resist cue-induced cravings.

4.7 Non-regulated products

Several non-regulated products exist, including nicotine containing water, e-cigarettes, hand gels and lollipops (Royal College of Physicians 2007). Most attention in recent years has focused on e-cigarettes. Advocates of e-cigarettes suggest they represent the most promising product for tobacco harm reduction yet, since they deliver a nicotine vapour without the products of tobacco combustion which cause the major negative health effects (Heavner et al, 2010).

4.7.1 Characteristics of electronic cigarettes:

The characteristics of e-cigarettes are (Trtchounian *et al.* 2011 [+]; Vansickel & Eissenberg 2012 [-]):

- delivery of nicotine as an aerosol, within a solvent (usually propylene glycol); the process is known to users as 'vaping'
- there is a learned behaviour of drawing a gas in and out of the mouth; experienced users appear able to derive higher levels of nicotine from e-cigarettes than naive users
- there is a time and motion experience similar to smoking.

Electronic cigarettes originated in China and widely distributed via internet suppliers. They are currently unregulated as medicines or medical devices although are regulated by the General Product Safety Directive (Medicines and Healthcare Products Regulatory Agency 2011b). This directive covers consumer safety within the EU for products not covered by specific sector legislation (Medicines and Healthcare Products Regulatory Agency 2011b).

4.7.2 How the electronic cigarette works:

The e-cigarette consists of a power source (battery), a nicotine solution and an atomiser (Trtchounian *et al.* 2011) [+]. The e-cigarette releases vapour containing nicotine and the process is described as vaping (rather than smoking). It is not currently understood how nicotine is absorbed from e-cigarettes i.e. whether there is absorption through the mucosa of the mouth, or through the alveoli of the lungs. A 'COMMERCIAL IN CONFIDENCE' report commissioned by MHRA revealed the presence of potentially toxic chemicals such as diethylene glycol in the liquid (Medicines and Healthcare Products Regulatory Agency 2011a) [++].

The nicotine solution (known as e-liquid) consists of a solvent such as propylene glycol or glycerine, water and flavourings (various flavours are available) (Trtchounian *et al.* 2011) [+].

To date, smokers have tended to use e-cigarettes to help them quit smoking, rather than reduce their level of smoking (Foulds *et al.* 2011 [+]; Medicines and Healthcare Products Regulatory Agency 2011b).

The MHRA has launched a public consultation on whether/how to bring unlicensed nicotine-containing products, including e-cigarettes, into regulation. This would require all currently unlicensed nicotine-containing products on the market to apply to the MHRA for a medicines Marketing Authorisation. Furthermore the MHRA anticipate applications for approval of e-cigarettes (Medicines and Healthcare Products Regulatory Agency 2011b)

4.7.3 British Medical Association statement on e-cigarettes

The British Medical Association (BMA) has, in March 2012, advised UK doctors not to recommend the use of e-cigarettes as aids to smoking cessation or as a lower risk option than continuing to smoke. The summary of the BMA briefing states:

- "e-cigarettes are not regulated as a tobacco product or as a medicine in the UK and there is no peer-reviewed evidence that they are a safe and effective nicotine replacement therapy
- the use of e-cigarettes may undermine smoking prevention and cessation by reinforcing the normalcy of cigarette use in public and workplaces
- health professionals should not recommend the use of e-cigarettes as smoking cessation aid or a lower risk option than continuing to smoke due to a lack of evidence of their safety and efficacy."

(BMA, 2012)

4.8 Safety and risk

Risk is defined as the probability of an adverse outcome based upon the exposure and potency of the hazardous agent(s). Hazard refers to intrinsic toxic properties (Casarett & Doull 2008).

An assessment of the safety of a drug includes the detection, assessment, understanding and prevention of adverse effects and is also known as pharmacovigilance or post market surveillance (Casarett & Doull 2008).

The main concern regarding the harm reduction approach is that it proposes a longer term exposure to NRT than has been previously encountered when NRT is used for smoking cessation programs. Cessation involving NRT products typically lasts two or three months during which time abstinence is advised. There are suggestions that approval of NRT for smoking cessation required a lower level of safety evidence because the use in cessation was expected to be of a short duration (typically 12 weeks) and in the absence of cigarette smoking, the individual would be exposed to less nicotine through NRT administration than if he/she continued to smoke (Food and Drug Administration 2010).

The pharmacological nature of nicotine presupposes four main safety concerns for the long term use in a smoking reduction initiative:

- Concerns about the carcinogenic properties of nicotine

- Concerns about the effects of nicotine on the cardiovascular system
- Concerns about the risk of dependence on the NRT product itself
- Concerns that encouraging reduction may make smokers less likely to quit.

In 2007, the Royal College of Physicians, in their report 'Harm reduction in nicotine addiction: helping people to quit' concluded: "evidence on the safety of long term use of NRT is lacking, but there are no grounds to suspect appreciable long term adverse effects on health" (Royal College of Physicians 2007).

Another issue regarding adopting a harm reduction approach is that greater use of therapeutic nicotine and availability of nicotine preparations in the home may represent a greater risk of childhood poisoning. The Summary of Product Characteristics (SPC) for nicotine patches warns that the contents may cause severe toxicity in small children and may be fatal, hence used patches should be disposed of carefully. All NRT medications represent some risks for childhood exposure; the high concentrations of nicotine in e cigarette cartridges and refill bottles may constitute considerable risk of harm (Cobb *et al.* 2010)

4.8.1 FDA Workshop, 2010

Proceedings of a US Food and Drug Administration (FDA) workshop address issues particularly relevant to this review (Food and Drug Administration 2010). The agenda was as follows:

- What is known about the long-term safety of nicotine from animal studies?
- What is known about the long-term safety of nicotine from human studies?
- What is known about abuse of/ addiction to NRT products?

Daniel Mellon, FDA: Non clinical requirements for Nicotine Replacement Therapy Products 2010

The presentation highlighted that some data are lacking, which are necessary to support a indication for long term use of NRT. When FDA approved NRT to support smoking cessation the following issues were highlighted:

- Approval of NRT for use in smoking cessation was granted in the knowledge that smokers had been receiving nicotine from cigarettes at levels comparable to those likely to be achieved through using NRT
- When the NRT products were approved for cessation, this was done in the absence of long term toxicity data (the period of use in a quit attempt is typically 12 weeks (Joint Formulary Committee 2011)

- The current non clinical requirements for a chronic indication are chronic toxicity in two species and carcinogenic assessment in two species. There are gaps in the data for nicotine, namely route specific concerns and questions concerning carcinogenicity.
- Safety of impurities would have to be re-evaluated to take into account the increased duration of use.

5 Methods

5.1 Aims of the review

The aims of this review are:

- to summarise evidence on the safety, or risks, of tobacco harm reduction strategies, both in people who continue to smoke and in smokers who quit but continue to use NRT products indefinitely
- to summarise the pharmacokinetic factors which influence the safety, or risks, of tobacco harm reduction strategies when used as above, principally NRT products.

5.2 Scope of the review

The scope of this review is bounded by the scope of the NICE guideline, available at: http://guidance.nice.org.uk/PHG/Wave23/23/Scope/pdf/English.

The scope of this review is summarised in the table below.

PICO table to summarise the review scope

Population

Included groups are smokers of all ages who:

- want to quit smoking but feel unable to do so abruptly or
- smoke and do not feel willing or able to quit but want to reduce the amount they smoke.

Excluded groups:

- Pregnant women.

Intervention

Included products:

- licensed nicotine containing medicines (both prescription only medications and those available over the counter)
- non licensed nicotine containing products (e.g. e-cigarettes).

Excluded products:

- Tobacco in any of its forms and any tobacco containing product, including potential reduced exposure products (PREPs)
- Medicines that do not contain nicotine but that are licensed for use in the UK for smoking cessation: bupropion and varenicline.

Comparison

- Safety, risk and pharmacokinetic profiles of different products are compared.
- No intervention – data from studies of people who smoke.
- Possibly data from smoking cessation programmes.
- Data from studies of ex-smokers

Outcomes

- Adverse events, serious adverse events, tolerability. These may be patient- or clinician-reported.
- Pharmacokinetic profile including Cmax, Tmax, t1/2 , AUC, bioavailability
- Drug interactions

This review studies NRT products used alone and in combination, in people who continue to smoke and also in people who stop smoking altogether. Of particular interest is evidence for the safety of using NCPs as a long term smoking harm reduction strategy.

NICE emphasised that the review should explore whether special pharmacokinetic or safety considerations arise from the evidence, concerning use of NCPs as part of smoking harm reduction in the following groups:

- People with low socio-economic status
- People in black and ethnic minority groups
- Sub-groups based on age
- People taking psychiatric medication
- Breast feeding mothers.

5.3 Subsequent decision to review evidence on Swedish snus

After reviewing evidence presented by Cedar in October 2011, the PDG concluded that the evidence presented to date does not answer the question of whether it is safe to use medicinal NRT indefinitely (e.g. as a life-long strategy), the concern being whether nicotine itself causes harm after long term exposure. The PDG noted that in Sweden many people are exposed to nicotine by using snus, a type of moist, oral tobacco. The smokeless tobacco industry attributes low smoking-related mortality rates that are observed for Sweden to the fact that Swedish men in particular tend to use snus as an alternative to smoking cigarettes (ESTOC, 2012). The implication is that Swedish snus may be, relatively speaking, a 'cleaner' source of nicotine than other forms of tobacco. Some public health academics have stated that although the use of snus is not hazard-free, it is less harmful than cigarette smoking (Britton & Edwards, 2008). The PDG requested a review of the safety of long term exposure to nicotine from snus, as a surrogate for long term exposure to NRT. This is presented in Section 18.

5.4 Research questions

Question 1

What specific risks have been associated with the technologies within the scope of the review? What adverse events or serious adverse events have been identified and how frequently do they occur? Is there any evidence that use of the technologies may cause significant drug interactions? Of particular concern is whether there are any interactions between nicotine and psychiatric medication since smoking prevalence is much higher among individuals with mental illness.

Question 2

What data are available to support the safety of long term use of the technologies?

Question 3

What are the risks associated with use of NCPs which are currently unlicensed? (Questions especially relevant to the e-cigarette: What is the nature of the absorbent material? Are there

other components present in the nicotine solution used in this device? Do these represent risks to the user? Are any harmful chemicals released when the nicotine solution is heated?)

Question 4

Do the data suggest the technologies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Question 5

Do the data suggest the combination of nicotine replacement therapies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Question 6

Are kinetic data available which allow comparison of the relative bioavailability of different technologies i.e. maximum (peak) concentration (Cmax), time to peak concentration (Tmax) and half life (t ½)?

Question 7

Do the data support the safety of an approach where smokers receive doses of medicinal nicotine (potentially by different routes) while continuing to smoke. Is there a greater risk of adverse effects?

Question 8

There are marked differences in smoking rates among socioeconomic groups, Black and minority ethnic (BME) groups, age (lifestage) and people with mental illness. Do the data suggest there may be inequalities among these groups with respect to the risk, safety and pharmacokinetics of smoking harm reduction technologies?

5.5 Literature search methods

The review protocol describes in detail the literature search methods and is available in full in Appendix 3. The methods are summarised here.

The aim of the literature search was to identify evidence on the safety, risks and pharmacokinetic profiles of tobacco harm reduction strategies (principally non-tobacco based, nicotine containing products). The literature search sought evidence that is:

- of the highest quality available, considering the hierarchy of evidence
- applicable to the UK
- valid.

The literature search was constructed and performed by Information Specialists at SURE, Cardiff University (FM).

The literature search used:

- 18 electronic databases to identify sources made available since 1980
- 7 websites representing pharmacological databases
- 28 websites representing tobacco and smoking research organisations, public health organisations and regulatory organisations.

All searches were restricted to English language, but were not restricted to studies of humans.

5.6 Call for evidence via NICE

To enable interested parties to submit evidence to be considered for this review, NICE issued a call for evidence via its website:

http://guidance.nice.org.uk/PHG/Wave23/23/EvidenceConsultation.

The period for submission of evidence was between 4th August 2011 and 30th August 2011.

5.7 Study selection

Two reviewers (SJ and AC) independently reviewed all titles and abstracts identified. Disagreements were resolved by consensus, and there was no need to consult a third reviewer. The following groups of study were particularly sought:

- randomised controlled trials and systematic reviews of randomised controlled trials of smoking harm reduction interventions that meet the scope of this review and report safety data
- Non randomised studies with a strong focus on safety and risks of using NRT
- pharmacokinetic studies (both randomised and non randomised), particularly those with a high frequency of measurement of pharmacokinetic parameters over the study period, in order to inform the pharmacokinetic model

- studies of any design that address special pharmacokinetic or safety considerations that arise, concerning use of NCPs as part of smoking harm reduction in the following groups:
    - People with low socio-economic status
    - People in black and ethnic minority groups
    - Sub-groups based on age
    - People taking psychiatric medication
    - Breast feeding mothers.

5.8 Study quality assessment

Quality of included studies was assessed and a quality rating (++, + or -) applied using the quality appraisal checklist for quantitative intervention studies, from the NICE CPHE document 'Methods for the development of NICE public health guidance (second edition)', available at: http://www.nice.org.uk/media/2FB/53/PHMethodsManual110509.pdf.

5.9 Data extraction

The reviewers (SJ and AC) devised and used a data extraction form for each included study. The source data for this review are presented in evidence tables for each research question in Appendices 4-7.

5.10 Evidence synthesis

The evidence is presented in two ways:

- evidence summaries i.e. concise statements that summarise the findings and strength of the evidence to answer the research questions
- pharmacokinetic model i.e. a simulated set of scenarios (based on numerous sources of data) that illustrate graphically the profile of plasma nicotine achieved over time through use of different NCPs, together with narrative interpretation.

6 Results

The literature search identified 5860 references, which were handled using Reference Manager v12 software. 81 papers were shortlisted as sources of evidence. Evidence tables are provided as Appendices 4-7.

6.1 Results: question 1

Question 1: What specific risks have been associated with the technologies within the scope of the review? What adverse events or serious adverse events have been identified and how frequently do they occur?

6.1.1 Characteristics of studies included for question1

Volume	▪ 9 randomised controlled trials ▪ 2 non randomised intervention studies ▪ 1 systematic review & meta analysis of randomised trials ▪ 1 resource for health professionals
Quality ++, +, -	Overall, evidence quality is moderate (+) to strong (++): ▪ (Batra *et al.* 2005) + ▪ (Bolliger *et al.* 2000) ++ ▪ (Carpenter *et al.* 2003) + ▪ (Carpenter *et al.* 2004) ++ ▪ (Etter *et al.* 2002) ++ ▪ (Haustein *et al.* 2004) + ▪ (Joseph *et al.* 2008) + ▪ (Kralikova *et al.* 2009) + ▪ (Moore 2011) ++ ▪ (Rennard *et al.* 2006) ++ ▪ (Wennike *et al.* 2003) + ▪ (Malone *et al.* 2003) + ▪ (McNally 2009) +
Applicability (high, moderate, low)	Moderate: the trials are of smoking harm reduction using licensed nicotine replacement therapies in people who continue to smoke. However the primary outcomes were measures of efficacy in smoking reduction. The period of use of NRT does not extend beyond 18 months. The studies on serotonin have poor applicability to NRT, because the participants absorbed nicotine from cigarette smoke.
Consistency	The 9 randomised trials are generally consistent in their findings on adverse events. In the meta analysis (Moore 2011) [++] there was generally high consistency, but substantial heterogeneity of results in the meta-analysis of serious adverse events. Evidence consistently suggests that smokers have poorer psychological outcomes than non-smokers.

6.1.2 Evidence summary – adverse events

Evidence from ten randomised controlled trials strongly suggests that adverse events are common when NRT is used for smoking harm reduction, but these tend to be mild or moderate and are rarely severe (Batra *et al.* 2005 [+]; Bolliger *et al.* 2000 [++];Carpenter *et al.* 2003 [+]; Carpenter *et al.* 2004 [++]; Etter *et al.* 2002 [++]; Haustein *et al.* 2004 [+]; Joseph *et al.* 2008 [+]; Kralikova *et al.* 2009 [+]; Rennard *et al.* 2006 [++]; Wennike *et al.* 2003) [+]. No authors have attributed serious adverse events to NRT when used as part of smoking harm reduction. NRT is generally well tolerated when used in this setting. Frequently reported adverse events depend on the route of administration but include throat irritation, coughing, nausea, vertigo / dizziness, vomiting or palpitations. There is no evidence of increased cardiac events in patients with existing cardiac disease treated with NRT for 18 months (Joseph *et al.* 2008) [+]. The duration of use of NRT in these studies varied from 1 month to 18 months. Follow up did not extend beyond 24 months, so the randomised trials do not provide safety data for longer term use.

Evidence from a meta-analysis (Moore 2011) [++] of 2767 participants drawn from several of the randomised trials cited above plus two unpublished sources corroborates the findings shown above. The unpublished trials used NRT for 9 months and 12 months. The results suggest that there is no difference between NRT (used for between 6 and 18 months) and placebo in terms of mortality, serious adverse events or discontinuation of therapy due to adverse events, but that nausea occurs more frequently with active NRT (OR 1.69, 95% CI 1.21-2.36). Use of the meta-analysis has two caveats:

- the meta-analysis re-iterates a substantial body of the same data from randomised trials cited above (Batra *et al.* 2005 [+]; Bolliger *et al.* 2000 [++]; Etter *et al.* 2002 [++]; Haustein *et al.* 2004 [+]; Rennard *et al.* 2006 [++]; Wennike *et al.* 2003) [+].
- there was substantial heterogeneity of results in the meta-analysis of serious adverse events.

6.1.3 Evidence summary – cardiovascular risk markers

Evidence from five randomised trials (Batra *et al.* 2005 [+]; Bolliger *et al.* 2000 [++]; Joseph *et al.* 2008 [+]; Kralikova *et al.* 2009 [+]; Rennard *et al.* 2006) [++] and one non-randomised, controlled study (Haustein *et al.* 2004) [+] suggests that there are no substantial changes in risk markers for cardiac disease in people treated with NRT as part of smoking harm reduction. This evidence is cited from a Cochrane review of the randomised trials (Stead & Lancaster 2007) [+]. Risk markers

studied included white blood cell count, fibrinogen, CRP, lipids, F2-isoprostanes, NNAL, 1-HOP. One study (Bolliger *et al.* 2000) [++] found favourable changes in both NRT and placebo groups. No study reported increases in risk markers for cardiovascular disease arising from NRT. Follow up did not extend beyond 24 months.

6.1.4 Nicotine, psychological outcomes and serotonin

There is established evidence that smokers have poorer psychological outcomes than non-smokers, as summarised by McNally (2009) [+]. Evidence is lacking on whether long term exposure to NRT lowers serotonin levels. A limited amount of data from a subgroup analysis of depressed human subjects suggests that smoking correlates with reduced serotonin levels (Malone 2003) [+]. A study of human brain tissue found a similar association (Benwell et al. 1990) [+]. One study in rats found that nicotine exposure over a 40 day period correlates with reduced serotonin (Benwell and Balfour, 1979) [+].

Further study details

Batra, 2005 [+]

This study randomized 364 healthy smokers with no intention of quitting smoking in the next month to either nicotine gum or placebo for 12 months treatment. Adverse events were assessed up to 12 months from study outset. In total there were 506 adverse events in the treatment group versus 370 in the placebo group. Only hiccups was reported as statistically significantly higher in the active treatment group (28 events) than in the placebo group (3 events), $p<0.0001$. The authors concluded that no serious adverse events arose from the nicotine treatment, and there were no discontinuations of use due to adverse events. There were no statistically significant changes in any cardiovascular risk markers (white blood cell count, fibrinogen CRP) between baseline and month 12 in the 20 successful sustained reducers.

Bolliger, 2000 [++]

This was a randomized study of nicotine inhaler versus placebo in 200 healthy smokers who were unable/unwilling to quit, treated for between four months and 18 months, and followed up until the 2 years from study outset. There were 227 adverse events in the active treatment group and 193 adverse events in the placebo group. There were 53 serious adverse events in total, none of which were attributed to nicotine treatment. Throat irritation and coughing were more common in the active treatment group than the placebo group (throat irritation: 14 events versus 4 respectively, 95% CI for OR 1.13-15.6; coughing: 13 events versus 4 respectively, 95% CI for OR 1.1-

10.6). The study did not report point estimates for odds ratios. In 19 NRT treated patients who sustained reduced smoking at 24 months there was a change in a range of risk markers for cardiac disease including cholesterol/HDL ratio, haemoglobin and pulse rate.

Carpenter 2003 [+]

This study randomized 67 smokers to a reduce to quit intervention, i.e. choice of NRT (patch, gum or inhaler) or no medication for 4 weeks prior to setting a quit date (with behavioural support), versus standard treatment, which was to offer NRT only if patients set a quit date at outset. The proportion of patients experiencing any adverse event while using NRT was 48% in the reduce to quit group versus 50% in the usual care group X^2 =0.1, p=0.9. All adverse events were mild, resolved without treatment and did not cause subjects to withdraw from the study.

Carpenter 2004 [++]

This larger (n=616) subsequent randomized study by Carpenter also studied smokers who were not interested in quitting smoking, using a reduce to quit intervention: NRT (gum or patch) was described and offered for 6 weeks, at which point NRT was only made available if a quit date was set. A second study arm was motivational support, with provision of NRT if a quit date was set (cessation group), and a third control arm provided no intervention. The proportion of NRT treated patients experiencing adverse events was greater in the reduce to quit group (i.e. with concurrent smoking) at 39 patients (21%) compared to those using NRT in the cessation group: 17 patients (9%); X2 = 13.8, P<0.01. In total 54 subjects reported 61 adverse events; 92% were mild, 7% were moderate and 2% were severe (1 case of vertigo/dizziness requiring hospitalisation). There were no study withdrawals due to adverse events. The rate of serious adverse events was 0.3%.

Etter, 2002 [++]

This study randomized 923 smokers to NRT (choice of patch, gum or inhaler) or equivalent placebo products, or to no treatment. Subjects in the first two groups could change products or combine the use of products. The paper provided only very brief adverse event data, stating that two patients in the NRT group died during the study, one of cerebral metastasis from bronchial adenocarcinoma and one from cerebral haemorrhage. The rate of serious adverse events was not statistically different between the nicotine and placebo groups (p=0.25).

Haustein 2004 [+]

This non randomised, prospective study grouped non abstainers treated with NRT as reducers (where CPD was <50% of baseline) and relapsers (where CPD was > 50% of baseline) and

measured hemorheological parameters over a 26 week period. There was no worsening of values of hemorheological parametersin reducers or relapsers compared to baseline including plasma fibrinogen, plasma viscosity, haematocrit, reactive capillary flow, erythrocyte deformability, expired CO, tcpO2, plasma SCN, WBC, platelets, blood pressure and heart rate. In general reducers had better (healthier) values than relapsers.

Joseph 2008 [+]

In this randomized trial, 152 smokers with existing heart disease and who were unable or unwilling to quit smoking within the next 30 days were allocated to either an 18 month counselling smoking harm reduction programme, supported by a choice of nicotine gum or nicotine patch, or to usual care i.e. a single, brief in person visit, stressing the importance of abstinence from smoking. Maximum follow up was 18 months from study outset. There were no statistically significant differences between treatment groups at any follow up point (1, 3, 6, 12 and 18 months) in prevalence of angina or, in patients reporting symptoms of angina in the last week, frequency of those symptoms. There was also no statistically significant difference in the need for urgent cardiac care at any follow up point, with the exception of at 6 months, where zero patients in the harm reduction arm required care, compared to 5 patients in the usual care group (p=.021, student's t test). Markers of inflammation and oxidation including WBC count, fibrinogen, CRP and F2-isoprostanes showed minimal change. Total NNAL and 1-HOP decreased slightly but to a similar extent in both treatment groups.

Kralikova 2009 [+]

This study randomly allocated 314 smokers to either NRT (choice of nicotine gum or inhaler) or placebo (choice of gum or inhaler). Random allocation was 2:1 (NRT:placebo). Participants were urged to reduce their level of smoking, or quit smoking, with both aims given equal emphasis. Treatment duration was 6 months, plus a three month period of voluntary tapering of therapy. Follow up assessment was at 9 months and at 12 months. There were more adverse events in the NRT group (82 events in 209 subjects) than the placebo group (26 events in 105 subjects). Of the 82 events in the NRT group, 47 (57%) were mild, 28 (34%) moderate and 7 (9%) severe. Of the 26 events in the placebo group, 22 (85%) were mild, 3 (12%) moderate and 1 (4%) severe. The most common events were throat/mouth irritation and cough. Signs of possible nicotine-related systemic events were reported in 6 subjects in the NRT group (2 nausea, 3 vertigo, 1 palpitation) compared to 1 in the placebo group (vertigo). All adverse events were tolerated. Amongst reducers there was little change in white blood cell count.

Moore 2010 [++]

This study was a meta-analysis of 2767 participants studied in a total of seven randomised controlled trials. Six are already cited in this review (Batra *et al.* 2005 [+]; Bolliger *et al.* 2000 [++]; Etter *et al.* 2002 [++]; Haustein *et al.* 2004 [+]; Rennard *et al.* 2006 [++]; Wennike *et al.* 2003) [+] whereas Moore and co workers [++] also included data from two unpublished smoking harm reduction trials (Haustein: 980 CHC 9021-0013 and Wood-Baker 98 NNCG-017). The meta analysis found that there was no statistically significant difference between NRT and placebo groups in the odds of death (OR 1.0, 95% CI 0.25-4.02), serious adverse events (OR 1.09, 95% CI 0.79-1.50) or discontinuation of therapy due to adverse events (OR 1.27 95% CI 0.64-2.51). Participants in the NRT group were more likely to experience nausea (OR 1.69 95% CI 1.21-2.36).

Whilst this meta-analysis has greater power to detect differences in rates of adverse events than the individual trials, two caveats should be considered:

- presentation of the original studies plus the meta-analysis presents some of the data twice.
- The extent of heterogeneity in the meta-analysed studies was low in all analyses except for serious adverse events, where $I^2 = 55.3$, p=0.048, meaning that approximately 55% of the variation of results seen in the original studies arose from heterogeneity, rather than chance (interpretation based on Centre for Reviews and Dissemination 2008 'Systematic reviews. CRD's guidance for undertaking reviews in health care, University of York). Authors of a Cochrane review (Stead & Lancaster 2010) [+] considered it acceptable to meta-analyse efficacy data from many of the trials cited here (but did not meta-analyse adverse event data) whereas authors of a third systematic review (Hughes 2007) opted not to perform meta-analysis with (to a degree) the same source data, citing methodological differences and heterogeneity of results between as two of their reasons.

Rennard, 2006 [++]

This study randomly allocated 429 smokers to either nicotine inhaler or placebo inhaler for a 12 month treatment period with follow up at 15 months. Participants were instructed to reduce their smoking as much as possible with a non mandatory goal of quitting from month 6. Adverse events were common: reported by 159 subjects in NRT group and 147 subjects in the placebo group. Most adverse events were mild or moderate and unrelated to study treatment. The incidence of

adverse events that were considered possibly treatment related was 11 in active group and 5 in placebo group. 28 serious adverse events occurred (15 events were reported by 9 subjects in NRT group and 13 events were reported by 11 subjects in placebo group). None were related to study treatment. The most common treatment related adverse events were throat irritation (15 in the NRT group and 6 in the placebo goup, p=NS) and cough (12 in the NRT group and 5 in the placebo group, p=NS). There was no difference across treatment groups in any cardiovascular risk marker.

Wennike, 2003 [+]

This study randomly allocated 411 smokers who were unwilling or unable to quit smoking to either nicotine gum (with dose titrated to FTND score) or placebo gum. Treatment duration was 12 months with follow up at 12 months and 24 months. There was no statistically significant difference in the number of adverse events in the NRT group (166) compared to the placebo group (147). Two patients in each study arm withdrew from treatment early due to adverse events. Six subjects in the NRT group experienced nausea, vomiting or palpitation compared with four subjects in the placebo group. Of the adverse events in the NRT group, 61% were mild, 34% were moderate and 4% were severe. None of 21 serious adverse events were assessed as related to study treatment.

McNally (2009) [+]

This resource for smoking cessation practitioners reported that smoking is identified as a significant risk factor for the onset and worsening of mental health problems, particularly depression and anxiety {McNally, 2009 8983 /id}.

Malone et al. (2003) [+]

This study measured CSF 5-HIAA (a metabolite of serotonin) in a subgroup of 162 depressed patients in a larger study of 347 smokers and non smokers. In depressed subjects CSF 5-HIAA level was negatively correlated with the amount of cigarette smoking, suggesting that higher levels of smoking are associated with lower levels of serotonin. This study cited an experiment performed in rats (Benwell and Balfour, 1979) [+] which suggested that rats injected with nicotine for 40 days had lower brain levels of serotonin and 5-HIAA. Another study cited by Malone et al. (2003) (Benwell et al. 1990) [+] of human brain tissue from cadavers of smokers (7-20 cigarettes/day for 30 years), also suggested that smoking was associated with lower levels of brain serotonin and 5-HIAA.

6.2 Results: question 2

Question 2: What data are available to support the safety of long term use of the technologies?

6.2.1 Characteristics of studies included for question2

Volume	▪ 1 large, multicentre randomised controlled trial of smoking cessation in patients with early stage COPD ▪ 4 randomised controlled trials of NRT smoking cessation in patients with cardiovascular disease ▪ 1 prospective study of NRT in patients with coronary artery disease ▪ 2 retrospective studies of NRT used in intensive care
Quality ++, +, -	▪ (Joseph *et al.* 2008) [+] ▪ (Joseph *et al.* 1996) [+] ▪ (Lee *et al.* 2007) [-] ▪ (Leja *et al.* 2007) [+] ▪ (Mahmarian *et al.* 1997) [+] ▪ (Murray *et al.* 1996) [+] ▪ (Murray *et al.* 2009) [+] ▪ (Paciullo *et al.* 2009) [-] ▪ (Tzivoni *et al.* 1998) [+]
Applicability (high, moderate, low)	The best available evidence comes from an indirect source: a study of NRT in smoking cessation, but where a large number of patients continued to smoke. Cardiac adverse events are relevant because nicotine has cardiovascular effects. However the studies of NRT in patients with existing cardiovascular disease are of relatively short duration NRT only.
Consistency	There is inconsistency between the higher quality studies that find no evidence of increased harm through use of NRT and poorer quality retrospective studies that suggest there may be increased mortality through the use of NRT in intensive care patients.

6.2.2 Evidence summary

There are no studies available of NRT safety used in SHR in the long term (maximum duration of NRT use is 5 years). The strongest evidence available for the long term safety of NRT with concurrent smoking comes from a large subgroup of patients studied the five year Lung Health Study of NRT in smoking cessation, where a large patient group continued to smoke and continued to use NRT (Murray *et al.* 1996) [+] (Murray *et al.* 2009) [+]. The results of this multicentre randomized controlled trial suggest that long term use of NRT is not associated with an increased

incidence of harm, including cardiovascular events or cancer, with the latest analysis of outcome at 12.5 years from study outset.

Six studies evaluated the safety of NRT in patients with cardiac disease (Mahmarian *et al.* 1997) [+] (Paciullo *et al.* 2009) [-] (Leja *et al.* 2007) [+] (Tzivoni *et al.* 1998) [+] (Joseph *et al.* 2008) [+] (Joseph *et al.* 1996) [+] and did not find any increased incidence of cardiovascular events or any other adverse events.

Two retrospective case-control studies have found an increased mortality associated with nicotine replacement therapy among critically ill patients (Paciullo *et al.* 2009) [-](Lee *et al.* 2007) [-]. However the confidence intervals around the odds ratios for mortality are wide indicating significant uncertainty surrounding the size of the effects..

6.2.3 Further Study details

Murray et al, 1996 [+]

The Lung Health Study, a multicentre randomized controlled trial involving 5,887 subjects provides good quality evidence for the long term safety of NRT. The population was all aged between 35 and 60 years and had evidence of early stage Chronic Obstructive Pulmonary Disease (COPD). The study randomized 3,923 participants to a special intervention which included a smoking cessation program. All subjects were encouraged to stop smoking and provided nicotine gum (nicotine polacrilex). Over the course of the five year study, smoking behaviour and NRT gum use were regularly monitored. By the end of the study 15% of quitters were still using NRT gum and 5% of smokers were still using NRT gum. Adverse effects were reported by the subjects but hospitalization by members of the special intervention group was reviewed by an independent panel of physician, with particular emphasis on cardiovascular or respiratory conditions and cancer. Ex-smokers who used gum reported a lower incidence of hospitalisation (overall 2.23 hospitalisations per 100,000 person-days) than ex-smokers who did not use gum (5.78). This relationship was maintained in all years of the study. No serious adverse events were reported during the study. Data on side effects were collected at regular intervals throughout the study (Murray *et al.* 1996) [+].

Murray et al, 2009 [+]

Participants in the original Lung Health Study were followed up for a further 7.5 years to assess a relationship between NRT use and cancer. Of the subjects randomized to smoking intervention, 3,320 (85%) were studied. During the five year period smoking behaviour and NRT use had been

recorded. Subsequently 75 lung cancers, 33 gastrointestinal cancers and 203 cancers from all causes were identified in this cohort. Regression modeling indicated no relationship between NRT use and subsequent lung cancer (p = 0.67), gastrointestinal cancer (p = 0.61) or cancer of any cause (p = 0.94) (Murray *et al.* 2009) [+].

Joseph et al, 1996 [+]

This randomised, double blind trial recruited 584 participants (576 male) all of whom had a history of serious cardiovascular disease, were over 45 years old, and smoked at least 15 cigarettes a day. The participants were required to give up smoking and were randomized to nicotine patches or placebo patches, they were then monitored for 14 weeks. During the trial 126 serious adverse events were reported, 62 in the placebo group, and 64 in the nicotine patch group. No statistically significant difference in adverse events or side effects were found between the two groups (Joseph *et al.* 1996) [+].

Leja et al, 2007 [+]

55 smokers were recruited to this trial and randomised to nicotine patches or placebos patches.. All smoked at least 20 cigarettes per day and had stress induced myocardial iscaemia. The participants smoked as normal for the first week, and then were encouraged to give up smoking for a further three weeks. No statistically significant differences in safety outcomes (total or ischemic perfusion defect size) were reported in patients from either group (Leja *et al.* 2007) [+].

Tzivoni et al, 1998 [+]

This was a two week randomised, controlled, double blinded trial. 106 smokers with a history of cardiovascular disease were randomised to nicotine patches or placebo patches. The number of cigarettes smoked per day was recorded and patients assessed for cardiovascular effects. Three patients experienced worsening angina, two of whom were randomised to nicotine patches. There were no other statistically significant changes in cardiovascular symptoms in either group (Tzivoni *et al.* 1998) [+].

Joseph et al, 2008 [+]

In this randomized trial, 152 smokers with existing heart disease and who were unable or unwilling to quit smoking within the next 30 days were allocated to either an 18 month counselling programme, with a choice of nicotine gum or nicotine patch, or to usual care i.e. a single, brief in person visit, stressing the importance of abstinence from smoking. Maximum follow up was 18

months from study outset. There were no statistically significant differences between groups in prevalence or frequency of angina at any follow up point. There was also no statistically significant difference in the need for urgent cardiac care at any follow up point, with the exception of at 6 months, where zero patients in the harm reduction arm required care, compared to 5 patients in the usual care group (p=.021, student's t test). Markers of inflammation and oxidation including WBC count, fibrinogen, CRP and F2-isoprostanes showed minimal change. Total NNAL and 1-HOP decreased slightly but to a similar extent in both treatment groups (Joseph *et al.* 2008) [+].

Mahmarian et al, 1997 [+]

40 smokers (35 male) with existing heart disease, and a strong desire to quit smoking, were given 14 mg nicotine patches for 3 or more days followed by 21mg patches for 3 or more days. Patients had an abnormal exercise SPECT to be included in the study, and these were repeated after after a minimum of 3 days with each patch. Patients were weaned off anti-angina medication prior to the study commencing. During treadmill excersice testes, rest heart rates were similar at baseline and during treatment. 14 patients had exercise induced ST segment depression during the baseline tests. In these patients the time to 1mm ST segment depression significantly increased from 352 at baseline to 436 on 14mg nicotine and 417 on 21mg nicotine. Four patients had resolution of their ST segment depression after the baseline study. A significant reduction in the total exercise induced perfusion defect size (PDS) was observed from baseline (17.5) to treatment with 14mg (12.6)and 21mg (11.8) patches. This was associated with a significant reduction in cigarettes smoked per day and exhaled CO levels. This occurred despite significant increases in treadmill exercise duration and nicotine and cotinine blood levels.
11 of the 36 patients had a ≥9% increase in their total PDS from baseline to 14mg patches and 10 of 34 patients from baseline to 21mg patch (expected = 1 – 2 patients in 36). Patients whose defects decreased ≥9% had a significantly greater reduction in CO and a lesser increase in serum nicotine levels.
Four patients withdrew from the study, two due to adverse effects from the nicotine patches (nausea and vomiting) (Mahmarian *et al.* 1997) [+].

Paciullo et al, 2009 [-]

This retrospective matched cohort pilot study included smokers treated as patients in intensive care following coronary artery bypass graft (CABG) surgery and compared those treated with NRT patch (7, 14 or 21mg) (n=67) with controls (n=67). There was no increased rate of mortality associated with use of the NRT patch. In the subgroup who underwent off pump CABG, the study found a significant increase in mortality in the NRT treated group (OR 6.49, 95% CI 1.29-32.56 (Paciullo *et al.* 2009) [-].

Lee et al, 2007 [-]

This retrospective study compared critically ill smokers (with numerous primary diagnoses) admitted to a medical ICU and treated with (RT (n=90) with control smokers who were admitted to the same ICU but did not receive NRT (n=90). NRT was an independent risk factor for hospital mortality with an odds ratio of 24.6 (95% CI 3.6-167.6), p=0.0011. When adjusted for severity of illness and invasive ventilation, NRT was an independent risk factor for hospital mortality with an odds ratio of 19.7 (95% CI 3.5-109.9)(Lee *et al.* 2007) [-].

6.3 Results: question 3

What are the risks associated with use of NCPs which are currently unlicensed? (Questions especially relevant to the e-cigarette: What is the nature of the absorbent material? Are there other components present in the nicotine solution used in this device? Do these represent risks to the user? Are any harmful chemicals released when the nicotine solution is heated?)

6.3.1 Characteristics of studies included for question 3

Volume	▪ 1 randomized crossover study of acute effects of e-cigarettes ▪ 1 prospective study of acute effects of e-cigarettes ▪ 2 laboratory based, chemical analyses of constituent chemicals of e-cigarettes ▪ 1 physical evaluation of e-cigarettes ▪ 1 survey of e-cigarette users ▪ 1 media report
Quality ++, +, -	Overall, evidence quality is moderate, with two laboratory studies of high quality: ▪ BBC 2011 - ▪ (Bullen *et al.* 2010) + ▪ (Foulds *et al.* 2011) + ▪ (Medicines and Healthcare Products Regulatory Agency 2011a) ++ ▪ (Trtchounian *et al.* 2011) + ▪ (Vansickel *et al.* 2010) + ▪ (Westenberger 2009) ++
Applicability (high, moderate, low)	Moderate: the studies are all focused on e-cigarettes and do not address other NCPs
Consistency	The two laboratory studies are highly consistent in their findings on chemical constituents (Medicines and Healthcare Products Regulatory Agency 2011a [++]; Westenberger 2009) [++] The two studies of acute effects are also consistent in their findings (Bullen *et al.* 2010) [+] (Vansickel *et al.* 2010) [+]

6.3.2 Evidence summary: question 3

All available evidence relates to e-cigarettes. There is no evidence on the long term safety of e-cigarettes, whether used alone or with concurrent cigarette smoking. There isn't a large volume of reliable evidence on the short term safety of e-cigarettes. One randomized crossover trial (Bullen et al. 2010) [+] found that the rate of acute adverse events arising from e-cigarette use (occurring on the first day of use) were intermediate between placebo e-cigarette and licensed nicotine

inhalator. A non randomised study also found no acute effect on heart rate from the use of two models of e-cigarette (Vansickel et al. 2010) [+].

Stakeholder statements submitted to NICE by the Electronic Cigarette Consumer Association of the United Kingdom (ECCA UK 2011) [-], suggest that there is increasing and widespread use of e-cigarettes in the UK since 2006. Evidence from a survey of established e-cigarette users in the US also suggests that use is widespread (Foulds et al. 2011) [+].There are no firm cases of harm that are directly attributable to e-cigarette use. One news article in the British press (BBC, 2011) [-] reported a death from lipoid pneumonia where e- cigarette use was implicated by a treating clinician. The inquest to the death recorded an open verdict.

E-cigarettes are not regulated as medicines and their regulation is limited to the General Product Safety Directive of the European Parliament. Personal communication with MHRA suggests that post market surveillance of e-cigarettes, as required by the directive, is problematic in practice (Medicines and Healthcare Products Regulatory Agency 2011b) [-] There is evidence from laboratory analyses that e-cigarettes can contain nicotine derived nitrosamine contaminants and diethylene glycol, a highly toxic substance (Westenberger 2009 [++]; Medicines and Healthcare Products Regulatory Agency 2011a) [++]. Most e-cigarettes include propylene glycol. This chemical is generally considered to be of low toxicity although there appears to be insufficient data concerning its inhalational toxicity and Healthcare Products Regulatory Agency 2011a) [++]. A physical evaluation of e-cigarettes found that e-cigarettes (including their constituent parts and instruction manuals) lack important information regarding contents, use and essential warnings (Trtchounian et al. 2011) [+]. The same study found that e-cigarettes frequently leak, presenting a hazard, and that there are currently no methods for proper disposal of e-cigarettes, including cartridges (Trtchounian et al. 2011) [+].

6.3.3 Further study details: question 3

Bullen et al, 2010 [+]

This crossover trial randomized 40 healthy adult smokers to either the Ruyan V8 e cigarette, Nicorette inhaler, usual cigarette or placebo e-cigarette for a single day's use. Nicotine concentrations were measured for a sub set (n = 9) and all participants reported acute adverse effects at the end of each study day. There were a total of 65 adverse events among the e cigarette group, compared to 49 among the placebo group and 75 among the inhalator group. Rates of mouth and throat irritation, and were 88% with the inhalator, 22%the 0 mg e-cigarette (22%), and 38% with the 16mg e-cigarette ($p<0.001$). Nausea was most commonly reported after

16 mg e-cigarette use, but, as with the other between-product differences in adverse events occurrence, was not significant. No serious adverse events (i.e. deaths or events requiring hospitalisation) occurred during the study.

Trtchounian et al. 2010. [+]

This study evaluated six brands of e-cigarettes in terms of issues of safety, namely nicotine content, variations in design, labeling of cartridges, wrappers and packs, leakiness of cartridges, defective parts, instructions, disposal and advertisement claims. The findings suggested poor quality control. Most cartridges assessed leaked nicotine containing fluid and spent cartridges retained fluid. Labelling was poor, and a high number of errors were made in filling orders (cartridges were sent with the wrong strength of nicotine) (Trtchounian *et al.* 2011) [+].

BBC News, 28th March 2011 [-].

This BBC news story reported the fatality of a man from lipoid pneumonia in England in March 2011. The doctor who treated him was of the opinion that the lung disease may have been associated with his use of e-cigarettes. The article also reported that the related inquest recorded an open verdict.

MHRA 2011, (COMMERCIAL IN CONFIDENCE**)**

A report of the analysis of nicotine solution extracted from e-cigarette cartridges. Four e cigarettes were tested, namely 'Regular High 18 mg', 'TAB high', 'Ultimo Cartridges Supersmoker Normal Exp' and 'Gamucci Tobacco Flavour-regular'. The report notes that the main constituents nicotine, propylene glycol and glycerine were found in all e cigarettes tested. 'Regular high 18 mg' contains 1,3-bis(3-phenoxyphenoxy) benzene as a major constituent (approximately 26%). The authors are uncertain what role this laboratory reagent plays in the formulation.

FDA 2009

This analysis used a sparging apparatus (used to simulate use of e cigarette and trap constituents of the released vapour). Two e-cigarette brands (Njoy and Smoking Everywhere) were tested. Nicotine was detected. The cartridges labeled as containing nicotine were found to contain nicotine. Tobacco specific nitrosamines were detected at very low levels. One cartridge contained diethylene glycol (highly toxic) (FDA 2009).

Vansickel et al, 2010 [+]

This study of smokers (n = 32) naïve to e cigarettes compared the plasma nicotine, subjective effects (by questionnaire) and heart rate following use of two types of e cigarettes, their own brand cigarettes and sham cigarettes (unlit). The study used a Latin-square order for these conditions and smokers used all interventions in a manner approximating ad libitum cigarette smoking. No significant changes in plasma nicotine concentration or heart rate were observed for e cigarettes or sham cigarettes (Vansickel *et al.* 2010) [+] The authors listed the ingredients of the NJOY e-cigarette as nicotine, propylene glycol, water, ethanol, glycerol, acetylpyrazine, guaiacol, mysomine, cotinine and vanillin and the ingredients of the Hydro e-cigarette as nicotine, propylene glycol, water and tobacco flavouring.

- Own brand cigarette
- Sham smoking (puffing unlit cigarette)
- 'NPRO' (NJOY) e-cigarette with 18 mg nicotine cartridge
- 'Hydro' e-cigarette with 16 mg nicotine cartridge

Continuous heart rate monitoring was performed. Compared to initial measurement, a significant increase in heart rate was only observed for the own brand cigarettes (from an average of 65.7 bpm at baseline to a peak of 80.3 bpm five minutes after first administration). No significant changes in heart rate were observed for the e-cigarettes or sham smoking condition.

6.4 Results: question 4 and question 5

Question 4

Do the data suggest the technologies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Question 5

Do the data suggest the combination of nicotine replacement therapies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

6.4.1 Characteristics of studies included for questions 4 and 5

Volume	▪ 4 randomised cross over trials ▪ 10 non-randomised studies ▪ 3 reviews
Quality ++, +, -	Study quality is fair: ▪ (Ebert *et al.* 1984) [+] ▪ (Fagerstrom *et al.* 2002) [+] ▪ (Foulds *et al.* 1992) [+] ▪ (Pickworth *et al.* 1994) [+] ▪ (Russell *et al.* 1976) [+] ▪ (Zevin *et al.* 1998) [+] ▪ (Fagerstrom & Hughes 2002) [-] ▪ (Holm 1992) [+] ▪ (Hughes 2000) [-] ▪ (Hughes & Carpenter 2005) [+] ▪ (Jarvis *et al.* 2001) [+] ▪ (Russell *et al.* 1981) [+] ▪ (Russell *et al.* 1987) [-] ▪ (Vansickel & Eissenburg 2012) [-] ▪ (Rose et al, 2010) [+] ▪ (Gourlay & Benowitz, 1997) [+] ▪ Henningfield et al, 1993 [+]
Applicability (high, moderate, low)	Moderate: these are experimental studies which aimed to measure nicotine concentrations under NRT use with concurrent smoking. A drawback is that none of the included studies address combinations of different NRTs (question 5). Some studies of compensatory smoking are studies of tobacco products.
Consistency	Consistency is reasonable: the studies find similar trends in nicotine blood levels. However the conclusions drawn by authors differ regarding whether users self regulate their smoking habit or whether smoking habit is unchanged by NRT. Studies are consistent in reporting that compensatory smoking occurs.

6.4.2 Evidence summary

Evidence from controlled studies suggests that nicotine concentrations with smoking alone are typically in the range 22-30 ng/ml. When NRT use is accompanied by smoking, nicotine concentrations can rise to higher levels (Ebert et al. 1984) [+], (Fagerstrom et al. 2002) [+], (Foulds et al. 1992) [+], (Pickworth et al. 1994) [+], (Russell et al. 1976) [+], (Zevin et al. 1998) [+]. The highest value observed was 63.4ng/ml when a 44mg patch was used with ad libitum smoking

(Pickworth et al. 1994) [+]. Some authors suggest that smoking behaviour self regulates to maintain a constant nicotine concentration but evidence (particularly for patches) suggests that this is imprecise.

Despite increased nicotine concentration with concomitant use, the available evidence suggests there are no increases in the incidence of side effects or significant changes in physiological parameters such as blood pressure and heart rate (Pickworth et al. 1994) [+] (Zevin et al. 1998) [+].

Compensatory smoking

Compensatory smoking is a mechanism whereby smokers, who have reduced the number of cigarettes they smoke per day, modify their smoke intake, e.g. by puffing more frequently or more intensely, and thus titrate their nicotine intake (Hughes and Carpenter, 2005) [+]. Studies correlating reductions in expired CO with reductions in the number of cigarettes per day have demonstrated that some compensation occurs, but that the reduction in CO is significant (Hughes 2000 [-], Hughes and Carpenter, 2005 [+]). A narrative review of studies Fagerstrom & Hughes 2002 [-] suggests that for acute NRT forms (gum, lozenge, inhalator, nasal spray) a reduction in CO is accompanied by little change in plasma nicotine, suggesting close titration by subjects. In contrast the same study found for nicotine patches, plasma nicotine increased, suggesting poor titration for the transdermal route.

Studies of snuff use and low yield cigarettes also indicate that users are able to manage their intake to achieve a plasma nicotine level of typically 35-37 ng/ml (Holm et al. 1992 [+], Jarvis et al. 2001 [+], Russell et al. 1981 [+]). One study showed that users of nasal snuff can generate similar plasma nicotine levels to those generated by smoking a cigarette, in approximately equal time (10 minutes) Russell et al. 1981 [+]).

Nicotine absorption routes from NRT and e-cigarettes

The routes of absorption of medicinal nicotine are buccal (lozenge, gum, microtab, inhalator), dermal (patches) and nasal mucosa (nasal spray). Notably nicotine is mainly absorbed from the inhalator via the oral mucosa, with minimal absorption via the lungs. The degree of absorption of nicotine from electronic cigarettes is uncertain and published studies suggest the delivery of nicotine by these devices is via buccal absorption. (Russell *et al.* 1987) [-], (Vansickel & Eissenberg, 2012) [-].

Nicotine in arterial and venous blood

Following administration of nicotine by any route, nicotine has a different concentration profile over time in arterial blood compared to venous blood Henningfield et al, 1993 [+]. Few studies report arterial nicotine concentrations because venous blood samples are easier to collect.The arterial concentration relative to venous concentration (expressed as a ratio of the two concentrations) indicates the potential for distribution to the brain via the arterial circulation (Gourlay & Benowitz, 1997) [+].

Nicotine in cigarette smoke is rapidly absorbed in the lungs and quickly reaches the brain via the left side of the heart and the arterial circulation. One experimental study (Rose et al, 2010) [+] found that brain nicotine accumulation from cigarette smoking begins approximately 7 seconds after nicotine is first detected in the oral cavity and that maximum brain accumulation occurs at 290 seconds in dependent smokers and 210 seconds in non dependent smokers. The same study suggests that during typical smoking patterns, there are no spikes in brain nicotine concentrations, although there are puff-associated oscillations in the rate of nicotine accumulation which could affect nicotine receptor function (Rose et al, 2010) [+]. The authors concluded that dependent smokers accumulate nicotine more slowly than non-dependent smokers, due to reduced nicotine washout from the lungs (Rose et al, 2010) [+].

Another experimental study (Gourlay and Benowitz, 1997) [+] found that during cigarette smoking, median ratios between the arterial and venous plasma concentration of nicotine at the time of arterial Cmax were 4.6 (nasal spray), 2.3 (smoking) and 1.6 (intravenous).

6.4.3 Further study details

Russell et al, 1976 [+]

This double blind, placebo controlled crossover trial investigated plasma nicotine concentrations among smokers using 2 mg nicotine gum and smoking freely. There was no significant difference in nicotine concentrations between smokers using the gum (27.4 ng/ml (SE ± 1.4)) and smokers using a placebo gum (24.7 ng/ml (SE ± 1.4) (Russell *et al.* 1976) [+].

Ebert et al, 1984 [+]

This study investigated the effects of chewing placebo gum and nicotine gum (at 2mg and 4 mg strengths). Throughout the study subjects smoked whenever they felt the urge. There was no significant increase in plasma nicotine concentration while chewing 2 mg nicotine gum (30.9 ng/ml ± SD 13) compared to placebo (29.5 ng/ml ± SD 14). The nicotine concentration measured while

chewing 4 mg gum (40.7 ng/ml ± SD 15) was significantly increased compared to the measurement for placebo (Ebert *et al.* 1984) [+].

Fagerstrom et al, 2002 [+]

Among subjects of this study comparing a cigarette substitute and nicotine inhaler, who continued to smoke as few cigarettes as they could without experiencing discomfort, the average nicotine concentration for smokers using the inhaler (11.4 ng/ml) was significantly lower than the average concentration amongst the smoking group (21.7 ng/ml) (Fagerstrom *et al.* 2002) [+].

Foulds et al, 1992 [+]

Several authors have suggested a model of smoking behaviour where concomitant use of NRT and smoking is associated with regulation of smoking behaviour to maintain a fairly constant nicotine concentration. This study suggests that the down-regulation may be imprecise. In a crossover trial comparing 16 hour NRT patches to placebo patches, nicotine concentrations after smoking a cigarette showed a similar boost regardless of which patch was applied. Despite the higher plasma nicotine concentrations (active 44.5 ng/ml (SD 10.8) vs placebo 36.6 (SD9.4)), the study did not report any increases in the incidence of side effects. The only symptoms whose incidences were significantly greater for patch compared to placebo were localized itching (21 vs 10, $p < 0.001$) and feeling 'high' (5 vs 0, $p<0.05$) (Foulds *et al.* 1992) [+].

Pickworth et al, 1994 [+]

This small (n =10), randomized trial with a double blind, crossover design found that nicotine concentrations increased with increasing dose of nicotine patch (0 mg (placebo), 22 mg and 44 mg treatments were compared). Subjects were able to smoke freely throughout the 7 day exposure (patches were applied daily). Nicotine concentrations (ng/ml) at baseline (ad libitum smoking), placebo, 22 mg patch and 44 mg patch were 29.6 (± 5.2 SEM), 18.7 (± 3.3), 39.2 (± 4.7) and 63.4 (± 8.5) respectively (Pickworth *et al.* 1994) [+]. The authors report small increases in heart rate and blood pressure when the 22 mg patch was worn (compared to placebo) and none of the subjects complained of nicotine related symptoms.

Zevin et al, 1998 [+]

This crossover, single blind trial of healthy smokers assigned to daily transdermal doses of nicotine of 0, 21, 42 and 63 mg for four days while smoking freely also demonstrated an increase in plasma nicotine concentration with increasing dose. For the 63 mg treatment arm, mean plasma nicotine

concentration exceeded 60 ng/ml. The authors report that two of the subjects treated at the highest dose had symptoms of toxicity 2 to 4 hours after application of the patches. The protocol was subsequently adjusted by staggering patch administration at four hourly intervals for the next eight subjects with no occurrences of toxicity. Although nicotine concentrations with concomitant smoking were higher than those usually seen among smokers there were no significant changes in heart rate or blood pressure. (Zevin *et al.* 1998) [+]. Benowitz et al (1998) [+] reported the effects on nicotine intake and carbon monoxide for these study participants separately (Benowitz *et al.* 1998) [+].

Hughes 2000 [-]

This narrative review examined compensatory smoking and found that reductions in CO are usually approximately 75% of the reduction in self reported cigarettes/day, suggesting that some compensation occurs. The author concluded that the median reduction in CO (27%) is nevertheless substantial.

Hughes and Carpenter 2005 [+]

This systematic review updated and built upon the work by Hughes (2000) cited above and calculated an index to measure the degree of compensatory smoking that occurs in people who reduced the number of cigarettes they smoke per day, as follows:

% compensation = (1-[% reduction in marker/% reduction in CPD]) x 100

Thus complete compensation has a value of 100% and zero compensation 0%. The most frequent marker studied was carbon monoxide. In ten studies of NRT-based reduced smoking, the percentage reduction in marker had range 4-46% and the percentage compensation had range 17-64%. Overall the reduction in marker was approximately a third less than the reduction in cigarettes per day. There was no correlation between the % reduction in cigarettes per day and the % compensation (i.e. no trend whereby smokers who made large reductions in cigarettes per day compensated to a greater degree). The authors concluded that compensatory smoking occurs, but is generally <50% of the reduction in cigarettes per day, and that the observed reductions in CO remain significant.

Fagerstrom & Hughes 2002 [-]

This narrative review included data from observational studies of smokers instructed to reduce their level of smoking while using NRT or to smoke ad libitum while using NRT. Across all included studies of acute NRT delivery routes (gum, inhalator, lozenges) there was a 50% reduction in the

number of cigarettes smoked per day, but with very little change in plasma nicotine levels (total average percent reduction 1%). There was a 28% reduction in exhaled CO across studies. For transdermal NRT, there was a similar reduction in the number of cigarettes smoked per day (43%) and in exhaled CO (31%) but in contrast to acute NRT, transdermal NRT had a total average increase in plasma nicotine concentration: 54% for doses <23mg and 190% for doses >22mg. The authors concluded that smokers titrate their nicotine levels quite well with acute NRT forms but not as well with nicotine patches, that all NRT systems equally and consistently decrease cigarette consumption and, to a somewhat lesser degree, CO intake, and that very few and mild adverse reactions occurred, even when nicotine concentrations were elevated 2 or 3 times with use of very high doses of nicotine from patches.

Holm et al. (1992) [+]

This study of nicotine dependence compared plasma nicotine levels between smokers and Swedish Snus users and found similar concentrations of plasma nicotine: 36.6 ng/ml in the snuff takers and 36.7 ng/ml in the smokers.

Jarvis et al. (2001) [+]

This cross sectional survey correlated salivary cotinine with nominal nicotine yield from different brands of cigarette in 2031 smokers. There was only a low degree of correlation between salivary cotinine and the measured nicotine yield of cigarettes determined for each brand ($r=0.19$, $p<0.001$). There was wide variation in cotinine concentrations at any given yield of nicotine. At any level of nominal yield, smokers achieved high nicotine intakes (approximately half of smokers achieved cotinine levels in excess of 300ng/ml). Estimated nicotine intake per cigarette was 1.17 mg in smokers of brands yielding less than 0.4 mg of nicotine (average yield = 0.14 mg), 1.22 mg from brands yielding between 0.4 mg and less than 0.8 mg (average yield = 0.57 mg), and 1.31 mg from brands yielding 0.8 or more (average yield = 0.91 mg).

Russell et al. 1981 [+]

This prospective case series compared plasma nicotine levels minutes after taking snuff (27 subjects) with that of smoking a cigarette (13 subjects, and also 136 heavy smokers previously seen at a smoking cessation clinic). Multiple doses of snuff produced massive increases in plasma nicotine concentrations (mean 53.3ng/ml). Daily snuff users also had a similar mean plasma nicotine concentration (35.6 ng/ml) to that of heavy smokers (36.2 ng/ml). In the 136 smokers Tmax was approximately 2 minutes after finishing the cigarette. In snuff takers Tmax and 6-15

minutes after taking snuff. The authors concluded that at 10 minutes after taking snuff, plasma nicotine levels approximate those seen at the end of the 10 minute period it takes to smoke a cigarette.

Russell et al, 1987[-]

This small study (n=8) measured the delivery of nicotine from a new smoke-free cigarette used by human subjects with a varied smoking history. The protocol involved an initial period of controlled use (one puff every 40 seconds for six minutes) followed by a twenty minute period where participants inhaled as hard and frequently as possible. Pharmacokinetic and safety outcomes were reported, with measurement of venous plasma nicotine concentration, heart rate and blood pressure and documentation of adverse effects. A mean peak nicotine concentration of 18.7 ng/ml (± 6.6 SD) was reported approximately ten minutes after participants stopped puffing (Tmax 35 minutes from starting puffing). Heart rate and blood pressure increased with increasing nicotine concentration. Local irritation was reported by all subjects. Five out of eight subjects complained of nausea, pallor, sweatiness and cool extremities. All participants except for one regular smoker experienced slight dizziness and light-headedness. The pharmacokinetic profile for nicotine led the authors to conclude that absorption had occurred at the mouth, throat and large airways rather than the alveoli.

Vansickel and Eissenberg (2012) [-]

This small study (n=8) investigated the delivery of nicotine by e-cigarettes among a group of experienced e-cigarette users. The participants were permitted to use their preferred e-cigarette device and e-liquid. Nicotine concentrations (venous) were measured during periods of controlled (ten puffs with a thirty second inter-puff interval) and ad libitum e-cigarette use (sixty minutes). Other reported outcomes were physiological measurement and subjective questionnaire, although details of these were not provided. A mean venous blood nicotine concentration of 16.3 (SE 2) ng/ml was reported after approximately 75 minutes of continuous e-cigarette use. Although the authors do not speculate on the route of absorption, the slow and gradual increase in nicotine concentration would be consistent with buccal absorption.

Rose et al, 2010[+]

This experimental study (n= 23) compared the brain accumulation of nicotine among 13 dependent (DS) and 10 non dependent smokers (NDS). Each subject was scanned (by PET) following a single puff of 11C-labelled nicotine. Head and chest scans were performed in separate

PET sessions. Brain nicotine accumulation began approx 7 seconds after radioactivity was detected in the oral cavity (7.0 ± 1.5 s (DS) and 6.9 ± 1.2 s (NDS)). Maximal accumulation occurred at 290 ± 30s and 210 ± 40s. Under typical smoking conditions puff associated spikes in brain nicotine concentration do not occur. DS have a lower brain nicotine accumulation rate than NDS. Significantly lower nicotine concentrations were observed for DS than NDS over the first 3 minutes, half maximal accumulation values of brain nicotine accumulation were 1.8 times longer for DS than NDS. This reduced accumulation in DS is a consequence of reduced nicotine washout from the lungs. Over the first 240 seconds, the residual fraction of the inhaled nicotine dose in the lung tissue was higher in DS versus NDS ($p<0.05$). T 1/2 of nicotine washout in DS was almost three times that of NDS (89 ± 18s and 27 ± 5 s, $p<0.01$).

Henningfield et al, 1993[+]

This experimental study (n= 8) measured arterial and venous concentrations of nicotine in human subjects before and after smoking a cigarette. Although smoking leads to an increase in both arterial and venous nicotine concentrations, the increase is much greater for arterial blood. At five minutes after light-up, mean arterial and venous blood concentrations of nicotine were 53ng/ml and 24 ng/ml, respectively. At ten minutes after light up, the respective values were 30 ng/ml and 19 ng/ml. The differences between arterial and venous levels decline rapidly. Much inter-subject variation was reported with respect to the magnitude and time course of arterial concentrations. The arterial concentrations measured are likely to underestimate the true Cmax due to the timings of the sampling procedure.

Gourlay and Benowitz, 1997[+]

This experimental study (n=12) studied the differences in arterial and venous nicotine concentrations among male smokers after smoking their usual cigarettes (one puff per minute for ten minutes), administering nicotine nasal spray (0.5 mg of nicotine administered to each nostril) or receiving a nicotine infusion (2 µg/kg per minute for 30 minutes). The peak arterial plasma concentrations of nicotine (Cmax) after smoking or administration of nicotine nasal spray were on average twice those of venous plasma. For nicotine nasal spray the time to Cmax was much shorter for arterial than for venous plasma (median 5 versus 18 minutes, $p<0.01$). The median ratios between the arterial and venous plasma concentration of nicotine at the time of arterial Cmax were 4.6 (nasal spray), 2.3 (smoking) and 1.6 (intravenous). Mean heart rate increased with all three methods of delivery, reaching a peak just after the mean tmax in arterial plasma.

6.5 Results: question 6

Are kinetic data available which allow comparison of the relative bioavailability of different technologies i.e. maximum (peak) concentration (Cmax), time to peak concentration (Tmax) and half life (t ½)?

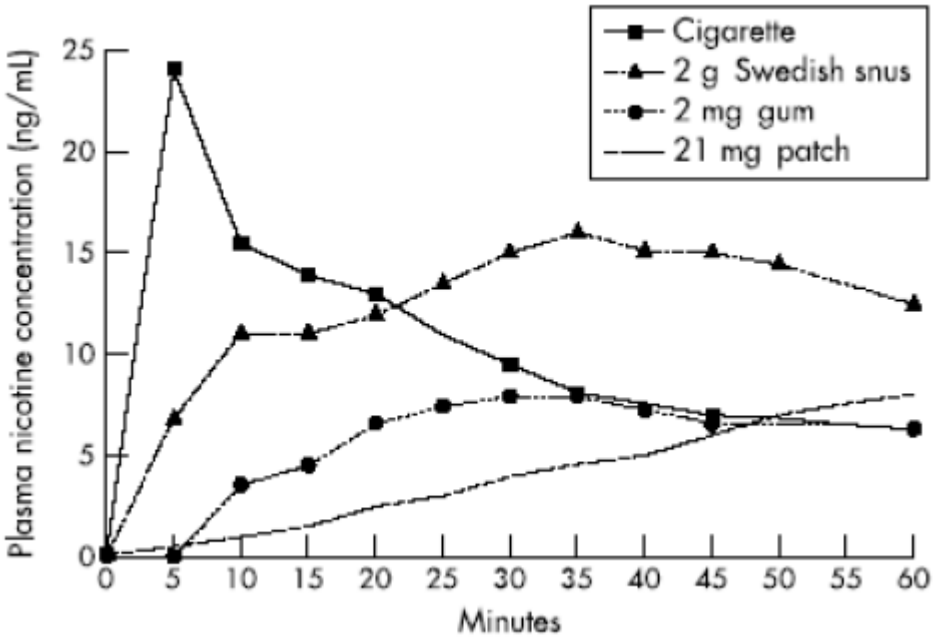
6.5.1 Pharmacokinetic model

Cedar commissioned Professor Glyn Taylor as an independent expert to construct a pharmacokinetic model using data from published pharmacokinetic studies. The source studies are summarised in Appendix 8. The pharmacokinetic model is a stand alone report for consideration by the PDG and is attached as Appendix 1.

6.5.2 Summary of source pharmacokinetic data

The figure below is reproduced from Foulds et al. (2003) and shows venous blood concentrations over the period of an hour for smoking a cigarette, using 2g of Swedish snus, 2mg of NRT gum and a 21mg NRT patch. The figure indicates that of the four products, the cigarette provides the most rapid rate of absorption of nicotine, hence the spiky PK profile. The other routes all give rise to flatter profiles and the 21mg patch markedly so, although it should be noted that for all products other than the patch, blood nicotine concentration begins to fall within one hour, whereas nicotine continues to be absorbed from the patch; patches are typically worn for 12-24 hours.

Figure: venous blood concentrations (ng/ml) of nicotine over time for various nicotine delivery systems, adjusting for baseline differences. From Foulds et al. 2003, Tobacco Control, 2003, 12, 349-59, reproduced with permission from the BMJ Publishing Group, copyright license no. 2877691043297, 28th March 2012



In addition, Cedar provided narrative summaries of the pharmacokinetic data from papers which Cedar provided to Professor Glyn Taylor for the purpose of constructing the pharmacokinetic model (Appendix 1). The narrative summaries of source data are described below.

6.5.2.1 Lozenges / tablets (5 studies, 28 study populations)

Total dose data were available for all lozenge / tablet population groups and ranged from one single 1mg dose to 48mg over twelve hours in 12 or 24 divided doses. Individual doses ranged from 1mg to 12mg (data available for all populations). Smoking abstinence prior to the study period ranged from none (9 populations)to 24 hours (4 populations). All other studies reported a minimum of 12 hours abstinence. Latest blood samples taken ranged from 90 minutes post exposure (1 report) to 48 hours post exposure (3 reports)with data available for 20 study populations.

Cmax (ng/ml) was available for all populations and ranged from 2.3 to 30.07.

Dose	Single Dose / Multiple Doses	No of Populations	Mean Cmax ng/ml	Cmax Range ng/ml
1mg	Single	2	2.67	2.3 – 3.04
2mg	Single	1	4.5	3.8 – 4.94
3mg	Single	3	8.2	-
4mg	Single	8	6.5	4.9 – 8.63

6mg	Single	2	12.95	9 – 16.9
12mg	Single and Multiple	3	14.03	10.6 – 20.5
20mg	Multiple	3	11.5	10.3 – 12.1
24mg	Multiple	4	16.91	13.2 – 22.5
48mg	Multiple	2	28.57	27.07 – 30.07

14 populations were given 4mg or less as a single dose. The mean Cmax in these patients was 5.62 (range 2.3 – 8.63) Eight of these populations had the latest blood sample taken at 8 hours post exposure. 14 populations were given between 6 and 48mg in single or divided doses. The mean Cmax in these patients was 16.23 (range 9-30.07).

Cmin was available for five study populations. Each of these involved patients who had received twelve doses over twelve hours of a total 12, 24 or 48mg nicotine resulting in a mean Cmax of 15.75ng/ml (range 8.1 – 25.32). Tmax was reported in 25 populations, mean 48.66 minutes , range 10 minutes to 168 minutes. Mean T1/2 was 3.03 hours, and was reported in 3 studies (range2.7 – 3.6 hours).

AUC 0-t was available for seven study populations, these all involved single doses of 4mg or less with a mean of AUC of 13.31h.ng.ml (range 7.78 – 22). AUC0-∞ (h.ng/ml)was available for 13 study populations all of whom had been administered single doses of 1 – 6mg. The mean AUC0-∞ was 21.98(h.ng/ml), range 7.54 – 36.5. AUC t-twas available for 13 study populations all of whom had been administered single doses of 1 – 6mg. The mean was 21.98(h.ng/ml), range 7.54 – 36.5. This parameter showed differences in the route of administration with three study populations using single doses of 3 to 12mg showing a mean AUC t-t of 75(h.ng/ml), range 37 – 103.1, while seven populations using 10 – 12 doses of 1 – 2mg of nicotine (total dose of 12 – 24mg over 10 – 12 hours) found a mean AUC t-t of 11.99 h.ng/ml with a range of 9.2 to 20.2)

6.5.2.2 Gum (8 studies, 14 study populations)

Total dose data were available for all population groups and ranged from one single 2mg dose to 48mg over twelve hours in 12 divided doses. Single populations received one – off doses of 2mgs and 8mg respectively. Ten populations were given single doses of 4mg , while 2 populations received 24mg in 12 doses over 12 hours, and two received 48mg in 12 divided doses over 12 hours. Smoking abstinence prior to the study was reported in all populations. This ranged from 90

minutes to 24 hours, with three populations being asked to smoke a cigarette 90 minutes prior to the use of nicotine gum. No pharmacokinetic data were available for these three populations. Of the remainder, abstinence ranged from 8 – 24 hours with a mean of 15.27 hours.

Cmax (ng/ml) was available for 11 populations and ranged from 2.9 to 30.5. Reported data in populations where 8mg or less was administered (8 populations) had a mean Cmax of 10.46 (range 2.9 – 14.9). In the three populations administered divided doses totalling 24 or 48 mg where Cmax was reported the mean was 22.62 (range 11.4 – 30.5). Cmin was only available for two populations with levels of 9.3ng/ml and 19ng/ml for a 2mg and 4mg dose respectively (Mean 14.15). T1/2 was also reported for two with a mean of 2.85 hours. One population used a single 2mg dose of nicotine resulting in a T1/2 of 2.5, the other used twelve 2mg doses over twelve hours and had a T1/2 of 3.2. Tmax was available for 10 populations, all of whom had been administered 2 – 4mg of nicotine. The mean Tmax = 38.5, with a range of 20 – 56.3ng/ml.

AUC 0-t (min.ng/ml) was available for 6 populations each administered 2 – 4mg nicotine as a single dose. The mean result was 1216.98min.ng/ml (20.28 h.ng/ml), range 467 – 1967 min.ng/ml (7.78 – 32.75 h.ng/ml). AUC0-∞ was measured in three populations each using 2 – 4mg of gum as a single dose. These had a range of 13.8 – 53.17h.ng/ml, resulting in a mean of 29.53 h.ng/ml. AUCt-t was also reported in three populations, with a mean of 17.1 h.ng/ml (range 10.2 – 27.5). Two of these (AUCt-t 10.2 and 27.5) were given as twelve multiple doses of 2mg and 4mg respectively while the third (AUC 13.5) was given a single dose of 4mg> All three studies had levels measured at 11-12 hours.

6.5.2.3 Nasal spray (5 studies, 12 populations)

Total dose data were available for all populations ranging from 0.5mg – 2.5mg administered over 5 minutes or less. All patients and been abstinent from nicotine use for 10 – 12 hours or “overnight”. Latest blood samples were taken at 15 minutes to 6 hours (mean = 118.78 minutes) and was reported for all populations.

All of the 14 populations reported Cmax and Tmax with respective means of 10.7ng/ml (range 4.58 – 23.5) and 11.67 minutes (range 0 – 30 minutes). AUC 0-t was reported for four populations all of whom had received 2 – 2.5mg nicotine with latest blood samples at 30 – 60 minutes. These ranged from 186.8 – 403 min.ng/ml with a mean of 309.3min.ng/ml. Three populations from one study reported AUC0-∞. These all involved 2mg of nicotine with a latest blood sample taken at 6 hours post use. These reported a mean AUC0-∞ of 17.6 with a range of 15.9- -18.9h.ng/ml.

6.5.2.4 Patch (4 studies, 7 study populations)

Total dose data were available for all populations, with a mean dose of 24.6mg, this ranged from 15mg (16 hour patch) to 40mg (24 hours patch). Dosing period was reported for 6 populations and ranged from 8 hours (two study) to six months (one study) the three remaining studies used patches for 16 hours, 24 hours and 5 days. Only three study populations reported a period of tobacco abstinence with a mean of 20 hours (range 12 – 24 hours). Two populations were not abstinent prior to the study period while in the remaining two, prior nicotine use was unclear.

Cmax was reported in five of the populations with a mean of 18.7ng/ml, range 14.5 – 26.1ng/ml. Cmax was not reported in the two studies carried out over a six month period. Tmax was available for three of the seven populations with a range of 6 – 12 hours (mean 8.67). Three populations reported AUC0-∞ with a mean of 276.1 and a range of 202.3 – 382.36 h.ng/ml. AUC 0-t (h.ng/ml) was reported more frequently with data available for five studies, however this data varied widely - possibly due to a variance in time to measurement and ranged from 50.3 to 370.91 h.ng/ml (mean 180.01h.ng/ml).

6.5.2.5 Inhalator (3 studies. 4 study populations)

Three populations were abstinent from nicotine use for 12 hours or overnight while the remaining population had no period of abstinence. Two populations used the inhalators freely, one over 8 weeks, the other over a day while two used the inhalator for 20 minutes/ hour for 11 hours. Three studies reported Cmax and Tmax with a mean Cmax of 22.8 ng/ml (range 2.1 – 34.2)and a mean Tmax of 27.3 minutes (range 19.8 – 23 minutes). AUCt-t was reported in two studies with AUC 11-12 of 30.9 and 29.5 (mean 30.2h.ng/ml).

6.5.2.6 E-cigarette (3 studies, 5 study populations)

Each population had an overnight or 12 hours period of smoking abstinence prior to the study. One population used a 16 mg e-cigarette for 5 minutes, while the remainder used a single 16 or 18mg e-cigarette initially followed by another after more than 60 minutes.

For the study with a 5 minutes e-cigarette use, Cmax and Tmax were reported as 1.3ng/ml and 19.6 minutes respectively. These parameters were not available for the other studies, however nicotine levels were measured and reported for two studies at 5, 15 and 30 minutes post use of each e-cigarette with levels ranging from 2.2 – 3.5ng/ml (mean 2.7).

6.5.2.7 Cigarettes (6 studies, 8 study populations)

Smoking abstinence was reported as 12 – 12.5 hours or overnight in 7 populations with no abstinence in the remaining population. Dose ranged from 1.5 - 2 cigarettes over 10 minutes in

two studies to smoking freely over 8 weeks with a mean use of 23.3 cigarettes per day in another study. Cmax and Tmax values based on venous blood samples (3 studies) suggest that when 1-2 cigarettes are smoked venous blood Cmax has mean 16.9 ng/ml (range 13.4-18.8 ng/ml) in Tmax mean 10.4 min (range 5-14.3 min). The figure from Foulds et al. (2003) shown above, indicates that a cigarette can generate a venous Cmax of 24 ng/ml in 5 minutes. Data for arterial blood indicate a higher Cmax of 39.8 ng/ml in a rapid Tmax of 8.2 min.

T1/2 and AUC0-t were both reported in two populations following use of 16x550cc of cigarette smoke via a metered device. Mean T1/2 was 139.2 minutes (152 and 126.4 minutes reported) and mean AUC0-t was 2017.95ng/ml.min, with levels of 2123.5 and 1912.4 reported.

6.5.2.8 Snus (2 studies, 3 study populations)

Total dose in each study was a 30 minutes use of snus, with each patient having a period of tobacco abstinence of 12-14 hours prior to snus use. Latest blood samples were taken at 8 hours (two studies) and 90 minutes (one study). Cmax and Tmax were available for all three populations and showed a mean of 14.87 ng/ml (range 13.7 – 16.1) and mean 34.7mins (range 30 – 37.1) respectively. AUC0-t was available for one study (with 90 minutes latest sample) with a level of 1038ng.min/ml. AUC0-∞ was available for the remaining two studies with levels of 3062 and 2829 ng.min/ml resulting in a mean of 2945.5ng.min/ml.

6.6 Results: question 7

Do the data support the safety of an approach where smokers receive doses of medicinal nicotine (potentially by different routes) while continuing to smoke. Is there a greater risk of adverse effects?

Note: on reviewing the available evidence we concluded that there is no useful distinction between studies that answer this question and those that answer question 1. We agreed with NICE technical staff to present all relevant data under question 1.

6.7 Results: question 8

There are marked differences in smoking rates among socioeconomic groups, Black and Minority ethnic (BME) groups, age (lifestage) and people with mental illness. Do the data suggest there may be inequalities among these groups with respect to the risk, safety and pharmacokinetics of smoking harm reduction technologies?

6.7.1 Characteristics of studies included for question 8

Volume	▪ 5 randomised controlled trials ▪ 1 randomised intervention study ▪ 6 non-randomised intervention studies
Quality ++, +, -	Overall, evidence quality is moderate (+) to strong (++): ▪ (Roddy et al. 2006) + ▪ (Lin et al. 1993) + ▪ (Schnoll et al. 2009) + ▪ (Malaiyandi et al. 2006) + ▪ (Berg et al. 2010) + ▪ (Moolchan et al. 2005) ++ ▪ (Smith et al. 1996) + ▪ (Hurt et al. 2000) + ▪ (Rubinstein et al. 2008) ++ ▪ (Molander et al. 2001) + ▪ (Stapleton et al. 2008) – ▪ (Dalack et al. 1999) ++
Applicability (high, moderate, low)	Moderate: these studies are concerned with the defined special groups although NRT is used within the short duration of cessation studies rather than the longer term exposure expected with the harm reduction approach.
Consistency	Data for each special group is sparse but there are no obvious inconsistencies in the findings. The studies of ethnicity / genetics make many references to 'tailoring' nicotine replacement therapy. This is currently poorly defined but involves identifying individuals who are most likely to benefit from NRT. Most available research concentrates on efficacy of NRT rather than safety of NRT.

6.7.2 Evidence summary: Socioeconomic groups

Few data were found which investigate the safety of nicotine with respect to socioeconomic groups although it is widely accepted that smoking prevalence is far higher among people from manual as opposed to non manual socio-economic groups. One community-based randomised controlled trial studied NRT in young smokers who were socioeconomically deprived. 98 subjects

were recruited and randomised to nicotine patch or placebo patch. The authors suggest NRT appears to be safe in this group (on the basis of few reported side effects). However it is worth noting that the adherence to therapy was very low (only eight subjects (3 with active treatment and 5 with placebo) completed the full six week treatment course) and 63 subjects did not attend any follow up (Roddy *et al.* 2006) [+].

6.7.3 Evidence summary: Black and Minority Ethnic groups

No data were found which specifically study the relative safety of NRT among different BME groups although there is evidence to suggest there are differences in nicotine metabolism among different BME groups.

Much of this evidence concerns the well studied genetic polymorphism in the hepatic detoxifying system (Cytochrome P450 family of enzymes). Variant alleles resulting in reduced enzyme activity are more commonly found among Asian populations (Chinese, Japanese and Korean) compared with Caucasian. Two open label clinical trials have found significantly increased plasma nicotine concentrations among slow metabolisers receiving NRT patches (Malaiyandi *et al.* 2006 [+]; Schnoll *et al.* 2009) [+]. Where NRT nasal spray was used, slow metabolisers used significantly fewer doses but maintained a similar plasma nicotine concentration (Schnoll *et al.* 2009) [+]. This trial of 568 smokers did not find any association between the measures of metabolic rate (3-HC/cotinine ratio) and patch related side effects although the 3-HC/cotinine ratio was considered a significant predictor of quit rates.

These studies show that the influence of CYP 2A6 genotype on nicotine metabolism may affect usage of NRT, the nicotine concentrations obtained during use and the efficacy of treatment (for cessation). Authors have suggested there may be some value in assessing pretreatment nicotine metabolism rate when considering the use of NRT since slow metabolisers are considered better candidates for this form of treatment. Alternative therapies (such as bupropion) may be more beneficial for faster metabolisers (Schnoll et al. 2009) [+]. The 3-HT/Cot ratio (ratio of 3-hydroxycotinine to cotinine) is regarded as a useful marker of the rate of nicotine metabolism and CYP 2A6 activity generally (Dempsey et al. 2004).

A review article concludes that the genetics nicotine dependence may involve contributions of hundreds of genes, interacting with each other and with the environment (Bierut 2009). These genes may include nicotine receptors, metabolic pathways and dopaminergic pathways.

There may be differences among ethnic groups in the metabolism of nicotine by the process of glucuronidation. This detoxifying process adds glucuronide to substrates such as nicotine and cotinine to make them more water soluble and more readily excreted. The evidence of one open label clinical trial suggests glucuronidation is significantly lower among African Americans compared to European Americans (Berg *et al.* 2010) [+].

6.7.4 Evidence summary: Age (lifestage)

Adolescence

Four separate clinical trials dealt with safety of NRT in the adolescent group. Two of these involved NRT patch monotherapy, one involved patch or gum in combination with cognitive behavioural therapy and one involved the NRT nasal spray. One trial was a double-blind randomized controlled trial, one was a randomized, open label trial and two were non-randomized, open labelled studies.

A double-blind, randomized trial of the safety and efficacy of nicotine patch and gum in a sample of 120 adolescents (13 to 17 year olds) treated for 12 weeks found that a total of 745 adverse events were documented throughout the trial. Incidence of sore throat (gum), hiccups (gum), shoulder/arm pain (patch), pruritis (patch and gum) and erythema (patch) were significantly greater with NRT than with placebo. There was a mean reduction in self reported smoking (CPD) for all three groups (gum, patch and placebo) and this exceeded 80% reduction in each case. The authors suggest that the pattern of adverse events reported in this trial was similar to those reported in adult trials (Moolchan *et al.* 2005) [++]. Similar findings were reported by Smith et al (Smith *et al.* 1996) [+] and Hurt et al (Hurt *et al.* 2000) [+] in non randomised open label trials of patch therapy in 22 and 101 adolescents respectively.

The evidence from one randomized, open label trial suggests there may be safety concerns regarding the use of NRT nasal spray among adolescents (Rubinstein et al, 2008) [++]. This study randomly assigned 23 subjects to the nicotine nasal spray and 17 to control group. 38.9% of individuals using the spray were of the opinion that there were lots of side effects. The most common adverse effect was nasal irritation (34.8%), followed by complaints about taste and smell (13%). The authors suggest that the symptoms may explain a low rate of use and that such poor adherence may explain the low overall quit rates observed (Rubinstein *et al.* 2008) [++].

Older people

One pharmacokinetic study was found which suggests the clearance of nicotine is significantly decreased by approximately 25% in elderly subjects (65 to 76 years) compared with younger

adults (22 to 43 years). The maximal nicotine concentration was higher in the elderly subjects (16.8 ± 7.8 ng/ml vs 10.4 ± 3.5 ng/ml) following an intravenous infusion of 0.028 mg/kg of nicotine over 10 minutes. The maximal heart rate increase was significantly (p = 0.0062) lower in elderly subjects than younger adults (15 ± 6 bpm vs 21 ± 8 bpm) and there were no differences in the systolic and diastolic blood pressure responses between the two groups. There were no differences in the adverse events experienced by the subjects, either in terms of the type of event or severity (Molander *et al.* 2001) [+].

6.7.5 Evidence summary: Individuals with psychiatric illness

Safety of NRT use in people with psychiatric illness

One study was found which explores the safety of NRT in individuals with mental illness. Stapleton et al (2008) [-] evaluated a consecutive series of 412 smokers receiving smoking cessation treatment, 111 (27%) of whom reported that they were being treated for a mental illness. Subjects could choose NRT (whichever licensed preparation they preferred) or varenicline. The study was powered to detect a difference in the primary outcome measure (abstinence) but also measured tobacco withdrawal symptoms and adverse drug reactions as secondary outcomes. In terms of efficacy, cessation rates were greater with varenicline than NRT. The authors report the incidence of adverse events for NRT and varenicline groups but did not analyse the frequency of adverse events in the NRT treated subjects with and without mental illness (Stapleton *et al.* 2008) [-].

Pharmacokinetics of NRT in people with psychiatric illness

A placebo controlled crossover trial measured nicotine concentrations following cigarette smoking and NRT nasal spray use among a group of 31 patients diagnosed with schizophrenia or schizoaffective disorder. Blood samples were taken for nicotine measurement before and after administration of cigarette or nasal spray. When subjects received two sprays of NRT to each nostril the mean nicotine plasma concentrations were 9.1 ng/ml. Administration of four sprays to each nostril resulted in a mean nicotine concentration of 22.4 ng/ml (Smith *et al.* 2002) [+].

Effects on psychiatric symptoms

A randomised, double blind, balanced crossover study of withdrawal and psychiatric symptoms in nineteen cigarette smokers with schizophrenia found that there were no significant changes in psychiatric symptoms during three days of smoking abstinence with or without nicotine replacement (Dalack *et al.* 1999) [++].

6.7.6 Further study details

Roddy et al, 2006 [+]

This community-based randomised controlled trial studied NRT in young (aged 14 to 20 years) smokers who were socioeconomically deprived. 98 subjects were recruited and randomised to nicotine patch or placebo patch. Treatment lasted for six weeks and the active treatment was tapered from 15 mg to 5 mg over this period. The authors suggest NRT seemed safe in this group (on the basis of few reported side effects). Two subjects withdrew from the study because of adverse effects (one from active and one from placebo group). There were a total of 30 adverse events among the active treatment compared to 17 among the placebo group. However it is worth noting that the adherence to therapy was very low (only eight subjects (3 with active treatment and 5 with placebo) completed the full six week treatment course) and 63 subjects did not attend any follow up.

Lin et al, 1993 [+]

This pharmacokinetic study adopted a randomised open label single treatment design to compare PK parameters for dermally absorbed nicotine in Taiwanese and American smokers. Results showed that the input rate of nicotine (Ri/Vi) into the central compartment was statistically higher in Taiwanese than in American Smokers ($p < 0.05$) following administration of a novel transdermal delivery system but there were no significant differences in any other pharmacokinetic parameters. The transdermal plasma profiles of nicotine in both ethnic groups are relatively similar.

Xu et al, 2002

This review discusses variation in human cytochrome P450 2A6 (CYP2A6) and its consequences. This enzyme is the main enzyme involved in the metabolism of nicotine to cotinine and is also responsible for the further oxidation of cotinine to 3-hydroxycotinine. This particular P450 isoenzyme has a relatively narrow substrate specificity. So the CYP2A6 is very important to the metabolism of nicotine. There are significant interindividual and interethnic differences in the activity of CYP2A6. This is known as a genetic polymorphism.

Poor metabolizers (PMs) are individuals who have two copies of the inactive gene and consequently no enzymatic function (e.g. CYP2A6*4/*4). Extensive metabolizers (EMs) have one or two copies of active gene alleles (e.g wildtype homologous CYP2A6*1/*1) and fast metabolizers (FMs) have two copies of the active gene (gene duplication CYP2A6*1/*1 x 2)

CYP2A6 allelic frequencies amongst ethnic groups

CYP2A6 allele	Activity	Caucasian (%)	Chinese (%)	Japanese (%)	African American (%)
*1A	Full	66.5	43.2	40.0 – 42.0	
*1B	Full	30.0	40.6	38.0 – 41.0	
*2	Inactive	1.1 – 3.0	0.0 – 0.7	0.0	0.3
*4	Inactive	0.5 – 4.9	6.6 – 15.1	20.0 – 31.0	
*5	Unknown	0.0 – 0.2	1.0	0.0	
*6	Reduced activity for nicotine			0.4	
*7	Reduced activity for nicotine	1.0	2.2	6.3	
*8	Full	0.0	3.5	1.6	
*9	Reduced activity for nicotine	5.2	15.7		
*10	Reduced activity for nicotine	0.0	0.4	1.6	
*1 x 2	Increased activity (gene duplication)	0.7	0.4	0.0	
*11	Reduced activity to CYP2A6 substrates				
*12	Reduced activity to CYP2A6 substrates				

Schnoll et al. 2009 [+]

This open label study found that among a sample of 576 adult smokers (>10 cpd), the 3-HC/cotinine ratio measured at baseline was a significant predictor of quit rates (OR=0.66, 95% CI: .48 - .91; p<0.05). Subjects with lower 3-HC/cotinine ratios (slower nicotine metabolisers) showed higher quit rates at week 8. However the 3-HC/cotinine ratio at baseline was not associated with patch-related side effects. The authors suggest the quit rates obtained by transdermal NRT among slow metabolisers are comparable to varenicline

Malaiyandi et al, 2006 [+]

This open label clinical trial studied the effects of slow nicotine metabolism (as determined by CYP2A6 genotype) on smoking behaviour and pharmacokinetics during treatment with NRT patches or nasal spray. 394 smokers were randomised to treatment with NRT patch or nasal spray for 8 weeks duration. Both arms received group counselling. At baseline significantly fewer cigarettes per day were smoked by slow metabolisers (20 ±7 vs 24 ±10; p=<0.04). For the nicotine patch group, plasma nicotine concentrations were significantly higher for slow metabolisers (22.8

± 4.6 ng/ml) than normal metabolisers (15.8 ± 7.6 ng/ml); p=0.02. For those in the nasal spray group significantly fewer doses were used per day by slow metabolisers (4.8 ± 3.6 vs 10.5 ± 8.0; p<0.02) although plasma nicotine concentrations were not significantly different between the two groups

Berg et al. 2010 [+]

An open label clinical trial which analysed nicotine and its metabolites in plasma and urine for African American and European American smokers during NRT patch treatment. Glucuronide conjugation of nicotine and cotinine was significantly lower among African Americans compared with European Americans although absorbance of nicotine from NRT patch did not vary significantly by ethnicity. In contrast, African Americans received a higher dose of nicotine per cigarette than European Americans. This is thought to be due to differences in smoking behaviour.

Moolchan et al. 2005 [++]

This double-blind, randomized trial studied the safety and efficacy of nicotine patch and gum in a sample of 120 adolescents (13 to 17 year olds). Psychiatric assessments showed that 75% of these subjects had at least one current psychiatric diagnosis (according to the Diagnostic Interview for Children and Adolescents). Of these diagnoses, oppositional defiant disorder was most frequent (40%). Treatment with patch or gum was for duration of 12 weeks, with a follow up visit three months after the end of treatment. A total of 745 adverse events were documented throughout the trial. There were statistically significant increases in the incidence of sore throat (gum compared to placebo, p = 0.0007), hiccups (gum compared to placebo, p = 0.014), shoulder/arm pain (patch compared to placebo, p = 0.0011), pruritus (patch compared to placebo, p = 0.033, gum compared with placebo, p = 0.003) and erythema (patch compared to placebo, p = 0.0045). There was a mean reduction in self reported smoking (CPD) for all three groups (gum, patch and placebo) and this exceeded 80% reduction in each case. The authors suggest that the pattern of adverse events reported in this trial was similar to those reported in adult trials

Smith et al. 1996 [+]

A nonrandomized, open-label trial to evaluate the safety, tolerance and efficacy of a 24 hour NRT patch in a group of 22 adolescent smokers reached a similar conclusion with respect to the safety of treatment. The treatment comprised daily nicotine patch therapy for 8 weeks (22 mg/day for 6 weeks followed by 11 mg/day for 2 weeks). Participants also received group counselling sessions. Adverse events were self reported. Fifteen subjects (68%) experienced a skin reaction (erythema,

oedema or vesicle formation); this was compared to a similar study in adults where 64% (58 of 90) subjects reported a skin reaction over the 8 week course of treatment. Other common symptoms reported by the adolescents included headache (41%), nausea and vomiting (41%), tiredness (41%), dizziness (27%) and arm pain (23%). None of these episodes were more than moderate intensity; none were serious or life-threatening

Hurt et al. 2000 [+]

Hurt et al, in their non-randomized, open label trial of nicotine patch therapy in adolescents. Of the 101 participants recruited to the trial, eighty-seven reported experiencing at least 1 adverse event during 6 weeks of treatment. Upper respiratory tract infections (44%), headache (43%), nausea and vomiting (13%), skin reactions (12%) and sleep disturbance (10%) were the most commonly reported adverse events.

Rubinstein et al. 2008 [++]

This randomized, open label trial suggests there may be safety concerns regarding the use of NRT nasal spray among adolescents (Rubinstein et al, 2008) [++]. The study randomly assigned 23 subjects to the nicotine nasal spray and 17 to control group. Both groups received counselling. Of the group using the spray 38.9% were of the opinion that the spray had lots of side effects. The most common adverse effect was nasal irritation (34.8%), followed by complaints about taste and smell (13%). The authors suggest that the symptoms may explain a low rate of use and that such poor adherence may explain the low overall quit rates observed.

Molander et al. 2001 [+]

This pharmacokinetic study describes the effects of advanced age on the kinetics of nicotine in humans. The hepatic clearance of high extraction drugs such as nicotine is expected to reduce with increasing age due to reduced hepatic blood flow and reduced renal function. Following an intravenous infusion of 0.028 mg/kg of nicotine over 10 minutes, the clearance of nicotine was significantly decreased by approximately 25% in elderly subjects (65 to 76 years) compared with younger adults (22 to 43 years). The maximal nicotine concentration was higher in the elderly subjects (16.8 ± 7.8 ng/ml vs 10.4 ± 3.5 ng/ml). Despite this, the maximal heart rate increase was significantly ($p = 0.0062$) lower in elderly subjects than younger adults (15 ± 6 bpm vs 21 ± 8 bpm) and there were no differences in the systolic and diastolic blood pressure responses between the two groups. There were no differences in the adverse events experienced by the subjects, either in terms of the type of event or severity.

Stapleton et al, 2008 [-]

Stapleton et al (2008) [-] evaluated a consecutive series of 412 smokers receiving smoking cessation treatment at a tobacco dependence clinic. Of these subjects 111 (27%) reported that they were receiving treatment for mental illness. Subjects could chose NRT (at whichever licensed preparation they preferred) or varenicline. The study was powered to detect a difference in the primary outcome measure (abstinence) but also measured tobacco withdrawal symptoms and adverse drug reactions over the course of treatment. In terms of efficacy, cessation rates were greater with varenicline than NRT. The authors report a similar incidence of adverse events for NRT and varenicline groups but did not analyse the frequency of adverse events in the NRT treated subjects with and without mental illness.

Daleck et al, 1999

A randomised, double blind, balanced crossover study of withdrawal and psychiatric symptoms in nineteen cigarette smokers with schizophrenia found that there were no significant changes in psychiatric symptoms during three days of smoking abstinence with or without nicotine replacement

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8 Appendix 1. Pharmacokinetic model

Modelling Nicotine Pharmacokinetics – Professor Glyn Taylor, November 2011

Disclaimer: The pharmacokinetic analysis has been performed by Professor Taylor in his individual capacity and the views expressed may not be those of Cardiff University.

Summary

In order to provide an overview of nicotine pharmacokinetics (i.e. the time course of nicotine circulating in blood) studies were selected from the published literature in which plasma or blood concentration measurements of nicotine were provided in sufficient detail to allow comprehensive analyses. Nicotine has been studied using many different forms and is delivered to the bloodstream by several routes of administration. The selection of studies has endeavoured to highlight by example the pharmacokinetics (PK) which have been reported using all of the major reported routes of administration. The technique of PK modelling used in this review, has been applied to the collected body of nicotine concentration data to allow further predictions to be made from the reported data, e.g. by changing the dose or frequency of dosing. Wherever possible the data selected for inclusion were from studies in smokers. Much of the required information in the published literature is only presented in graphical form and in these cases, nicotine concentrations were determined by estimation and detailed analysis of the graphical information. The limitations of accuracy in published graphical data should be taken into account when using this type of data source. Analyses of the concentration data and simulations of concentrations were performed using, the industry standard PK modelling programme, WinNonlin Professional (v2.1, Pharsight Corporation). This type of PK modelling involves portraying the body as a series of "compartments" and "rate constants" which define the movement of nicotine into, around (and out of) the body by transfer from one compartment to another. "First-order rate constants" are associated with very high initial rates of nicotine transfer which progressively decrease, with the rate of transfer halving after every "half-life". Conversely "zero-order rate constants" are defined by a constant rate of nicotine transfer until all of it has been moved to another compartment.

The key findings from the intravenous PK studies establish that nicotine is rapidly distributed from the blood to other tissues in the body, with a half-life of around 9 minutes and then more slowly removed (eliminated) from the body with a half-life of approximately 2 hours.

During cigarette smoking, nicotine is very rapidly absorbed from the lung with an absorption half-life of approximately 3 minutes, thus blood concentrations increase rapidly and are likely to reach a maximum within a few minutes after finishing a cigarette. Inhalation of nicotine from vapour inhalers and electronic cigarettes generally seems to be less efficient than from cigarette smoking.

Some studies report rapid absorption of nicotine following dosing via a nasal spray, with maximum concentrations occurring at a similar time to that seen after cigarette smoking whilst other studies report more variability and prolonged absorption.

Absorption of nicotine from the oral cavity is fairly rapid with half-lives of around 6-12 minutes. Peak plasma concentrations are however likely to be prolonged in part due to release rates from lozenge or gum formulations.

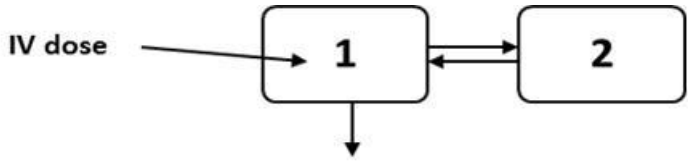
Transdermal nicotine formulations are designed to release nicotine over prolonged periods at controlled rates and whilst the time to reach maximum plasma concentrations may be several hours after a single application of a patch, subsequent patches are designed to maintain the concentrations with limits that are similar to those seen after smoking a single cigarette.

The remit of this pharmacokinetic report was to review and comment of blood or plasma concentrations of nicotine. The relationship between these concentrations and any effects, risk or safety of nicotine is beyond the scope of this review.

Intravenous (IV) Pharmacokinetics

Knowledge of intravenous pharmacokinetics (PK) is vital, not because this is an important route of administration but is needed as a reference to determine the absorption of nicotine from other routes. There are relatively few reports of intravenous nicotine PK and in these cases nicotine has been administered by infusion (Benowitz and Jacob, 1994; Feyerabend et al, 1985). From these studies and other reports measuring nicotine concentrations after cigarette smoking, the consensus of opinion is that nicotine PK are characterised by a rapid distribution phase (with a half-life of approximately 9 minutes) upon initial exposure to the systemic circulation. Characterisation of this distribution phase is important since if NRT products need to produce circulating nicotine concentrations which exactly mimic cigarette smoking then it is important to acknowledge that the kinetics of the distribution phase strongly influence the PK profile seen immediately after cigarette smoking.

Figure 1: IV PK Model

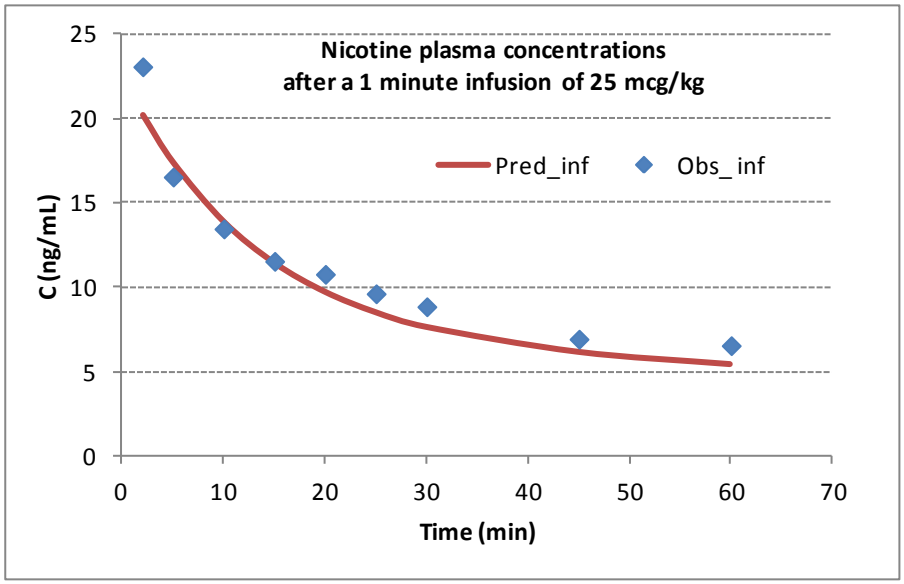


Notes: The distribution phase is very rapid and there is some evidence, although not sufficient data, for an additional distribution compartment.

The IV model (Figure 1) was adapted to IV infusion studies, in which the infusions were given over different time periods (Figures 2 &3). The parameters of the model were estimated from a review of the literature in terms of published concentration data and appropriate PK analyses in smokers. Data from non-smokers were excluded since a number of PK parameters, for example clearance, are reportedly different in this population (Tutka et al, 2005). Precision of the selected model parameters was tested against published concentration data. The pharmacokinetics of nicotine show large inter-subject variability (Benowitz et al, 1997) and thus any simulation will not perfectly match all of the published data but in this report the simulations are used to highlight general outcomes and potentials form different routes of administration and delivery systems.

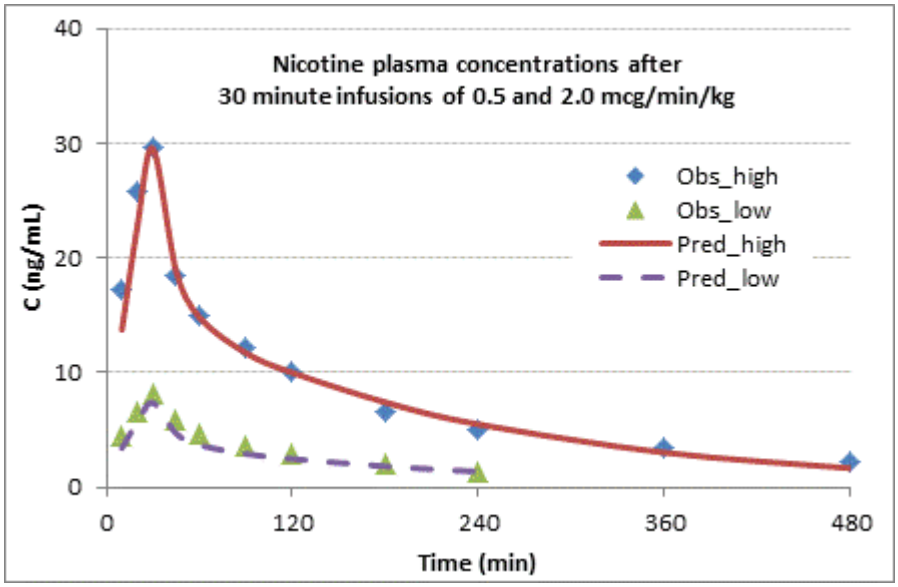
In Figure 2 the model is shown to be a reasonable prediction of the reported concentrations (Feyerabend et al, 1985). A much closer simulation could have been produced to match the specific data in this report, however, as discussed above, the parameters are derived from evaluations of a number of studies. Additionally the distribution half-life used is that reported in the study and the early “mismatch” may be partially attributable to the presentation of the plasma concentrations as mean (arithmetic average) data rather than the more representative geometric mean data.

Figure 2



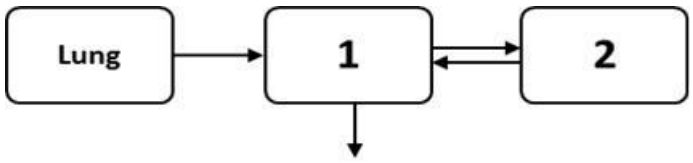
In a separate study (Figure 3) nicotine was infused over a longer period of time (30 minutes). One effect of using a longer infusion time is that the distribution phase will appear to be less pronounced. The values selected for PK modelling again show a reasonable concordance with the published concentration data (Benowitz and Jacob, 1994).

Figure 3



Pharmacokinetics after Cigarette Smoking

Figure 4: Inhaled PK Model

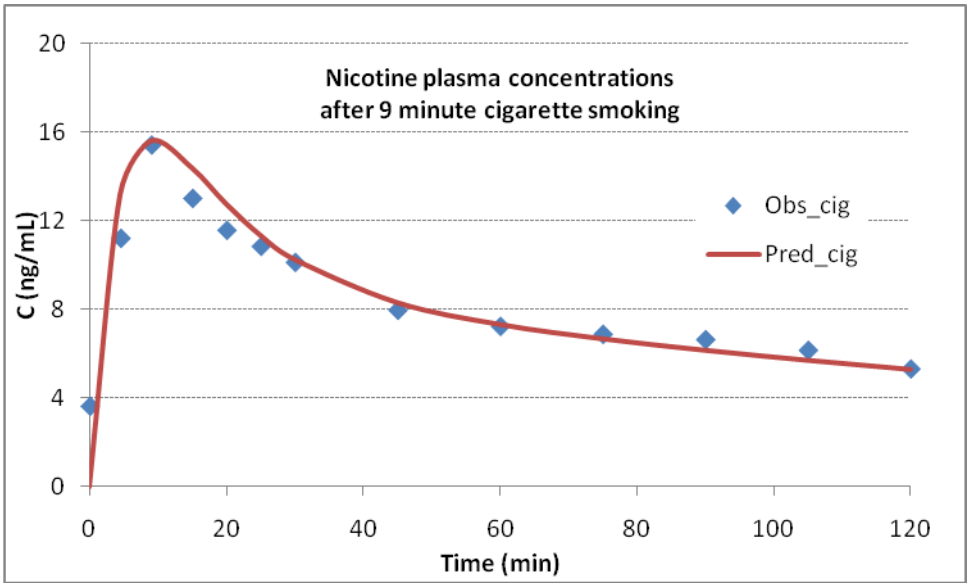


Notes: The absorption is very rapid and there is little likelihood of mucociliary clearance with subsequent g-i absorption (hence is not included). Any incomplete absorption, or first-pass metabolism in the lung will be "masked" in lung deposited dose.

Nicotine is very rapidly absorbed from the small airways of the lung and has been reported to give rise to arterial concentrations greater than those arising from IV dosing (Henningfield et al, 1993; Rose et al, 1999). The rapid increase in systemic nicotine concentrations may be associated with dependence (Benowitz 1990, Henningfield and Keenan 1993) hence if this is a usage factor, then modelling the PK after typical smoking episodes is important.

In Figure 5, average nicotine plasma concentrations for 10 (male) subjects (Benowitz et al, 1988) are seen to be modelled using the same PK disposition parameters described previously and with a first-order absorption half-life of 3 minutes. Other input functions, including zero-order were investigated but the first-order model gives the best fit to the sparse data. The relatively long half-life may seem incongruous with other observations that inhaled nicotine can produce increases in arterial blood concentrations exceeding those of IV but is most likely a reflection that under "typical" smoking conditions, subjects initially inhale rapidly and deeply to produce a rise in nicotine levels and then subconsciously reduce and titrate subsequent inhalations to control blood/brain concentrations. From a PK perspective it seems that if mimicking nicotine concentrations from smoking is the desired end goal of NRT, then this should be set against a typical smoking pattern, not what is the maximum achievable by inhalation.

Figure 5



In Figure 5 the model with a 3 minute absorption half-life is a reasonable prediction of the reported concentrations. The slight "mismatch" immediately after cessation of smoking (at 9 minutes) may be a reflection of some retention of nicotine in lung tissue or simply an increase in

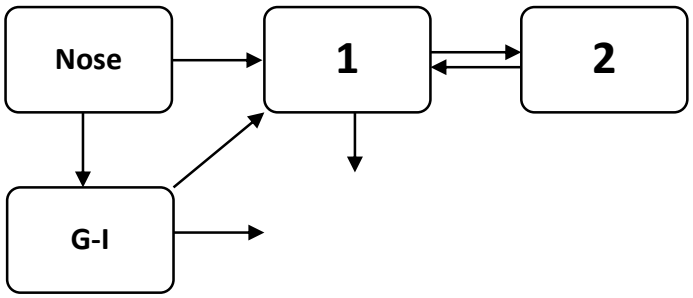
nicotine intake by the subjects towards the end of their allotted smoking time. Either of these hypotheses could be supported by the analysis of nicotine input rate (Benowitz et al 1988, Fig. 2) in which there is some evidence of a secondary peak during the smoking phase and a much smaller tertiary peak at approximately 20 minutes after the start of smoking.

Pharmacokinetics after Inhalation of Nicotine from Vapour Inhalers and Electronic Cigarettes

The PK model in Figure 4 was used to assess the absorption of pulmonary delivered nicotine. Determining the dose of nicotine delivered to the lung, whether that is via cigarettes or NRT devices is notoriously difficult. Estimates using in-line filters, breathing simulators and similar approaches end to indicate that approximately 80% of inhaled nicotine is absorbed into the systemic circulation (Hukkanen, et al. 2005). Absolute bioavailable fraction from a nicotine vapour inhaler (Molander, et al. 1996) is reported as somewhat lower, at 56%, however the sparse blood sampling regimen in this study, may have underestimated the bioavailable faction and time to reach peak concentration (0.5 hours). In another study (Bullen, et al. 2010) the Ruyan ENDD (electronic cigarette) resulted in 10-fold lower peak concentrations of nicotine compared with normal cigarette smoking (1.3 vs. 13.4 ng/mL) , the peak was however achieved at similar times (19.6 vs. 14.3 min) after the start of product use. Similar electronic devices tested in other studies (Vansickel et al. 2010) also report small and non-significant increases in nicotine plasma concentrations.

Figure 6: Nasal Cavity PK Model

Nasal (nasal spray)

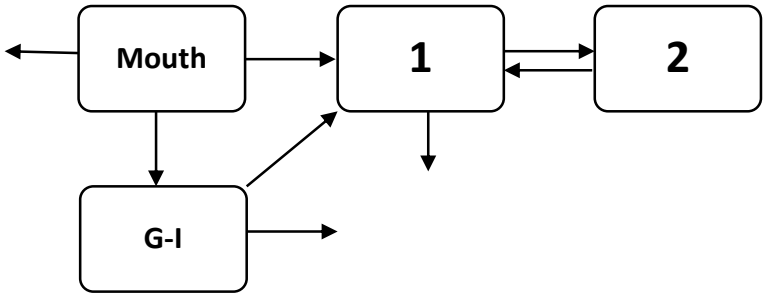


Notes: The absorption is rapid but mucociliary clearance with subsequent g-i absorption is possible. Any incomplete absorption, or first-pass metabolism in the nose will be “masked” in nasal delivered dose.

Nicotine is absorbed rapidly from the nasal cavity and can produce PK profiles similar to those seen after cigarette smoking (Sutherland et al 1992, Guthrie et al, 1999). Peak plasma concentrations can be achieved at around 6 mins (Sutherland et al 1992) to 15 minutes (Lunell et al, 1995) after dosing. The bioavailable fraction, from the Lunell data is estimated to be around 60% (with the clearance estimates used elsewhere in the modelling). The effects of rhinitis and use of a vasoconstrictor, xylometazoline, did not significantly affect the bioavailable fraction (Lunell, et al 1995), however the time to reach peak plasma concentration was significantly increased from approximately 15 to 30 minutes. The reported times to peak concentration are longer in this report than in the Sutherland paper, in part due the nasal dose being delivered with a 5 minute interval between 2 administrations. In other reports the time to reach peak concentrations in venous samples is variable, ranging from 8 to 70 minutes after nasal spray dosing in 6 male smokers (Gourlay et al, 1997) and 9 to 60 minutes in 9 female smokers (Guthrie et al, 1999).

Figure 7: Oral Cavity PK Model

Oral (gums, lozenges, sublingual tablets, etc.)



Notes: There is significant g-I delivery from swallowing saliva and thus nicotine released from dosage forms intended to be retained in the mouth. Absorption is relatively slow and there is a likelihood of binding, incomplete release, etc. with certain dosage forms, as indicated by the additional exit from "Mouth" compartment.

A number of comparator studies between nicotine lozenges (Nitcotinell) and nicotine gum (Nicorette) are reported by Dautzenberg et al, 2007. This group of studies report bioequivalence between 1 mg lozenge and 2 mg gum formulations, with the performance of 2mg lozenges, in terms of delivered dose, lying between the 2 and 4 mg gum formulations. The pharmacokinetics resulting from administration of these products is potentially highly complex, since the stimulation of saliva by chewing or sucking inevitably leads to the swallowing of unknown quantities of nicotine released from these products. This swallowed nicotine will be subject to first-pass metabolism if subsequently absorbed from the intestine (Benowitz et al, 1987). Additionally, all of the nicotine may not be released from these products within 30 minutes, leading to losses when the products are ejected or swallowed. Significant residual amounts of nicotine in lozenges were reported by Dautzenberg et al, 2007 and these amounts were used in adjusted parameter calculations. Without adjustments the absolute bioavailable fraction of nicotine from the oral lozenge is approximately 60%, the high variability in systemic clearance and the absence of IV PK for this cohort of subjects should be borne in mind when using this estimate. The bioavailable fraction of nicotine from (Nicotinell) gum products in this study was approximately half of that observed with the lozenge. Such large differences between lozenge and gum formulations have not been reported in other studies (J&J NCT01084603). The absorption rate from the oral cavity may be an important factor in the efficacy of NRT products. Times to reach peak concentration are longer than after inhalation at approximately 30-60 minutes. The much slower absorption from the oral cavity results in much lower peak concentrations (Dautzenberg et al, 2007; Figures 8 and 9) than are seen after inhalation (Figure 5). It is noteworthy that repeated intake of a 1 mg lozenge, or 2 mg gum every hour does not result in the likely peak concentration seen after a typical smoking episode (Figure 5). The plasma nicotine concentrations from the repeated lozenge and gum dose study reported by Dautzenberg, with blood samples taken during the accumulation and decline phases (Figures 8 and 9) has allowed the modelling of nicotine concentrations and

enabled testing of whether nicotine is retained in oral cavity tissues with prolonged release into the blood. In both cases, absorption half-lives of 6-12 minutes from the oral cavity can be used to give reasonable predictions of the observed data. Prolonged residence in buccal or other oral cavity tissues would be manifest as a slower decline after reaching steady-state. This is not seen to any appreciable extent in either Figure 8 or 9. The slight deviations in predicted concentrations beyond 15 hours may be some evidence for prolonged retention but this represents a small proportion of the dose in each case.

Figure 8

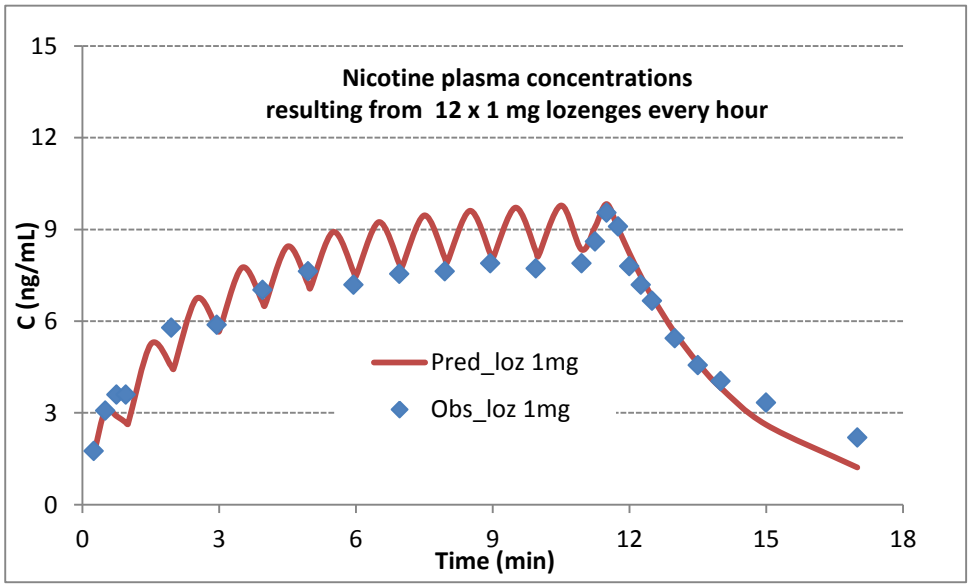
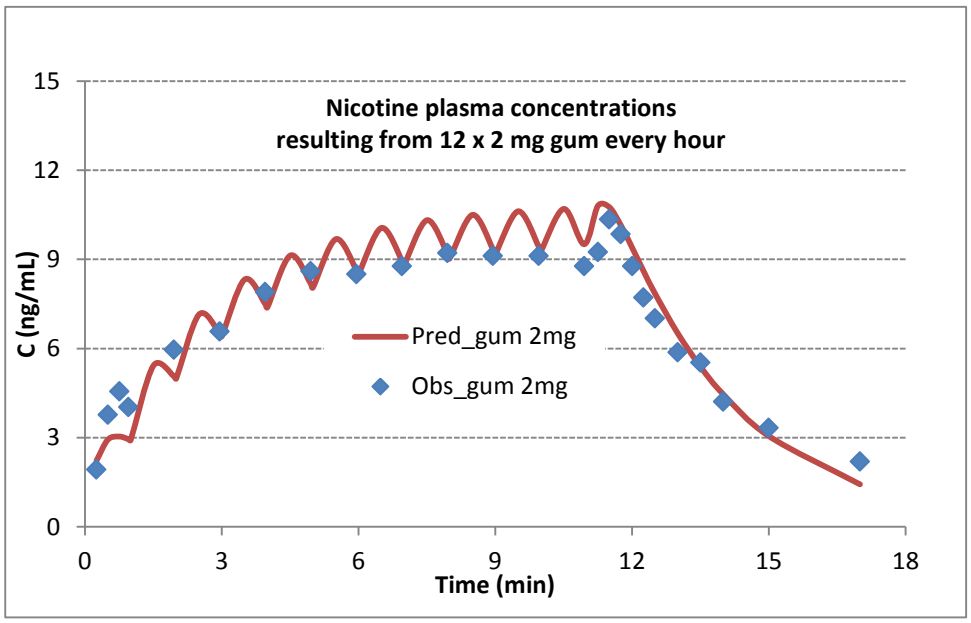


Figure 9

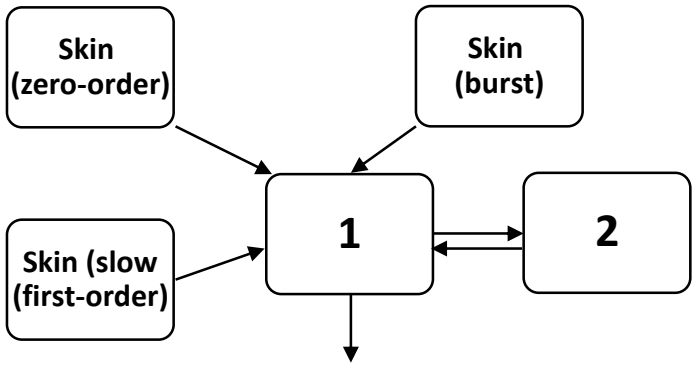


Administration of nicotine using a vapour inhaler delivery to the buccal region (Molander et al, 1996) resulted in concentrations similar to those achieved after normal cigarette smoking but with a peak concentration achieved at 20 minutes, the overall time of administration using the inhaler. This result also suggests that nicotine is not subject to prolonged residence in the buccal tissues.

The use of a 2 mg nicotine sub-lingual tablet formulation resulted in a PK profile similar to that from dosing with 2 mg nicotine gum in the same subjects (Molander and Lunell, 2001). Incorrect use of the tablets by chewing and immediate swallowing reduced the bioavailable fraction, most likely due to first-pass metabolism of the swallowed dose. The reduction, of approximately 20% in AUC, is however much less than would be anticipated from the reported bioavailaibility of 20-45% (Hukkanen et al, 2005) and this may indicate that a significant proportion of the nicotine dose partitions into tissues of the oral cavity after tablet chewing.

Figure 10: Transdermal PK Model

Transdermal (patches)

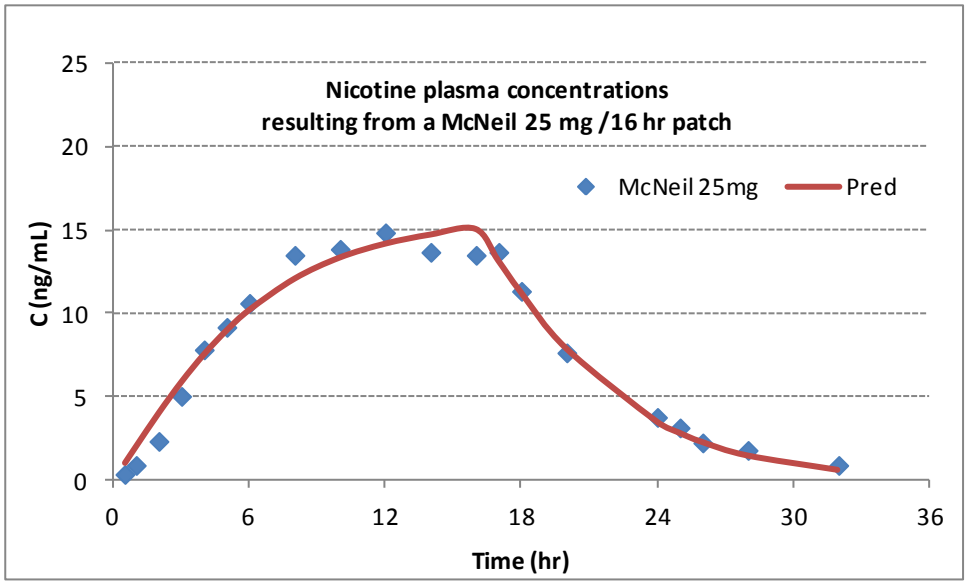


Notes: These dosage forms should provide zero-order release over a specified time period but for some devices there may be evidence of both an initial burst of delivery and reduced delivery before exhaustion (both will be modelled as first-order events).

Most transdermal patch delivery systems aim to control drug release by means of a rate controlling membrane from a reservoir in the delivery device. A zero-order release and input into the bloodstream will maintain constant plasma concentrations upon consecutive application of patches, providing that patches are replaced before the time of reservoir exhaustion. Deviations from this scheme may occur in a number of ways. The nicotine input rate may increase soon after application resulting in a "burst" of drug input. There may be some time lag before the nicotine starts to be released at a constant rate. The rate of release may not be consistent (zero-order) process but shows a gradual diminution over time, resembling a slow first-order process which will result in absorption rate limited kinetics. There may also be some delayed transit through the skin, leading to a prolonged increase to reach peak concentrations. This might be expected to be device independent, however the extent of skin hydration with different devices may also have a significant influence.

DeVeaugh-Geiss, et al (2010) compared the PK of two nicotine transdermal systems in 50 healthy (29 male, 21 female) smokers in a single-dose cross-over study. The plasma profiles are summarised in Figures 11 and 13.

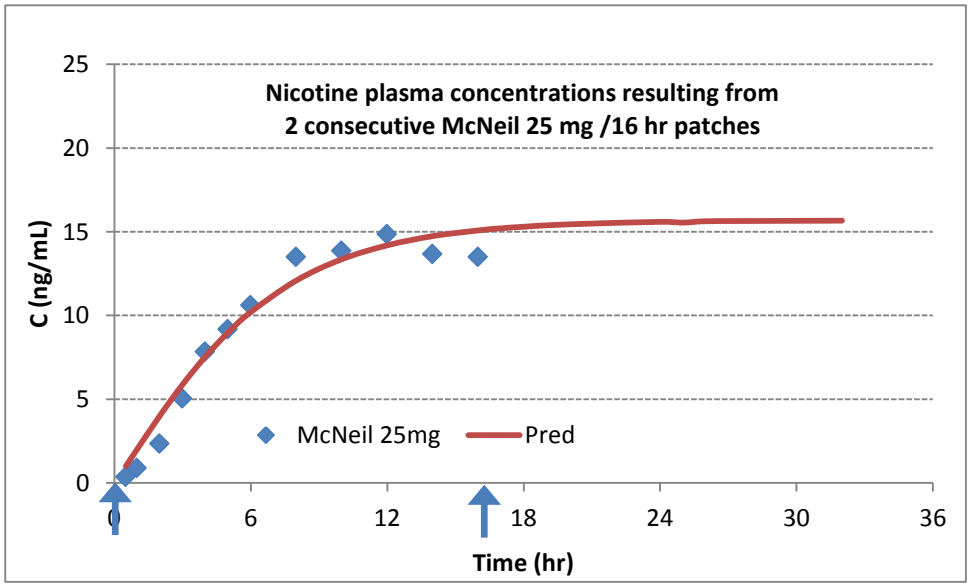
Figure 11



The data presented in Figure 11 for the McNeil 25mg/16 hour patch (Nicorette Invisi 25 mg Patch) provide some evidence of a short lag-time of around 30 minutes before the plasma concentrations start to markedly increase but the overall profile is generally consistent with a zero-order drug input. After removal of the patch at 16 hours, the similarity of 16 and 17 hour concentration provides evidence of some prolonged residence in the skin. The post-17 hour half-life is however consistent with the range of elimination half-lives seen after intravenous studies indicating that any prolonged skin residence is not of great importance in determining the PK profile from this delivery system. By contrast, the half-lives measured post-removal (at 16 hours) for another Nicorette patch applied to three different skin sites (Sobue et al 2005) were much longer at 4-5 hours, suggesting a prolonged absorption through the skin in these subjects (19 Japanese male smokers).

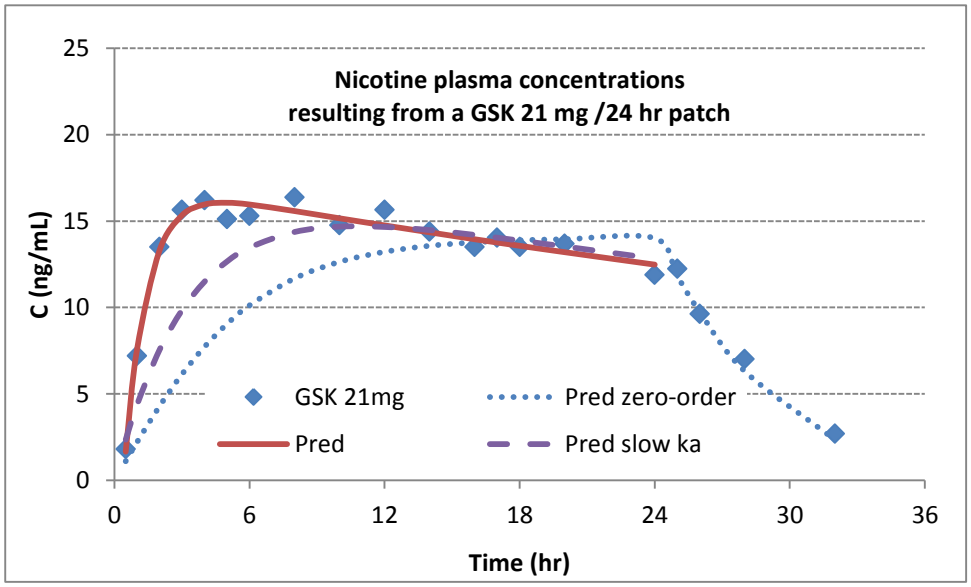
Simulated concentrations following removal and application of a second McNeil patch at 16 hours are shown in Figure 12. As illustrated, the concentrations remain relatively constant. This is a consequence of the data being consistent with zero-order input.

Figure 12



The comparator transdermal device in the DeVeaugh-Geiss et al (2010) study was NiQuitin 21 mg Transdermal Patch. The data in Figure 13 compare the reported concentrations with a simple zero-order release ("Pred zero-order") using distribution and elimination half-lives consistent with average IV data and with those used for the same cohort of subjects in Figure 11. The data clearly demonstrate a "burst effect" in which the early drug release produces a rapid rise in plasma nicotine concentrations during the first 2-3 hours. The half-life associated with this early phase of approximately 0.7 hours is shorter than is consistent with the nicotine elimination half-life and most probably a reflection of the absorption half-life through the skin. The data cannot be modelled as a slow first-order release ("Pred slow ka") unless again a burst phase is added to the simulation.

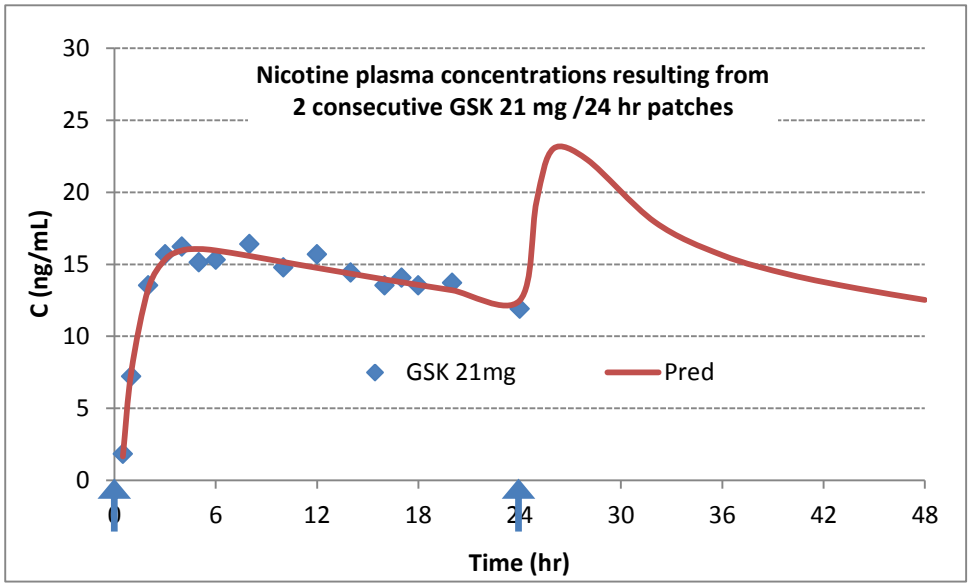
Figure 13



Simulated concentrations following removal and application of a second GSK patch at 24 hours are shown in Figure 14. In contrast to the McNeil patch, the concentrations show a rapid increase to reach a peak at around 2 hours after application of the new patch with a slow decline to the concentrations seen at 24 hours. This profile is a consequence of the data being consistent with a rapid release "burst dose" followed by a prolonged input. This simulation is based upon an absorption rate limited model (slow ka) plus a burst. Similar results would be obtained with zero-order input plus a burst, however that simulation, less accurately reflects the reported data after a single patch application.

The AUCs from the GSK patch are reported to be around 50% higher than the McNeil patch and this difference increases to around 87% higher with dose normalisation. This may be reflection of a number of factors including incomplete release from the delivery systems or differences in the method of expressing doses in the patches. IV studies were not reported for this cohort of subjects, however a bioavailability of approximately 100% from the GSK patch is estimated if this cohort of subjects has a clearance similar to that reported for IV dosing.

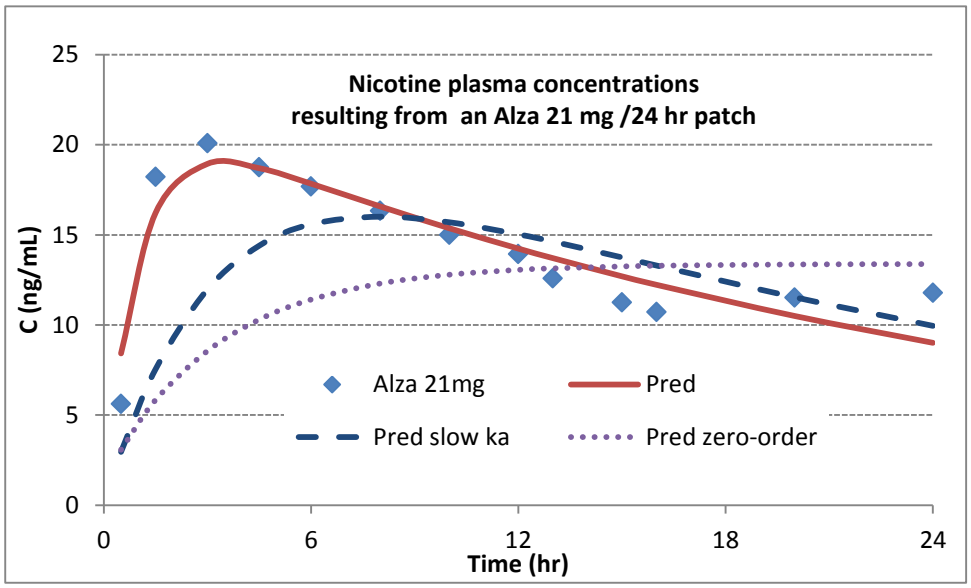
Figure 14



Fant, et al (2000) compared the PK of three nicotine transdermal systems in 25 healthy (16 male, 9 female) smokers in a single-dose cross-over study. The plasma profiles are summarised in Figures 15 to 17 together with PK model predictions.

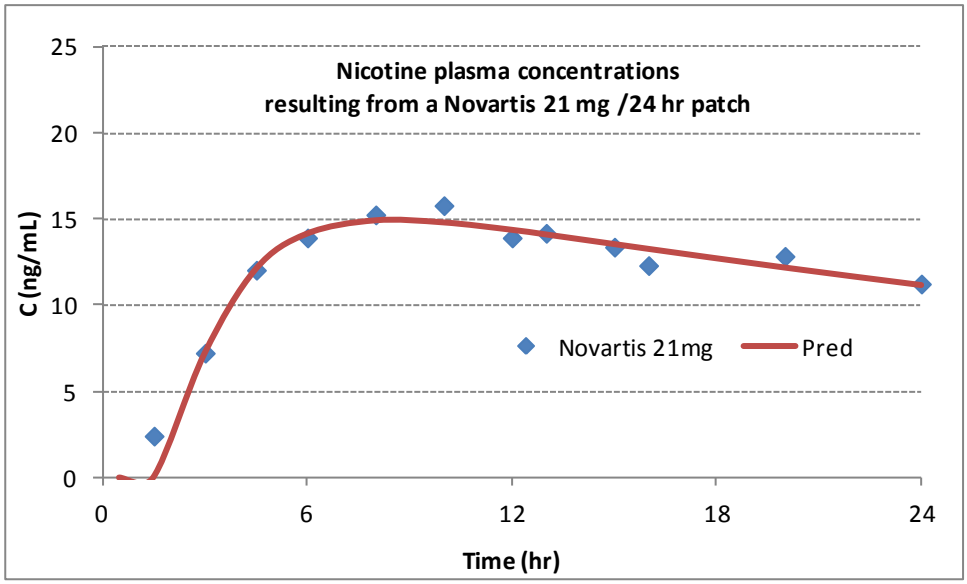
Data from an Alza patch are presented in Figure 15 and there are some distinct similarities with the data for the GSK patch shown in Figures 13 and 14. The ratio of the peak (at 3.8 hours) to the 24 hour concentration is however less than reported with the GSK patch. There are some commonalities in the technology used in the two systems, although information on the precise dosage form being used in the Fant paper is lacking. In common with the analysis of the GSK patch data, there is good evidence of a burst dose in this formulation as shown by the simulations of simple zero-order (pred zero-order) or absorption rate limited (slow ka) models. In this study two further patches were applied and plasma concentrations measured after the third patch showed a distinct spike at 2.8 hours after application.

Figure 15



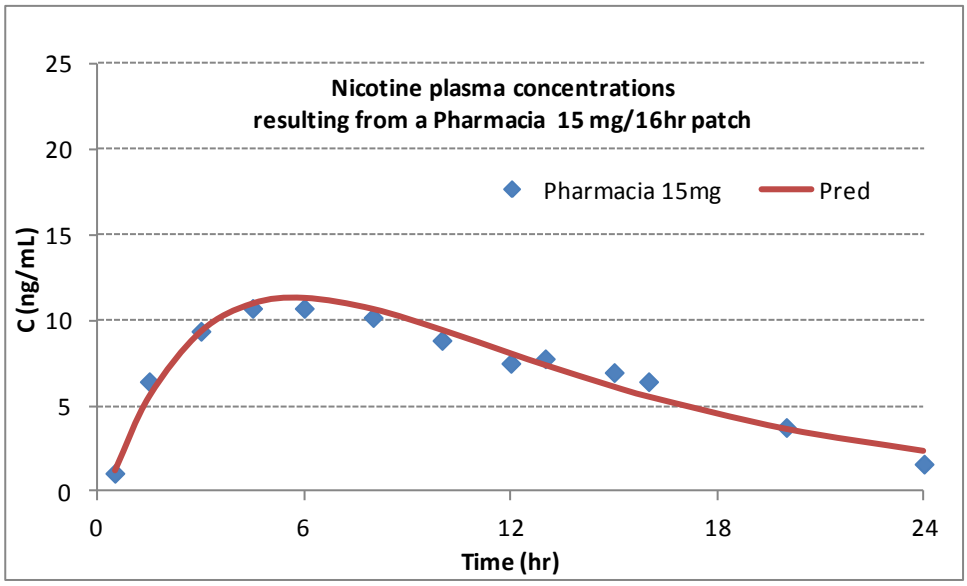
Data from a Novartis patch are presented in Figure 16 and in contrast with the Alza patch data, a simple absorption rate limited model (pred) with a time lag is a reasonable simulation of the observed data. Consistent with the lack of a burst dose is the observation that the predicted peak concentration occurred at 10 hours after the third application of this patch.

Figure 16



Data from a Pharmacia patch are presented in Figure 17 and show marked PK similarities with the Novartis patch data. Consistent with the lack of a burst dose is the observation that the predicted peak concentration would occur at 6 hours after the third application of this patch.

Figure 17



The dose normalised AUCs from the Alza patch are reported to be around 40% higher than the Pharmacia patch and 13% higher than the Novartis patch. Comparsion of AUCs with the DeVeaugh-Geiss, et al (2010) study shows similarity in AUC 0-24 hr of 328 hr.ng/mL for the Alza product and AUC 0-32 of 371 hr.ng/mL for the GSK product.

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9 Appendix 2: Nicotine interactions with drugs

Source: Baxter, K. (2011). Stockley's Drug Interactions 8th edition. Pharmaceutical Press.

Interaction	Description
Nicotine + Adenosine	Nicotine appears to enhance the effects of adenosine. In healthy subjects the circulatory effects of a 70 mcg/kg/min infusion of adenosine were increased by NRT gum (2mg). Increase in heart rate due to nicotine (5.5 bpm) was further increased to 14.9 bpm by adenosine. In another study nicotine increased the chest pain and duration of AV block when given to healthy subjects with IV boluses of adenosine.
Nicotine + Alcohol	NRT patch may enhance the effect of alcohol on heart rate and reduce the time to peak alcohol levels. Concurrent use of alcohol and NRT nasal spray did not affect the pharmacokinetics of either drug.
Theophylline + Nicotine (tobacco)	Polycyclic hydrocarbons found in tobacco smoke induce the cytochrome P450 isoenzyme CYP1A2. Increased enzyme activity results in a more rapid excretion of theophylline (the mean half life is 4.3 hours in smokers compared to 7 hours in non-smokers). Consequently heavy smokers may need much greater daily doses of theophylline than non-smokers. Large doses are not needed for those who chew NRT gum. Significant reductions in the daily doses of theophylline will be required when a smoker stops smoking since the CYP1A2 induction is gradually lost.
Antidiabetics + Nicotine (tobacco)	Smoking or, to a lesser extent, nicotine patches may increase insulin resistance, and stopping smoking can improve glycaemic control in both type I and type II diabetes. Heavy smokers may need up to 30% more subcutaneous insulin than non-smokers.
Bupropion + Nicotine	A higher risk of hypertension has been described when the two drugs are combined.
Bupropion + Nicotine + Pseudoephedrine	One isolated case report of acute myocardial ischaemia in a 21 year old male following combined use of pseudoephedrine (270 mg over a 3 day period), bupropion and nicotine (from smoking cigarettes).
H2 receptor antagonists + Nicotine (tobacco)	Smoking may reduce the plasma levels of cimetidine and ranitidine. Cimetidine and ranitidine reduce the clearance of nicotine from the body in non-smokers.
Opioids + tobacco	Smokers who stop smoking require more opioid analgesics for postoperative pain control than non-smokers. This has been seen with both fentanyl and morphine.
Neuromuscular blockers + tobacco	Smokers may need more vecuronium and possibly more rocuronium, but less atracurium to achieve the same effects as non-smokers. Results are variable and significance is uncertain.

Interaction	Description
Nicotinic Acid + nicotine	One isolated report of a flushing reaction which developed in a female taking nicotinic acid 250 mg bd who started to use nicotine transdermal patches.
Vasopressin + Nicotine	Marked hypotension and bradycardia in a female during surgery, attributed to the combined effects of vasopressin and nicotine from a transdermal patch.

10 Appendix 3 – Review protocol

10.1 Background

In the past, public health strategies with respect to smoking have focused on discouraging people from starting to smoke and helping smokers to quit the habit completely. There remains a group of smokers who either want to quit but feel unable to stop abruptly or otherwise are not willing or able to quit but may be prepared to reduce the amount they smoke. The healthiest course of action for all smokers is to stop smoking but harm reduction measures attempt to limit the risks by reducing exposure to the toxic chemicals found in tobacco smoke (Royal College of Physicians, 2007).

Harm reduction is defined as "policies, programmes, services and actions which aim to reduce the harm to individuals, communities and society that are associated with the use of drugs". Such measures are pragmatic, recognising that the reduction of harms may be more feasible than complete elimination of drug use (UK Harm Reduction Alliance).

Smokers continue to smoke predominantly due to nicotine addiction but in so doing expose themselves to a large number of chemicals, many of which are established carcinogens. Tobacco smoke contains over 3000 chemicals, including carbon monoxide, nitrosamines, polycyclic aromatic hydrocarbons, nitrogen oxides, hydrogen cyanide and heavy metals.

The Royal College of Physicians estimate that if only 0.4% of the population of smokers in the UK switch from smoking to less harmful nicotine sources each year, this would save approximately 25 000 lives in 10 years.

There are some suggestions that medicinal nicotine may have a role in harm reduction.

From the DOH publication Drug Misuse and Dependence: UK Guidelines on Clinical Management: "Given the high rates of smoking and the low quit rates in drug misusers, it may be reasonable to consider harm reduction approaches to smoking such as replacing cigarettes with clean nicotine in the form of patches for some of the day. This may be particularly useful in alleviating the symptoms of tobacco withdrawal while a patient is within a residential or inpatient drug treatment facility" (DOH, 2007).

The MHRA have launched a public consultation regarding whether unlicensed nicotine containing products (NCPs) should be brought into regulation. Currently a number of NCPs such as electronic cigarettes are unlicensed so have not been assessed for safety, efficacy and quality. NCPs which do

not claim or imply medicinal use can currently be sold and used without the safeguards inherent in the regulation of medicines. There was support for regulation from medical professional bodies, royal colleges, NHS bodies, public health bodies and trading standards. Many importers of electronic cigarettes and their users opposed regulation. The MHRA has also identified further scientific and market research which will be required and expect a final decision regarding nicotine regulation to be made in Spring 2013 (MHRA, 2011).

The health benefits of cutting down smoking rather than quitting have not been established. The US Institute of Medicine, in its 2001 report conclude that the reduction of the risk of disease by reducing exposure is feasible, but harm reduction measures would need to be evaluated. Overall the net effect of such measures on public health is unknown (Stratton et al, 2001).

Although harm reduction strategies have been successful in other areas, when applied to tobacco they are controversial. Bates (2002) described the various approaches, for example there may be unintended consequences of adopting harm reduction measures such as ex-smokers relapsing to the harm reduction option and young persons starting off with the harm reduction option in the belief that it is safer. In such cases it is possible the benefits may be overwhelmed by more widespread uptake of harm reduction measures. Another criticism levelled against harm reduction measures is that they represent an admission of defeat and still leave the smoker exposed to harm (Bates, 2002).

10.1.1 Guidelines and salient publications

Bates C, 2002. 'Harm reduction: an introduction to the issues. Background paper for Harm reduction seminar 16th May 2002'

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Stratton K, Shetty P, Wallace R et al, 2001. 'Clearing the smoke: assessing the science base for tobacco harm reduction- executive summary', Tobacco Control; 10: 189-195.

10.2 Aims

The aims of this review are:

- To summarise evidence on the safety, or risks, of tobacco harm reduction strategies when used in people who may continue to smoke. This includes smokers who successfully quit but continue to use NRT products indefinitely.
- To summarise the pharmacokinetic factors which influence the safety, or risks, of tobacco harm reduction strategies when used as above, principally NRT products.

10.3 Scope

10.3.1 Groups that will be covered:

This literature review will study smokers of all ages (including children and young people) who:

- want to quit smoking but feel unable to do so 'abruptly' (that is, they want to cut down before quitting)
- are not willing or able to quit, but want to reduce the harm that smoking is doing to their health (or to the health of those around them)
- want to quit smoking but are not willing or able to stop using nicotine (so they will continue to use nicotine following a successful quit attempt)
- want to stop smoking temporarily, for example, while at work.

The review will focus, in particular, on groups who are more likely to smoke (this includes those in routine and manual occupations.

10.3.2 Groups that will not be covered

This review will not cover pregnant women.

10.3.3 Activities / interventions that will be covered

- licensed nicotine containing medicines (both prescription only medications and those available over the counter), including
- nicotine chewing gum
- nicotine transdermal patches
- nicotine inhalers
- nicotine microtabs
- nicotine nasal spray
- nicotine lozenges
- non licensed nicotine containing products (e.g. electronic cigarettes)

10.3.4 Activities / interventions that will not be covered

- Tobacco (oral moist tobacco [snus], oral compressed tobacco, oral loose tobacco, bidis, pipe tobacco, snuff)
- Tobacco containing products, including those that are potential reduced exposure products (PREPS):
- combustible products that are smoked e.g. low nitrosamine or low tar cigarettes
- cigarette-like products that heat, rather than burn tobacco
- Medicines that do not contain nicotine but that are licensed for use in the UK for smoking cessation: bupropion and varenicline.

10.4 Other aspects of the scope

The review will include evidence for NRT products used alone and in combination, in people who continue to smoke and in people who stop smoking altogether but use NRT as a long term strategy.

10.5 Overview of project

NICE is commissioning Cedar, Cardiff & Vale University Local Health Board (UHB) to produce the following products and services during the Financial Years 2011/12 and 2012/13:

- The review of the safety, risk and pharmacokinetic profiles of tobacco harm reduction technologies

- Delivery of the above product will involve submitting a 1st draft review to the NICE Team by 16th September 2011 and undertaking any amendments to the draft following comment, prior to providing a revised draft (2nd draft) by 30th September 2011 for mailing to the PDG.
- Presentation of the review to the PDG meeting on 18th October and undertake any amendments to the review following comment from the PDG. Submission of a 3rd draft review following comments from the PDG, by 25th November 2011
- Provision of written contributions and technical support during and after the completion of the review, as required during the development of the public health programme guidance. This will include:
    - Supporting the NICE Team in responding to any stakeholder comments on the review and the draft recommendations
    - Attendance at PDG meetings as required (dates for these meetings are outlined in Annex 2).
    - Submission of a final review document following public consultation, by 22nd February 2013.

The project is the first of three components of work, which will inform the NICE public health guideline on tobacco harm reduction. The other two components are:

- Two reviews of effectiveness and one review of barriers and facilitators
- An economic analysis (cost effectiveness review and economic model).

10.6 Review questions

10.6.1 Question 1

What specific risks have been associated with the technologies within the scope of the review? What adverse events or serious adverse events have been identified and how frequently do they occur? Is there any evidence that use of the technologies may cause significant drug interactions? Of particular concern is whether there are any interactions between nicotine and psychiatric medication since smoking prevalence is much higher among individuals with mental illness.

10.6.2 Question 2

What data are available to support the safety of long term use of the technologies?

10.6.3 Question 3

What are the risks associated with use of NCPs which are currently unlicensed? (Questions especially relevant to the e-cigarette: What is the nature of the absorbent material? Are there other components present in the nicotine solution used in this device? Do these represent risks to the user? Are any harmful chemicals released when the nicotine solution is heated?)

10.6.4 Question 4

Do the data suggest the technologies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

10.6.5 Question 5

Do the data suggest the combination of nicotine replacement therapies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

10.6.6 Question 6

Are kinetic data available which allow comparison of the relative bioavailability of different technologies i.e. maximum (peak) concentration (Cmax), time to peak concentration (Tmax) and half life (t ½)?

10.6.7 Question 7

Do the data support the safety of an approach where smokers receive doses of medicinal nicotine (potentially by different routes) while continuing to smoke. Is there a greater risk of adverse effects?

10.6.8 Question 8

There are marked differences in smoking rates among socioeconomic groups, Black and minority ethnic (BME) groups, age (lifestage) and people with mental illness. Do the data suggest there may be inequalities among these groups with respect to the risk, safety and pharmacokinetics of smoking harm reduction technologies?

10.6.9 PICO table to support review questions

Population
Smokers of all ages who: want to quit smoking but feel unable to do so abruptly or smoke and do not feel willing or able to quit but want to reduce the amount they smoke. Particular attention will be paid to the following: Socio-economic status Black and minority ethnic groups Age (lifestage: children, adults, older people) People taking psychiatric medication.
Intervention
Interventions identified as suitable for harm reduction but excluding tobacco containing products: licensed nicotine containing pharmacotherapies unregulated nicotine containing products (e.g. e-cigarettes) Use of the above alone or in combination. These will be considered in people who continue to smoke and also in people who cease smoking.
Comparison
Comparing risk and safety of different technologies. No intervention – data from studies of people who smoke. Possibly data from smoking cessation programmes. Data from studies of ex-smokers
Outcomes
Safety: Adverse effects, serious adverse effects, safety reports, acceptability/ tolerability. These

may be patient- or clinician- reported.

Pharmacokinetic: Pharmacokinetic profile, documentation of pharmacokinetic parameters (Cmax, Tmax, t1/2 , AUC, bioavailability)

Adverse effects associated with use of the intervention

Drug interactions associated with the use of the intervention.

Specify pharmacokinetic parameters, such as time to peak blood levels, half life, metabolism, excretion.

10.7 Methods

10.7.1 Literature search

The aim of the literature search is to identify evidence on the safety, risks and pharmacokinetic profiles of tobacco harm reduction strategies (principally non-tobacco based, nicotine containing products). We will seek evidence that is:

- of the highest quality available, considering the hierarchy of evidence
- applicable to the UK
- valid.

The following sources will be searched from 1980 onward to identify relevant evidence/studies in the English language. Both published and unpublished literature that is publicly available, including trials in press ("academic in confidence") will be considered.

A draft search strategy has been developed for Ovid Medline [Appendix 1] and once approved this will be translated for use in all other sources detailed below.

10.7.2 Electronic database sources:

- AMED (Allied and Complementary Medicine)
- ASSIA (Applied Social Science Index and Abstracts)
- British Nursing Index
- CINAHL (Cumulative Index of Nursing and Allied Health Literature)
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Cochrane Public Health Group Specialized Register [based at SURE, Cardiff University]
- Database of Abstracts of Reviews of Effectiveness (DARE; 'other reviews' in Cochrane Library)
- Current Contents
- EMBASE
- HMIC (or King's Fund catalogue and DH data)
- Medline

- UK Clinical Research Network Portfolio Database
- PsycINFO
- Sociological Abstracts
- Social Policy and Practice
- Social Science Citation Index
- Web of Knowledge (Science and Social Science Citation Indexes)

10.7.3 Other sources

- US Food and Drug Administration (FDA) http://www.fda.gov/
- Drug Information Online http://www.drugs.com/
- Electronic Medicines Compendium (eMC) http://www.medicines.org.uk/emc/
- National electronic library for medicines http://www.nelm.nhs.uk/en/
- UK Medicines Information http://www.ukmi.nhs.uk/default.asp
- Toxbase http://www.toxbase.org
- Smoke free http://smokefree.nhs.uk
- NHS Centre for Smoking Cessation and Training http://www.ncsct.co.uk/
- Action on Smoking and Health (ASH) http://www.ash.org.uk
- Treat tobacco.net http://www.treatobacco.net/en/index.php
- Society for Research on Nicotine and Tobacco http://www.srnt.org
- International Union Against Cancer http://www.uicc.org
- WHO Tobacco Free Initiative (TIF) http://www.who.int/tobacco/en
- International Tobacco Control Policy Evaluation Project http://www.itcproject.org
- Tobacco Harm Reduction http://www.tobaccoharmreduction.org/index.htm
- Current controlled trials http://www.controlled-trials.com
- Association for the treatment of tobacco use and dependence (ATTUD) http://www.attud.org
- National Institute on drug abuse- the science of drug abuse and addiction http://www.nida.nih.gov/nidahome.html

- NICE http://www.nice.org.uk/
- Public health observatories http://www.apho.org.uk/
- Scottish Government http://home.scotland.gov.uk/home
- Welsh Government http://wales.gov.uk/?lang=en
- NHS Evidence http://www.evidence.nhs.uk/
- Joseph Rowntree Foundation http://www.jrf.org.uk/
- OpenGrey http://www.opengrey.eu/
- The Centre for Tobacco Control Research (University of Stirling) http://www.management.stir.ac.uk/research/social-marketing/centre-for-tobacco-control-research/
- UK Centre for Tobacco Control Studies http://www.ukctcs.org/ukctcs/index.aspx
- Tobacco Control Research Group (University of Bath) http://www.bath.ac.uk/health/tobacco/
- Medicines and Healthcare products regulatory agency (MHRA) http://www.mhra.gov.uk/index.htm
- US Food and Drug Administration (FDA) http://www.fda.gov/
- Drug Information Online http://www.drugs.com/
- Electronic Medicines Compendium (eMC) http://www.medicines.org.uk/emc/
- National electronic library for medicines http://www.nelm.nhs.uk/en/
- UK Medicines Information http://www.ukmi.nhs.uk/default.asp

Information on studies in progress, unpublished research or research reported in the grey literature will be identified through searching a range of relevant databases including Conference Proceedings Citation Index: Science (ISI), Inside Conferences, National Technical Information Service (NTIS) and Clinical Trials.gov and manufacturer marketing materials.

To identify published resources that have not yet been catalogued in the electronic databases, recent editions of key journals will be hand-searched. Advice on appropriate journals will be sought from the pharmacokinetics expert Professor Glyn Taylor and other members of the advisory group. The protocol will be updated to include details of all journals handsearched.

Registered stakeholders and manufacturers of all relevant technologies will be contacted to request relevant evidence/ information. Further details are provided in Appendix 2. Protocols for the submission of commercial in confidence data will be agreed with NICE.

To supplement the database and hand searches and improve the sensitivity of the search, Cedar will carry out additional methods (see Manual section 4.4.2): Following up reference lists of relevant primary and review-level studies, searching specific web sites for additional and grey literature, contacting experts in the field (including authors, the Trials Search Coordinator of the Cochrane Tobacco Addiction Group and the UK Tobacco Control Research Network) and unpicking relevant systematic reviews and evidence-based guidelines.

10.7.4 Restrictions

The literature search strategy is restricted to English Language resources. The strategy is not restricted to human studies only because extrapolation from animal studies may be relevant, if there is a paucity of high quality human pharmacokinetic data e.g. for long term use of NRT. However, all else being equal, evidence from human studies will be viewed as more applicable to the scope than that from animal models.

10.7.5 Gathering evidence, conducting searches and documenting the process

Results of the literature searches will be imported into Reference Manager 12. A copy of the de-duplicated database will be provided to NICE, along with a Microsoft Word document detailing results that could not be added to the file

As outlined in Appendix C of the CPHE Manual, the following information will be provided to document the search and study selection processes (for each database/source searched):

- Database name
- Database host
- Database coverage dates
- Searcher
- Search date
- Search strategy checked by
- Number of records retrieved
- Name of RefMan library

- Number of records loaded into RefMan
- Reference numbers of records in RefMan library
- Number of records after de-duplication in RefMan library

10.7.6 Reviewing the evidence

Studies will be selected on the basis of relevance to the scope of this review and considering in particular:

- The hierarchy of evidence: randomised controlled trials and systematic reviews / meta analyses are robust sources of evidence
- Relevance to the PICO table described above

Applicability to the United Kingdom: we will report on technologies that are only available in other countries e.g. USA, in case they are available in the UK in future. However we will consider technologies available in the UK as most applicable. Importantly, we will consider inclusion of technologies used for smoking cessation, if studies provide data on people who continued to smoke while using for example, NRT products. We will discuss this carefully with the expert panel and team at NICE since such extrapolated data will have limitations.

Availability of evidence: if high quality evidence is not available we will pragmatically select the best available evidence e.g. observational studies, retrospective studies and case series.

10.7.7 Title/ abstract screening

All results of the searches will be screened independently by two Cedar reviewers (Andrew Cleves (AC) & Stephen Jones (SJ)) using clear inclusion criteria, to be defined according to the considerations listed above. AC and SJ will discuss any disagreements and resolve them where possible. If there is still disagreement after discussion, a third reviewer from SURE, Fiona Morgan (FM) will adjudicate.

10.7.8 Full-paper screening

Full paper copies will be obtained for all studies selected based on title and abstract. On reading all information in the full papers, screening will be performed according to relevance to the scope. Screening will be performed independently by two reviewers (AC & SJ) and any differences resolved by discussion, and if needed, adjudication (FM). A flow chart will be prepared to illustrate how many papers were selected and discarded at each stage. Reasons for exclusion of papers at

this stage will be documented. During the screening process papers will be tagged for relevance to specific questions and populations of interest.

10.7.9 Assessment of study quality and data extraction

Selected studies will be reviewed for quality using an appropriate quality appraisal checklist (as outlined in the CPHE Methods Manual). This will assess the internal and external validity of the studies. Studies will be rated ++, + or – for both internal and external validity in accordance with the CPHE Methods Manual. Any identified limitations of the studies will be documented.

Data will be extracted for key outcomes including:

- Safety and risk: adverse events
- Pharmacokinetics: dose and administration route of active agents, Tmax, Cmax

Quality assessment and data extraction will be performed independently by two reviewers (AC & SJ) and any differences resolved by discussion, and if needed, adjudication (FM). Quality assessment records will be retained by Cedar. Study characteristics, quality score and outcome data from all included studies will be compiled in evidence tables. A distinction will be drawn between clinical importance and statistical significance, and study results will be accompanied by appropriate statistics where available (e.g. test statistics, p values, confidence intervals).

10.8 Evidence synthesis

10.8.1 Evidence summaries

Concise, narrative statements will be constructed to summarise the key findings of the evidence for the PDG. The evidence summaries will be supported by more detail in the evidence tables and will include:

- The message given by the evidence
- The strength of the evidence (based on quality of the source studies)
- The applicability of the results to the UK

10.8.2 Pharmacokinetic modelling

Where suitable source data are available we will construct a pharmacokinetic model for nicotine derived from NRT. Pharmacokinetic models are mathematical models designed to explain and predict the complex physiological processes associated with drug absorption and elimination. They can utilize data from numerous sources to model pooled parameters including:

- Tmax: the time after administration of a drug where maximum plasma concentration is reached
- Cmax: the maximum plasma concentration of the drug.

We will construct pharmacokinetic models on the basis of suitable source data and applicability to likely real life scenarios. These may include:

- Use of a single NRT while continuing to smoke, but smoking fewer cigarettes than prior to commencing NRT
- Use of two or more NRTs while continuing to smoke, but smoking fewer cigarettes than prior to commencing NRT
- Use of single or two or more NRTs as a long term (possibly lifelong) strategy, either with continuation of smoking at a lesser rate as above, or with complete cessation of smoking.

The pharmacokinetic models will be constructed using non linear regression, which does not make assumptions about the standard error of model parameters. Important parameters to include in the pharmacokinetic models are:

- Route of administration of nicotine (e.g. inhaled, ingested, through the mucosa of the mouth, transdermally etc)
- Concentration of nicotine in the NRT product (e.g. NRT skin patches are available in different strengths)
- Degree of concurrent smoking (e.g. cigarettes / day)
- Presence or absence of diseases / conditions that effect pharmacokinetics (e.g. chronic obstructive pulmonary disease).
- Interactions with psychiatric medications

Outputs of the model will be Tmax and Cmax, used to create pharmacokinetic profiles over time. These will be interpreted in the context of seeking an optimized, therapeutic level of plasma nicotine that is sufficient to sustain reduced smoking or cessation of smoking, without reaching a level where nicotine itself becomes harmfully toxic.

10.9 Timetable

Task	Date to be completed (5pm on day)
Contract start date	Mon 25th July 2011
CEDAR submits draft review protocol	Mon 25th July 2011
NICE provides comments on draft review protocol	Weds 27th July 2011
Final review protocol agreed by NICE and CEDAR	Fri 29th July 2011
CEDAR submits draft search protocol and strategies	Mon 25th July 2011
NICE provides comments on search protocol and strategies	Weds 27th July 2011
Final search protocol and strategies agreed by NICE and CEDAR. CEDAR begins searches.	Mon 1st August 2011
Searches completed	Fri 5th August 2011
Draft evidence tables sent to NICE team	Tues 30th August
First draft review sent to NICE team for comment To include draft evidence summaries.	Fri 16th September 2011
NICE team to provide comments on draft review	Fri 23rd September 2011
Second draft review submitted to NICE team ready for mailing to PDG. To include final evidence summaries.	Fri 30th September 2011
Submit PowerPoint slides	Fri 14th October 2011
Attendance at and presentation of review to PDG	Tues 18th October 2011
Any required revisions undertaken and third draft review submitted to NICE team	Fri 25th November 2011

10.10 Example search strategy

The search strategy shown below is designed for the Ovid MEDLINE(R) database, covering the period 1948 to July Week 1 2011 and will be adapted for use in the other databases listed in section 6.1.

1. Smoking Cessation/ or exp Smoking/ 111863
2. ((Nicotine adj4 (therapy or gum* or inhal* or replace* or lozenge* or tablet* or microtab* or nasal spray* or patch* or delivery device* or delivery system* or gel*)) or ((smok* or tobacco or nicotine or cigarette*) adj10 NRT)).ti,ab. 3434
3. 1 and 2 2771
4. (exp smoking/ or smoking cessation/) and harm reduction/ 152
5. nicotine/th 2
6. (Cigarette* adj2 substitut*).ti,ab. 40
7. ("electronic cigarette*" or e-cigarette* or ecigarette* or ecig* or e-cig*).ti,ab. 26
8. (vaping or (personal adj4 vapori?er)).ti,ab. 3
9. (Nicotine adj4 (therapy or gum* or inhal* or replace* or lozenge* or tablet* or microtab* or nasal spray* or patch* or delivery device* or delivery system* or gel*)).ti,ab. 3428
10. (Pastille* and (smok* or tobacco or nicotine or cigarette*)).ti,ab. 0
11. (Nicorette or Nicotinell or Niconil or NiQuitin or Polacrilex or Habitrol or Nicabate or NicoDerm or Nicotex or Nicotrol or ProStep).ti,ab. 195
12. ((Stoppers or Commit or pharmacotherap*) adj3 (smok* or tobacco or nicotine or cigarette*)).ti,ab. 363
13. (Stubit or super-25).ti,ab. 0
14. (pharmacotherapy/ or drug therapy/) and (smok* or tobacco or nicotine or cigarette*).ti,ab. 197
15. (((reduc* or declin* or quit* or stop* or cess* or cease* or cut down or giv* up) adj4 (smok* or tobacco or cigarette*)) and nicotine).ti,ab. 4717

16. pharmacokinetics/ 6361
17. toxicology/ 7558
18. exp Drug Toxicity/ 26939
19. (Pharmacokinetic* or drug kinetic* or Toxicokinetic* or toxicolog* or metaboli*).ti,ab. 778282
20. (ADME or ADMET or LADME).ti,ab. 767
21. Blood-brain barrier.ti,ab. 19791
22. Nicotinic cholinergic receptors.ti,ab. 378
23. Cytochromes/ or ((Cytochrome adj P450) or CYP450).ti,ab. 34025
24. (CYP 2A6 or CYP2A6).ti,ab. 860
25. Cotinine/ or Cotinine.ti,ab. 3704
26. halflife/ or (halflife or half-life).ti,ab. 69824
27. Biological transport/ or (biologic* adj5 transport).ti,ab. or (nicotine adj10 distrib*).ti,ab. 84396
28. (Pharmacovigilance or Toxicovigilance).ti,ab. 1333
29. substance withdrawal syndrome/ or Withdrawal symptom*.ti,ab. 18982
30. Adverse Drug Reaction Reporting Systems/ 4618
31. Drug Interactions/ or (drug? adj interact*).ti,ab. or (safe or safety or side-effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or event or events or outcome or outcomes or experience or experiences))).ti,ab. 800656
32. or/3-15 6457
33. or/16-31 1674274
34. 32 and 33 2259
35. Limit 34 to (english language and yr="1980 - Current") 2101

10.11 Call for evidence

10.11.1 Registered stakeholders

NICE will issue a call for evidence to all registered stakeholders in the guideline development process. The list of stakeholders includes some manufacturers of products which fall within the guideline scope. Stakeholder evidence with be received in the normal way using the stakeholder response forms on the NICE website.

10.11.2 Manufacturers that are not registered stakeholders

Where we identify manufacturers of relevant products that are not registered as stakeholders, Cedar staff (AC and SJ) will make contact by email requesting evidence on the relevant product, and requesting that manufacturers send their responses direct to Cedar.

We will use the content shown below to be clear on what type of evidence is relevant to the guideline.

10.11.3 Wording of the call for evidence

The National Institute for Health and Clinical Excellence (NICE) has been asked by the Department of Health to develop public health guidance on the use of tobacco harm reduction approaches to smoking cessation. See the final scope for this guidance for more information.

To inform the development of the guidance NICE has commissioned a number of reviews and an economic analysis. One of the reviews focuses on tobacco harm reduction technologies and aims to:

- summarise the evidence on the safety, or risks, of tobacco harm reduction technologies when used by people who may or may not continue to smoke. This includes people who may use nicotine replacement therapy (NRT) or other nicotine containing products (NCPs) indefinitely.
- summarise the pharmacokinetic factors which influence the safety, or risks, of tobacco harm reduction technologies when used as above, principally NRT and other nicotine containing products.

We would like to receive details of evidence that relate to the above aims and more specifically address the questions set out below:

Question 1: What specific risks have been associated with the technologies within the scope of the review? What adverse events or serious adverse events have been identified and how frequently

do they occur? Is there any evidence that use of the technologies may cause significant drug interactions? Of particular concern is whether there are any interactions between nicotine and psychiatric medication since smoking prevalence is much higher among individuals with mental illness.

Question 2: What data are available to support the safety of long term use of the technologies?

Question 3: What are the risks associated with use of NCPs which are currently unlicensed? (Questions especially relevant to the e-cigarette: What is the nature of the absorbent material? Are there other components present in the nicotine solution used in this device? Do these represent risks to the user? Are any harmful chemicals released when the nicotine solution is heated?)

Question 4: Do the data suggest the technologies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Question 5: Do the data suggest the combination of nicotine replacement therapies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Question 6: Are kinetic data available which allow comparison of the relative bioavailability of different technologies i.e. maximum (peak) concentration (Cmax), time to peak concentration (Tmax) and half life (t ½)?

Question 7: Do the data support the safety of an approach where smokers receive doses of medicinal nicotine (potentially by different routes) while continuing to smoke. Is there a greater risk of adverse effects?

Question 8: There are marked differences in smoking rates among socioeconomic groups, Black and minority ethnic (BME) groups, age (lifestage) and people with mental illness. Do the data suggest there may be inequalities among these groups with respect to the risk, safety and pharmacokinetics of smoking harm reduction technologies?

Appendix B of the guidance scope lists some further issues that we anticipate the Programme Development Group (PDG) will consider in relation to the approaches considered for the guidance.

We are interested in a broad range of different types of evidence. This includes quantitative or qualitative research, published or unpublished.

Please note we not need to receive evidence on the following as they will not be covered by the guidance:

- Pregnant women
- Any products containing tobacco. This includes products which are claimed to deliver reduced levels of toxicity (such as 'low tar' cigarettes) or which reduce exposure to tobacco smoke, for example, by warming instead of burning it
- Products that are smoked that do not contain tobacco, such as herbal cigarettes
- Smokeless tobacco products such as gutka, or paan (these products are associated with a number of health problems and are the focus of NICE guidance in development – see section 6.)
- 'Snus' or similar oral snuff products as defined in the European Union's Tobacco Product Directive (European Parliament and the Council of the European Union 2001)
- Alternative or complementary therapies, such as hypnotherapy or acupuncture. (Note: non-NHS services, including complementary therapies, were reviewed for NICE public health guidance 10 on 'Smoking cessation services'.)
- Behavioural, social or educational interventions e.g. support groups, counselling.

In terms of **published** material, we are interested in identifying studies that have been published since 1980 that relate to the questions outlined above. The studies may be published in journals, texts or monographs.

In terms of **unpublished** material, we are interested in identifying unpublished manuscripts relating to research conducted since 1980, or any ongoing research that is being conducted, and which relates to the review questions outlined above.

Please note that the following material is not eligible for consideration:

- Promotional material
- Undocumented assertions of effectiveness
- Opinion pieces

Forms with electronic attachments of published material, or hard copies of published material. For copyright reasons, we cannot accept these copies. However, if you give us the full citation, we will obtain our own copy Instructions for published material.

Please send either full reference details (which are to include author/s, title, date, journal or publication details including volume and issue number and page numbers), - not a PDF/Word attachment or hard copy - by **5pm on 30 August 2011** to <*relevant contact email*>

Instructions for unpublished material

If you are aware of trials/ongoing research relevant to our questions which are in progress please could you help us to identify that information by providing relevant information such as a link to a registered trial with the Cochrane Central Register of Controlled Trials (Clinical Trials), or with the US National Institutes of Health trials registry.

If you wish to submit academic in confidence material (i.e. written but not yet published), or commercial in confidence (i.e. internal documentation), please could you highlight which sections are confidential by using the highlighter function in Word. Such content will not be made public. Please refer to section 4.4 of the Process Manual for further information on submissions of confidential material.

We look forward to receiving information on this and thank you in advance for your help.

Products that will be covered

- Licensed nicotine containing medicines (both prescription only medications and those available over the counter), including
- nicotine chewing gum
- nicotine transdermal patches
- nicotine inhalers
- nicotine microtabs
- nicotine nasal spray
- nicotine lozenges
- Non licensed nicotine containing products (e.g. electronic cigarettes).

Products that will not be covered

- Tobacco (oral moist tobacco [snus], oral compressed tobacco, oral loose tobacco, bidis, pipe tobacco, snuff) Tobacco containing products, including those that are potential reduced exposure products (PREPS):
- combustible products that are smoked e.g. low nitrosamine or low tar cigarettes
- cigarette-like products that heat, rather than burn tobacco
- Medicines that do not contain nicotine but that are licensed for use in the UK for smoking cessation: bupropion and varenicline.

Groups that will be covered

Smokers of all ages who:

- want to quit smoking but feel unable to do so abruptly or
- smoke and do not feel willing or able to quit but want to reduce the amount they smoke.

Particular attention will be paid to following:

- Socio-economic status
- Black and minority ethnic groups
- Age (lifestage: children, adults, older people)
- People taking psychiatric medication.

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11 Appendix 4. Evidence table: questions 1 & 7

What specific risks have been associated with the technologies within the scope of the review?

What adverse events or serious adverse events have been identified and how frequently do they occur?

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Design

Randomised controlled trial

Participants

(n=364) smokers of age ≥ 18y yrs and who smoke ≥ 20 cigarettes/day and who were willing to change their smoking behaviour but unwilling to quit smoking. Also:

- expired-air CO level of at least 15 ppm
- had made at least 1 failed quit attempt within 2 years before the study but not within the previous 6 months.

Exclusions:

- intent to quit smoking within the next month
- current use of other NRT or involvement in other smoking cessation / smoking reduction programs.
- angina pectoris or myocardial infarction within the preceding 3 months
- psychiatric treatment or medication
- alcohol or drug problems.

Interventions / comparators

- (n=184) nicotine chewing gum 4mg (6-24 pieces daily) for 12 months versus:
- (n=180) placebo gum for 12 months

Smoking behaviour / co-interventions

Smoking habit at baseline was mean 28 (range 20-70) cigarettes/day. Participants were instructed to reduce their smoking level during the study by substituting gum.

The number of cigarettes smoked at 13 months was 5.25 (n = 4; SD, 5.5; range, 0-10) in the placebo gum group and 9.14 in the nicotine gum group (n = 7; SD, 6.3; range, 4-20).

Pharmacokinetic outcomes

No data presented

Safety Outcomes

n (%) of patients seen at follow-up visits:

	4 months	13 months	13 months after reminder letter
Active gum (n=184)	124 (67%)	98 (53%)	138 (75%)
Placebo (n=180)	105 (58%)	69 (38%)	111 (62%)

Mean no. pieces of gum used per day (and no. patients using gum):

	2 weeks	4 months	12 months
Active gum (n=184)	6.5 (116)	6.5 (54)	6.1 (15)
Placebo (n=180)	6.4 (108)	6.5 (38)	4.3 (13)

Adverse events:

		severity		
	n (AEs)	mild	moderate	severe
Active gum (n=184)	506	16%	44%	40%
Placebo (n=180)	370	13%	46%	40%

Selected adverse events:

	Nausea	Hiccups	Dyspepsia	Oral discomfort
Active gum (n=184)	19	28	12	8
Placebo (n=180)	11	3	5	3
p value, Fisher exact test	NS	p<0.0001	NS	NS

The authors report that no serious adverse event was related to nicotine treatment. There were no discontinuations attributed to side effects.
In patients who successfully reduced their smoking levels by 50% compared to baseline, there was no statistically significant difference at month 4 or at month 12 compared to baseline levels in white blood cell count, fibrinogen and CRP.

Study quality comments

Overall Quality Score: +

- Method of randomisation not reported.
- Intention to treat analysis
- Double blind study

Bolliger, Zellweger, Danielsson, van, X, Robidou, Westin, Perruchoud, Sawe, Bolliger, Zellweger, Danielsson, van Biljon, Robidou, Westin, Perruchoud & Sawe . Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. BMJ 321[7257], 329-333. 2000.

Design

Two centre, double blind, placebo controlled randomised clinical trial. Four month trial with a two year follow up.

Participants

n = 200.
Smokers (≥ 15 cigarettes per day). Carbon monoxide concentration is expired air ≥ 10 ppm.
All unwilling or unable to quit but interested in reducing their smoking.

Interventions / comparators

Two arms:

- Nicorette inhaler (using cartridge consisting of 10 mg nicotine and 1 mg menthol)
- Placebo inhaler (identical appearance, containing only 1 mg menthol)

Smoking behaviour / co-interventions

Participants were asked to reduce the number of cigarettes they smoked by as much as possible, an initial reduction of 50% was suggested. Inhalers were used as needed, with a recommendation to use between six and twelve cartridges over 24 hours.
Decreased use of inhalers after four months was encouraged, but treatment for up to 18 months was permitted.

Inhaler use decreased over time

Time	Numbers using the inhaler every day
Week 6	222/368 (60%)
Month 4	146/318 (46%)
Month 12	39/331 (12%)
Month 18	30/289 (10%)

Pharmacokinetic outcomes

Safety Outcomes

Safety assessment consisted of reports of adverse effects and plasma cotinine concentrations.

	Active inhaler	Placebo	95% CI for OR
n (AEs)	227	193	NR
Throat irritation	14	4	1.13 to 15.6
Coughing	13	4	1.1 to 10.6
Nausea/ nausea and vomiting	9	8	NR
Palpitation	1	2	NR

Even distribution of total numbers of adverse effects relating to symptoms associated with nicotine (nausea, vomiting and palpitations)
53 serious events occurred, none of which was related to treatment.
Authors conclude that the combination of reduced smoking and use of the nicotine inhaler was well tolerated.

Study quality comments

Overall Quality Score: ++
Recruitment described
Randomisation by a computer generated list.

Withdrawals: 28% of placebo group. 17% of active group. Intention to treat analysis. Baseline parameters were comparable for active and placebo groups. Cotinine concentrations not reported.

Carpenter, Hughes & Keely . Effect of smoking reduction on later cessation: a pilot experimental study. Nicotine.Tob.Res. 5[2], 155-162. 2003.

Design

Randomised controlled trial

Participants

(n=67) smokers (predominantly middle aged women) with no interest in quitting in the next 30 days with a history of at least one quit attempt

Interventions / comparators

- quit intervention, i.e. choice of NRT (patch7, 14, 21mg, gum 4mg or inhaler 10mg) or no medication for 4 weeks prior to setting a quit date (with behavioural support at weeks 0, 1, 2, 3 & 4). Brief advice to quit smoking was given at week 4 following reduction, although for participants not interested in quitting were told that reduction may be better then doing nothing
- standard treatment, which was to offer NRT only if patients set a quit date at outset, and brief advice given only at the initial visit.

Smoking behaviour / co-interventions

Existing smoking habit: at least 10 cigarettes per day, verified with CO>10ppm

Pharmacokinetic outcomes

Not reported

Safety Outcomes

The proportion of patients experiencing any adverse event while using NRT was 48% in the reduce to quit group versus 50% in the usual care group X^2 =0.1, p=0.9. All adverse events were mild, resolved without treatment and did not cause subjects to withdraw from the study.

Study quality comments

Pilot study: randomisation method, power calculation and ITT/per protocol analyses not described.

Overall Quality Score: +

Carpenter, Hughes, Solomon & Callas . Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. J.Consult Clin.Psychol. 72[3], 371-381. 2004.

Design

Randomised controlled trial

Participants

(n=616) smokers aged over 18 years who were not interested in quitting smoking (mostly middle aged women)

Interventions / comparators

- n=212 reduce to quit intervention (24 weeks): NRT (4mg gum or 7, 14, 21 mg patch) was described and offered for 6 weeks followed by tapered dose, at which point NRT was only made available if a quit date was set.
- n=197 cessation group: motivational support (24 weeks), with provision of NRT (6 weeks followed by tapered dose) if a quit date was set
- n=207 control arm provided no intervention.

In total 300 participants used NRT.

Smoking behaviour / co-interventions

Existing habit: > 10 cigarettes per day

Pharmacokinetic outcomes

Not reported

Safety Outcomes

Of 183 subjects using NRT for harm reduction, 39 (21%) reported an adverse event. Of 201 using NRT for a quit attempt, 17 (9%) reported an adverse event.

The proportion of NRT treated patients experiencing adverse events was greater in the reduce to quit group (i.e. with concurrent smoking) at 39 patients (21%) compared to those using NRT in the cessation group: 17 patients (9%); $X2 = 13.8$, $P<0.01$. In total 54 subjects reported 61 adverse events; 92% were mild, 7% were moderate and 2% were severe (1 case of vertigo/dizziness requiring hospitalisation). There were no study withdrawals due to adverse events. The rate of serious adverse events was 0.3%.

Study quality comments

Three groups were fairly similar at study outset.
Intention to treat analysis
Overall Quality Score: ++

Etter, Laszlo, Zellweger, Perrot & Perneger . Nicotine replacement to reduce cigarette consumption in smokers who are unwilling to quit: A randomized trial. Journal of Clinical Psychopharmacology 22[5], 487-495. 2002.

Design

Randomised controlled trial

Participants

General population, Switzerland.
n= 923

Interventions / comparators

Three arms:

1. Nicotine (n = 265). Participants could choose from a patch (25 mg, delivering 16 mg over 16 hours), a gum (4mg, delivers 2 mg) and an inhaler (10 mg, delivers 5 mg) or a combination.
2. Placebo (n = 269). Participants could choose from placebo patch, gum or inhaler.
3. No treatment (n = 389)

Participants in the nicotine and placebo groups could switch between products or use several products at the same time.
Education was limited to a booklet sent by mail; participants received no medical advice.

Smoking behaviour / co-interventions

Participants smoked more than 20 cigarettes per day and had no intention to quit in the next 6 months.

Pharmacokinetic outcomes

Not included.

Safety Outcomes

Participants completed questionnaires by mail at 3 months and 6 months after randomisation. Reminders were sent. Non responders to a fifth reminder answered the questionnaire over the phone.
Main outcome of the study was the number of cigarettes smoked per day (CPD). Results were also collected for participant assessed “pleasure of smoking” and “psychoactive benefits of smoking”. Also smoking-related self efficacy. The study also assessed abstinence.

Among daily users at 6 months 72% used the patch, 48% used the gum and 30% used the inhaler. Compliance with recommended treatment patterns was better for the patch (median 1 patch per day) and gum (median 6 pieces per day) than for the inhaler (median 3.5 plugs per day (up to 12 per day can be administered))

For those who were still smoking at the 6 month follow up (n= 844), self perceived dependence on cigarettes was lower in the nicotine group (7.4 on a scale of 0 to 10) than in the placebo (7.8)and control (8.3) groups.

Adverse events
Authors provide very little detail regarding adverse events but indicate that two participants in the nicotine group died during the study (one from cerebral metastasis of a bronchial adenocarcinoma and one from a cerebral hemorrhage).
“The difference in the rate of serious adverse events in the nicotine and placebo groups was not statistically significant (Fisher’s exact test: p = 0.25).”

Study quality comments

Overall Quality Score: ++
Sample size calculations performed to select group size to detect difference in change of 3.3 cigs/day between groups. 250/ group for nicotine and placebo, 360 in control (no treatment) group.

Recruitment procedure described: newspaper advertisements, invitation letters.
Randomisation by computer-generated list of random numbers.
There were few differences among the three groups at baseline (but fewer women in the nicotine group (46%) than in the control group (51%).
Adverse events were reported either by the participants themselves or by their physicians.
Participants were blinded (receiving package labelled “nicotine or placebo”). Investigators were aware of which treatment the participants were provided but had no in-person contact with the participants and minimal telephone contact (questionnaire at 6 months was completed by telephone only if the postal form had not been returned).
Authors claim the lack of medical advice represents a real world setting, relevant to over the counter purchase.

Haustein, Krause, Haustein, Rasmussen & Cort . Changes in hemorheological and biochemical parameters following short-term and long-term smoking cessation induced by nicotine replacement therapy (NRT). International Journal of Clinical Pharmacology and Therapeutics 42[2], 83-92. 2004.

Design

Prospective, parallel group intervention study

Participants

2 Groups:
(n=164) smokers motivated to quit
(n=33) control smokers not motivated to quit

Interventions / comparators

- (n=164) smokers motivated to quit received NRT (15mg patch and 4mg gum as duotherapy)and were instructed to stop smoking. At 26 weeks smokers were analysed as:
    - abstainers or
    - nonabstainers. Nonabstainers were subgrouped as:
        - reducers: <50% of baseline CPD
        - relapsers: >50% baseline CPD
- (n=33) control smokers not motivated to quit.

Abstinence was verified by CO measurement.

Smoking behaviour / co-interventions

Existing habit: >20 cigarettes per day ≥5 FTND CO > 10 ppm

Pharmacokinetic outcomes

Not reported

Safety Outcomes

Plasma fibrinogen: In reducers and relapsers, values dropped to a minimum at week 4 and in relapsers at weeks 8 and 12 baseline values were reached.

Plasma viscosity: In reducers there was a significant decline in viscosity throughout the study, while in relapsers there was little change from baseline.

Hematocrit: In reducers values reduced to a minimum at week 8 (42.86% versus 44.9% at baseline, p = 0.0002). In relapsers at 4 weeks a significant decrease was detected (43.84% vs 45.42% at baseline, p<0.0001).

Reactive capillary flow: No significant changes in base value in relapsers or reducers between baseline and week 26. There was no statistically significant change in t-pmax in relapsers.

Erythrocyte deformability: deformability was similar across all groups.

Expired CO: in reducers and relapsers CO dropped at at 4 weeks (p<0.0001) but in relapsers at the end of the study (26 weeks) showed no difference from baseline.

tcpO2: In reducers mean base values increased significantly from baseline to week 26. In relapsers values increased initially but then reduced over time.

Plasma SCN: at week 26 values were reduced in reducers at week 26 (8.9ng/ml) compared to baseline (11.4ng/ml) p=0.0001. In relapsers values were reduced at 4, 8 & 12 weeks p=0.0011 but then gradually increased to baseline values.

WBC: In reducers WCB count was reduced over the whole test period, and a slight decrease was seen in relapsers.

Blood platelets: No changes observed in reducers or relapsers.

Blood pressure: In reducers SBP reduced at week 12 and throughout the remainder of the study. No change was observed in relapsers.

Heart rate: In reducers HR decreased at 26 weeks from 81 to 77 (p=0.02). There were no changes in relapsers.

Reviewer's conclusion: no parameter appears to worsen compared to baseline in reducers or abstainers.

Study quality comments

Data are not presented in an easy to interpret manner.
Non randomised study.
Overall Quality Score: +

Joseph, Hecht, Murphy, Lando, Carmella, Gross, Bliss, Le & Hatsukami . Smoking reduction fails to improve clinical and biological markers of cardiac disease: A randomized controlled trial. Nicotine and Tobacco Research 10[3], 471-481. 2008.

Design

Randomised controlled trial

Participants

(n=152) smokers aged 18-80 who smoke ≥15 cpd and had one of the following cardiovascular disorders:

- history of myocardial infarction
- coronary artery bypass surgery
- angioplasty
- stent placement
- thrombolytic therapy
- angina
- arrhythmia
- cardiac arrest
- >50% coronary artery stenosis by angiography
- ischaemia on exercise tolerance test
- congestive heart failure.

As well as unwilling or uninterested in setting a stop smoking date in next 30 days.

Exclusions:

- unstable angina in past 2 weeks
- unstable psychiatric or substance use disorders
- contraindications to NRT (incl. pregnancy or intention to become pregnant)

Interventions / comparators

- (n=78) Smoking reduction (SR): behavioural and pharmacological components (NRT). Counselling visits at 1 and 2 weeks, and at 1, 2, 3, 4, 6, 12, 18 months. Nicotine gum (4 mg) and if using >6 pieces to switch to nicotine patches.
- (n=74) Usual care (UC): brief in-person visit, and encouraged to seek smoking cessation assistance from their health care provider – no additional counselling or pharmacological treatments.

Smoking behaviour / co-interventions

Baseline smoking habit: SR 27.69 cpd; UC 27.04 cpd.

Pharmacokinetic outcomes

None presented

Safety Outcomes

No differences in need for urgent cardiac care at 1, 3, 12, 18 months. At 6 months statistically significant difference in need for urgent cardiac care (SR: 0; UC: 5; p=0.02).

No significant difference in other serious cardiac events and non-cardiac adverse events.

Study quality comments

Overall Quality Score: +

- Randomised using computer-generated scheme
- Assessors not blinded

Kralikova, Kozak, Rasmussen, Gustavsson & Le . Smoking cessation or reduction with nicotine replacement therapy: a placebo-controlled double blind trial with nicotine gum and inhaler. BMC Public Health 9, 433. 2009.

Design

Randomised controlled trial

Participants

(n=314) smokers of age ≥ 18 yrs who smoke ≥ 15 cpd,

- smoked regularly for 3 yrs
- CO level of ≥ 10 ppm
- wanted to reduce smoking
- at least one failed quit attempt

Exclusions:

- current use of NRT or other nicotine products,
- current involvement in smoking cessation/reduction programs
- unstable angina, myocardial infarction in previous 3 months
- pregnancy/lactation or intended pregnancy
- psychiatric treatment and medication, co-existing alcohol or other drug problems

Interventions / comparators

- (n=209) Active NRT: either inhaler (nicotine 10 mg) or gum (nicotine 4 mg), participants free to decide
- (n=105) placebo (inhaler or gum), participants free to decide

6 months full treatment, followed by ≤3 months of voluntary tapering.

Smoking behaviour / co-interventions

Mean baseline cigarette consumption was 25 cpd (range 13-70). Fagerstrom Test of Nicotine Dependence: active NRT 5.8 ± 2.1; placebo 6.2 ±2.1.

Subjects instructed to reduce their smoking by replacing as many cigarettes as possible with treatment (gum/inhaler). Subjects received brief behavioural smoking reduction/cessation support.

Pharmacokinetic outcomes

Not reported

Safety Outcomes

No unexpected adverse events.

Adverse Events

	Mild	Moderate	Severe
Active NRT	47	28	7
Placebo	22	3	1

Treatment related AEs

	Cough	Heartburn	Mouth, throat, tongue irritation (inhaler)	Mouth & throat irritation	Salivation	Upset stomach & hiccups (gum)
Active NRT	9	3	15	2	2	3
Placebo	3	0	1	1	0	0

Study quality comments

Overall Quality Score: +

- Method of randomisation not reported
- Intention to treat analysis
- Double blind

Moore . Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. BMJ 2009. 11 Apr. 338[7699]. 867.

Design

Systematic review of randomised trials

Participants

n=2767 predominantly middle aged smokers who were unwilling or unable to stop smoking abruptly and who entered one of 7 randomised trials aimed at smoking reduction.
Exclusions: heart disease, psychiatric medications, pregnant / lactating women, other drug problems

Interventions / comparators

Trial eligibility criteria:

- NRT used in smoking reduction programmes
- use of nicotine gum or inhaler (alone or in combination) versus placebo or no treatment.

Of 7 randomised controlled trials, 4 used gum, 2 used inhaler, 1 used a patch, gum or inhaler at the participant's choice.
Doses: gum: 2mg or 4mg nicotine, patches: 15mg/16hr, inhaler: not stated. NRT was used for between 6 and 18 months.

Smoking behaviour / co-interventions

Participants aimed to reduce their level of smoking while using NRT. Participants in the trials generally received either behavioural support or booklet information to assist reduction.

Pharmacokinetic outcomes

No data presented

Safety Outcomes

Active treatment: n=1384
Placebo: n=1383
Data are combined for gum-treated & inhaler-treated patients.

	NRT	Placebo	Peto OR (95% CI)	Heterogeneity analysis
Deaths	4/1384	4/1383	1.0 (0.25-4.02)	I^2=25.7% p=0.257
SAE	86/1119	79/1114	1.09 (0.79-1.50)	I^2=55.3% p=0.048
Discontinue therapy due to AE	6/215	6/214	1.27 (0.64-2.51)	I^2=0% p=0.636
Nausea	96/1119	59/1114	1.69 (1.21-2.36)	I^2=0% p=0.797

In no cases were SAEs judged likely to have been due to treatment.

Study quality comments

Quality score ++

- Study selection process documented.
- Primary studies were assessed for quality using the CRD York checklist.
- Study selection and data extraction were quality checked by a second reviewer, and disagreements resolved using a third reviewer.
- Primary studies were assessed as being of high quality. In all trials participants were blinded to active treatment or placebo but the authors note that blinding of subjects is not completely feasible because nicotine is psychoactive.
- Full methods for the meta-analysis are not described.
- Heterogeneity of results of the meta-analyses was generally low, except for SAEs, where it was moderate with I^2 = 55.3%.

Rennard, Glover, Leischow, Daughton, Glover, Muramoto, Franzon, Danielsson, Landfeldt, Westin, Rennard, Glover, Leischow, Daughton, Glover, Muramoto, Franzon, Danielsson, Landfeldt & Westin . Efficacy of the nicotine inhaler in smoking reduction: A double-blind, randomized trial. Nicotine & Tobacco Research 8[4], 555-564. 2006.

Design

Double-blind, parallel group, randomised, multicentre study.

Participants

n = 429

Interventions / comparators

Two arms:

- 10 mg nicotine inhaler (including 1 mg menthol) (n = 215): ad libitum use (recommended 6 -12 cartridges/day) for up to 12 months.
- Placebo inhaler (also contained 1 mg menthol) (n = 214): same mode of use as nicotine inhaler.

Nine clinic visits (8 within the 12 month treatment period and one follow up visit at 15 months). Various assessments were made: self reported smoking status, CO measurement, inhaler use questionnaire, blood samples for cotinine and thiocyanate concentrations, Tobacco dependence (FTND), quality of life, smoking related symptoms, biomarkers of cardiac disease and adverse events.

Smoking behaviour / co-interventions

Participants (who initially smoked at least 20 cigarettes/day) were instructed to reduce their smoking as much as possible, with a long term goal of cessation from month 6 (not mandatory).

Pharmacokinetic outcomes

Not included.

Safety Outcomes

Overall Quality Score: ++

Primary outcome was self reported reduction in the number of cigarettes smoked per day. Also intention to quit smoking, smoking related symptoms, quality of life and risk markers for cardiovascular disease.
Adverse events were assessed at each visit by open ended questions.
Adverse events were common: reported by 159 subjects in nicotine group and 147 subjects in the placebo group. Most were mild or moderate and unrelated to study treatment.
Incidence of adverse events possibly treatment related: 11 in active group, 5 in placebo group.
28 serious adverse events reported (15 events reported by 9 subjects in active group, 13 events reported by 11 subjects in placebo group), none related to study treatment.
Most common treatment related adverse events were throat irritation (15 active vs 6 placebo: not significant) and cough (12 active vs 5 placebo: not significant).
Concomitant use of the inhaler and smoking was well tolerated, with no unexpected or serious treatment-related adverse events. The incidence of symptoms of possible nicotine overdose was similar in the active and placebo groups.

Study quality comments

Study used newspaper advertisements to enrol smokers who wanted to reduce.
Subjects were randomised to nicotine or placebo but method of randomisation was not provided.
Baseline characteristics of nicotine and placebo groups were very similar although the proportion of males/ females was greater for the placebo group (104 males, 110 females) than the nicotine group (88 males, 127 females)
Adverse events were self reported.
High drop-out rate (126/215 active treatment, 149/214 placebo): reasons given were “not willing to participate”, lost to follow up and “unable to reduce smoking”. Because the rate is higher for placebo, there is no evidence to show that compliance is a bigger problem for the active treatment e.g. due to side effects but possibly an efficacy issue.
Analysis on an intention to treat basis: withdrawals were classified as failures.

Power calculation provided for detecting a reduction in smoking by at least 50% in 20% of the active group. Study would not have sufficient power to detect less common adverse effects.

Stead LF, Lancaster T. Interventions to reduce harm from continued tobacco use. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005231. DOI: 10.1002/14651858.CD005231.pub2.

Design

Systematic review. Stated aims: To assess the effect of interventions intended to reduce the harm from smoking on the following: biomarkers of damage caused by tobacco, biomarkers of tobacco exposure, number of cigarettes smoked, quitting, and long-term health status.

Participants

n =16 studies

Studies were of smokers who did not currently wish to try to quit. Trials which did not assess motivation were included if an aim was to reduce cigarette consumption.

Interventions / comparators

Study selection criteria:
Randomized or quasi-randomized controlled trials of interventions in tobacco users to reduce amount smoked, or to reduce harm from smoking by means other than cessation. Outcomes were change in cigarette consumption, markers of cigarette exposure and any markers of damage or benefit to health, measured at least six months from the start of the intervention.

- 16 randomised trials were included
- 3 trials which tested the effects of using products designed to reduce damage, such as Potentially Reduced Exposure tobacco Products (PREPs).
- 11 trials tested nicotine replacement therapy (NRT) as an aid to cutting down.

Smoking behaviour / co-interventions

Study protocols included those that permitted concurrent smoking with the harm reduction intervention e.g. ‘cut down to quit’

Pharmacokinetic outcomes

Not included.

Safety Outcomes

Data on biomarkers of disease risk came from 5 trials oflow tar cigarettes, carbon-filter cigarettes, and a cigarette-like device that heats tobacco rather than burning. Changes from baseline were assessed in those available for assessment and typically showed improvements over time but not between groups.

Study	n (subjects)	Design	Results: risk markers
Batra 2005	364	NRT versus placebo	No statistically significant change in any cardiovascular risk markers (white blood cell count, fibrinogen, CRP) between baseline and month 12 in the 20 successful sustained reducers/abstainers.
Bolliger 2000	400	NRT versus placebo	Comparison between 25 (19 active 6 placebo) sustained reducers and 285 others present at 24m. Both groups had significant favourable changes from baseline in a range of risk markers. The difference between the groupswas statistically significant for cholesterol/HDL ratio, haemoglobin and pulse rate.
Joseph 2008	152	NRT + counselling programme versus single counselling session	Markers of inflammation and oxidation including WBC count, fibrinogen, hs-CRP and F2-isoprostanes showed minimal change. Total NNAL and 1-HOP decreased slightly but to a similar extent in both treatment groups
Kralikova 2009	314	NRT versus placebo	No significant changes in white blood cell count amongst reducers.
Rennard 2006	429	NRT versus placebo	No differences across treatment groups in any markers. Exploratory analyses of successful reducers at 4m showed significant change frombaseline in HDL but no other markers

Study quality comments

Overall Quality Score: ++

- The date of most recent search was June 2010.
- Study selection and data extraction verified by a second reviewer
- Methods adequately reported; risk of bias in primary studies is assessed
- Significant overlap in terms of sources of data with other included systematic reviews.

Wennike, Danielsson, Landfeldt, Westin, Tonnesen, Wennike, Danielsson, Landfeldt, Westin & Tonnesen . Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. Addiction 98[10], 1395-1402. 2003.

Design

Randomised controlled trial

Participants

(n=411) healthy smokers aged ≥ 18 yr and smoking ≥ 15 cigarettes / day who were unwilling or unable to quit smoking, having failed a serious quit attempt in the last 24 months, but interested in reducing their smoking, with no intention to quit smoking within the next month. Exhaled CO had to be ≥ 15 ppm after at least 15 smoke-free minutes.

Exclusion criteria:

- current use of NRT or any other smoking cessation/reduction intervention
- use of other nicotine-containing products (e.g. cigars, pipes or snuff)
- unstable angina or MI within last 3 months
- psychiatric care or medication, or alcohol or other drug problem

Interventions / comparators

Treatment duration was 12 months. Participants were randomised to nicotine gum or placebo. The dose of gum was selected according to FTND score at baseline:

FTND ≤ 5: 2mg gum (n=65) versus placebo gum (n=68)
FTND >6: 4mg gum (n=140) versus placebo (n=138)

Mean (SD) number of gums used daily at 2 weeks:
2mg: 7.8 (4.3)
4mg: 9.8 (5.1)

Mean (SD) number of gums used daily at 12 months:
2mg: 10.8 (8.3)
4mg: 10.6 (5.8)

Smoking behaviour / co-interventions

Smoking habit at baseline was mean 24 cigarettes / day. Subjects were permitted to smoke but urged to cut down or quit. Subjects received behavioural support at follow-up visits at weeks 2, 6, 10 and months 4, 6, 9 and 12.

Pharmacokinetic outcomes

No data presented.

Safety Outcomes

Attendance at follow up:
12 months: 41%
24 months: 37%

	Active gum	**Placebo**	
n (AEs)	166	147	p=NS
Stop treatment prematurely	2	2	NR
Nausea, vomiting and palpitation	6	4	NR

Severity of AEs in active gum group:
61% mild, 34% moderate and 4% severe.
None of the 21 serious adverse events were assessed as related to study treatment.

Study quality comments

Quality score +

- Double-blinded study
- Study shows significant loss to follow-up, but with a similar pattern between active gum & placebo groups.
- Intention to treat analysis.
- Results are aggregated for the two doses of gum given.
- Method of randomisation not described.

Study

McNally, L. (2009) A Guide to Implementing Stop Smoking Support in Mental Health Settings. Section 2.3 Smoking & Mental Health. Does Smoking Influence Mental Health? Quitting in Mind, Smoke Free Minds & London Development Centre. Quitting in Mind.

Design

Narrative review – provides a training resource for practitioners in cessation programmes.

Participants

Various primary studies in smokers with or without psychiatric illness.

Interventions / comparators

Various

Smoking behaviour / co-interventions

Various: effects of smoking, withdrawal and cessation

Safety Outcomes

Provides general background on smoking and mental health

- Although smoking has the potential to have rewarding psychological effects, these effects are likely to be very transient and be unlikely to produce improvements that can be said to benefit mental health or increase an individual's quality of life.
- There is sufficient evidence to identify smoking as a significant risk factor for the onset and worsening of mental health problems, particularly in the case of depression and anxiety.
- While acute nicotine administration has been shown to promote serotonin release, chronic administration results in serotonin depletion in brain areas such as the hippocampal formation and reduces firing of serotonergic neurons. These effects may trigger depression and increase the predisposition to suicidal behaviour (cites primary source as Malone et al., 2003).

Study quality comments

Overall Quality Score: +

Contains a vast compilation of studies; does not report study identification methods (is not presented as a systematic review, but is compiled with support from a panel of experts).

Study

Malone, K. M., Waternaux, C., Haas, G. L., Cooper, T. B., Li, S. & Mann, J. J. (2003) Cigarette smoking, suicidal behavior, and serotonin function in major psychiatric disorders. Am.J.Psychiatry, 160: 773-779.

Design

Case series. Aim: to test the hypothesis that that the relationship that may exist between cigarette smoking and suicidal behaviour may be associated with lower serotonin function and the presence of impulsive/aggressive traits.

Participants

347 patients with a psychiatric disorder (175 with depression, 127 with schizophrenia, and 45 with other disorders). Fifty-three percent of the subjects (N=184) had a lifetime history of suicide attempt, and 47% (N= 163) had never attempted suicide.

Interventions / comparators

Studies of serotonin function were conducted in a subgroup of depressed patients (N=162). Patients with schizophrenia were excluded from these analyses.

Smoking behaviour / co-interventions

Measurements commenced at 8.00 am, patients were expected to abstain from smoking for 12 hours.

Safety Outcomes

In depressed subjects CSF 5-HIAA (a metabolite of serotonin) level was negatively correlated with the amount of cigarette smoking ($r_s = -0.32$, N=88, $p<0.003$). This result held true in a regression analysis, controlled for key clinical variables.

This study cited an experiment performed in rats (Benwell and Balfour, 1979) [+] which suggested that rats injected with nicotine for 40 days had lower brain levels of serotonin and 5-HIAA. Another cited study (Benwell et al. 1990) [+] of human brain tissue from cadavers of smokers (7-20 cigarettes/day for 30 years), also suggested that smoking was associated with lower levels of brain serotonin and 5-HIAA.

Study quality comments

Overall Quality Score: +

12 Appendix 5. Evidence table: question 2

Question 2: What data are available to support the safety of long term use of the technologies?

Joseph, Hecht, Murphy, Lando, Carmella, Gross, Bliss, Le & Hatsukami . Smoking reduction fails to improve clinical and biological markers of cardiac disease: A randomized controlled trial. Nicotine and Tobacco Research 10[3], 471-481. 2008.

Design

Randomized controlled trial

Participants (n= 152)

Inclusion criteria:

- Smokers aged 18-80
- Smoking at least 15 cigarettes / day
- With one of 11 cardiovascular disorders (history of myocardial infarction; coronary artery bypass surgery; angioplasty;
- Unwilling or uninterested in setting a stop date in the next 30 days

Exclusion criteria

- Unstable angina in the past two weeks
- Unstable psychiatric or substance use disorders
- Contraindications to nicotine replacement therapy (including pregnancy or intention to become pregnant)

Interventions / comparators

- (n=78) Smoking reduction (SR) group, substitution of 4mg Nicotine gum for each cigarette eliminated, or nicotine patches, plus regular cessation counselling
- (n=74) Usual care (UC), initial brief counselling session only.

Smoking behaviour / co-interventions

The goal was to reduce smoking by at least 50% of the base line level but also by as much as possible.

Smoking reduction group

Cessation counsellors trained in the interventional protocol saw subjects in person at weeks 1 and 2, and months 1 and 3. Telephone care took place at months 2, 4, 6, 12 and 18. If subjects expressed an interest re-initiating reduction treatment further visits could be scheduled over the 18 months. Participants were encouraged to substitute a piece of 4mg nicotine gum for each cigarette they eliminated. If more than 6 pieces were used it was suggested that they switch to nicotine patches. If participants did not accomplish reduction with nicotine gum, they were invited to try nicotine patches alone.

Usual Care Group

The usual care group had an initial brief in person visit. The counsellor reiterated the importance of abstinence from cigarette smoking for patients with heart disease. Participants were encouraged to seek smoking cessation assistance from their health care provider but no other support or treatment was offered.

Outcomes -

At 6, 12 and 18 month follow up approximately the same number of participants in the SR and UC groups reported abstinence from smoking.

Pharmacokinetic outcomes

No data available

Safety Outcomes

Clinical markers of heart disease were compared at 1, 3, 6 , 12 and 18 months. There were no significant differences at any time point in the prevalence or frequency of angina, or distributions of CCSC (Canadian Cardiovascular Society Classification). There were no differences between groups in the quality of life index

at any point. At 18 months there was a greater decline in distance walked in UC subjects, but a significant increase in the proportion of subjects completing the 6 minute walk.
Adverse events – There were no differences in need for urgent cardiac care other than at 6 months (n=0 in the SR group, n=5 in UC group). Serious cardiac events were roughly equally distributed between groups.

Study quality comments

Overall Quality Score: +

Recruitment clearly described
Computer generated randomization
Clear aim
Appropriate follow up period
Clear outcomes
Baseline parameters comparable for the two groups.
Objective outcome measures
Acknowledgement of study limitations.

Joseph, Norman, Ferry, Prochazka, Westman, Steele, Sherman, Cleveland, Antonuccio, Antonnucio, Hartman & McGovern . The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. The New England Journal of Medicine 335, 1792-1798. 1996.

Design

Multicentre, randomised, double-blind placebo controlled trial.
Based at ten centres, assigned a ten week course of transdermal nicotine or placebo. Subjects monitored for 14 weeks, follow up telephone call at 24 weeks

Participants

584 participants (576 male; 8 female)
Inclusion criteria:

- Aged 45 years or older
- Smoked at least 15 cigarettes per day
- Smoked for at least 5 years
- Made a minimum of 2 previous attempts to quit
- CO level in expired air at least 8ppm
- One or more diagnosis of: history of myocardial infarction; history of coronary-artery bypass surgery or angioplasty; stenosis of at keast 50% in at least one coronary artery; clinical history of angina/congestive heart failure/cor pulmonale/peripheral vascular disease/ cerebrovascular disease.

Exclusion criteria (any of the following in the two weeks before randomisation)

- Unstable angina
- Myocardial infarction
- Coronary artery bypass surgery
- Angioplasty
- Hospitalisation for cardiac arrhythmias
- A history of continuous use of transdermal nicotine for more than 48 hours
- Current use of (and unwillingnessto stop using) other tobacco products or nicotine gum
- The presence of unstable psychiatric illness or an unstable disorder involving the use of alcohol or controlled substances
- A history of severe dermatitis
- Pregnancy

Interventions / comparators

- (n= 294) Transdermal nicotine given as 21mg patch for 6 weeks; 14mg patches for 2 weeks and 7mg patches for 2 weeks.
- (n=290) Placebo group given patches of identical size, appearance and odour.

Smoking behaviour / co-interventions

Subjects returned to hospital for outpatient visits at the end of the 1st, 6th and 14th weeks. They received the National Cancer Institutes pamphlets at baseline visit. The also received brief behavioural conselling sessions lasting 10-15 minutes at baseline, week one and week 6.
Efficacy defined as subject not having smoked for at least 8 weeks as verified at the end of the 14th week, verified by expired co level of 10ppm or less at end of week 14

Pharmacokinetic outcomes

No data

Safety Outcomes

Serious Adverse Events According to study group

Side Effect	Subjects with event	Event

	Nicotine (n=294)	Placebo (n=290)	P Value	Nicotine (n=294)	Placebo (n=290)	P Value
	no (%)			no.		
Primary end points						
Death	1	6		1	6	
Myocardial Infarction	0	1		0	1	
Cardiac Arrest	1	1		1	1	
Admission for increased severity of angina	7	10		8	12	
Addmission for arrhythmia	5	3		6	6	
Admission for congestive heart Failure	2	2		3	3	
Total	16 (5.4)	23 (7.9)	0.23	19	29	0.10
Secondary end points	3	5		3	5	
Admission for peripheral vascular disease	4	3		5	4	
Admission for other reasons	16	13		21	16	
Outpatient visit for increased severity of atherosclerotic cardiovascular disease	12	7		16	8	
Total	35 (11.9)	28 (9.7)	0.37	45	33	0.23
All end points	48 (16.3)	47 (16.2)	0.97	64	62	0.39

Severe side effects of transdermal nicotine therapy according to study group

Side Effect	Subjects with event			Event		
	Nicotine (n=294)	Placebo (n=290)	P value	Nicotine	Placebo	PValue
	no (%)			no.		
Sleep disturbance	10	6		10	6	
Skin Rash	6	3		6	4	
Gastrointestinal distress	5	6		6	7	
Other	15	12		18	13	
Total	36 (12.2)	27 (9.3)	0.25	40	30	0.24

Study quality comments

Overall Quality Score: +

Recruitment described
Mainly males included
Randomisation by a computer generated list.
Double blind
No of patients lost to follow up not reported
No of patients non compliant not reported
Smoking cessation verified by CO measurement

Lee, Afessa, Lee & Afessa . The association of nicotine replacement therapy with mortality in a medical intensive care unit. Critical Care Medicine 35[6], 1517-1521. 2007.

Design

Retrospective, case controlled.

Participants

(n=180)
Critically ill smokers admitted to a medical ICU between Feb 1st 2001 and Feb 9th 2005
Patients who received the first NRT after 24 hours of ICU admissions were not included.

Interventions / comparators

Comparison of critically ill smokers admitted to a medical ICU from February 1 2001 to February 9 2005 who received nicotine replacement therapy (NRT) (n=90) with control smokers who were admitted to the same ICU but did not receive NRT (n=90)

Smoking behaviour / co-interventions

All included participants were smokers. No details available on amount smoked or amount of NRT given.

Pharmacokinetic outcomes

No data available

Safety Outcomes

Patients were admitted with 40 different diagnoses (there were no significant differences in the admission diagnosis between the two groups), the most common diagnosis being drug overdose (59% of patients in NRT group, 47% in control group). There was no significant difference in the Acute Physiology Score, APACHE III score and predicted mortality rates between the two groups. There were no significant differences in the worst daily mean arterial pressure and heart rate during their first three ICU days. Overall predicted mean hospital mortality rate was 9.8%. The overall mean hospital rate observed was 13.3%: 20% for the NRT group and 7% for the control group. The mean 28-day ICU free days were higher for the control group. There was no significant difference in the mechanical ventilation-free days between the two groups. When adjusted for severity of illness and invasive ventilation, NRT was an independent risk factor for hospital mortality with an odds ratio of 24.6 (95% confidence interval). None of the 95 patients treated for drug overdose died. For the remaining patients, when adjusted for severity of illness and invasive ventilation, NRT was an independent risk factor for hospital mortality with an odds ratio of 19.7.

Study quality comments

Overall Quality Score: -
Authors acknowledge limitations
Small sample size
As a single centre observational study limitations in terms of bias
Patients had 40 different diagnosis so few numbers in each patient group, although comparable between groups, this may introduce bias.

Leja, Case, Bateman, Iskandrian, Kronenberg, Chang, Iskander, Matthias, Strahs, Mishra, Kotler, Frias, Mahmarian & Pratt . Nicotine patches are safe to use in patients with coronary artery disease and stress-induced myocardial ischemia. Journal of the American College of Cardiology 49[9], 209A. 2007.

Design

Prospective, multicentre randomized, placebo controlled trial.

Participants

(n=55)

Inclusion criteria:

- Smokers
- Smoking >20 cigarettes/day
- all with quantified ≥9% stress induced myocardial ischaemia using single photon tomography (SPECT)

Interventions / comparators

Pts randomised to:

- 21mg nicotine patches or
- Placebo

Smoking behaviour / co-interventions

Baseline >20 cigarettes / day. Patients initially continued smoking, with SPECT repeated after week 1. Pts then encouraged to stop smoking, while using patches with repeat SPECT at week 4. Nicotine and exhaled CO measured before each SPECT.

Pharmacokinetic outcomes

No data

Safety Outcomes

No significant changes in total or ischemic PDS (perfusion defect size) observed in patients randomised to active treatment versus placebo.

Study quality comments

Overall Quality Score: +

Prospective, multicentre, randomised placebo controlled

Small study group

No details on method of randomisation

Lack of data due to abstract format

Subjective outcome measures

Mahmarian, Moye, Nasser, Nagueh, Bloom, Benowitz, Verani, Byrd, Pratt, Mahmarian, Moye, Nasser, Nagueh, Bloom, Benowitz, Verani, Byrd & Pratt . Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. Journal of the American College of Cardiology 30[1], 125-130. 1997.

Design

Prospective, single centre longitudinal study.

Aim

To determine if nicotine patch therapy when used to promote smoking cessation could effect the extent of exercise induced myocardial ischemia in patients with coronary artery disease.

Participants

(n=40) 35 male, 5 female

Inclusion criteria:

- coronary artery disease on angiography
- smoked ≥1 pack of cigarettes per day but had a strong desire to quit
- had a qualifying abnormal SPECT (Single-photon emission computed tomography) (≥5% exercise induced reversible perfusion defect)

Exclusion criteria:

- unstable angina
- recent (<3 months) coronary angioplasty or bypass surgery
- significant vavular heart disease
- intolerance to nicotine preparations

Interventions / comparators

- 14mg Nicotine patches for 3 or more days followed by 21mg patches for 3 or more days.

Smoking behaviour / co-interventions

Patients were weaned off anti-anginal medications prior to the study. In hypertensive patients angiotensin-converting enzyme inhibitors were substituted for beta blockers and calcium antagonists for blood pressure control. Patients were allowed to take sublingual nitroglycerin if needed for chest pain.

Patients were started on 14mg nicotine patches and encouraged to stop smoking. The patches were applied each morning and maintained for 24 hours. After a minimum of 3 days (mean 8.6), exercise SPECT was repeated. Patients were then given 21mg patches for a minimum of 3 days (mean 7.6) followed by a third SPECT.

Sixteen (44%) of the 36 patients smoked ≤cigarettes per day by the end of the study, and 19% had ceased entirely.

Pharmacokinetic outcomes

No data reported

Safety Outcomes

Treadmill exercise tests

The rest heart rates were similar at baseline and during treatment. 14 patients had exercise induced ST segment depression during the baseline tests. In these patients the time to 1mm ST segment depression significantly increased from 352 at baseline to 436 on 14mg nicotine ad 417 on 21mg nicotine. Four patients had resolution of their ST segment depression after the baseline study.

Group scintigraphic variables

A significant reduction in the total exercise induced perfusion defect size (PDS) was observed from baseline (17.5) to treatment with 14mg (12.6)and 21mg (11.8) patches. This was associated with a significant reduction in cigarettes smoked per day and exhaled CO levels. This improvement in myocardial perfusion

occurred despite significant increases in treadmill exercise duration and nicotine and cotinine blood levels.
Individual scintigraphic results
11 of the 36 patients had a ≥9% increase in their total PDS from baseline to 14mg patches and 10 of 34 patients from baseline to 21mg patch (expected = 1 – 2 patients in 36). Patients whose defects decreased ≥9% had a significantly greater reduction in CO and a lesser increase in serum nicotine levels.

Four patients withdrew from the study, two due to adverse effects from the nicotine patches (nausea and vomiting)

Study quality comments

Overall Quality Score: +

Small study group
Short follow up
Recruitment clearly described
Withdrawals described
Objective outcome measures
Clear aim
No control group

Murray, Bailey, Daniels, Bjornson, Kurnow, Connett, Nides, Kiley, Murray, Bailey, Daniels, Bjornson, Kurnow, Connett, Nides & Kiley . Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Lung Health Study Research Group. Chest 109[2], 438-445. 1996.

Design

Multicentre randomised control trial

Participants

n= 5,887

All between 35 and 60 years of age, with evidence of early stage COPD (ratio of FEV1 to FVC was no greater than 70% and baseline FEV1 values were between 55% and 90% of predicted normal)

Interventions / comparators

Randomised into one of three groups:

- Special Intervention (n = 3,923):
    1. Bronchodilator (ipratropium bromide):
    2. Placebo inhaler
- Usual care (n = 1,964)

The special intervention groups received a behavioural smoking cessation intervention. Participants were encouraged to quit smoking and use nicotine gum. The group program consisted of 12 meetings over the initial 3 month period. Further maintenance program involved monthly meetings for the next 4 years.
At 4 monthly intervals from randomisation participants visited a clinic for replacement of bronchodilator canister, measurement of CO in expired air, self report of smoking status and inhaler use, review and guidance in nicotine use. Salivary cotinine was sampled at baseline and at annual visits.

Smoking behaviour / co-interventions

Participants were encouraged to stop smoking and provided nicotine gum free of charge to help them do so.

Pharmacokinetic outcomes

Not provided

Safety Outcomes

Study of the safety of nicotine for a large sample population for an extended period of time (5 years). Throughout the study, whether participants were using nicotine gum, had used it and stopped, had started using it after a period of not using, and smoking status while using the gum, were all recorded (at 4 month intervals). Participants who had stopped using nicotine gum were asked why. Any problems which the participant thought was caused by or associated with the gum were recorded. If any participant had been hospitalised since their last visit, hospital records were obtained. Any records mentioning cardiovascular, cancer or respiratory conditions were reviewed by an independent panel of three specialist physicians.

Hospitalisations per 100,000 person-days among exsmokers:
NRT gum users: 2.23
Non NRT gum users: 5.78

NB Among ex-smokers, the hospitalisation rates are higher for those not using nicotine gum. Among smokers, rates for nicotine gum users is higher in some years and higher for non users in other years.

Regression analysis to study predictors of death or hospitalisation due to cardiovascular disease among 3,332 special intervention participants for whom a complete set of first 4 month data was available: nicotine gum use was not significantly related to outcome ($p = 0.53$). Coefficients suggest an initial protective effect of nicotine gum that attenuates over time (not statistically significant). Neither nicotine dose nor the interaction between nicotine dose and log of follow-up time were statistically significant. Interaction between nicotine use and concomitant smoking was not significant ($p = 0.63$).

The authors conclude that there is no evidence of a relationship between the dose of nicotine gum and

cardiovascular conditions.

Nicotine use was found to have a non significant protective effect against peptic ulcers (p = 0.06; risk ratio= 0.63).

Reporting of symptoms at first 4-month visit:
NRT gum use: 27%
Non NRT gum use: 29%
NB No gender differences in symptom reporting rates.

Levels of gum use were related to rates of reporting jaw muscle ache and hiccups in males and belching in females.

Symptom	Gum intake			
	Up to 5 pieces/day	6 to 10 pieces/ day	11 to 15 pieces/ day	16 or more pieces/ day
Jaw muscle ache (male users)	0%	2.3%	4.1%	5.3%
Hiccups (male users)	2.0%	3.3%	6.6%	1.3%
Belching (female users)	0%	1.6%	0%	5.7%

Concomitant Use of nicotine gum and cigarettes
Rates of side effects were compared for 389 smoking and 2554 nonsmoking nicotine gum users. None of the symptoms were significantly different between the two groups. 12% of the special intervention group were smoking while using the gum. The study found no evidence that concomitant use is dangerous (although study wasn't designed to test this).
5% of users reported quitting the gum in the first 4 months because of side effects.

Study quality comments

Overall Quality Score: +

Study was nonblinded
Described as randomised, method of randomisation not given.
Inclusion and exclusion criteria defined.
Participants were given instruction and monitored in proper use of nicotine gum. This was reviewed during a series of 12 meetings over a 3 month period. Where any problems had occurred participants were advised accordingly (reviewing chew and park method, recommending reduction or suspension of use or referral to physician).
Data on possible side effects were gathered continuously throughout the study. These were self-reported at 4 month intervals (participants were asked if they had experienced any problems which may have been caused or associated with the gum). Where hospitalisations occurred, hospital records were reviewed with emphasis on cardiovascular, respiratory and cancer outcomes.
Authors note minor differences at baseline between the special intervention and usual care groups.
A number of the participants in the usual care group would have sought help in quitting smoking and some of these (n = 49 in year 1) obtained nicotine gum. They probably would not have received such intensive instruction in proper use and reported certain symptoms more frequently than participants who received the special intervention. Dizziness and throat irritation was reported more frequently by men who received usual care, headache and throat irritation were reported more frequently by women who received the usual care.

Murray, Connett & Zapawa . Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. Nicotine & Tobacco Research 11[9], 1076-1082. 2009.

Design

Prospective study of cancer incidence in participants enrolled in the Lung Health Study (the original study enrolled 5,887 participants, 3,923 of whom were randomised to smoking intervention which included 2 mg nicotine gum). Original study (Murray, 1996) was a multi centre randomised clinical trial. This prospective study followed 85% of the smoking intervention patients for 7.5 years after the Lung Health Study.
Morbidity records were obtained for cancers only (cancer mortality data derived from the National Death Index).
Smoking and NRT exposure were estimated over the original 5 year Lung Health Study.

Participants

n= 3,320
These participants were encouraged to use NRT gum liberally for 6 months but some continued to use NRT well beyond that point.

Interventions / comparators

Use of NRT measured by self report by regular (4 monthly) visits during the original 5 year study (also at additional visits where participants obtained a supply of NRT).
Smoking exposure during the 5 year study calculated from reports made at annual visits (expressed as pack-years of smoking during the study).
Surveillance for cancer diagnoses following the five-year study (study ended in 1991, surveillance from May 1994 to December 2001): identified 75 lung cancer events, 33 gastrointestinal cancers and 203 cancers from all causes.

Smoking behaviour / co-interventions

Over the 5 year period, mean NRT gum use was as follows:
40.1% of participants used 0 pieces of gum/day,
25.5% used 0.05 to 1 pieces / day,
16.9% used 1.05 to 3.0 pieces/day,
17.5% used 3.05 or more pieces/day.

Pharmacokinetic outcomes

Not studied.

Safety Outcomes

Adjusted Cox proportional hazards regressions to assess the hazards of NRT and smoking

1. Lung Cancer

Model 1 indicates no relationship between NRT use and subsequent lung cancer HR 1.02 95%CI 0.95-1.09 (p = 0.67).
Model 2 indicates a significant relationship between cigarette use (pack-years over 5 years) during the Lung Health Study and subsequent lung cancer HR 1.08 95%CI 1.01-1.16 (p = 0.03).
Model 3 has both NRT and cigarette use: NRT use is not significant HR 1.04 95%CI 0.97-1.12 (p = 0.25) and cigarette use is significant HR 1.10 95%CI 1.02-1.19 (p = 0.02)

2. Gastrointestinal Cancers

Model 1 indicates no relationship between NRT use and subsequent gastrointestinal cancer HR 0.97 95%CI 0.86-1.10 (p = 0.61).
Model 2 indicates no relationship between cigarette use and subsequent gastrointestinal cancer HR 1.03 95%CI 0.93-1.14 (p = 0.59).
Model 3 has both NRT and cigarette use: neither NRT use HR 0.97 95%CI 0.82-1.14 (p = 0.68) or cigarette use HR 1.03 95%CI 0.91-1.17 (p = 0.64) are significant.

3. All cancers
Model 1 indicates no relationship between NRT use and subsequent cancer HR 1 95%CI 0.96-1.05 (p = 0.94).
Model 2 indicates no relationship between cigarette use and subsequent cancer HR 1.03 95%CI 0.99-1.08 (p = 0.17).
Model 3 has both NRT and cigarette use: neither NRT use HR 1.01 95%CI 0.97-1.06 (p = 0.62) or cigarette use HR 1.04 95%CI 0.99-1.09 (p = 0.14) are significant.

NRT use and cigarette use are negatively correlated in this study (Pearson's r = -0.23, p = 0.0001) indicating most participants used either NRT or cigarettes as instructed, rather than using both concurrently.

Authors conclude that this study adds credence to their theory that nicotine does not cause cancer.

Study quality comments

Quality score +
Authors identify confounding between historical smoking and current smoking and between current smoking and current nicotine replacement use.
Looking specifically for cancer incidence following a relatively short (5 year) exposure.
The authors assert that if the study is powered to demonstrate a risk of harm from smoking it has a reasonable chance of demonstrating harm from NRT.
One of the authors is an employee of a company providing services to GlaxoSmithKline Consumer healthcare (manufacturer of NRT products).

Paciullo, Short, Steinke, Jennings, Paciullo, Short, Steinke & Jennings . Impact of nicotine replacement therapy on postoperative mortality following coronary artery bypass graft surgery. Annals of Pharmacotherapy 43[7], 1197-1202. 2009.

Design

Retrospective matched cohort pilot study.

Participants

(n=134)

Inclusion criteria:

- patients who had undergone coronary artery bypass graft (CABG) surgery
- had received at least one transdermal nicotine patch (7, 14 or 21mg)

Exclusion criteria:

- any other surgical procedure performed at the same time as the (CABG)
- 18 years old or younger
- had incomplete medical record
- received any form of nicotine replacement therapy (NRT) other than transdermal patch.

Interventions / comparators

- Smokers treated post operatively with NRT (n=67)
- Smokers not treated post operatively with NRT (n=67)
- Non smokers (n=134)

Smoking behaviour / co-interventions

Phase 1 - 134 smokers matched to 134 non-smoking controls. Group 1 matched 67 patients treated post operatively with NRT, group 2 matched 67 smokers who did not receive any cessation therapy. Baseline characteristics were not significantly different.

Phase 2 – conducted to obtain baseline mortality rates among patients undergoing CABG and compare these with subsets of smokers and non smokers. This involved unmatched evaluation of all patients identified as having received NRT postoperatively in the ICU. These patients stratified into three groups: non-smokers and smokers with and without NRT. These were then further stratified to investigate the effects on and off pump CABG, NRT use and mortality.

Pharmacokinetic outcomes

No data available

Safety Outcomes

Phase 1 - Nonsignificant increases in mortality were noted: 3 (4.5%) patients in the NRT group died compared with 0 in the non-NRT group. There was no association between length of stay and pack year history.

Phase 2 - This provided a population based evaluation of mortality among 3 groups (non-smokers and smokers with and without NRT) Mortality was not significantly higher in the NRT smoker group. Smokers receiving NRT were not at increased risk of death compared with non-smokers. However, a significant increase in mortality was seen in among those smokers using NRT compared with smokers not using NRT and non smokers when the differences in age and atrial fibrillation were controlled.

Further stratification to evaluate for the effect of on or off pump CABG a significant increase in mortality was seen in those using NRT and having off pump CABG when adjusted.

Comparison of mortality rates

Group Comparison	Adjusted OR (95% CI)
NRT vs non-NRT	6.06 [1.65-22.21] NS
NRT vs non-NRT after on pump CABG	5.22 [0.57-47.85] NS
NRT vs non-NRT after off pump CABG	6.49 [1.29-32.56] *
NRT vs non-smokers	6.17 [1.62-23.59] *
NRT vs non-smokers after on pump CABG	6.04 [0.57-63.61] NS
NRT vs non-smokers after off pump CABG	6.08 [1.16-31.68] *
Non-NRT vs non-smokers	1.00 [0.37-2.71] NS

Non-NRT vs non-smokers after on pump CABG	1.85 [0.43-7.95] NS	
Non-NRT vs non-smokers after off pump CABG	0.67 [0.14-3.02] NS	

Study quality comments

Overall Quality Score: -

Smoking behaviour during study not described
Poor details on the amount of NRT given
Unclear how many patients included in phase 2
Few data on adverse events other than mortality rates

Study

Tzivoni D, et al. Cardiovascular safety of Transdermal nicotine patches in patients with coronary artery disease who try to quit smoking

Design

Two-centre, double blind, placebo controlled randomised study. Conducted over a two week period

Participants (n=106)

Inclusion criteria:

- Presence of coronary artery disease
- Stable angina pectoris
- Documented previous myocardial infarction
- Nicotine dependent, smoking at least 15 cigarettes a day for 5 years or more
- Fagerstrom score of 5 or more.

Exclusion criteria

- Hypersensitivity to any adhesive cutaneous application
- Myocardial infarction, coronary bypass surgery, coronary angioplasty or stroke within the 3 months prior to screening.
- >12 ischemic episodes during the 48 hour AEM
- Diastolic BP >200mmHg
- Reduced left ventricular function
- Clinical signs of congestive heart failure, complex ventricular arrhythmias, or episodes of supraventricular tachycardia >60 seconds duration.

Interventions / comparators

(n=52) Nicotinell patches

(n= 54) placebo group

81 patients were given 30cm2 patches as they smoked 20 or more cigarettes / day (40 patients in Nicotinell group, 41 in placebo group) the other patients were given 20cm2 patches. 30cm2 Nicotinell patches = 21mg nicotine; 20cm2 Nicotinell patches = 14mg nicotine. Placebo patches delivered 3mg and 2mg of nicotine per 24 hours to deliver identical odour and colour.

Smoking behaviour / co-interventions

Number of cigarettes smoked / day was noted and abstinence measured by CO in exhaled air.

Attendance in smoking cessation group

Pharmacokinetic outcomes

No data

Safety Outcomes

- No patient experienced symptomatic arrhythmias or worsening of palpitations.
- Three patients had worsening angina; two from the nicotine group, one from placebo group.
- No change in heart rate or diastolic blood pressure during the screening period (during regular smoking) compared with immediately after patch application, and 2 weeks after patch application.
- No indication of significant change in the number and duration of ischemic episodes during the trial.
- There was no change in the frequency of atrial and ventricular arrhythmia in all three stages of the study

Study quality comments

Overall Quality Score: +

Short study period

Unclear method of randomisation

Double blind placebo controlled

No data on study drop out rate

Obvective outcome measures

Clear research question

13 Appendix 6. Evidence table: question 3

What are the risks associated with use of NCPs which are currently unlicensed? (Questions especially relevant to the e-cigarette: What is the nature of the absorbent material? Are there other components present in the nicotine solution used in this device? Do these represent risks to the user? Are any harmful chemicals released when the nicotine solution is heated?)

BBC News England 28 March 2011 Gateshead doctor calls for research into 'e-cigarettes'. Last updated at 21:27. Available at: http://www.bbc.co.uk/news/uk-england-12887335

Design

News report. Primary source of data is a coroner's inquest (not seen)

Participants

None

Interventions / comparators

Relates to use of e-cigarrete

Smoking behaviour / co-interventions

Not known

Pharmacokinetic outcomes

No data

Safety Outcomes

Direct quote of news item:

"A doctor from Tyneside has called for more research into "electronic" cigarettes following the death of one of his patients. It comes after an inquest recorded an open verdict into the death of Terence Miller from Gateshead. Mr Miller, who used large quantities of the substitutes, had suffered from a lung disease - severe lipoid pneumonia. Dr Rob Allcock, who treated him at the Queen Elizabeth Hospital, believes this could be associated with his use. The 'e-cigarettes' are battery-powered and contain a cartridge of liquid nicotine. This is heated and the user inhales vaporised droplets of the drug and breathes out a mist rather than smoke. Supporters describe them as a healthy alternative to real cigarettes because their users can inhale nicotine without tar, tobacco or carbon monoxide. Dr Allcock said that the brand Mr Miller had been using seemed to involve a mixture of nicotine and some oil. 'There's extensive literature in the medical world on damage to the lungs due to inhaling oil, which looks very similar to his disease,' he said. 'There's some limited research merely mentioning what the chemical composition [of 'electronic' cigarettes] is, but there's no systematic research assessing the overall safety of inhaling these chemicals deep into the lungs over an extended period.' However, the Electronic Cigarette Industry Trade Association, has described the cigarettes as 'far safer than ordinary ones'. It said that 100% of users were former smokers and any damage to their lungs was going to be caused by that. It added 'electronic' cigarettes had been "tested vigorously" in various scientific studies around the world."

Study quality comments

Study quality score [-]

Bullen, McRobbie, Thornley, Glover, Lin & Laugesen . Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tobacco Control 19, 98-103. 2010.

Design

Single blind randomised repeated measures cross-over trial of the Ruyan V8 ENDD. The primary outcome was change in desire to smoke. Secondary outcomes included withdrawal symptoms, acceptability and adverse events.

Participants

n= 40 (nicotine concentrations obtained for 9 of these)
Mean age 47.6 (SD 12.4) years.
Mean level of nicotine dependence (FTND) = 5.4
Participants smoked an average of 20.2 cigarettes (SD 7.3) per day.

Interventions / comparators

Four arms (treatment period 1 day):

- Electronic cigarette (ENND – Ruyan Group (Holdings Ltd), Bejing) 16 mg
- Electronic cigarette 0mg nicotine (placebo)
- Nicorette inhalator 10 mg per cartridge
- Usual cigarette

All subjects abstained from smoking overnight (verified by CO ≤ 15 ppm in expired breath).
Participants randomised to using the ENDD were asked to puff the device as they would their usual cigarette for 5 mins. They remained in the study centre for 1 hour The device was then used for a further 8 hours.
When participants used the inhaler they were instructed to puff on the inhaler over 20 minutes in the first hour and then use the inhaler freely over the day (up to a maximum of 6 x 10mg cartridges)
When randomised to smoke their usual cigarettes, subjects smoked within the first 5 minutes of the first hour and then freely as they wished.
The subset of patients who had nicotine concentrations measured had bloods taken at 5, 10,15, 30 and 60 minutes after initial dosing.
There was a 3 day washout period between each study day.
Withdrawal was assessed using the Minnesota Nicotine Withdrawal Scale with additional items relating to craving. Participants also rated their satisfaction with the products compared to their usual cigarettes.

Smoking behaviour / co-interventions

Subjects were smokers (smoking at least 10 factory-made cigarettes per day for at least the last year).
All smoked their first cigarette of the day within 30 minutes of waking.
During the study period smoking rates were:

- 16mg ENDD: 2.8 usual cigarettes / day
- Placebo ENDD: 4.5 usual cigarettes / day
- Inhalator: 3.4 usual cigarettes / day

Pharmacokinetic outcomes

Nicotine concentration only measured in a proportion of the study group.

Product	Mean tmax (min) (95% CI)	Mean Cmax (ng/ml) (95% CI)
Usual cigarette (n = 9)	14.3 (8.8 to 19.9)	13.4 (6.5 to 20.3)
16 mg ENDD (n = 8)	19.6 (4.9 to 34.2)	1.3 (0.0 to 2.6)
Nicorette inhalator (n =10)	32.0 (18.7 to 45.3)	2.1 (1.0 to 3.1)

Authors suggest the ENDD is comparable to a NRT product in terms of nicotine delivery. Use of the 16 mg ENDD resulted in modest increases in blood nicotine levels. Also the ENDDs were not as consistent for puffing and nicotine delivery as the medicinal Nicorette inhalator. One third of participants showed no

increase in blood nicotine when using the ENDD. Some participants reported the device sometimes failed to produce mist when puffed.

Safety Outcomes

Outcomes were assessed at the end of the treatment day. The most frequently reported adverse events were mouth and throat irritation, and were most common with the inhalator (88%) and least common with the 0 mg ENDD (22%). The differences between active and placebo ENDDs and inhalator were statistically significant ($p<0.001$). Nausea was most commonly reported after 16 mg ENDD use, but, as with the other between-product differences in adverse events occurrence, was not significant. No serious adverse events (i.e. deaths or events requiring hospitalisation) occurred during the study. Table of results as presented in original publication:

Adverse events reported after 9 hours of product use

Adverse event	ENDD 0 mg		ENDD 16 mg		Nicorette inhalator	
	n/N*	(%)	n/N	(%)	n/N	(%)
Mouth/ throat irritation[y]	14/64	22	22/58	38	36/41	88
Aching jaws	4/35	11	3/37	8	2/37	5
Nausea	6/33	18	9/31	29	6/33	18
Flatulence/ belching/ hiccups/heartburn	6/111	5	6/113	5	11/147	23
Vertigo/ heartburn	9/69	9	14/66	21	12/66	18
Headache	7/32	22	6/34	18	6/33	18
Sweatiness/ clammy skin	3/75	4	3/77	4	2/76	3
Palpitations	0/38	0	2/38	5	0/39	0

ENDD, electronic nicotine delivery device.
*n = number of events, N = numbers of participants in each group. In some cases, groups were pooled because of similarity of symptoms, hence the large numbers.

Study quality comments

Study quality score +

Trial is funded by the e-cigarette manufacturer.
Subjects were allocated to one of the four treatment arms using a random sequence of four codes (each corresponding to one product) prepared in advance by the study statistician.
Participants and investigators were blinded only to assignment to the ENDD condition (16 or 0 mg).
Statistical power calculations relate to detecting the differences in desire to smoke.
Report of adverse events made at the end of the day. Events were self-reported. Later effects or chronic effects not covered by the study design.
PK parameters (Cmax, tmax) calculated based on plasma concentration-time data by model-independent methods using SAS version 9.2.
Crossover design to minimise variability, bias and confounding.
Study limited to smokers not intending to quit.
No period of familiarisation or test of functioning with ENDDs (this was the first exposure for both subjects and investigators).

Foulds, Veldheer & Berg . Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. The International Journal of Clinical Practice e publication[August 2011]. 2011.

Design

User survey

Participants

(n=104) American, experienced e-cigarette users attending an e-cigarette-focussed conference in Philadelphia ('Philly Vapefest, 2011')

Interventions / comparators

Participants completed an anonymous 55-item questionnaire designed to record data on:

- demographics
- e-cigarette use history
- tobacco use history
- beliefs about e-cigarettes

Smoking behaviour / co-interventions

Overall 12% of respondents continued to smoke tobacco. Participants had smoked for a mean of 16 (SD 10) years, at a rate of 25 (SD 13) cigarettes per day.

Pharmacokinetic outcomes

No data

Safety Outcomes

Data from the survey:

- Mean (SD) no. of previous quit attempts: 9 (16)
- % previously using a licensed NRT product as a quit attempt: 65%
- % who tried to quit 'cold turkey': 73%
- % using an e-cigarette for >20 days out of last 28 days: 89%
- % who believe they get equivalent or greater nicotine from an e-cigarette: 58%
- % who believe e-cigarette is less harmful to others: 80%
- % who believe it is less harmful to own health: 98%

Study quality comments

Study population are already established e-cigarette users; applicability to a wider population may be limited.

Overall Quality Score: +

Medicines and Healthcare Products Regulatory Agency 2011a. Assessment of the constituents of four e-cigarette products. Commission on Human Medicines.Working Group on Nicotine Containing Products (NCPs). COMMERCIAL IN CONFIDENCE

Design

Laboratory analysis of four different e-cigarettes: the nicotine solution was extracted from the cartridges and analysed by a semi-quantitative gas chromatography- mass spectroscopy (GC-MS) analysis.

Participants

No participants. Laboratory study

Interventions / comparators

E-cigarettes evaluated:

- Regular High 18mg
- TAB high
- Ultimo Cartridges Supersmoker Normal Exp
- Gamucci Tobacco Flavour - Regular

Smoking behaviour / co-interventions

Not applicable

Pharmacokinetic outcomes

None reported.

Safety Outcomes

Summary of chemical analyses for all four e-cigarettes

No	Name	Nominal* %				CAS No.
		Regular High 18mg	TAB High	Ultimo – Super smoker	Gamucci	
1	Unidentified nitrogenous compound	ND	ND	0.22	0.16	
2	1,3-bis(3-phenoxyphenoxy) Benzene	26.51	0.29	ND	ND	2455-71-2
3	Ethanol	0.81	0.12	ND	ND	64-17-5
4	Water	0.63	1.87	3.71	1.18	7732-18-5
5	Bicyclo[4.1.0]heptane, 3,7,7-trimethyl-, (1β,3β,6β)- (also known as Trans Carane)	ND	0.08	ND	ND	554-59-6
6	Acetic acid	ND	ND	0.07	ND	64-19-7
7	1-Methoxy-2-propanol	0.04	ND	ND	ND	107-98-2
8	2-Ethoxy Propane	0.02	ND	ND	ND	625-54-7
9	[R-(R*, R*)]-2,3-Butanediol	0.02	ND	ND	ND	24347-58-8
10	Propylene Glycol	46.13	64.24	46.00	79.79	57-55-6
11	2,2'-Oxybis-Ethanol (DEG)	0.14	ND	ND	ND	111-46-6
12	alpha, 3,4-tris[(trimethylsilyl)oxy]-benzeneacetic acid	0.37	ND	ND	ND	37148-65-5
13	2-Hydroxy-3-methyl-2-cyclopenten-1-one (also known as Corylone)	ND	3.95	ND	ND	80-71-7
14	3-Methyl-pentanoic acid	ND	ND	0.07	ND	105-43-1
15	2-Butanol	ND	ND	0.04	ND	78-92-2
15	Nicotine	8.02	19.43	9.99	4.06	54-11-5
16	3-(3,4-dihydro-2H-pyrrol-5-yl)-pyridine (also known as Myosmine)	ND	0.16	ND	ND	532-12-7
17	7-Chloro-1,3-Dihydro-5-Phenyl-1-(trimethylsilyl)-3-[(trimethylsilyl)oxy]-2H-1,4-Benzodiazepin-2-one	0.71	ND	ND	ND	55319-93-2
18	1,1,1,5,7,7,7-Heptamethyl-3,3-bis(trimethylsiloxy) Tetrasiloxane	0.44	ND	ND	ND	38147-00-1
19	Glycerin	16.14	19.43	39.90	14.82	56-81-5

All four products contain the major constituents nicotine, propylene glycol, and glycerine. Regular high 18mg has a distinct profile containing 1,3-bis(3-phenoxyphenoxy) benzene as a major constituent (nominally 26%) and a variety of other minor components including a trimethylsilyl derivative of a benzodiazepine oxazepam.

Diethylene glycol (DEG) is of particular toxicological interest and the authors report this as a serious problem, given that teething syrup contaminated with DEG caused the deaths of 84 children in Nigeria in 2008/2009.

Authors conclude:

The analysis of the contents of four e-cigarettes reveals a number of issues. There are no long term data on the safety of the delivery system excipents/solvents used in the devices. The rate of

delivery of nicotine-solvent solution is not characterised and there is no quality assurance concerning what is delivered from the cartridge into the subject.

Study quality comments

Overall Quality Score: ++

Authors report:

- The GC method employed may not detect some less volatile components that may be found in the sample, or where components are present in such low levels that they are below detection limits for the GC-MS method.
- The GC method employed was of the 'normalization type' where the detector response for each eluted component was set at the default value of 1.000 and the peak areas normalized to evaluate nominal area percentage value for each eluted component.
- The analysis is limited as following "atomization" the vapour that will be inhaled will probably contain a different balance of compounds and potentially the transformation of some compounds. This might be a particular issue for nicotine which can be degraded to tobacco specific nitrosamines (TSNA) which are of additional toxicological concern. It should also be remembered that this is not pyrolysis (complete or incomplete combustion) but rather atomisation of the constituents of a liquid into a vapour.

Trtchounian, Talbot, Trtchounian & Talbot . Electronic nicotine delivery systems: is there a need for regulation? Tobacco Control 20[1], 47-52. 2011.

Design

Physical evaluation / simulated use of e-cigarettes

Participants

No participants.

Interventions / comparators

Six brands (NJOY, NCIG, Liberty 6, Crown 7, Hydro, Smoking Everywhere gold and platinum, VapCigs), of ENDS were evaluated from a physical perspective, focussing on:

- design
- nicotine content
- labelling
- leakiness
- defective parts
- disposal
- errors in filling orders
- instruction manual
- quality
- advertising

Smoking behaviour / co-interventions

Not applicable – no study participants

Pharmacokinetic outcomes

No data presented

Safety Outcomes

The authors report the following as areas for concern:

- Difficulty distinguishing between types of battery within a brand
- Ambiguous labelling of nicotine dose (inter-product variability with use of terms 'low', 'medium' & 'high' nicotine content)
- No clear labelling of nicotine concentration, expiry date, manufacturer's name, product flavour
- Inconsistency between product markings and advertising website regarding nicotine content
- Lack of uniformity with packaging labelling of replacement cartridges; some products do not list cartridge ingredients
- Leakage from cartridge reservoirs of nicotine-containing fluid from most brands (causing contact with skin upon handling):
    - once removed from the wrapper
    - upon removal of protective plug
    - after use
- Poorly functioning indicator LEDs (to warn of battery discharge / too frequent use)
- No instructions for proper disposal of used cartridges (which contain residual liquid)
- Delivery of wrong products when ordered online
- Poor standard of instruction manuals (see table above)
- Spurious advertising claims,

Authors conclude:

- Batteries, atomisers, cartridges, cartridge wrappers, packs and instruction manuals lack important information regarding e-cigarette contents, use and essential warnings.
- e-cigarette cartridges leak, thereby creating the potential for unwanted nicotine exposure to children, adults, pets and the environment.
- There are currently no methods for proper disposal of e-cigarette products and accessories,

including cartridges.

- Data indicate that regulation of manufacturing, quality control, sales and advertisement of e-cigarette is needed.

Study quality comments

Overall Quality Score: +

Study methods only briefly described – no details of testing protocol.
Authors report no competing interests.

Vansickel, Cobb, Weaver, Eissenberg, Vansickel, Cobb, Weaver & Eissenberg . A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiology, Biomarkers & Prevention 19[8], 1945-1953. 2010.

Design

4 Latin square ordered conditions (different products) each separated by 48 hours.
Each experiment is repeated 60 minutes later.

Participants

n=32
Age: mean 33.6 years (SD 12)
Gender: 13 female, 19 male.
Ethnicity: 14 non-white.

Interventions / comparators

4 conditions:

- Own brand cigarette
- Sham smoking (puffing unlit cigarette)
- 'NPRO' (NJOY) electronic cigarette with 18 mg nicotine cartridge
- 'Hydro' electronic cigarette with 16 mg nicotine cartridge

Participants were instructed to puff normally and then puffed ad libitum 10 times (30s interpuff interval) from the product of the day (bout 1). At 5, 15, 30 and 45 min after the first puff, subjective measures were completed and blood sampled. Expired air CO was recorded at 15, 30 and 45 minutes. At time +60 min assessments were repeated, product was administered (bout 2), and identical subsequent assessments completed. The authors claim that this product administration equates to ad libitum cigarette smoking.

As well as nicotine plasma concentrations, heart rate was continually monitored. Subjective effect questionnaires were completed: Tiffany Drobes Questionnaire of Smoking Urges Brief, and Visual Analog Scales designed to assess nicotine abstinence symptom suppression and nicotine/ tobacco effects.

Smoking behaviour / co-interventions

All subjects were smokers (mean 22 cigarettes smoked/day (SD 8.8)). Verified by screening CO of at least 15 ppm and urine cotinine of at least 4 on a 7-point scale.

Study was preceded by > 12 hour tobacco/nicotine abstinence (verified by expired air CO ≤10ppm)

Pharmacokinetic outcomes

Raw data not provided. For own brand cigarette smoking, mean plasma nicotine increased from a pre-administration level of 2.1 ng/ml to a peak of 18.8 ng/ml five minutes after the first administration. No significant changes in plasma nicotine were observed for the e-cigarettes or sham smoking condition.

The authors conclude that compared to cigarette smoking, the e-cig delivered little to no nicotine.

Safety Outcomes

Continuous heart rate monitoring was performed. Compared to initial measurement, a significant increase in heart rate was only observed for the own brand cigarettes (from an average of 65.7 bpm at baseline to a peak of 80.3 bpm five minutes after first administration). No significant changes in heart rate were observed for the e-cigarettes or sham smoking condition.
Authors list ingredients of NJOY e-cigarette as nicotine, propylene glycol, water, ethanol, glycerol, acetylpyrazine, guaiacol, mysomine, cotinine and vanillin.
Authors list ingredients of HydroEC as nicotine, propylene glycol, water and tobacco flavouring.
Authors quote Federal Trade Commision finding that average cigarette yields 1.06 mg nicotine, 14.7 mg tar, 14.6 mg CO.

Study quality comments

Quality score +

Clinical laboratory study.

Inclusion/exclusion criteria described, reasons for exclusions and withdrawals provided.

Westenberger . Evaluation of e-cigarettes. US Food and Drug Administration . 2009.

Design

Laboratory analysis of e-cigarettes from two manufacturers

Participants

No participants

Interventions / comparators

Two e-cigarette brands were analyzed:

- Njoy e-cigarette with various cartridges
- Smoking Everywhere e-cigarette with various cartridges

Smoking behaviour / co-interventions

Not applicable

Pharmacokinetic outcomes

No data

Safety Outcomes

Authors conclude:

- nicotine is present in both products (including in the Smoking Everywhere product that claims to contain no nicotine)
- Diethylene glycol (DEG) was detected in one cartridge (Smoking Everywhere 555 high)
- Tobacco specific nitrosamines, representing tobacco based contaminants were detected in both brands
- Under simulated smoking conditions, nicotine was detected in both products.

Study quality comments

Objective laboratory analysis.

Overall Quality Score: ++

14 Appendix 7. Evidence table: questions 4 & 5

Question 4: Do the data suggest the technologies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Question 5: Do the data suggest the combination of nicotine replacement therapies could generate an appropriate blood concentration of nicotine, a concentration high enough to prevent craving and withdrawal symptoms, yet not high enough to result in nicotine toxicity?

Russell MAH et al, 1976. Effect of nicotine chewing gum on smoking behaviour and as an aid to cigarette withdrawal, BMJ, 1976, 2, 391-393.

Design

Double blind, placebo controlled, crossover trial

Participants

n= 43. 18 male, 25 female. Age range 21 to 57 (average 37) years.
Exclusions: any history of heart disease.

Interventions / comparators

Two arms:

- Nicotine chewing gum, 2 mg.
- Placebo gum, spiced to match taste of nicotine gum

Subjects were instructed to chew 10 pieces of gum per day and each piece chewed for at least 20 minutes. Blood samples were taken five times during regular visits throughout the study for analysis of nicotine concentration.

Smoking behaviour / co-interventions

For the first week of the study, participants used each gum (active and placebo) for two days. During this period they were allowed to smoke as they felt inclined (making no attempt to cut down cigarette consumption). For the second and third weeks they took each treatment for one week while trying to stop smoking.

Pharmacokinetic outcomes

	Initial levels before taking gum	Taking gum and smoking as inclined		Taking gum and trying not to smoke	
		Placebo gum	Nicotine gum	Placebo gum	Nicotine gum
Plasma nicotine (ng/ml)	30.1 (± 1.9)	24.7 (± 1.4)	27.4 (± 1.4)	7.3 (± 1.5)	10.7 (± 1.2)
Recorded CPD	33.3 (± 2.6)	23.0 (± 1.6)	20.9 (± 1.9)	3.9 (± 0.9)	4.1 (± 1.2)
COHb (%)	8.5 (± 0.4)	7.2 (± 0.5)	6.3 (±0.4)	2.9 (± 0.5)	2.3 (± 0.4)

Values are means ± SE of mean.

Safety Outcomes

Mild and transient side effects were experienced by 22 subjects. Symptoms were more severe in 10 subjects, eight of these had to discontinue the gum for a while.

Symptoms:

- Sore mouth or throat (11 subjects)
- Ulceration of tongue (2)
- Nausea (12)
- Vomiting (3)
- Flatulence/ indigestion/ epigastric burning (7)
- Hiccups (2)
- Faintness/ dizziness (3)
- Laxative effects (1)

Study quality comments

Study was double blinded.
Method of reporting adverse effects is not described.
Baseline characteristics of the study population were not provided.
No washout period in the first week of the study.
Community based study with regular clinic visits.
Allocation of treatment was randomised, method of randomisation was not described.

Overall Quality Score: +

Ebert RV et al, 1984. Effect of nicotine chewing gum on plasma nicotine levels of cigarette smokers. Clin Pharmacol Ther, 35;4: 495-498.

Design

Double blind, randomised crossover study.

Participants

n = 12. Mean age 55 years. All male, ambulatory and patients at an alcohol rehabilitation unit

Interventions / comparators

Three arms:

- Placebo gum (flavoured to resemble nicotine gum)
- 2 mg nicotine gum
- 4 mg nicotine gum

A four day study:
Day 1: smoking as usual, no gum use
Days 2,3 and 4: placebo, 2mg and 4 mg gums. One day's use for each. Random order. One piece of gum chewed per hour from 7 am to 4 pm on each study day.
Blood sample drawn between 1pm and 2 pm on each of the study days for nicotine concentration to be measured.

Smoking behaviour / co-interventions

Subjects were allowed to smoke at all times throughout the study, whenever they felt the desire.

Pharmacokinetic outcomes

	No of cigs smoked during experimental period	Peak CO level during day (ppm)	Plasma nicotine (ng/ml)
Initial smoking period	15.3 ± 3.2	40.8 ± 12.1	26.5 ± 13
Placebo gum	16.0 ± 6.2	40.0 ± 16.2	29.5 ± 14
2 mg nicotine gum	13.9 ± 3.9	35.2 ± 12.1	30.9 ± 13
4 mg nicotine gum	14.6 ± 6.1	33.5 ± 11.6	40.7 ± 15

Values are means ± SD.
The concentration measured while using 4 mg gum is significantly greater than the value for placebo gum ($p < 0.05$).

Safety Outcomes

Not provided.

Study quality comments

The study was performed in a general medical ward and subjects received the usual hospital diet. They were ambulatory during the study.
Double blind.
Method of randomisation is unclear.
Baseline characteristics of subjects were not provided.
Short study with small number of participants.
Physical act of chewing gum may make it impossible for subjects to maintain their usual smoking level.

Overall Quality Score: +

Fagerstrom KO et al. Long-term effects of the Eclipse cigarette substitute and the nicotine inhaler in smokers not interested in quitting. Nicotine and Tobacco Research, 2002, S141-S145.

Design

Open smoking trial (subjects chose their intervention based on preference following a crossover study)

Participants

n= 38.

All smokers (at least 5 CPD)

Interventions / comparators

- Eclipse cigarette (heats tobacco therefore out of scope of this review) n= 10
- NRT inhaler n=15
- Preferred cigarette n=13

Participants chose their own intervention following a crossover trial where they had used all three technologies.

8 week study with four clinic visits where amounts of products used, CPD, CO, withdrawal symptoms and subjective product evaluation were recorded. At two of these visits blood samples were taken.

Smoking behaviour / co-interventions

Subjects who chose to use the eclipse device or NRT inhaler were instructed to smoke as few cigarettes as possible without suffering discomfort.

Pharmacokinetic outcomes

All groups maintained their nicotine concentrations relative to baseline.

	CPD	CO (ppm)	Plasma nicotine (ng/ml)
Cigarettes	23.3	22.2	21.7
NRT Inhaler	6.6	12.5	11.4
Eclipse	2.6	32.5	15.8

All results are means.

Safety Outcomes

Nicotine dependence (FTND) recorded at the start and end of the study. For users of the inhaler, the measure of dependence had significantly decreased over the course of the study (from 5.6 to 3.5; p= <0.001).

Study quality comments

Baseline analysis was performed to examine 15 variables which might be associated with reduction.

Missing data (nicotine concentrations) for two subjects who used the inhaler.

Baseline nicotine concentrations not taken (used levels from previous study).

No randomisation; subjects chose their own intervention based on previous use.

Overall Quality Score: +

Foulds J et al. Effect of transdermal nicotine patches on cigarette smoking: a double blind crossover study. Psychopharmacology 1992; 106: 421-427.

Design

Randomised, double blind crossover study. Following a one week baseline period (smoking but not wearing a patch), subjects received nicotine patch for one week and placebo patch for one week. Randomisation to each group was carried out by staff not involved in the study.

Participants

n=30 (7 male, 23 female). Mean age 39 years (range 19 – 60). All were smokers (at least 10 CP). No subjects had respiratory or cardiovascular disease.

Interventions / comparators

Nicotine patch (15 mg/16 hr)
Placebo patch
One patch worn per day. Each subject received nicotine for 1 week and placebo for 1 week. Patch applied each morning (to a different position on the upper arm or torso) and removed at night.
The study measured the following: Number of cigarettes smoked per day (recorded by subjects in diary), Expired carbon monoxide (CO) (measured during each weekly visit), plasma nicotine, cotinine and thiocyanate (during weekly visits), subjective ratings from smoking and side effects. At each visit the subjects smoked a cigarette before the measures were made (biochemical measures were made before and after the cigarette was smoked)

Smoking behaviour / co-interventions

Participants were advised to smoke whenever they felt they needed to.

Pharmacokinetic outcomes

	No patch (NP)	Placebo (P)	Nicotine (N)	P-NP difference	N-P difference (95% CI)
Pre-cig expired CO	28.1 (10.6)	28.7 (10.3)	25.2 (12.1)	0.6	-3.5 (-5.7, -1.3) P<0.05
Post cig expired CO	32.5 (11.1)	32.5 (10.6)	28.4 (12.2)	0.0	-4.1 (-6.4, -1.7) P<0.01
Pre-cig plasma nicotine (ng/ml)	27.0 (9.9)	25.0 (10.3)	34.2 (12.9)	-2.0	9.2 (4.5, 13.9) P<0.001
Post-cig plasma nicotine (ng/ml)	36.9 (10.5)	36.6 (9.4)	44.5 (10.8)	0.5	7.9 (3.3, 12.5) P<0.01

Th authors conclude smokers reduce their CO and nicotine intake from cigarettes while wearing nicotine patches but do not down regulate their nicotine intake from cigarettes sufficiently to prevent a moderate increase in plasma nicotine concentration.

Safety Outcomes

No serious side effects of nicotine patches were reported. Six subjects reported “not serious” side effects while taking the nicotine patch (5 subjects reported such effects while taking the placebo patch).
Localised itching (12 vs 10, p<0.001) and feeling “high” (5 vs 0, p<0.05) were the only effects which showed a nicotine vs placebo difference in incidence.
The authors conclude subjects experience almost no toxic effects from smoking while wearing nicotine patches.

Study quality comments

Power calculation provided; sample size calculated to detect nicotine-placebo difference in expired CO.
No washout period between crossover.

Double blind (subjects and experimenters blind to conditions)
Small study size.

Overall Quality Score: +

Pickworth WB et al. Transdermal nicotine: reduction of smoking with minimal abuse liability. Psychopharmacology 1994; 115: 9 -14.

Design

Randomised, double blind crossover trial

Participants

n= 10, all male. Smokers recruited by newspaper advertisements. Mean age 33.1 years (range 20 to 35)

Interventions / comparators

Nicotine patch (22 mg)
Placebo patch (0 mg nicotine)
Three dose phases, each of 7 days duration: 0 mg(2x placebo), 22 mg(1 x active + 1 x placebo) and 44 mg (2 x active)
At 1400 hours each day, subjects smoked one cigarette to measure puff behaviour.
Physiological measures (heart rate, systolic and diastolic Blood Pressure), number of cigarettes smoked in 24 hrs, subjective measures and blood samples were taken for measurement of nicotine and cotinine concentration.

Smoking behaviour / co-interventions

Subjects had unrestricted access to their usual brand of cigarettes and were allowed to smoke ad libitum.

Pharmacokinetic outcomes

	Baseline	Placebo	22 mg patch	44 mg patch
Mean nicotine concentration ng/ml (SEM)	29.6 (± 5.2)	18.7 (± 3.3)	39.2 (±4.7)	63.4 (± 8.5)
Mean CPD (SEM)	18.1 (± 1)	17.01 (± 1)	15.3 (± 1)	13.4 (± 1)

Safety Outcomes

	Placebo	22 mg	44 mg
Heart Rate (bpm)	74.5 (± 1.2)	78.3 (± 1.3)	75.5 (± 1.3)
Systolic Blood Pressure (mmHg)	121.3 (± 1.2)	124.8 (± 1.3)	121.5 (± 1.2)
Diastolic Blood Pressure (mmHg)	68.3 (± 0.8)	70.8 (± 0.9)	69.9 (± 0.9)
Oral Temperature (°C)	36.7 (± 0.02)	36.8 (± 0.03)	36.8 (± 0.03)

Symptoms of skin irritation increased with increasing dose; all subjects had some evidence of skin irritation at the high dose condition. Two subjects in the 44mg treatment group had skin reactions that were rated as severe and one subject had to withdraw from the study. Skin irritation was maximal 6 hours after removal of the patch.

Study quality comments

During the study, participants resided on a clinical ward of the research centre.
Double blind.
Skin reactions: patch sites were evaluated daily by experimenters for erythema, dryness, pruritis, burning, edema and weeping using an intensity scale of 0 (none) to 3 (severe).
Small sample size.
Subjects did not want to quit and had not made any attempts to quit in the last year.
Method of randomisation was not described.

Overall Quality Score: +

Zevin S et al. Dose related cardiovascular and endocrine effects of transdermal nicotine. Clinical Pharmacology and Therapeutics 1998; 64(1): 87 – 95.

Design

Single blind, placebo controlled crossover study. Treatment sequence was balanced across subjects with Latin squares.

Participants

n= 12, all male. Ages 21 to 49 years (average 41 ± 6 years). Smokers (> 20 CPD)

Interventions / comparators

Four treatment blocks, each lasting 5 days:

- Placebo patch
- 1 x 21 mg nicotine patch
- 2 x 21 mg nicotine patches
- 3 x 21 mg nicotine patches

At the higher dose, patches were applied at 4 hourly intervals to avoid nicotine toxicity.
On days 4 and 5, blood samples were taken for determination of plasma nicotine, cotinine and carboxyhaemoglobin were measured every 4 hours.

Smoking behaviour / co-interventions

On days 1 -4 of each treatment block, subjects were free to smoke ad libitum. On day 5 subjects abstained from smoking.

Pharmacokinetic outcomes

The difference between average nicotine levels on day 4 and day 5 was significantly smaller with increasing nicotine dose ($p<0.05$).

Plasma nicotine with concurrent cigarette smoking

Nicotine patch dose (mg)	Plasma nicotine ng/ml
0	22
21	38
42	50
63	60

The number of cigarettes smoked was lower with 63 mg nicotine than with other treatment conditions (12 ± 5 versus 15 ± 7) but the difference was not statistically significant. Cigarette consumption did not differ between 0, 21 and 42 mg nicotine.

Safety Outcomes

Heart rate, systolic blood pressure and diastolic blood pressure measured over 24 hours did not differ significantly across the different nicotine doses. There were also no significant changes in hematocrit, white blood cell count, fibrinogen level or lipid profile across the different patch doses.
The authors conclude that high dose transdermal nicotine with concomitant cigarette smoking had no adverse effects on heart rate, blood pressure, fibrinogen level or lipid profiles of heavy smokers. These parameters with any dose of nicotine were similar to those with smoking alone.

Study quality comments

Subjects not interested in quitting smoking.
Study completed at a clinical study centre.
Small study.
Overall Quality Score: +

Fagerstrom, K. O. & Hughes, J. R. (2002) Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: A review. Nicotine and Tobacco Research, 4: S73-S79.

Design

Narrative review. Aims:

1. To review data on blood nicotine or cotinine concentrations resulting from concomitant cigarette smoking and use of NRT, due to concern that a possible increase in concentrations could lead to significant adverse effects
2. to review the data on number of cigarettes smoked and exhaled CO concentrations (gum and inhaler routes presented seperataly to the patch route).

Participants

Primary observational studies of smokers (n=416) instructed to reduce their level of smoking while using NRT or to smoke *ad libitum* while using NRT.

Interventions / comparators

NRT:

- Acute (gum, nasal spray, inhaler, tablet)
- Transdermal

Varied comparators including placebo, no comparator, *ad libitum* versus reduced smoking.

Smoking behaviour / co-interventions

Various. See above.

Safety Outcomes

1. Results for <u>acute</u> nicotine delivery systems (gum, lozenge, tablet): percent reduction in plasma nicotine, n(cigs)/day and exhaled CO

a) 5 primary studies where participants were <u>encouraged to reduce</u> the number of cigarettes smoked, over study periods of range 2 weeks to 260 weeks:

% change in blood nicotine concentration: -7%
% change in n(cigarettes smoked/day): -54%
% change in exhaled CO: -29%

b) 2 primary studies with <u>ad libitum</u> smoking (duration 2-4 days)

% change in blood nicotine concentration: -1%
% change in n(cigarettes smoked/day): -50%
% change in exhaled CO: -28%

2. Results for <u>transdermal</u> nicotine delivery systems (patch): percent reduction in plasma nicotine, n(cigs)/day and exhaled CO:

a) participants were <u>encouraged to reduce</u> the number of cigarettes smoked, over study periods of 3 days and 4 weeks:

% change in blood nicotine concentration: +48%
% change in n(cigarettes smoked/day): -65%
% change in exhaled CO: --41%

b) 3 studies with <u>ad libitum</u> smoking:

% change in blood nicotine concentration: +60%
% change in n(cigarettes smoked/day): -21%
% change in exhaled CO: -20%

Authors conclude that:

- smokers titrate (reduce intake from smoking) their nicotine levels quite well with acute NRT forms but not as well with nicotine patches.
- all NRT systems equally and consistently decrease cigarette consumption and, to a somewhat lesser degree, CO intake.

- very few and mild adverse reactions were reported with concurrent smoking and use of NRT, even when nicotine concentrations were elevated 2 or 3 times with use of very high doses of nicotine from patches.

Authors discuss possible reasons for poor titration to patches (i.e. compensatory smoking):

- Adaption may occur to slow release of nicotine from patches (i.e. no boost)
- Patch studies tended to have less intervention to cut down on smoking cf studies of acute NRT
- Administration of acute NRT (gum/lozenge) may interfere physically with smoking.

Study quality comments

Overall Quality Score: -

Methods for study identification & selection are not fully described. No meta-analysis was performed as the authors concluded that the studies had large variability in design. However, effects are summarised across studies as an average.

Funding source:
US National Institute on Drug Abuse

Holm, H., Jarvis, M. J., Russell, M. A. & Feyerabend, C. (1992) Nicotine intake and dependence in Swedish snuff takers. Psychopharmacology (Berl), 108: 507-511.

Design

Two studies:
1. PK case series (aim: to examine the rate of absorption of nicotine from Swedish Snus)
2. Prospective comparative study (aim: to compare nicotine dependence between Snus users and cigarette smokers

Participants

Study 1: 10 Snus users (9 men, 1 woman, mean age 32.6y), weekly snuff consumption averaged 160 g
Study 2: 27 regular snuff users (all men, 16 never smokers, 11 ex-smokers) and 35 cigarette smokers (12 men, 23 women).

Interventions / comparators

Study 1: Overnight abstinence verified by exhaled CO measurement. Each subject took 2.0 g snuff ("Ettan'), in the mouth for 30 min. before discarding. Venous blood specimens were taken prior to dosing and at 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 30, 35, 40, 45, 50, and 60min after placing the snuff in the mouth.

Study 2: No abstinence period was mandated. Subjects completed a questionnaire and took a pinch of their usual snuff or smoked one of their usual brand of cigarette. A venous blood sample was taken
1 min after extinguishing the cigarette, and 5-15 min after discarding the snuff. The questionnaire items enquired about current and past tobacco use and subjective aspects of dependence, with responses on anchored 3-, 4-, or 5-point scales (e.g. "Do you think that you are addicted to snuff/smoking?" Extremely/Fairly/Slightly/Not at all).

Smoking behaviour / co-interventions

As above

Pharmacokinetic outcomes

STUDY 1

Plasma nicotine concentrations following a single dose of 2g Swedish snuff

Average values:
Cmax: 17.0 (SD 5.6) ng/ml
Tmax: 35.5 (SD 11.7) min
AUC (0-60 min) 747.4 (SD 243)ng/ml/min

STUDY 2
Mean plasma nicotine after dosing:
Snuffers: 36.6 ng/ml (SD 14.4) in the snuffers
Smokers: 36.7 (SD 16.1) (p=NS)

Mean plasma cotinine:
Snuffers: 399.2 ng/ml (SD 160.5)
Smokers: 306.3 (SD 162.5).
On a univariate analysis, this difference was statistically significant (P= < 0.05), but was no longer so after controlling for age and sex (F= 3.44, P = 0.07).

There was no significant difference in plasma nicotine between never smokers and ex-smokers among the snuffers (32.4 ng/ml and 42.6 ng/ml, respectively).

Safety Outcomes

STUDY2:
On questionnaire measures of dependence, there was no difference between smokers and snuffers in self-assessed addiction, craving for tobacco, or difficulty in giving up. Snuffers reported stronger enjoyment of

the habit than did smokers: 2.59 vs 2.05 ($p<0.01$, multivariate) on a 3 point scale.

Study quality comments

Overall Quality Score: +

Hughes, J. R. (2000) Reduced smoking: an introduction and review of the evidence. Addiction, 95 Suppl 1: S3-S7.

Design

Narrative review which included the research questions:

1. how many smokers can reduce their smoking and maintain this reduction?
2. how much compensation occurs?
3. will reduced smoking significantly decrease the risk of smoking?
4. will reduction promote or undermine cessation?

Participants

Relevant data comes from 7 studies of smokers not interested in quitting.

Interventions / comparators

Smoking reduction strategies

Smoking behaviour / co-interventions

Smokers took part in reduction interventions.

Pharmacokinetic outcomes

Authors conclude:

- Reductions in CO are usually 75% of the reduction in self reported cigarettes/day, suggesting that some compensation occurs
- Nevertheless the median reduction in CO (27%) is substantial
- Conversely the MRFIT trial found no reduction in thiocyanate (biochemical marker of smoking) despite a self reported reduction in cigarettes per day of 26%.
- In summary – some compensation occurs, but exposure to toxins is reduced.

Study quality comments

Review article does not describe methods, or many characteristics of the primary studies.

Overall Quality Score: -

Funding source:
US National Institute on Drug Abuse; Pharmacia & Upjohn

Hughes, J. R. & Carpenter, M. J. (2005) The feasibility of smoking reduction: an update. Addiction, 100: 1074-1089.

Design

Systematic review addressing four research questions:

1. whether smokers reduce their smoking spontaneously
2. whether smokers who try to quit and fail return to smoking less
3. whether smokers can substantially reduce and maintain reduction via pharmacological and behavioral treatments
4. whether smokers compensate when they reduce.

Participants

Smokers not aiming to stop smoking, drawn from 15 studies. Abstainers excluded from analysis as they cannot compensate.

Interventions / comparators

Reduced smoking with NRT, bupropion or behavioural interventions, confined to reducing the number of cigarettes per day (not topography or cigarette length or low tar cigarettes)

Review uses a compensation index:

% compensation = (1-[% reduction in marker/% reduction in CPD]) x 100
i.e. complete compensation: 100%, zero compensation: 0%

Smoking behaviour / co-interventions

As above

Safety Outcomes

In studies of NRT (n=10):

- Reduction in marker: range 4-46%
- % compensation: range 17-64%

Overall the reduction in marker was approximately a third less than the reduction in cigarettes per day

In studies of behavioural interventions (n=5)

- Reduction in marker: range 10-26%
- % compensation: range 0-58%

There was no correlation between the % reduction in cigarettes per day and the % compensation (i.e. no trend whereby smokers who made large reductions in cigarettes per day compensated more).

Discussion of biological markers of exposure to cigarette smoke:

- CO: limited by short half life and reflects only recent smoking
- Cotinine: has longer half life than CO but is influenced by NRT
- Thiocyanate: longer half life but is less sensitive or specific than CO or cotinine.

Discussion of limitations:

- CO is known to be an imperfect marker of cigarette smoke exposure
- Author's intention-to-treat analysis reduced the estimate of reduction in exposure (cigarettes per day); therefore the estimates of compensation may be overestimates
- If patients exaggerate their reductions in cigarettes per day, this would over estimate the degree of compensation.

Authors conclude:

- Compensation occurs
- Compensation is generally <50% of the reduction in cigarettes per day, but significant reductions in

CO occur
- It is unclear whether using NRT abates compensatory smoking (only two studies provided data with inconsistent results)

Study quality comments

Methods adequately described including:

- Electronic databases & conference proceedings & research sources
- Retrieval of papers
- Data extraction
- Presentation of results
- Decision to not perform meta-analysis due to heterogeneity in study design.

Study quality was not assessed.
Statistical significance of results is not reported (and was not always reported in primary studies).
Authors performed an intention-to-treat analysis in which participants lost to follow-up were assumed to have returned to baseline levels of CPD

Overall Quality Score: +

Funding source:
US National Institute on Drug Abuse

Jarvis, M. J., Boreham, R., Primatesta, P., Feyerabend, C. & Bryant, A. (2001) Nicotine yield from machine-smoked cigarettes and nicotine intakes in smokers: evidence from a representative population survey. J.Natl.Cancer Inst., 93: 134-138.

Design

Cross sectional survey correlating salivary cotinine with nominal nicotine yield from different brands of cigarette.

Participants

2031 respondents (868 men, 1163 women) to the Health Survey for England conducted in 1998 who:

- were smokers who smoked a brand of cigarettes for which the nicotine yield had been calculated by the Laboratory of the Government Chemist using a machine smoking measurement
- provided a saliva sample for cotinine analysis

The 2031 subjects were drawn from 3496 smokers visited by a nurse in the survey. Exclusions were those smoking own rolled cigarettes (542), inadequate saliva volume (685) or missing data on cigarette brand/yield (238).

Characteristics of smokers and cigarettes tested by machine smoking

	nicotine yield (mg/cig)		
	0 to <0.4	**0.4-0.75**	**>0.75**
Mean nic yield mg	0.14	0.57	0.91
Mean CO yield	1.60	7.48	13.14
Mean cigs/day	13.5	13.3	15.5

Interventions / comparators

A saliva sample was taken from subjects for cotinine measurement, and compared with machine-measured cigarette nicotine yield.

Smoking behaviour / co-interventions

No change in smoking habit was mandated in the study.

Pharmacokinetic outcomes

Correlation of salivary cotinine and nicotine yield

There was only a low degree of correlation ($r=0.19$, $p<0.001$) between nicotine yield and salivary cotinine, with wide variation in cotinine concentrations at any given yield. At any level of nominal yield, smokers achieved high nicotine intakes (approximately half of smokers achieved cotinine levels in excess of 300ng/ml).

Multiple regression analysis

In multiple regression controlling for confounders (cigs/day, age, sex, BMI, car ownership, housing tenure, unemployment, occupation, education), the incremental proportion of variance explained by yield overall was low, at 0.79%, $p<0.001$.

Estimated nicotine intake based on other sources that estimate that 100ng/ml cotinine represents a daily nicotine intake of 6.7mg.

The authors noted imprecision in the estimated values of nicotine but note that there is only a slight tendancy for higher yield brands to result in higher estimated nicotine intakes. Estimated nicotine intake per cigarette was 1.17 mg in smokers of brands yielding less than 0.4 mg of nicotine (average yield = 0.14 mg), 1.22 mg from brands yielding between 0.4 mg and less than 0.8 mg (average yield = 0.57 mg), and 1.31 mg from brands yielding 0.8 or more (average yield = 0.91 mg).

Study quality comments

Overall Quality Score: +

Cotinine is not a perfect proxy for nicotine and the machine measurement of yield does not reflect actual

smoking patterns per cigarette, although these drawbacks are difficult to overcome.
The multivariate analysis used sensible confounding variables.

Russell, M. A., Jarvis, M. J., Devitt, G., Feyerabend, C., Russell, M. A., Jarvis, M. J., Devitt, G. & Feyerabend, C. (1981) Nicotine intake by snuff users. British Medical Journal Clinical Research Ed, . 283: 814-817.

Design

Prospective case series of snuff takers, results compared with a separate series of heavy smokers

Participants

Sample 1

- 27 people volunteered to take snuff (4 virgin snuffers, 12 occasional snuffers, 11 daily snuffers). 4 women, 23 men. 15 were smokers. 5 subjects were taking snuff competitively.
- 13 people smoked a cigarette

Sample 2:

- 136 heavy smokers (37 men, 99 women, mean 30 cigarettes/day), attending a smokers' clinic.

Interventions / comparators

Venous blood samples were taken one to two minutes before a pinch of snuff and then repeated between six and 17 minutes after taking the snuff (mean 101 + SD 2-4 minutes). Five subjects took multiple doses of snuff, two of them according to snuff taking championship rules. Blood was analysed for nicotine and cotinine concentrations.

Smoking behaviour / co-interventions

The 27 snuff takers smoked/snuffed ad libitum up to the study period (6pm-10pm)

Pharmacokinetic outcomes

Initial plasma nicotine and cotinine concentrations correlated well with each other ($r = 0.84$; $p < 0\text{-}001$) and with the smoking habits and amount of snuff use.

Changes in venous plasma nicotine concentration at mean 10.1 minutes after taking nasal snuff (sample 1)

	Nicotine increase (nmol/l)	SD	Nicotine increase (ng/ml)	SD
Virgin snuffers (n=4)	-3.1	0.5	-0.5	0.1
Occasional snuffers (n=12)	12.3	20.3	2.0	3.2
Daily snuffers (n=11)	77.7	70.3	12.4	11.2
Multiple-dose snuffers (n=5)	332.9	199.1	53.3	31.9
Cigarette smokers	62.3	48.1	10.0	7.7

Mean venous plasma nicotine concentrations from cigarette smoking and snuff use (sample 2)

	Mean plasma nicotine concentration (nmol/l)	SD	Mean plasma nicotine concentration (ng/ml)	SD
Cigarette smokers (n=136)	226.3	85.1	36.2	13.6
Daily snuffers (n=11)	222.6	130.7	35.6	20.9
Rapid smoking (n=15)	296.5	96.8	47.4	15.5
Multiple dose snuffing (n=5)	464.9	256.5	74.4	41.0

There was large individual variation in nicotine concentrations for both snuff users and cigarette smokers.

Larger increases in nicotine concentrations after using snuff were observed in heavier snuff users. Daily snuff users had a similar mean increase in plasma nicotine (12.4 ng/ml) to that of smoking a single cigarette (10.0 ng/ml). Multiple doses of snuff produced massive increases in plasma nicotine concentrations (mean 53.3ng/ml). Daily snuff users also had a similar mean plasma nicotine concentration (35.6 ng/ml) to that of heavy smokers (36.2 ng/ml). In the 136 smokers Tmax was approximately 2 minutes after finishing the cigarette. In snuff takers Tmax and 6-15 minutes after taking snuff.

Authors conclude that at 10 minutes after taking snuff, plasma nicotine levels approximate those seen at the end of the 10 minute period it takes to smoke a cigarette.

Study quality comments

Overall Quality Score: +

Heterogenous sample with regard to smoking habit. Sample 1 is predominantly men and sample 2 predominantly women.

The snuff takers were sampled at a snuff taking competition in 1980 and may not represent the snuff taking patterns elsewhere in the UK (or in the UK in 2011).

There was no washout period, so some nicotine in snuff takers may have come from cigarettes.

Some nicotine concentration data presented here are converted from nmol/l to ng/ml by a factor of 0.16 stated in the paper.

Russell MAH, Jarvis MJ, Sutherland G, Feyerabend C. 'Nicotine Replacement in Smoking Cessation', JAMA 1987; 257(23): 3262-3265.

Design

Experimental study of the plasma nicotine concentrations (venous samples) before, during and after the use of a smoke-free cigarette

Participants (n= 8)

All male, aged 29 to 54 years. Three were ex-smokers, three were occasional cigar smokers and two were current cigarette smokers (>25 per day)

Interventions / comparators

- Smoke-free cigarettes (Favor Regular) consisting of a plastic cylinder containing a plug of plastic sponge impregnated with nicotine. The plug contains 9.5 mg nicotine and the device releases on average 13 µg of nicotine per 50 ml puff.
- No comparator studied
- Two phases: first test cigarette puffed at intervals of 40 seconds (ten puffs in six minutes). This was followed by a period of maximal puffing where subjects puffed and inhaled as hard and frequently as possible for 20 minutes (every five minutes the cigarette was changed)
- Blood samples were taken for nicotine analysis, at -5 (before study commenced), 0, 2.5,5,7.5,10,15,20,25,30,35,40,45,50 and 60 minutes
- Heart rate and blood pressure were measured and recorded automatically

Smoking behaviour / co-interventions

Abstinence from smoking for 12 hours prior to the study (confirmed by measuring expired air CO)

Pharmacokinetic outcomes

Nicotine vapor smoke free cigarette:
Cmax (mean, 8 subjects) 18.7 (SD6.6) ng/ml
Tmax (mean, 8 subjects) 35 min

There was very little increase in nicotine concentration in the first ten minutes. After this time there was a steady increase in blood nicotine concentrations as a result of maximal puffing of the test cigarettes. Peak levels were reached at about 35 to 40 minutes (5 to 10 minutes after discontinuing puffing). The authors suggest much of the nicotine was absorbed through the mouth and upper airway rather than through the alveoli.
The PK data stated above were compared with historical data for tobacco cigarette and nicotine gum:
Cigarette Cmax 26ng/ml, Tmax 8min
Gum (2mg) Cmax 8ng/ml, Tmax 30min

Very little nicotine was absorbed from the vapour cigarette when it was smoked like a conventional cigarette. With maximal use, more nicotine is absorbed than when a single 2 mg nicotine gum is chewed. The authors conclude "even with intensive puffing and inhalation there was evidence that most nicotine vapour failed to reach the alveoli and was presumably deposited in the mouth, throat and large airways". There are two reasons for this assertion: the rate of absorption from the device was much slower than from a conventional cigarette and the plasma nicotine concentrations continued to rise even after puffing had ceased.

Safety Outcomes

Heart rate and blood pressure increased slowly in line with the rise in blood nicotine concentrations. Heart rate increased from a baseline of 73 ± 15.6 (SD) bpm to an average peak of 89 ± 11.7 bpm at 30 minutes ($p<0.05$). Average blood pressure increased from 126/73 to 135/84 mm Hg at 35 minutes ($p <0.01/0.05$).
All subjects experienced some irritation to the throat and trachea which was not severe and adaptation occurred within minutes.
Slight dizziness and light-headedness were experienced by 7/8 subjects. These became more prominent

during the maximal puffing phase and subsided after 35 minutes.
Nausea, cool extremities, sweatiness and pallor were experienced by 5/8 subjects.
Two out of the eight subjects were described as feeling quite ill.
One subject developed hiccups.

Study quality comments

Overall Quality Score: -

No selection, inclusion or exclusion criteria.
Protocol was described.
Puffing technique was exaggerated, difficult to relate to usual practice.
No comparator.

Vansickel, A. R. & Eissenberg, T. (2012) Electronic Cigarettes: Effective Nicotine Delivery After Acute Administration. Nicotine Tobacco Research Electronic publication ahead of print. Nicotine Tob Res (2012) doi: 10.1093/ntr/ntr316. First published online: February 6, 2012.

Design

Clinical laboratory study.

Participants (n=8)

3 females

8 Caucasian

Average age 33.4 years

All were former smokers who had quit smoking for an average 11.4 months prior to the study and had used electronic cigarettes for an average 11.5 months (experienced e-cigarette users)

Interventions / comparators

- Electronic cigarette and cartridge of participants choice
- 5 hour session (with continuous physiological measurement):
    - baseline measurement (blood nicotine concentration, subjective questionnaires)
    - 10 puffs with a 30 second inter puff interval (blood samples at 5 and 15 minutes after the first puff, subjective questionnaires)
    - 60 minute ad-libitum puffing (blood samples every 15 minutes, subjective questionnaires)
    - 2 hour rest period: no puffing (blood samples every 30 minutes, subjective questionnaires)

Smoking behaviour / co-interventions

Study did not describe nicotine exposure prior to the study (no mention of abstinence for instance). All participants were ex smokers.

Pharmacokinetic outcomes

Plasma nicotine increased from a baseline mean of 2 ng/ml (SE 0) to a mean of 10.3 ng/ml, (SE 2) at 5 minutes (during which participants took ten puffs). At 15 minutes participants started a 60 minute ad lib puffing period. Plasma nicotine remained elevated, and reached a maximum concentration of mean=16.3 ng/ml, (SE 4.5) by the end of the ad lib period.

Safety Outcomes

No data reported

Study quality comments

No comparator

Laboratory study, appropriate measurement of nicotine concentration.

Small study population

Overall Quality Score: -

Rose JE, Mukhin AG, Lokitz SJ et al, 'Kinetics of brain nicotine accumulation in dependent and nondependent smokers assessed with PET and cigarettes containing ^{11}C-nicotine. Proc Natl Acad Sci USA, 2010 Mar 16; 107(11): 5190-5.

Design

Experimental study of brain nicotine accumulation using PET. The study was performed in dependent and nondependent smokers.

Participants (n= 23)

Dependent smokers (DS): n= 13
Nondependent smokers (NDS): n=10
Inclusion and exclusion criteria were not provided and selection of study participants was not described.

Interventions / comparators

- The dynamics of brain nicotine accumulation during cigarette smoking was measured using PET with 3-s temporal resolution and ^{11}C-nicotine loaded into cigarettes.

Smoking behaviour / co-interventions

Study protocol was not included.

Pharmacokinetic outcomes

Main findings:
Under typical smoking conditions puff associated spikes in brain nicotine concentration do not occur. This is explained by insufficient cerebral perfusion to washout nicotine rapidly enough for peaks and troughs to develop. Brain nicotine accumulation began approx 7 seconds after radioactivity was detected in the oral cavity (7.0 ± 1.5 s (DS) and 6.9 ± 1.2 s (NDS)). Maximal accumulation occurred at 290 ± 30s and 210 ± 40s. These values of Tmax suggest nicotine after each puff is superimposed on a brain nicotine concentration that is increasing as a result of the previous puff. Cigarette smoking should be considered as a single, continuous source of nicotine treatment.

DS have a lower brain nicotine accumulation rate than NDS. Significantly lower nicotine concentrations were observed for DS than NDS over the first 3 minutes, half maximal accumulation values of brain nicotine accumulation were 1.8 times longer for DS than NDS. The authors suggest slow lung kinetics in DS can be partially explained by chronic cigarette smoking.

This reduced accumulation in DS is a consequence of reduced nicotine washout from the lungs. Over the first 240 s, the residual fraction of the inhaled nicotine dose in the lung tissue was higher in DS versus NDS ($p<0.05$). $T_{1/2}$ of nicotine washout in DS was almost three times that of NDS (89 ± 18s and 27 ± 5 s, $p<0.01$).

Overall brain nicotine accumulation can be closely approximated by a linear function but there is puff-associated oscillation in the rate of nicotine accumulation which the authors suggest could result in puff-associated changes in the function of nAChR receptors.

DS have a tendency to compensate for their slow nicotine kinetics by taking larger puffs (42.8 ± 2.8 ml vs 30.0 ± 2.4 ml, $p<0.003$)

Safety Outcomes

Not reported

Study quality comments

Overall Quality Score: +
No selection, inclusion or exclusion criteria.
Protocol was described.
Limitations of the method were described
Appropriate statistical analysis.

Henningfield JE, Stapleton JM, Benowitz NL et al, 'Higher levels of nicotine in arterial than in venous blood after cigarette smoking', Drug and Alcohol Dependence, 1993; 33:23-29.

Design

Experimental study measuring arterial and venous nicotine concentrations before and after smoking. The study was supplemental to a study involving PET scanning which required insertion of arterial and venous catheters.

Participants (n= 8)

All subjects were polydrug abusers in good health. Mean age 33.6 years (range 26 to 43).
All were smokers (mean 22.7 cigarettes per day (range 10 to 40)).

Interventions / comparators

Subjects smoked their usual brand of cigarettes over a period of approximately 5 minutes. Blood samples were taken before smoking a cigarette and at 5-6 minutes and 10-11 minutes after the cigarette was lit. Sampling was usually completed approximately 20 seconds earlier from the arterial than from the venous catheter. Subjects smoked in their usual way over the course of the study (a period of approximately 5 minutes). Four subjects smoked mentholated cigarettes and four smoked non-mentholated cigarettes. All brands were filter-tipped.
Two subjects had additional samples drawn at 1 and 3 minutes after light-up, one subject was also sampled at 3 minutes after light-up and one subject at 8 and 12 minutes after light-up.

Smoking behaviour / co-interventions

Participants had abstained from smoking for 5 to 8 hours before the study began.

Pharmacokinetic outcomes

Smoking one cigarette produced a statistically significant increase in both arterial and venous concentrations of nicotine, but the increase was much greater in arterial blood. Arterial levels were higher than venous levels at both 5 and 10 minutes after light-up. There was considerable inter-individual variation in the difference between arterial and venous (difference ranged from 0.6 to 79.8 ng/ml).
Comparing pre- and post- cigarette levels, there were statistically significant increases in both arterial and venous levels at 5-6 min and 10-11 min after smoking.
Age, number of cigarettes smoked per day and hours of smoking deprivation were not significantly correlated with arterial or venous nicotine or cotinine concentrations before smoking.

Mean arterial and venous concentrations of nicotine (ng/ml), before and after smoking one cigarette:

	Time after light up		
	Zero	**5min**	**10min**
Arterial	5	53	30
Venous	7	24	19

Smoke inhalation produces increases in drug concentration of much greater size in arterial plasma than in venous plasma. This difference declines rapidly. There is also considerable variability in arterial concentrations across subjects. The authors concede that to determine the maximum arterial-venous differences would require assessment within 15 seconds of the first puff (after this arterial concentrations fall due to dilution effect of arterial and venous blood mixing).These high arterial blood concentrations would be expected to cause a rapid and transient physiological perturbation.
The authors, in their discussion note that NRT gum and patches deliver nicotine into the venous circulation. The consequence of this is a gradual increase in the concentrations of nicotine in the blood and brain and would not produce high concentrations or rapid effects seen with smoke inhalation.
Post inhalation arterial drug levels should better reflect brain concentrations than venous levels, which reflect effluent concentrations from skeletal muscle. Venous blood levels of smoked nicotine may greatly underestimate the concentrations to which tissues are exposed.

Safety Outcomes

Not reported

Study quality comments

Overall Quality Score: +

Small study

Gourlay SG and Benowitz NL, 'Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine', Clin Pharmacol Ther 1997; 62: 453-63.

Design

Experimental study reporting arteriovenous differences following exposures to cigarettes, nicotine nasal spray and intravenous nicotine infusion.

Participants (n= 12)

Healthy male smokers (mean age 38 ± 10 years), mean number of cigarettes smoked per day= 23 ± 8, mean Fagerstrom Tolerance Score 7 ± 2, mean screening plasma cotinine concentration 224 ± 67 ng/ml.

Interventions / comparators

- 6 subjects were given nicotine by nasal spray (0.5 mg per nostril)
- 6 subjects smoked their usual cigarettes (one puff per minute for 10 minutes)
- Blood samples were taken (arterial and venous) at 0,2,4,6,8,10,15,20,25,30,45 and 60 minutes after dosing.
- 70 minutes later all 12 subjects received an IV infusion of 2 µg/kg/min radioactively labelled nicotine per minute for 30 minutes.

Blood samples were taken (arterial and venous) at 0,10,20,30,32,35,40,45,60,90,120,150,180,240,300 and 360 minutes after dosing.
Samples were analysed for nicotine, cotinine, epinephrine and norepinephrine.

Smoking behaviour / co-interventions

Prior to the study, subjects did not smoke (abstinence from smoking was supervised)

Pharmacokinetic outcomes

When inhaled in smoke, nicotine is directly absorbed through the pulmonary capillaries into the pulmonary venous circulation and to the left side of the heart. Arterial blood perfuses tissues, which take up a variable amount of nicotine before blood reaches a venous sampling site.
When taken intranasally, nicotine is absorbed into a submucosal venous plexus that drains into the facial, sphenopalatine and ophthalmic veins. Blood then passes into the jugular veins, superior vena cava, right side of the heart, lungs, and the left side of the heart before appearing in arterial blood.

Cmax and Tmax in arterial and venous blood for 3 administration routes for nicotine

Blood sample	PK parameter	Smoking 10min	1mg nasal spray	30min IV infusion at 2 µg/kg/min
Arterial	**Cmax ng/ml**	39.8	10.4	49.9
	Tmax min	8.2	4.7	29
Venous	**Cmax ng/ml**	18.6	5.4	29.5
	Tmax min	11.9	24.8	30

The median ratios between the arterial and venous plasma concentration of nicotine at the time of arterial Cmax were 4.6 (nasal spray), 2.3 (smoking) and 1.6 (intravenous).

Peak arterial plasma concentrations of nicotine (Cmax) after smoking or administration of nicotine nasal spray averaged twofold those of venous plasma. For nicotine nasal spray the time to Cmax was much faster for arterial than for venous plasma (median 5 versus 18 minutes, $p<0.01$)
Mean heart rate increased with all three methods of delivery, reaching a peak just after the mean tmax in arterial plasma.

Study quality comments

Overall Quality Score: +
Small study.
Artificial, laboratory environment, not natural smoking pattern.
Not clear how subjects were recruited or selected. Allocation to smoking/ nasal spray not described. Details of laboratory and statistical analysis were provided.

15 Appendix 8. Evidence table: question 6

Are kinetic data available which allow comparison of the relative bioavailability of different technologies i.e. maximum (peak) concentration (Cmax), time to peak concentration (Tmax) and half life (t ½)?

Dautzenberg, Nides, Kienzler & Callens . Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate lozenges (Nicotinell). BMC Clinical Pharmacology 7[pp 11], 2007.

Design

Randomised pilot study, 3-way crossover design: all participants received each treatment in turn.

Participants

n=9 male smokers who normally smoke at least 20 cigarettes per day

Interventions / comparators

Three treatment arms

- 1mg lozenge versus
- 2mg lozenge versus
- 2mg gum

Single dose given in each arm after 24hr smoking abstinence. Products were sucked/chewed for 30 minutes.
32hr measurement period post-dose: blood was sampled before dosing and at 15, 30, 45 min, 1, 1.25, 1.5, 2, 3, 4, 6, and 8 hrs after dosing.
7d washout between crossovers.

Smoking behaviour / co-interventions

Smoking was prohibited during the study.

Pharmacokinetic outcomes

Single dose PK parameters: mean (SD)

	1mg lozenge	2mg lozenge	2mg gum
Cmax ng/ml	2.3 (0.8)	4.8 (1.4)	2.9 (1.2)
Tmax h	1.1 (0.7)	0.8 (0.2)	0.8 (0.1)
AUC0-∞ h.ng.ml	10.7 (3.1)	20.0 (5.9)	13.8 (5.6)

In some participants the lozenges did not completely dissolve therefore results were adjusted to represent whole lozenges.
The authors concluded that the results suggest there is bioequivalence between 1mg lozenge and 2mg gum.

Safety Outcomes

There were 18 adverse events of which two were attributed so study medication: 2mg lozenge and gum, throat irritation. No adverse events were serious.

Study quality comments

+

Dautzenberg, Nides, Kienzler & Callens . Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate lozenges (Nicotinell). BMC Clinical Pharmacology 7[pp 11], 2007. 2007.

Design

Randomised, 2-way crossover study

Participants

n=24 male smokers who normally smoke at least 20 cigarettes per day

Interventions / comparators

2 treatment arms:

- 1mg lozenge versus:
- 2mg gum

12 doses were given, one each hour, starting after 22 hr of abstinence from smoking.
Gums were chewed for 30 min. Lozenges were sucked until completely dissolved (approx 30 min).
Measurements were made over 23 hrs. Blood was sampled pre-dose, 15, 30 and 45 min after the first dose. In addition, blood was sampled before each new dose (at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 hr) and after the last dose at 11.25, 11.5, 11.75, 12, 12.25, 12.5, 13, 13.5, 14, 15, 17, 19, 21, and 23 hr (all times after first dose).
There was a washout period of 7d between crossovers.

Smoking behaviour / co-interventions

Smoking was prohibited during the study.

Pharmacokinetic outcomes

Median tmax (0.76 versus 0.75 h), mean Cmax (4.2 ±1.8 versus 5.0 ± 1.6 ng/ml) and AUC0–1 (2.9 ± 1.4 versus 3.5 ± 1.3h.ng/ml) were similar for lozenge and gum after the first dose (0–1 h).
Plotting of plasma nicotine concentrations over time after repeated administration of 1mg lozenges and 2mg gum revealed that the plateau of concentration was reached after intake of six doses.
Results in steady state as presented in paper:

PK parameters in steady state after 12 hourly doses – mean [SD]

	1mg lozenge	2mg gum
Cmax ng/ml	10.6 [2.9]	11.4 [3.8]
Tmax h	0.54 [0.21]	0.47 [0.19]
AUC11-12 h.ng.ml	9.2 [2.6]	10.2 [3.4]

Safety Outcomes

12 volunteers had a total of 40 adverse events, which were mild to moderate, with complete recovery. Six were considered as drug related: salivation, hiccups, flatulence and throat irritation.

Study quality comments

Open label study +

Dautzenberg, Nides, Kienzler & Callens . Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate lozenges (Nicotinell). BMC Clinical Pharmacology 7[pp 11], 2007. 2007.

Design

Randomised, three-way cross-over study

Participants

n=31 male smokers who normally smoke at least 20 cigarettes per day

Interventions / comparators

Participants entered 3 treatment arms in turn:

- 1mg lozenge
- 2mg lozenge
- 4mg gum

Participants received 12 doses of the product, on each hour per 12 hr treatment session. Each session was preceded by 24hr abstinence from smoking and there was a washout period of 7d between crossovers Blood samples for determination of plasma nicotine were taken pre-dose and at 7 and 9 h. After intake of the last dose (11 h), blood was drawn at 11.25, 11.5, 11.75, 12.5, 13, 14, 15, 17, 19, 21, and 23hr.

Smoking behaviour / co-interventions

Smoking was prohibited during the study.

Pharmacokinetic outcomes

Mean [SD]: steady state after 12 horly doses of each product

	1mg lozenge	2mg lozenge	4mg gum
Cmax ng/ml	11.0[4.9]	22.5 [7.0]	30.5 [12.8]
Tmax h	0.5	0.5	0.5
AUC11-12 h.ng.ml	9.7 [3.9]	20.2 [6.8]	27.5 [11.4]

Safety Outcomes

Study quality comments

One participant withdrew from the study due to vomiting while on the 2mg lozenges. 16 people reported a total of 29 adverse events which were mild to moderate, including hiccups, throat irritation and nausea.

+

Dautzenberg, Nides, Kienzler & Callens . Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate lozenges (Nicotinell). BMC Clinical Pharmacology 7[pp 11], 2007. 2007.

Design

Case series, safety (escalating dose) study

Participants

n=24 male/female smokers who smoked at least 10 cigarettes per day.

Interventions / comparators

Participants were treated in one of three groups:

1. A: swallowed 3 x 1mg lozenges together
2. B: swallowed 6 x 1mg lozenges together
3. C: swallowed 12 x 1mg lozenges together.

In each group two participants were given the dose and observed. If the dose was well tolerated the remaining six participants were given the same dose. Each dose was followed by a 2d measurement period, in which smoking was prohibited for the first 12h. Measurement of plasma nicotine took place at pre-dose and 10, 20, 30, 40, 50 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 13, 16 and 48 h post-dose.

Smoking behaviour / co-interventions

No period of abstinence pre-study was required. All but one participant had measureable plasma nicotine at baseline. Smoking prohibited for first 12h following dose.

Pharmacokinetic outcomes

The highest mean nicotine concentration observed (20.5 ng/ml) fell within the range typically observed in active cigarette smokers (10-50ng/ml). The results were not corrected to account for baseline plasma nicotine levels.

PK parameters (mean [SD]) after swallowing lozenges without sucking

	3 x 1mg lozenge	6 x 1mg lozenge	12 x 1mg lozenge
Cmax ng/ml	8.2 [7.6]	16.9 [11.8]	20.5 [8.8]
Tmax h	2.7 [2.8]	2.8 [2.0]	2.2 [1.4]
AUC10min-12h (h.ng.ml)	37.0 [27.2]	84.9 [48.9]	103.1 [58.6]

Safety Outcomes

No clinically significant changes in cardiac (HR, BP, ECG) or laboratory parameters observed. No serious adverse events were reported. Only one minor adverse event occurred in groups A and B (headache during 1h). In group C, six volunteers reported stomach heaviness in the first hour after ingestion of the 12 lozenges. Gastric motor activity determined at 1 and 11 h post-dosing was normal (3 ± 0.5 cycles/min). Gastric half clearance times at 1 and 11 h post-dosing were within the standard range (55 ± 15 min) for subjects receiving 3 or 6 lozenges, but not for those receiving 12 lozenges; the latter complained about stomach heaviness at 1 h post-dosing and displayed shortened gastric half clearance times (26 and 34 min). These adverse events resolved spontaneously, and clearance half-times at 11 h post-dosing were again well within the standard range (49 and 62 min).

Study quality comments

Quality score [+]

Veaugh-Geiss, Chen, Kotler, Ramsay & Durcan . Pharmacokinetic comparison of two nicotine transdermal systems, a 21-mg/24-hour patch and a 25-mg/16-hour patch: a randomized, open-label, single-dose, two-way crossover study in adult smokers. Clinical Therapeutics 32, 1140-1148. 2010.

Design

Randomised, open-label, single-dose, 2-way crossover study comparing single dose PK of the 21-mg/24-hour patch and the 25-mg/16-hour patch. Also a post hoc exploratory analysis evaluated the PK assuming that the 21-mg patch was removed after 16 rather than 24 hours.

Participants

n= 50 healthy smokers (>10 cigarettes / day): 29 men, 21 women, 47 (94%) white. Mean (SD) age 31.5 (9.57) years (range, 20–53 years). Subjects reported smoking between 11 and 40 cigarettes per day before the study.

Interventions / comparators

Subjects were randomly allocated to receive:

- 21-mg patch worn for 24 hours followed by the 25-mg patch worn for 16 hours versus:
- 25-mg patch worn for 16 hours followed by the 21-mg patch worn for 24 hours.

Subjects underwent 2 study sessions, each consisting of:

- 24-hour baseline phase (approx. 12 times the nicotine t1/2)
- 32-hour treatment phase (a respective 16 or 24 hours of treatment and 16 or 8 hours of blood sampling after patch removal).

Blood samples were taken before patch application and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 17, 18, 20, 24, 25, 26, 28, and 32 hours after patch application.

Smoking behaviour / co-interventions

Smoking was prohibited during the study visit, except for the 16-hour interval between study sessions. Abstinence from smoking was confirmed based on measurement of expired CO before patch application and at 1.5, 8.25, 12.3, and 32 hours after patch application.

Pharmacokinetic outcomes

	21 mg 24h patch	25 mg 16h patch
Cmax ng/ml	18.34	16.56
Tmax h	6.0	12.0
AUC0-∞(h.ng.ml)	382.36	243.69

Safety Outcomes

Adverse events: 75.0% with the 21-mg patch, 89.8% with the 25-mg patch, mostly mild, including erythema (50.0% with the 21-mg patch, 77.6% with the 25-mg patch), pruritus (60.4% and 32.7%, respectively), and irritation (4.2% and 8.2%), also dizziness (12.5% and 4.1%) and headache (10.4% and 8.2%). One patient withdrew from the study due to nausea (25-mg patch).There were no serious or unexpected adverse events.

Study quality comments

Random allocation to treatment sequence was computer-generated.
The study was unblinded
Sample size based on at least 80% power to establish superiority based on a true AUC ratio (21 mg:25 mg) of approximately 1.13.
Analyses are not by intention to treat, but per protocol.
PK analyses were based (after excluded protocol violations) on 43 profiles for the 21 mg patch and 46 profiles for the 25 mg patch.
Factors standardised in the study:

- Meals, drinks & fasting relative to patch application.
- Water allowed ad libitum, apart from 1-hour either side of application.
- Medicines
- Environment
- Showering

+

Guthrie, Zubieta, Ohl, Ni, Koeppe, Minoshima, Domino, Guthrie, Zubieta, Ohl, Ni, Koeppe, Minoshima & Domino . Arterial/venous plasma nicotine concentrations following nicotine nasal spray. European Journal of Clinical Pharmacology 55[9], 639-643. 1999.

Design

Case series

Participants

n=19 smokers (10 men, 9 women) In good general health and on no medication except contraceptives. Mean age (women) 33.7 yr, (men) 30.4 yr

Interventions / comparators

Following overnight smoking abstinence (>10 h) verified by exhaled CO assessment, subjects were given a single dose of nasal nicotine spray (0.5mg nicotine / spray). Subjects received 2-5 sprays depending on tolerance. Arterial and venous forearm blood samples for plasma nicotine assessment were takes at baseline and at 3, 6, 10, 15, 20 and 30 minutes following dose.

Smoking behaviour / co-interventions

Existing smoking habit was 15-40 cigarettes / day.

Pharmacokinetic outcomes

Results did not change when adjusted for baseline plasma nicotine measurements.
PK results (mean [SD]):

	Arterial	Venous
Cmax ng/ml	17.0 [5.9]	8.2 [4.0]
Tmax h	5.1 [2.5]	17.6 [13.0]
AUC (h.ng.ml)	295.5 [128.7]	186 [93.5]

The mean number of sprays administered was 3.3 [1.0]

Arterial plasms nicotine levels were consistently higher than venous levels for the entire group of subjects ($p<0.01$, ANOVA) and varied over time ($P<0.01$, ANOVA). There was no statistically significant difference by gender for plasma nicotine Cmax, AUC, tmax or the ratio of arterial to venous Cmax or AUC.

Safety Outcomes

No data presented.

Study quality comments

Small sample size. One male was excluded from the analyses because too few blood samples were obtained for analysis: data presented are for 18 subjects.
+

Molander & Lunell . Pharmacokinetic investigation of a nicotine sublingual tablet. European Journal of Clinical Pharmacology 56, 813-819. 2000.

Design

Crossover study

Participants

n=24 healthy smokers (13 men age 20-48y, 11 women age 24-48)

Interventions / comparators

Subjects received both treatments sequentially:

- 2mg nicotine sublingual tablet versus;
- 2mg nicotine gum.

There was 12h abstinence from smoking before the study and 24h washout period between treatments. Each product was given as 12 doses, one each hour over 11 hours. Tablets were given sublingually for 30 minutes, then any residual tablet chewed and swallowed. Gum was chewed for 30 minutes with use of a metronome (1 chew every 2s) and saliva was swallowed every minute.
Venous blood samples were taken at 0, 2, 4, 6, 8, 10 and 11 h and at 10 minute intervals during hours 11-12.

Smoking behaviour / co-interventions

Existing smoking habit: >10 cigarettes per day

Pharmacokinetic outcomes

PK parameters (mean [SD]) unless otherwise stated

	Sublingual tablet	2 mg gum
Cmax ng/ml	13.2 [3.1]	14.4 [2.3]
Median Tmax min	20 (range 10-40)	20 (range 10-40)
AUC11-12(h.ng.ml)	12.4 [3.0]	13.5 [2.3]

Mean tablet disintegration time: 26 min.
After 30 minutes chewing, mean (SD) amount of nicotine extracted from chewed gum: 1.55 (0.12)mg.
There were no statistically significant differences between the two treatments for any pharmacokinetic measure.
Authors conclude: the 2mg sublingual tablet had similar pharmacokinetic properties (Cmax, tmax, AUC) to the 2mg gum when used according to the same hourly dosing schedule.

Safety Outcomes

5 (gum) and 6 (tablet) subjects reported adverse events, including hiccups, throat irritation, abdominal discomfort, cough, headache, nausea, restlessness and tachycardia.

Study quality comments

2 (tablet) and 3 (gum) subjects were excluded due to high baseline plasma nicotine levels: 22 and 21 subjects were analysed, respectively.
+

Molander & Lunell . Pharmacokinetic investigation of a nicotine sublingual tablet. European Journal of Clinical Pharmacology 56, 813-819. 2000.

Design

Three way, crossover randomised trial

Participants

n= 21 healthy smokers (10 men, age 24-45, 11 women age 22-48).

Interventions / comparators

Subjects fasted from midnight to treatment and no food or drink was permitted until 1 hour after treatment administration. There was 12h abstinence from smoking before the study and 24h washout period between treatments. Subjects received 3 treatments in randomised order:

- 1 x 2 mg sublingual tablet, versus:
- 2 x 2mg sublingual tablet, versus:
- 3 x 2mg mg sublingual tablet.

Saliva was swallowed once every minute. Venous blood samples were taken at baseline and at 10,20, 30, 45, 60, 90 min and 2, 3, 4, 5, 6, 7, and 8h after drug administration.

Smoking behaviour / co-interventions

Existing smoking behaviour: 20 cigarettes per day or more, representing 1mg nicotine / day

Pharmacokinetic outcomes

PK parameter	Treatment		
	1 tablet	**2 tablets**	**3 tablets**
Cmax, ng/ml	3.8 (1.0)	6.8 (2.1)	9.0 (3.3)
Cmax normalised for dose ng/ml	-	3.4 (1.0)	3.0 (1.1)
Ratio for normalised Cmax (95% CI)	Ref	0.88 (0.78-1.00)	0.76 (0.67-0.85)
AUC∞, ng/ml	17.0 (5.0)	27.6 (7.6)	36.5 (13.1)
Relative bioavailability (ratio AUC∞)	Ref	0.82 (0.73-0.95)	1.71 (0.63-0.82)

Authors conclude: the ratio of the dose-normalised AUC∞ using the one-tablet (2mg) dose as reference was significantly lower than expected (deviates from linearity) for the two-tablet dose (4mg) and three-tablet dose (6mg), the most plausible explanation being that a larger fraction of higher doses is swallowed, and subject to first pass elimination in the liver.

Safety Outcomes

Frequency of adverse events:

- 1 tablet: 10
- 2 tablets: 19
- 3 tablets: 27

The most common adverse events were hiccups (15), heartburn (14) and nausea (11).
Three cases at the highest dose (3 tablets) were graded as severe (hiccups, heartburn, nausea).

Study quality comments

4 subjects were excluded due to high baseline plasma nicotine levels (>4ng/l).

Andy: the ratio value 0.82 doesn't make sense to me if it is a ratio of the values in the row above.

+

Molander & Lunell . Pharmacokinetic investigation of a nicotine sublingual tablet. European Journal of Clinical Pharmacology 56, 813-819. 2000.

Design

Open label, three way randomised crossover study

Participants

19 healthy smokers (10 men, 9 women) age 24-47 yr

Interventions / comparators

Subjects were given 1 x 2mg sublingual tablet every hour 9 hours (10 administrations). The three comparisons were:

- Place the tablet sublingually and let it disintegrate, while swallowing saliva once each minute
- Chew and immediately swallow the tablet
- Chew the tablet but delay swallowing for as long as possible.

Venous blood was sampled at baseline and at 1, 2, 3, 4, 5, 6, 7, 8 and 9h and every 10 min between 9h and 10h post administration.

Smoking behaviour / co-interventions

Existing smoking habit: > 10 cigarettes per day

Pharmacokinetic outcomes

PK results (mean [SD] unless otherwise stated)

	Correct use	Chew & immediate swallow	Chew & delayed swallow
Cmax ng/ml	12.1 [2.3]	10.3 [3.3]	12.1 [2.9
Median Tmax min (range)	20 (10-60)	20 (10-60)	20 (10-60)
AUC9-10 (h.ng.ml)	11.6 [2.4]	9.6 [3.1]	11.2 [2.7]

In the chewing and delayed swallow, the median time to swallowing was 20 min (range 1-20min).

PK parameter	**Treatment**		
	Recommended use	**Chew & immediate swallow**	**Chew & delayed swallow**
Mean ratio AUC9-10h (95% CI)	Ref	0.80 (0.74-0.88)	0.96 (0.89-1.07)
Mean ratio Cmax (95% CI)	Ref	0.82 (0.76-0.90)	0.99 (0.93-1.10)
Mean ratio tmax (95% CI)	Ref	0.86 (0.62-1.19)	0.77 (0.55-1.07)

The lower bioavailability in the chew & immediate swallow treatment is interpreted ay the authors as due to a larger fraction of the dose being swallowed than in the other two treatments.

Safety Outcomes

Chewing and immediately swallowing the tablets produced slightly more adverse events (10) than either recommended use (4) or chewing with delayed swallow (3). The most common adverse events were hiccups and heartburn.

Study quality comments

Non blinded study.

+

Molander & Lunell . Pharmacokinetic investigation of a nicotine sublingual tablet. European Journal of Clinical Pharmacology 56, 813-819. 2000.

Design

Open label, randomised, 4 way crossover study

Participants

20 healthy smokers (>10 cigarettes / day), 11 males age 22-48, 9 females, age 23-47 yr.

Interventions / comparators

2 x 2mg nicotine sublingual tablets were given as a single 4mg dose in each treatment arm, with a wash out period between treatments of 48hr. Treatment arms were:

- Control: no pH modification
- Acidic mouth: 10ml orange juice given every 30s for 2 min prior and 30 min post nicotine tablet administration.
- Alkaline mouth: antacid lozenges (containing Ca and Mg carbonate - 'Rennie') sucked for 2 min prior and 30 min post nicotine tablet administration
- Alkaline stomach: 150mg dose of ranitidine 2h before treatment and 10ml of antacid mixture (Novaluzid) before, and at 2, 4 and 6h after administration.

Venous blood was sampled at baseline and at 10, 20, 30, 45, 60, 75 and 90 min and 2, 3, 4, 5, 6, 7 and 8h after administration.

Smoking behaviour / co-interventions

Existing cigarette habit: >10 / day.

Pharmacokinetic outcomes

Mean oral pH:

- Control: 6.6 (SD 0.6)
- Acidic mouth: 5.9 (SD1.0)
- Alkaline mouth: 7.2 (SD0.6)

PK results: mean [SD] unless otherwise stated

	Control	Acidic mouth	Alkaline mouth	Alkaline stomach
Cmax ng/ml	5.6 [1.9]	4.9 [1.8]	6.1 [2.1]	6.2 [2.2]
Median Tmax min (range)	75 (30-180)	90 (30-240)	60 (30-120)	75 (30-120)
AUC0-∞ (h.ng.ml)	26.5 [9.4]	25.5 [10.0]	26.7 [10.8]	26.3 [10.0]

The authors conclude that the strategies intended to alter oral or gastric pH did not have any effect on the bioavailability of nicotine.

Safety Outcomes

23 adverse events were reported by 17 subjects, mostly mild/moderate and all resolving within 30min.

Study quality comments

Non blinded study.

+

Molander, Lunell, Andersson & Kuylenstierna . Dose released and absolute bioavailability of nicotine from a nicotine vapor inhaler. Clinical Pharmacology and Therapeutics 59, 394-400. 1996.

Design

Open label, randomised, three-way crossover study

Participants

14 healthy smokers (8 women, 6 men), age range 23-48

Interventions / comparators

Smokers were required to abstain from smoking for 12 hours prior to the study commencing and for the whole study period. There were three interventions:

- IV administration of nicotine solution: total dose 2mg, given at 0.1mg/min for 20min
- Two vapour inhaler treatments, where the inhaler was used for 20 minutes every hour for 11 hours (12 administrations)
    - Pulmonary mode: one deep inhalation for 5s with inhalations per minute, for a total of 20 minutes (80 inhalations) per hour.
    - Buccal mode: 'pipe smoking method', one suck each second for 10s with mouth closed & nasal breathing. Vapour is not inhaled. After a 10s break the sucking is repeated. This continues for 20min per hour

Venous blood was sampled for plasma nicotine measurement as follows:

- Vapour treatments: before the first inhaler dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11 hours after the first dose and at 10, 20, 30, 40, 50 and 60 minutes after the start of the last dose
- IV treatment: before administration and at 5, 10, 20, 30, 45, 60 and 90 minutes and at 2, 3, 4, 6 and 8 hours from infusion start.

Smoking behaviour / co-interventions

Baseline smoking habit: >10 cigarettes / day.

Pharmacokinetic outcomes

PK results for the last dosing interval (11-12h): mean [SD]

	Buccal mode	Pulmonary mode
Cmax ng/ml	32.0 [8.7]	34.2
Tmax h	0.33	0.50
AUC11-12(h.ng.ml)	29.5	30.9

Safety Outcomes

Adverse events were more common after pulmonary, than buccal inhalation (15 versus 7), including hiccups (6) coughs (5) and also headache, nausea, dizziness, hoarseness and feeling a lump in the throat.

Study quality comments

Patients could use over the counter medicines freely. Prescription medications were not permitted, except for contraceptives.+

Fagerstrom, Hughes, Callas, Fagerstrom, Hughes & Callas . Long-term effects of the Eclipse cigarette substitute and the nicotine inhaler in smokers not interested in quitting. Nicotine & Tobacco Research 4 Suppl 2, S141-S145. 2002.

Design

Prospective, non randomised, comparative study.

Participants

Participants were drawn from a previous crossover study (n=50) in smoking harm reduction. Of these, 39 agreed to continue to this subsequent study of smoking harm reduction. Eligibility: age 20-65yr, good health, smoking 5 cigarettes / day or more.

Interventions / comparators

After a two-week washout period from the preceding study, subjects self selected one of three strategies to be used for 8 weeks:

- Eclipse cigarette (tobacco-containing, reduced harm smoking substitute; outside of guideline scope) with concurrent smoking (n=10)
- Nicotine inhaler (10mg nicotine per whole inhaler) with concurrent smoking (n=15)
- Smoking alone (n=13)

Blood samples were taken for plasma nicotine measurement at 2 weeks and at 8 weeks

Smoking behaviour / co-interventions

Existing smoking habit was 5 cigarettes per day. In the Eclipse and nicotine inhaler groups, subjects were instructed to smoke as few cigarettes as possible to satisfy craving, while use of the Eclipse / inhaler was encouraged. In the smoking group, participants smoked *ad libitum*.

Pharmacokinetic outcomes

	Cigarette group (n=13)	**Nicotine inhaler & cigarette group (n=15)**
Baseline no. cigarettes / day	21.3	20.4
Average no. cigarettes / day, study period	23.3	6.6
Average no. of episodes of inhaler use	NA	7.9*
Baseline plasma nicotine (ng/ml)	18.5**	15**
Average plasma nicotine (ng/ml)	21.7	11.4

* 7.9 episodes is the mean of 7.5 episodes at 2 weeks follow up and 8.3 episodes at 8 weeks follow up.
**Baseline values from preceding study were used. Values shown inferred from figure in published paper.

Safety Outcomes

No data presented.

Study quality comments

Of 50 subjects in the preceding study, eleven refused to enter this subsequent study.
The authors analysed 15 demographic and baseline variables for distribution across the three self selected groups and found no statistically significant trend in distribution.
No baseline plasma nicotine measurement was made in this subsequent study, so the original baseline values from the preceding study were used.
Plasma nicotine values were not available for 2 subjects in the inhaler group.
The authors do not quantify the dose of nicotine delivered by an 'episode' of inhaler use, or by smoking a cigarette.
=

Gourlay, Benowitz, Forbes, McNeil, Gourlay, Benowitz, Forbes & McNeil . Determinants of plasma concentrations of nicotine and cotinine during cigarette smoking and transdermal nicotine treatment. European Journal of Clinical Pharmacology 51[5], 407-414. 1997.

Design

Retrospective analyses of blood samples taken from prospective case series.

Participants

n=466 and n=12 healthy smoking subjects, age 18-70 yr and not using other nicotine products. Exclusions – medicines that may affect nicotine metabolism, co-morbidity, pregnancy, potential pregnancy, lactation.

Interventions / comparators

1. Smoking cessation study

Prior to the study, subjects (n=466) smoked *ad libitum*. Subjects started a 12 week course of nicotine patches (beginning with 21mg per 24 hours for 28 days) in decreasing dose (no further details presented). Venous blood was taken at baseline, at follow up (4-10 days from baseline) and over a six month period.

2. Pharmacokinetic study

Subjects wore 1 15mg /16 hr nicotine patch for 16 hr on 5 consecutive days. On the 5th day venous blood was sampled every 4 hours for 12 hours.

Smoking behaviour / co-interventions

Existing smoking habit: 15 cigarettes / day or more for at least 3 years. In both studies subjects were asked to abstain from smoking.

Pharmacokinetic outcomes

Smoking cessation study

Plasma concentration of nicotine [ng/ml)	Baseline smoking	Transdermal nicotine and not smoking
Mean	10.6 [SD 6.9]	9.3 [SD 5]
Median	9.4	8.6
Range	1.6-39	2-28

PK study

Plasma concentration of nicotine	Baseline smoking	Transdermal nicotine and not smoking
Mean	17.0 [7.5]	9.2 [3.6]
Median	13.7	7.6
Range	6.7-30	6-16

Safety Outcomes

No data presented.

Study quality comments

Cessation study: subjects with undetectable plasma nicotine or plasma nicotine below 20mg/ml were assumed to have violated the protocol and were excluded from analyses.

Study presents mean values for plasma nicotine and not changes over time.

+

Gourlay, Benowitz, Gourlay & Benowitz . Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clinical Pharmacology & Therapeutics 62[4], 453-463. 1997.

Design

Prospective volunteer experimental study

Participants

(n=12) healthy male smokers with mean age (SD) 38 (10) yr, Fagerstrom tolerance score 7 (SD 2).

Interventions / comparators

The following cannulas were inserted:

- Radial artery, non dominant arm (for arterial blood sampling)
- Antecubital vein, contralateral arm (for venous blood sampling)
- Antecubital vein, nondominant arm (for IV nicotine administration).

Nicotine doses:

- n=6 received 0.5mg nicotine nasal spray at 60 minutes from baseline
- n=6 began smoking cigarettes at 1 puff/min for 10 min i.e 1.5-2 cigarettes
- 70 minutes later all subjects received IV nicotine at 2ug/kg/min for 30 minutes.

Arterial & venous blood was sampled at:

- 0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45 and 60 minutes after nicotine dosing (nasal spray & smoking).
- 0, 10, 20, 30, 32, 35, 40, 45, 60, 90, 120, 150, 180, 240, 300 & 360 minutes after nicotine dosing (IV nicotine)

Smoking behaviour / co-interventions

Existing smoking habit: 23 (SD 8) cigarettes / day. Abstinence from smoking and fasting during the night preceding the study was supervised.

Pharmacokinetic outcomes

Average dose of nicotine administered (SD):

- IV infusion: 5.1 (0.6) mg
- nasal spray 0.8 (0.1) mg i.e. absorbed dose
- smoking 2.4 (0.7) mg

Cmax and Tmax in arterial and venous blood for 3 administration routes for nicotine

Blood sample	PK parameter	Smoking 10min	1mg nasal spray	30min IV infusion at 2 µg/kg/min
Arterial	**Cmax ng/ml**	39.8	10.4	49.9
	Tmax min	8.2	4.7	29
Venous	**Cmax ng/ml**	18.6	5.4	29.5
	Tmax min	11.9	24.8	30

Safety Outcomes

No data presented.

Study quality comments

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Bullen, McRobbie, Thornley, Glover, Lin & Laugesen . Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tobacco Control 19, 98-103. 2010.

Design

Single blind randomised repeated measures cross-over trial of the Ruyan V8 ENDD. The primary outcome was change in desire to smoke. Secondary outcomes included withdrawal symptoms, acceptability and adverse events.

Participants

n= 40 (nicotine concentrations obtained for 9 of these)
Mean age 47.6 (SD 12.4) years.
Mean level of nicotine dependence (FTND) = 5.4
Participants smoked an average of 20.2 cigarettes (SD 7.3) per day.

Interventions / comparators

Four arms:

- Electronic cigarette 16 mg
- Electronic cigarette 0mg nicotine (placebo)
- Nicorette inhalator 10 mg per cartridge
- Usual cigarette

All subjects abstained from smoking overnight (verified by CO ≤ 15 ppm in expired breath).
Participants randomised to using the ENDD were asked to puff the device as they would their usual cigarette for 5 mins. They remained in the study centre for 1 hour The device was then used for a further 8 hours.
When participants used the inhaler they were instructed to puff on the inhaler over 20 minutes in the first hour and then use the inhaler freely over the day (up to a maximum of 6 x 10mg cartridges)
When randomised to smoke their usual cigarettes, subjects smoked within the first 5 minutes of the first hour and then freely as they wished.
The subset of patients who had nicotine concentrations measured had bloods taken at 5, 10,15, 30 and 60 minutes after initial dosing.
There was a 3 day washout period between each study day.
Withdrawal was assessed using the Minnesota Nicotine Withdrawal Scale with additional items relating to craving. Participants also rated their satisfaction with the products compared to their usual cigarettes.

Smoking behaviour / co-interventions

Subjects were smokers (smoking at least 10 factory-made cigarettes per day for at least the last year).
All smoked their first cigarette of the day within 30 minutes of waking.

Pharmacokinetic outcomes

Nicotine concentration only measured in a proportion of the study group.

Product	Mean tmax (min) (95% CI)	Mean Cmax (ng/ml) (95% CI)
Usual cigarette (n = 9)	14.3 (8.8 to 19.9)	13.4 (6.5 to 20.3)
16 mg ENDD (n = 8)	19.6 (4.9 to 34.2)	1.3 (0.0 to 2.6)
Nicorette inhalator (n =10)	32.0 (18.7 to 45.3)	2.1 (1.0 to 3.1)

Authors suggest the ENDD is comparable to a NRT product in terms of nicotine delivery. Use of the 16 mg ENDD resulted in modest increases in blood nicotine levels. Also the ENDDs were not as consistent for puffing and nicotine delivery as the medicinal Nicorette inhalator. One third of participants showed no increase in blood nicotine when using the ENDD. Some participants reported the device sometimes failed to produce mist when puffed.

Safety Outcomes

Table of results as presented in original publication:

Adverse events reported after 9 hours of product use

Adverse event	ENDD 0 mg		ENDD 16 mg		Nicorette inhalator	
	n/N*	(%)	n/N	(%)	n/N	(%)
Mouth/ throat irritation[y]	14/64	22	22/58	38	36/41	88
Aching jaws	4/35	11	3/37	8	2/37	5
Nausea	6/33	18	9/31	29	6/33	18
Flatulence/ belching/ hiccups/heartburn	6/111	5	6/113	5	11/147	23
Vertigo/ heartburn	9/69	9	14/66	21	12/66	18
Headache	7/32	22	6/34	18	6/33	18
Sweatiness/ clammy skin	3/75	4	3/77	4	2/76	3
Palpitations	0/38	0	2/38	5	0/39	0

ENDD, electronic nicotine delivery device.
*n¼number of events, N¼numbers of participants in each group. In some cases, groups were pooled because of similarity of symptoms, hence the large numbers.
yENDD 0 mg versus inhalator p<0.001; ENDD 16 mg versus inhalator p<0.001.

When using the 16 mg ENDD participants smoked on average 2.8 usual cigarettes over the day, compared with 4.5 cigarettes when using the 0 mg ENDD and 3.4 cigarettes when using the inhalator.

Study quality comments

Subjects were allocated to one of the four treatment arms using a random sequence of four codes (each corresponding to one product) prepared in advance by the study statistician.
Participants and investigators were blinded only to assignment to the ENDD condition (16 or 0 mg).
Statistical power calculations relate to detecting the differences in desire to smoke.
Report of adverse events made at the end of the day. Events were self-reported. Later effects or chronic effects not covered by the study design.
PK parameters (Cmax, tmax) calculated based on plasma concentration-time data by model-independent methods using SAS version 9.2.
Crossover design to minimise variability, bias and confounding.
Study limited to smokers not intending to quit.
No period of familiarisation or test of functioning with ENDDs (this was the first exposure for both subjects and investigators).
+

Eissenberg . Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. Tobacco Control 19, 87-88. 2010.

Design

4 Latin square ordered conditions (different products) each separated by 48 hours.
Each experiment is repeated 60 minutes later (hence results given for bouts 1 and 2).

Participants

n=16
All subjects were smokers (mean 18.5 cigarettes smoked/day)
Age: mean 29.8 years (SD 10.7)
Gender: 5 female, 11 male.
Ethnicity: 8 non-white.

Interventions / comparators

4 conditions:

- Own brand cigarette
- Sham smoking (puffing unlit cigarette)
- 'NPRO' (NJOY) electronic cigarette with 16 mg nicotine cartridge
- 'Hydro' electronic cigarette with 16 mg nicotine cartridge

Participants were instructed to puff normally and then puffed ad libitum 10 times (30-s interpuff interval) from the product of the day (bout 1). At 5, 15, 30 and 45 min after the first puff, subjective measures were completed and blood sampled. At time +60 min assessments were repeated, product was administered (bout 2), and identical subsequent assessments completed.

As well as nicotine plasma concentrations, heart rate was continually monitored. Craving was also assessed using a visual analogue scale (0 to 100 scale).

Smoking behaviour / co-interventions

Study was preceded by > 12 hour tobacco/nicotine abstinence (verified by expired air CO <10ppm)

Pharmacokinetic outcomes

Plasma nicotine concentrations measured :

Bout 1

Condition	Nicotine conc at 5 mins ng/ml (SEM)	Nicotine conc at 15 mins ng/ml (SEM)	Nicotine conc at 30 mins ng/ml (SEM)
Own brand cigarette	16.8 (3.4)	11.2 (1.6)	8.7 (1.2)
Hydro e cig	2.5 (0.2)	2.3 (0.2)	2.2 (0.1)
NPRO e cig	3.5 (0.5)	2.8 (0.3)	2.6 (0.2)

Bout 2

Condition	Nicotine conc at 5 mins ng/ml (SEM)	Nicotine conc at 15 mins ng/ml (SEM)	Nicotine conc at 30 mins ng/ml (SEM)
Own brand cigarette	20.0 (3.3)	15.4 (2.0)	12.9 (1.7)
Hydro e cig	2.5 (0.3)	2.3 (0.2)	2.3 (0.1)
NPRO e cig	3.0 (0.3)	3.1 (0.4)	2.9 (0.3)

All p values less than 0.05.
Nicotine concentrations did not exceed 2.0 ng/ml in any occasion (this is the assay's limit of quantification)
The authors conclude that compared to cigarette smoking, the e-cig delivered little to no nicotine.

Safety Outcomes

Continuous heart rate monitoring was performed. Compared to initial measurement, a significant increase in heart rate was only observed for the own brand cigarettes (at 5 and 15 minutes after bouts 1 and 2). NPRO decreased craving significantly 5 minutes after bout 2 only ($p<0.05$)

Study quality comments

Clinical laboratory study.

+

Kotlyar, Mendoza-Baumgart & Li . Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge . Tobacco Control 16[2], 138-142. 2007.

Design

Randomised crossover study

Participants

n=10

All subjects were male. Average age 30.9 years (range 20 to 49).

Interventions / comparators

The following nicotine containing products were evaluated:

- Ariva (smokeless tobacco lozenge)
- Copenhagen (moist snuff)
- Stonewall (smokeless tobacco)
- Revel (smokeless tobacco)
- Commit (4 mg medicinal nicotine lozenge)

Of these, only Commit is within the scope of this review.

Nicotine concentrations were obtained during product use and for 1 hour after use. Subjective measurements of withdrawal, craving and drug effects/ liking were also made.

Subjects placed the assigned product between their cheek and gum for 30 min after which the product was removed and subjects rinsed their mouth with water. Blood was drawn immediately before and at 1, 5, 10, 15, 20, 25, 30, 45, 60, 75 and 90 min after product placement.

Smoking behaviour / co-interventions

All had used Copenhagen smokeless tobacco daily for at least 1 year.

12 hour pre-session abstinence was required. A further 2 hr period of abstinence prior to investigations.

Pharmacokinetic outcomes

Nicotine area under the concentration–time curve and maximal nicotine concentration for Commit nicotine lozenge (95% CI):

AUC0–90 (ng x min/ml): 467 (361 to 604)
Cmax (ng/ml): 7.3 (5.5 to 9.8)

(AUC0–90, area under the concentration-time curve for time 0 to 90 minutes; Cmax, maximal nicotine concentration.)

The paper does not provide mean nicotine concentrations at the different sampling times.

Tmax for Commit not provided, although the paper states that for those three products for which nicotine concentration increased significantly above baseline (Commit lozenges and two other smokeless tobacco products), the Cmax was observed at an average of 27 to 33 minutes after starting product use.

Safety Outcomes

Subjects were asked if they experienced any bad effects, felt alert, relaxed, light-headed/dizzy, drowsy, energetic, jittery or had any tremor. There were no specific concerns documented for Commit but it was stated that the results for Copenhagen ST showed a higher score regarding experiencing a fast/pounding heart.

Study quality comments

One subject completed only one laboratory session and was excluded from the analysis.

12 hour abstinence was required, paper does not mention whether this was verified.

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Vansickel, Cobb, Weaver, Eissenberg, Vansickel, Cobb, Weaver & Eissenberg . A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiology, Biomarkers & Prevention 19[8], 1945-1953. 2010.

Design

4 Latin square ordered conditions (different products) each separated by 48 hours.
Each experiment is repeated 60 minutes later.

Participants

n=32
Age: mean 33.6 years (SD 12)
Gender: 13 female, 19 male.
Ethnicity: 14 non-white.

Interventions / comparators

4 conditions:

- Own brand cigarette
- Sham smoking (puffing unlit cigarette)
- 'NPRO' (NJOY) electronic cigarette with 18 mg nicotine cartridge
- 'Hydro' electronic cigarette with 16 mg nicotine cartridge

Participants were instructed to puff normally and then puffed ad libitum 10 times (30-s interpuff interval) from the product of the day (bout 1). At 5, 15, 30 and 45 min after the first puff, subjective measures were completed and blood sampled. Expired air CO was recorded at 15, 30 and 45 minutes. At time +60 min assessments were repeated, product was administered (bout 2), and identical subsequent assessments completed.
The authors claim that this product administration equates to ad libitum cigarette smoking.

As well as nicotine plasma concentrations, heart rate was continually monitored. Subjective effect questionnaires were completed: Tiffany Drobes Questionnaire of Smoking Urges Brief, and Visual Analog Scales designed to assess nicotine abstinence symptom suppression and nicotine/ tobacco effects.

Smoking behaviour / co-interventions

All subjects were smokers (mean 22 cigarettes smoked/day (SD 8.8)). Verified by screening CO of at least 15 ppm and urine cotinine of at least 4 on a 7-point scale.

Study was preceded by > 12 hour tobacco/nicotine abstinence (verified by expired air CO ≤10ppm)

Pharmacokinetic outcomes

Raw data not provided. For own brand cigarette smoking, mean plasma nicotine increased from a pre-administration level of 2.1 ng/ml to a peak of 18.8 ng/ml five minutes after the first administration. No significant changes in plasma nicotine were observed for the e-cigarettes or sham smoking condition.

The authors conclude that compared to cigarette smoking, the e-cig delivered little to no nicotine.

Safety Outcomes

Continuous heart rate monitoring was performed. Compared to initial measurement, a significant increase in heart rate was only observed for the own brand cigarettes (from an average of 65.7 bpm at baseline to a peak of 80.3 bpm five minutes after first administration). No significant changes in heart rate were observed for the e-cigarettes or sham smoking condition.
Authors list ingredients of NJOY e-cigarette as nicotine, propylene glycol, water, ethanol, glycerol, acetylpyrazine, guaiacol, mysomine, cotinine and vanillin.
Authors list ingredients of HydroEC as nicotine, propylene glycol, water and tobacco flavouring.
Authors quote Federal Trade Commision finding that average cigarette yields 1.06 mg nicotine, 14.7 mg tar,

14.6 mg CO.

Study quality comments

Clinical laboratory study.
Inclusion/exclusion criteria described, reasons for exclusions and withdrawals provided.
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Johnson & Johnson (2011b) Single-dose Nicotine Pharmacokinetics With a New Oral Nicotine Replacement Product. Available at:

http://clinicaltrials.gov/ct2/show/NCT01084603

Design

Pharmacokinetics Study. Randomised, open label study in healthy smokers.

Participants

n= 45
21 female, 24 male. All aged between 18 and 65 years (mean not specified)

Interventions / comparators

This study compares a new oral Nicotine Replacement Therapy (NRT) product with NiQuitin™ lozenge 4 mg and Nicorette®gum 4 mg, after 12 hours of nicotine abstinence, with respect to nicotine pharmacokinetics, during 12 hours after start of administration. Single doses of each treatment are given once in the morning during five separate treatment visits scheduled in a crossover setting with randomized treatment sequences. The study will include 45 healthy smokers between 18-50 years, who have been smoking at least 15 cigarettes daily during at least one year preceding inclusion. Subjects and study personnel will be aware of which treatment is administered at a given visit.

5 Arms:
Oral Nicotine 1 (Experimental): Oral administration of 1mg of nicotine (new nicotine product).
Oral Nicotine 2 (Experimental): Two oral administrations of 1mg of nicotine (new nicotine product).
Oral Nicotine 4 (Experimental): Four oral administrations of 1mg of nicotine (new nicotine product).
Niquitin TM Nicotine Lozenge (Active Comparator) : one 4mg nicotine lozenge.
Nicorette Gum (Active Comparator): one 4 mg gum chewed for 30 minutes.

Participant flow:

1. Baseline (2 subjects withdrew from study at this stage)
2. NiQuitin TM Lozenge (1 subject withdrew at this stage)
3. Washout Period 1
4. Nicorette Gum (1 subject withdrew at this stage)
5. Washout period 2
6. Oral Nicotine 1 ((1 subject withdrew at this stage)
7. Washout Period 3
8. Oral Nicotine 2
9. Washout Period 4 (1 subject withdrew at this stage due to adverse event)
10. Oral Nicotine 4

Smoking behaviour / co-interventions

Subjects were healthy smokers (smoking at least 15 cigarettes daily during at least 1 year), BMI between 17.5 and 30.0 kg/m2.

Pharmacokinetic outcomes

	Oral Nicotine 1	**Oral Nicotine 2**	**Oral Nicotine 4**	**NiQuitinTM Lozenge 4 mg**	**Nicorette® Gum 4 mg**
Number of Participants Analyzed	40	40	39	42	41

Maximum Plasma Concentration Cmax (ng/ml) mean ± SD	3.04 ± 1.47	4.94 ± 2.06	8.63 ± 2.96	6.44 ± 2.06	7.36 ± 2.66
Bioavailability [units: h*ng/ml] mean ± SD **AUC to last measurable concentration** **AUC to infinity**	5.85 ± 3.7 7.54 ± 4.10	11.50 ± 3.98 13.30 ± 4.20	21.96 ± 9.00 24.10 ± 9.35	22.0 ± 11.05 24.30 ± 11.91	19.69 ± 7.95 21.62 ± 8.43
Nicotine Plasma Concentration [units: (h*ng/ml)] mean ± SD (AUC at 10 minutes)	0.43 ± 0.23	0.56 ± 0.33	0.87 ± 0.42	0.29 ± 0.20	0.29 ± 0.20
Time of Maximum Concentration [units: (hours)] Median (Full Range)	0.17 (0.07 to 1.50)	0.21 (0.07 to 1.00)	0.17 (0.07 to 1.50)	0.75 (0.17 to 2.02)	0.50 (0.33 to 1.00)
Terminal Elimination Rate Constant [units: (1/hr)] mean ± SD	0.29 ± 0.13	0.29 ± 0.10	0.30 ± 0.10	0.26 ± 0.07	0.31 ± 0.10
Released Nicotine [units: (ng/ml)] mean ± SD (amount of nicotine released from Nicorette gum during 30 minutes chewing)					2.70 ± 0.27

Safety Outcomes

Serious Adverse Events

	Oral Nicotine 1	Oral Nicotine 2	Oral Nicotine 4	NiQuitinTM Lozenge 4 mg	Nicorette® Gum 4 mg
Total, serious adverse events # participants affected / at risk	0/41 (0.00%)	1/42 (2.38%)	0/43 (0.00%)	0/43 (0.00%)	0/42 (0.00%)
Gastrointestinal disorders Appendicitis # participants affected / at risk	0/41 (0.00%)	1/42 (2.38%)	0/43 (0.00%)	0/43 (0.00%)	0/42 (0.00%)

Other Adverse Events

	Oral Nicotine 1	Oral Nicotine 2	Oral Nicotine 4	NiQuitinTM	Nicorette®

				Lozenge 4 mg	Gum 4 mg
Total, other (not including serious) adverse events # participants affected / at risk	11/41	11/42	24/43	7/43	9/42
Gastrointestinal disorders Nausea # participants affected / at risk	2/41 (4.88%)	3/42 (7.14%)	4/43 (9.30%)	2/43 (4.65%)	2/42 (4.76%)
Hiccups # participants affected / at risk	2/41 (4.88%)	1/42 (2.38%)	10/43 (23.26%)	0/43 (0.00%)	3/42 (7.14%)
Throat Irritation # participants affected / at risk	2/41 (4.88%)	4/42 (9.52%)	6/43 (13.95%)	0/43 (0.00%)	2/42 (4.76%)
Nervous system disorders Dizziness # participants affected / at risk	0/41 (0.00%)	1/42 (2.38%)	3/43 (6.98%)	2/43 (4.65%)	1/42 (2.38%)
Headache # participants affected / at risk	7/41 (17.07%)	1/42 (2.38%)	6/43 (13.95%)	5/43 (11.63%)	4/42 (9.52%)
Respiratory, thoracic and mediastinal disorders Nasopharyngitis # participants affected / at risk	3/41 (7.32%)	5/42 (11.90%)	2/43 (4.65%)	1/43 (2.33%)	0/42 (0.00%)

Study quality comments

Randomised, open label, pharmacokinetics study with crossover assignment.
Six subjects withdrew from the study; it is not clear if they were included in the analyses.
Details about the new oral NRT product not provided.
+

Lewis, Subramanian, Pandey & Udupa . Pharmacokinetic evaluation of a developed nicotine transdermal system. Indian Journal of Pharmaceutical Sciences 69[2], 309-312. 2007.

Design

Prospective volunteer experimental study

Participants

(n=6) healthy South Indian adult male smokers age 25-40y, weight 50-60kg without any illness, medication, alcohol or drug use.

Interventions / comparators

Application of a novel nicotine patch, area 12cm^2, loaded with 40 mg nicotine, designed to release 27 mg nicotine over 24h (i.e. 95$ug/cm^2/h^2$

Venous blood was sampled at 0, 1, 2, 4, 6, 8, 10, 12, 18 and 24h after patch application

Smoking behaviour / co-interventions

Each subject was required to abstain from smoking for 12h prior to the study and was supervised throughout t maintain abstinence.

Pharmacokinetic outcomes

Trace amounts of plasma were detected at baseline (1.04 ng/ml, SD 0.26ng/ml).

Parameters (SD):

Cmax (ng/ml) 14.5 (3.6)
t1/2 (h) 4.78 (1.54)
tmax (h) 8.00 (1.40)
Kel (h-1) 0.145 (0.10)
AUC0-24 181.0 (54.0)
AUC0-∞ 202.3 (67.0)

Safety Outcomes

There were few adverse events; one subject had mild erythema at the application site, which lasted one hour.

Study quality comments

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Perkins, Stiller & Jennings . Acute tolerance to the cardiovascular effects of nicotine. Drug and Alcohol Dependence 29, 77-85. 1991.

Design

Small experimental study

Participants

(n=3) healthy male smokers drawn from a larger group (n=12) with mean age 19.2yr (SE 0.4yr)

Interventions / comparators

Subjects were given a nicotine dose via a nasal spray in 5 equal fractions (one every 60 seconds). Subjects received the following doses in total on four different days:

- zero (placebo)
- 0.5mg
- 1.0mg
- 2.0mg

Doses were given after overnight abstinence from smoking (verified by CO measurement), food and caffeine.

Blood was taken from the 3 subjects at baseline, 1st, 3rd & 5th dose fraction and at 1, 3, 5, 10 and 15 min after the final dose fraction.

Smoking behaviour / co-interventions

Existing smoking habit was 15 cigarettes per day or more for the last year.

Pharmacokinetic outcomes

PK results read from graphic in paper:

	0.5mg dose	1.0mg dose	2.0mg dose
Cmax ng/ml	10	15	24
Tmax min	6	5	6

NB from baseline (time zero) the dose was given in five equal fractions at minutes 1, 2, 3, 4, 5.

Safety Outcomes

No data presented.

Study quality comments

The paper does not present plasma nicotine values following administration of the placebo nasal spray.
+

Nemeth-Coslett, Henningfield, O'Keeffe & Griffiths . Nicotine gum: Dose-related effects on cigarette smoking and subjective ratings. Psychopharmacology 92[4], 424-430. 1987.

Design

Case series

Participants

(n=8) healthy smokers, 5 women, 3 men, mean age 27.5yr

Interventions / comparators

All subjects attended a total of 16 sessions, in which they were exposed to four different doses of nicotine gum, four times each. Sessions took place 1-3 days apart. Doses were:

- Zero (placebo)
- 2mg
- 4mg
- 8mg

Subjects were requested to smoke a cigarette 90 min prior to the study, and following administration of the gum, subjects could smoke *ad libitum*.

Gum was chewed for 20 minutes at a rate of 1 chew every 3 seconds, guided by an audible tone. Blood was sampled (once only per dose) following the 20 minute chewing period.

Chewed gum was retained for measurement of residual nicotine.

Smoking behaviour / co-interventions

Existing smoking habit: mean 30.6 cigarettes / day for mean 14.1 years

Pharmacokinetic outcomes

Residual nicotine in chewed gum:
2 mg dose: 51% (1.02 mg) (range 37-62%),
4 mg dose: 59% (2.39 mg) (range 45-69%) and
8mg dose: 65% (5.2mg) (range 60-71%).

Blood nicotine concentrations (* value read from graphic in published paper)

	Before gum chewing	After gum chewing (20 minutes)*
Placebo gum:	29.9 ± l.7ng/ml	23
2 mg gum:	30.08 ± l.4ng/ml	27.5
4 mg gum:	31.3± 1.1 ng/ml	31
8 mg gum:	29.08 ± 1.8 ng/ml	34

Safety Outcomes

No data presented.

Study quality comments

Subjects were blinded to the dose of gum they received; the placebo gum was deliberately flavoured to be similar to the active dose gums.

+

Lunell, Molander, Andersson, Lunell, Molander & Andersson . Relative bioavailability of nicotine from a nasal spray in infectious rhinitis and after use of a topical decongestant. European Journal of Clinical Pharmacology 48[1], 71-75. 1995.

Design

Randomised, 3-way crossover study

Participants

15 healthy smokers age 20-40yr

Interventions / comparators

Subjects underwent two treatments in succession in randomised sequence:

- Nicotine nasal spray applied while subject has rhinitis
- Nicotine nasal spray plus vasoconstrictor spray while subject has rhinitis

When subjects had recovered from rhinitis they received:

- Nicotine nasal spray

Dose for nicotine nasal spray: Nicorette 10mg/ml delivers 0.5mg nicotine in each spray. One spray was applied to each nostril and then again, 5 minutes later. Total dose = 2mg.
Dose for vasoconstrictor: xylometazoline 1mg/ml delivers 0.14mg xylometazoline in each spray. One spray was applied to each nostril. Total dose = 0.28mg, administered 30min before nicotine spray.
There were no restrictions on over-the-counter medicines. No prescribed drugs were permitted except contraceptives.
Venous blood for plasma nicotine measurement was taken at 0 (immediately before 1st dose) and 15, 30, 45, 60 and 90 min and at 2, 3, 4, 5 and 6 h after 1st dose.

Smoking behaviour / co-interventions

Participants were required to abstain from smoking for 12hr prior to the study.

Pharmacokinetic outcomes

Mean [SD] values

	Normal	Rhinitis	Rhinitis + xylometazoline
Cmax ng/ml	6.03 [3.36]	4.71 [2.27]	4.58 [2.30]
Tmax h	0.25	0.40	0.50
AUC h.ng.ml	17.9 [7.69]	15.9 [5.81]	18.9 [6.67]

AUC0-∞ and Cmax were corrected for baseline nicotine concentration.

Safety Outcomes

The most commonly reported adverse events were sneezing, throat irritation and headache. All events were mild except for one moderate headache in a subject with rhinitis, which could not be distinguished from the disease itself.

Study quality comments

Common cold and rhinitis were carefully defined.
Only the sequence of the two rhinitis treatments was randomised. The treatment given in the disease-free state was performed as soon as possible after the episode of rhinitis.
Drugs were administered meticulously: spray pumps were primed and the spray carefully directed within the nasal cavities. Subjects were required to blow their noses prior to the first spray of vasoconstrictor.
+

Johnson & Johnson (2011a) Multiple-dose Nicotine Pharmacokinetics With a New Oral Nicotine Replacement Product. Available at: http://clinicaltrials.gov/ct2/show/NCT01084707

Design

Pharmacokinetics study. Randomised, open label, crossover assignment.

Participants

n= 40 started trial, 34 completed.
18 female, 22 male.
Healthy smokers, smoking at least 20 cigarettes daily during at least one year preceding inclusion and BMI between 17.5 and 30.0 kg/m2.

Interventions / comparators

5 Arms:
Oral Nicotine 24-SA: Experimental (12 doses of 2mg nicotine once every hour by self administration)
Oral Nicotine 24: Experimental (12 doses of 2mg once every hour by study personnel)
Oral Nicotine 48: Experimental (24 doses of 2mg once every 30 mins by study personnel)
NiQuitin™ Lozenge 4 mg: Active Comparator (12 doses of 4 mg once every hour by study personnel)
Nicorette® Gum 4 mg: Active Comparator (12 doses of 4mg, chewed for 30 minutes, once every hour)

Smoking behaviour / co-interventions

Pharmacokinetic outcomes

	Oral Nicotine 24-SA	**Oral Nicotine 24**	**Oral Nicotine 48**	**NiQuitinTM Lozenge 4 mg**	**Nicorette® Gum 4 mg**
Number of Participants Analyzed [units: participants	39	35	32	35	32
Maximum Plasma Concentration (Cmax) [units: (ng/ml)] Geometric Mean ± Standard Deviation	15.43 ± 6.12	16.49 ± 4.99	30.07 ± 9.77	27.07 ± 10.95	25.96 ± 8.55
Average Concentration [units: (ng/ml)] Geometric Mean ± Standard Deviation	13.33 ± 5.55	14.04 ± 4.50	27.50 ± 9.18	23.70 ± 9.86	22.15 ± 7.49
Time of Maximum Concentration [units: (minutes)] Median (Full Range)	15.0 (5.0 to 42.0)	10.0 (5.0 to 45.0)	10.0 (5.0 to 23.0)	25.0 (13.0 to 55.0)	30.0 (10.0 to 50.0)
Minimum Plasma	11.54 ± 4.71	11.67 ± 4.04	25.32 ± 8.41	22.14 ± 9.71	19.00 ± 7.00

Concentration [units: (ng/ml)] Mean ± Standard Deviation					
Peak-Trough Fluctuation [units: Percent Fluctuation] Mean ± Standard Deviation	35.6 ± 14.2	38.4 ± 14.9	21.7 ± 8.7	29.1 ± 10.7	36.3 ± 12.8
Nicotine Plasma Concentration [units: (h*ng/ml)] Geometric Mean ± Standard Deviation (AUC at 10 minutes)	0.43 ± 0.23	0.56 ± 0.33	0.87 ± 0.42	0.29 ± 0.20	0.29 ± 0.20
	0.17 (0.07 to 1.50)	0.21 (0.07 to 1.00)	0.17 (0.07 to 1.50)	0.75 (0.17 to 2.02)	0.50 (0.33 to 1.00)
Terminal Elimination Rate Constant [units: (1/hr)] Mean ± Standard Deviation	0.29 ± 0.13	0.29 ± 0.10	0.30 ± 0.10	0.26 ± 0.07	0.31 ± 0.10
Released Nicotine [units: (ng/ml)] Mean ± Standard Deviation (amount of nicotine released from Nicorette gum during 30 minutes chewing)					2.70 ± 0.27

Safety Outcomes

Study quality comments

+

Shiffman, Zettlersegal, Kassel, Paty, Benowitz & Obrien . Nicotine Elimination and Tolerance in Nondependent Cigarette Smokers. Psychopharmacology 109[4], 449-456. 1992.

Design

Experiment (comparing PK parameters in regular smokers and "chippers" exposed to a controlled dose of cigarette smoke)

Participants

n= 22. Eleven regular smokers (20 to 40 cigarettes/day) and eleven "chippers" (averaged no more than 5 cigarettes/day and smoking at least 4 days per week). Each group consisted of 7 females and 4 males.
Caucasian subjects (authors note substantial ethnic differences in the prevalence of very light smoking).
All subjects were advised to abstain from smoking overnight (tested by CO breath testing – levels below 15 ppm)

Interventions / comparators

Subjects inhaled 16 puffs of cigarette smoke using a fixed-dose smoking device (delivered 50 cc of smoke in an inhaled total volume of 550 cc). Subjects inhaled over a period of 2 s and held in the puff for 3 s.
Puffs were delivered from four cigarettes (four puffs for each cigarette) and puffs were delivered once every 45 s.
At baseline physiological measures (heart rate, BP, temperature) and blood samples were taken.

Smoking behaviour / co-interventions

Study involved smoking.

Pharmacokinetic outcomes

	Regular Smokers (RS)	"Chippers" (CH)
Area under plasma nicotine concentration curve: Mean (SD)	2123.5 ng/ml x min (619.0)	1912.4 ng/ml x min (913.8)
Nicotine concentration increase from baseline: Mean (SD)	16.4 ng/ml (6.0)	17.2 ng/ml (7.1)
Half-life: Mean (SD)	152.0 min (37.1)	126.4 min (45.8)
Baseline nicotine concentration	1.7 ng/ml	0.4 ng/ml

Authors conclude that chippers eliminate nicotine at the same rate as regular smokers. Therefore they cannot maintain a significant plasma nicotine concentration between cigarettes and their smoking is not motivated by withdrawal avoidance.

Safety Outcomes

Not included

Study quality comments

Small sample size limits statistical power.
Smoking device draws a fixed volume of smoke from a burning cigarette and injected it into a plastic chamber from which the subject inhaled.
Exclusions were explained.
Study groups were matched for characteristics, including age, age at smoking initiation, number of years smoking, and gender. The groups did not differ significantly in height, weight, education or socioeconomic class.
+

Shiffman, Cone, Buchhalter, Henningfield, Rohay, Gitchell, Pinney & Chau . Rapid absorption of nicotine from new nicotine gum formulations. Pharmacology Biochemistry and Behavior 91[3], 380-384. 2009.

Design

Single dose, randomized, crossover study.

Participants

n = 14 (9 male, 5 female) smokers. Average age 29.8 years (SD 10.7)
Subjects smoked on average 11.6 cigarettes/day (SD 6.2) for the past 9.1 years (SD 7.9) and were nicotine dependent (smoked first cigarette within 30 mins of waking).

Interventions / comparators

3 arms:
Nicorette Freshmint NRT gum (contains nicotine polacrilex 4 mg)
NHTG2 (new gum formulation containing nicotine tartrate 4 mg)
NHTG1 (new gum formulation containing nicotine tartrate 4 mg)

Each subject participated in three sessions, with a 24 hr washout period between each session.
Subjects received a single dose of each of the nicotine gums and chewed the gum for 30 minutes. A chew rate of 30 chews/minute was determined by a metronome in an attempt to standardize dosing across products.

Smoking behaviour / co-interventions

Subjects were expected to abstain from smoking/ tobacco products within 12 hrs prior to the study (confirmed by CO sampling). Tobacco use was not permitted during the study.

Pharmacokinetic outcomes

Blood samples were obtained pre-dose (-5 min) and at 2, 4,6,8,10, 15, 30, 45, 60, 90 and 180 minutes timed from the start of gum chewing.
Lower limit of nicotine quantitation in plasma was 0.5 ng/ml.

Mean (± SD) pharmacokinetic parameter estimates. (n = 12)

Measure	NHTG2	NHTG1	Nicorette
AUC 0-10 min ng/ml	25.9 (19.5)	14.3 (12.7)	6.6 (5.0)
AUC 0-30 min ng/ml	206.8 (75.5)	141.1 (80.4)	118.6 (51.3)
AUC 0-180 min ng/ml	1967.8 (709.8)	1467.5 (460.5)	1583.0 (430.6)
Cmax ng/ml	14.9 (4.9)	11.4 (4.0)	12.6 (2.7)
Tmax, min	53.8 (16.3)	51.3 (17.5)	56.3 (14.5)

Safety Outcomes

12 of 14 subjects (85.7%) reported one or more AEs. A total of 39 AEs were reported and all were rated as mild.

Treatment	Number of subjects	Number of (%) subjects with ≥ 1 AE	Number of AEs	Probably treatment related	Possibly treatment related	Unlikely treatment related
NHTG2	14	10 (71.4%)	17	47.1%	35.3%	17.6%
NHTG1	14	9 (64.3%)	10	70.0%	30.0%	0.0%
Nicorette	14	10 (71.4%)	12	75.0%	25.0%	0.0%

Listing of adverse events and frequency by treatment group (N=14)

Adverse event	NHTG2 n	NHTG1 n	Nicorette n	Total n

				(% of the total AEs)
Pharyngitis	5	3	5	13 (33.3%)
Circumoral paresthesia	2	4	4	10 (25.6%)
Headache	3	1	0	4 (10.3%)
Dizziness	0	1	3	4 (10.3%)
Tooth disorder	0	1	0	1 (2.6%)
Vomiting	1	0	0	1 (2.6%)
Lacrimation disorder	1	0	0	1 (2.6%)
Rhinitis	1	0	0	1 (2.6%)
Stomatitis	1	0	0	1 (2.6%)
Eructation	1	0	0	1 (2.6%)
Hiccup	1	0	0	1 (2.6%)
Dyspepsia	1	0	0	1 (2.6%)
Total	17	10	12	39

Study quality comments

Subjects and investigators blinded to the NHTG1 and NHTG2 treatments. Nicorette is a coated gum (the other two are uncoated) so subjects and investigators were potentially unblinded to those conditions.
Session order was randomised (Williams square design).
Adverse effects were subject-reported and tabulated using COSTART system organ class and preferred term, by severity (mild, moderate or severe) and by relationship to study medication (not related, unlikely, possible, probable, or not assessable)
Two exclusions from the pharmacokinetic analysis were explained (one patient had a missed baseline specimen, the other had three missing sequential blood specimens).
+

Sutherland, Russell, Stapleton, Feyerabend & Ferno . Nasal Nicotine Spray - A Rapid Nicotine Delivery System. Psychopharmacology 108[4], 512-518. 1992.

Design

Crossover study

Participants

n = 10. 8 males, 2 females. Mean age 36.7 years. Five were cigarette smokers, two were occasional cigar smokers and three were ex-smokers.

Interventions / comparators

Two interventions:

1. Nasal Nicotine Aerosol (NNA): metered dose inhaler containing CFC propellant gases mixed with nicotine solution in a multi-dose canister.
2. Nasal Nicotine Spray (NNS): delivers a fixed dose of nicotine solution through a plastic nozzle held in the nostril.

Each device administers 0.25 mg of nicotine for each "shot". Subjects took eight shots over a 30 second period (total dose of 2 mg nicotine).
Subjects completed testing with both devices with a 3 month interval between testing.
Blood samples were taken before and at 2.5, 5, 7.5, 10, 15, 20, 30, 45 and 60 minutes after the 2 mg nicotine dose. Heart rate and BP were monitored.

The two subjects who developed the highest and lowest nicotine concentrations were subsequently tested with repeated doses (2mg doses at 0, 20 and 40 minutes) and blood samples taken at 2.5, 5, 7.5, 10, 15 and 20 minutes after each of the three doses.

Smoking behaviour / co-interventions

Subjects abstained from smoking for at least 12 hours (verified by expired air CO of < 10ppm).

Pharmacokinetic outcomes

Single (2 mg) nicotine dose

Plasma nicotine	Nasal Nicotine Spray (NNS) Mean (SD)	Nasal Nicotine Aerosol (NNA) Mean (SD)
C max (ng/ml)	12.4 (7.1)	11.7 (6.2)
T max (min)	6.0 (2.1)	10.8 (9.4)
Rise (ng/ml) 0 – 2.5 min	8.7 (8.1)	8.5 (6.2)
Rise (ng/ml) 0 – 5.0 min	11.2 (7.3)	9.7 (6.8)
AUC 0-60 (ng . min/ml)	403 (135)	352 (133)

Repeated doses of 2 mg nicotine (total of 6 mg): only two subjects studied.
Maximal levels were 39.6 and 19.6 ng/ml at 7.5 and 5 min after the third dose. Nicotine was rapidly absorbed by the nasal route, with a similar pattern being observed for both products. A mean nicotine boost was observed which is similar to the average boost per cigarette during usual smoking throughout the day. With repeated use blood nicotine levels comparable to those with smoking were obtained within one hour. Using a nasal spray ad libitum a blood level of nicotine similar to those seen in smoking, can be obtained.

Safety Outcomes

Lightheadedness (8/10)

Paraesthesia (1/10)
Transient tinnitus (1/10)
Palpitations (2/10 : one smoker, one ex-smoker)
Nausea (1/10 with NNS but not NNA, 1/10 with NNA but not NNS)
Dysphoria (1/10 with NNA but not NNS)
Local irritancy – nose and eyes (5/10 with NNS, 3/10 with NNA)

Study quality comments

Prior to the testing, subjects were given instructions and practised using the device.
Adverse events were self reported and subjective.
Small sample size.
No placebo controls.
+

Vanakoski, Seppälä, Sievi & Lunell . Exposure to high ambient temperature increases absorption and plasma concentrations of transdermal nicotine. Clinical Pharmacology and Therapeutics 60, 308-315. 1996.

Design

Open randomised crossover study.

Participants

n = 12 (7 male, 5 female), Age range 21 to 31 years. Weight range 48 to 88 kg.

Interventions / comparators

Patches were applied 4.5 hours before the session. Two patches were applied (10 mg/ 16 hr Nicorette and 15 mg/ 16 hr Nicorette) to the lateral aspect of the right arm of each subject for their first session and to the left arm for the second session one week later.
Two open sessions. One week washout period between the sessions.
Sauna bathing session: 3 x 10 min stays in a sauna bath (mean temperature 82 C; temperature range 25 to 27 C)
Control session: subjects remained in a resting room at 23 C.
Patches were removed 8 hours after application.
Blood sampling: samples were taken for nicotine concentration measurement before patch application (- 5 hrs), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75 and 3 hours after the beginning of the session.

Smoking behaviour / co-interventions

All subjects were smokers (≥ 12 cigarettes/ day for at least 1 year). Subjects were prohibited from smoking, consumption of other nicotine products or alcohol, excessive physical exercise and sauna bathing for 24 hours before the session.

Pharmacokinetic outcomes

Mean [SEM]

	Control	Sauna
Cmax ng/ml	18.0 [1.4]	26.1 [1.8]
Amount absorbed (mg)	15.9 [0.3]	17.2 [0.4]
AUC0-1 h.ng.ml	17.8 [1.5]	25.1 [1.6]
AUC0-3 h.ng.ml	50.3 [3.9]	59.6 [3.6]

Authors conclude that absorption and plasma concentrations of transdermally delivered nicotine may be increased during exposure to high temperatures, probably due to enhanced skin blood flow. It is not clear whether this effect is due to increased absorption of nicotine from the patch or increased transport of nicotine from subcutaneous tissues into systemic circulation.

Safety Outcomes

None provided.

Study quality comments

Method of randomisation not described.
+

16 Appendix 9. Evidence table: question 8

There are marked differences in smoking rates among socioeconomic groups, Black and Minority ethnic (BME) groups, age (life stage) and people with mental illness. Do the data suggest there may be inequalities among these groups with respect to the risk, safety and pharmacokinetics of smoking harm reduction technologies?

Roddy E et al, 2006. Use of nicotine replacement therapy in socioeconomically deprived young smokers: a community-based pilot randomised controlled trial. Tobacco Control 2006;15: 373-376.

Design

RCT

Participants

n= 98

Interventions / comparators

Subjects randomised to

- Nicotine patch (tapering treatment: 15 mg to 10 mg to 5 mg per day for 2 weeks each)
- Placebo patch

Participants reviewed weekly by the study doctor for side effect monitoring. All participants received weekly behavioural counselling.

Smoking behaviour / co-interventions

Cessation study; smoking was discouraged

Pharmacokinetic outcomes

Not provided.

Safety Outcomes

There were a total of 30 adverse events among the active treatment compared to 17 among the placebo group (itching: 16 cases (nicotine) versus 7 (placebo); rash: 6 versus 3; pain or paraesthesia: 6 versus 4; dizziness, nausea or headache: 2 versus 3). Two subjects withdrew from the study because of adverse effects (one from active and one from placebo group).
The authors conclude that NRT seemed safe in this group.

Study quality comments

Baseline characteristics analysed
Community use of NRT
Study powered to detect an increase in cessation rates from 15% in placebo group to 22% in the active group. Unable to recruit sufficient participants and retain them for the duration of the study.
Study participants were motivated to quit smoking and were keen to use some form of NRT.
Overall Quality Score: +

Lin et al, 1993. Development of a new nicotine transdermal delivery system: in vitro kinetics studies and clinical pharmacokinetic evaluations in two ethnic groups. Journal of Controlled Release 1993; 26: 175 – 193.

Design

Open label, randomised single treatment PK study.

Participants

American group: n= 32. 19 female, 13 male. Mean (SD) age 36 (± 8). Smokers of an average 30 (SD ± 13) CPD.

Taiwanese group: n = 33. All males. Mean age 31 (±6) years. Smokers of an average 19.3 (± 7) CPD.

Interventions / comparators

Four arms:

- One unit of 10 cm^2 transdermal nicotine
- Two units of 10 cm^2 transdermal nicotine
- Three units of 10 cm^2 transdermal nicotine
- Six Nicorette gums

Smoking behaviour / co-interventions

Subjects abstained from smoking one day before the study and for the whole of the study.

Pharmacokinetic outcomes

Mean [SEM]

	Treatment patch size	American	Taiwanese	Ratio American/Taiwanese
Plasma nicotine concentration in steady state period 8-24 h	A 10cm2	4.73 [0.32]	4.66 [0.57]	1.02
	B 20cm2	8.33 [0.74]	8.35 [0.67]	1.00
	C 30 cm2	11.60[1.84]	13.78 [1.55]	0.84
Ri/Vi	A 10cm2	1.40 [0.14]	1.90 [0.32]	0.74
	B 20cm2	2.57 [0.20]	2.89 [0.38]	0.89
	C 30 cm2	4.30 [1.08]	4.66 [0.85]	0.92
AUC0-36	A 10cm2	112.69 [12.34]	105.83 [10.12]	1.07
	B 20cm2	199.00 [19.74]	208.17 [13.73]	0.96
	C 30 cm2	276.66 [41.73]	335.20 [36.86]	0.83

Of the pharmacokinetic parameters only the Ri/Vi ratio showed a statistically significant difference between the two groups of smokers. This ratio reflects the input rate of nicotine into the central compartment.

Safety Outcomes

None reported.

Study quality comments

Differences in gender distribution among the two groups.
Exclusion criteria provided.
Method of randomisation not described.
Inpatient environment.
Overall Quality Score:+

Schnoll et al, 2009. Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: A validation study. Pharmacology, Biochemistry and Behaviour 2009; 92:6-11.

Design

Open label trial of transdermal NRT

Participants

n= 576. 55% male, average age 45 years (SD 10.3). 84% were Caucasian. All smokers (average 21.2 CPD (SD 9.2), average FTND score 5.2 (SD 2.1).

Interventions / comparators

All participants received 8 weeks of open label 21 mg transdermal NRT. Behavioural counselling was also provided.

Rate of nicotine metabolism was measured at baseline (blood sample taken for analysis of plasma nicotine and determination of the 3-HC/cotinine ratio). The authors indicate that the 3-HC/cotinine ratio is a stable measure of individual differences in nicotine metabolism.

Primary outcome was cessation at week 8. After the first week of treatment plasma nicotine concentration, patch-related side effects, nicotine craving and positive and negative affect were measured.

Severity of each side effect was graded from 0 to 3.

Smoking behaviour / co-interventions

Cessation verified biochemically (CO<10ppm)

Pharmacokinetic outcomes

Not provided.

Safety Outcomes

Baseline log 3-HC/cotinine ratio was a significant predictor of week 8 point prevalence quit rates (OR=0.66 [95% CI:0.48 – 0.91]; p=<0.05) i.e. slower nicotine metabolisers showed higher quit rates at week 8.

There was no association between baseline log 3-HC/cotinine ratio and patch use (r = 0.07,ns), patch related side effects (r=-0.02, ns), nicotine withdrawal (r = -0.02, ns), nicotine craving (r = -0.2, ns), negative effect (r=0.02, ns), or positive effect (r=-0.03, ns).

Study quality comments

Baseline characteristics provided. Baseline 3-HC/cotinine ratio was associated with age, gender and ethnicity (older individuals, females and Caucasians had higher baseline values).

Individuals committed to quitting smoking.

Inclusion and exclusion criteria were provided.

Study did not include placebo to observe effect on 3-HC/cotinine ratio. Short term follow up only. Authors suggest extending the study to racial/ethnic groups as a future study.

Overall Quality Score: +

Malaiyandi V et al. Impact of CYP2A6 genotype on pretreatment smoking behaviour and nicotine levels from and usage of nicotine replacement therapy. Molecular Psychiatry 2006; 11: 400- 409.

Design

Randomised, Open label clinical trial.

Participants

n= 394. All Caucasian

Interventions / comparators

- Nicotine patch (n=193)
- Nicotine nasal spray (n=201)

Study period: 8 week treatment with 12 month follow up.
CYP2A6 genotyping assays allowed classification as normal (100% activity), intermediate (75% activity) or slow (50% or less activity).
Plasma nicotine concentration measured before treatment and at 1 week after treatment commenced.

Smoking behaviour / co-interventions

Biochemically confirmed abstinence

Pharmacokinetic outcomes

Plasma nicotine concentrations were significantly greater in the slow metabolisers (22.8 ± 4.6 ng/ml) than in normal metabolisers (15.8 ± 7.6 ng/ml); p=0.02. For those in the nasal spray group significantly fewer doses were used per day by slow metabolisers (4.8 ± 3.6 vs 10.5 ± 8.0; p<0.02) although plasma nicotine concentrations were not significantly different between the two groups

Safety Outcomes

Slow metabolisers smoked fewer cigarettes per day compared to normal metabolisers (20 ± 7 vs 24 ± 10, p <0.04)

Study quality comments

Baseline characteristics described.
Some variants are poorly represented in the sample.
Diet and drug history may affect CYP2A6 activity but were not studied.
Overall Quality Score: +

Berg JZ et al, 2010. Nicotine metabolism in African Americans and European Americans: variation in glucuronidation by ethnicity and UGT2B10 Haplotype.

Design

Open label clinical trial

Participants

n= 105

Interventions / comparators

Nicotine patch (21 mg)

Baseline smoking assessment with 24 hr urine collection while smoking as usual. Subsequently patch was used and subjects abstained from smoking. BP and heart rate monitored on days 5 to 7. 70 subjects provided plasma on days 5 to 7.

Smoking behaviour / co-interventions

Subjects abstained from smoking throughout the 8 day study

Pharmacokinetic outcomes

Urinary nicotine and % nicotine glucuronide

Metabolite	Nicotine patch		Baseline Smoking	
	African American	European American	African American	European American
Free nicotine (nmol/l)	12.9	9.9	8.8*	6.0*
Total nicotine (nmol/l)	15.6	13.7	19.4	15.1
% nicotine glucuronide	18.1*	29.3*	51.4	57.4

*P<0.05

Multivariate linear regression models:

For both participants using the NRT patch, and for participants at baseline smoking, the following independent variables were statistically significant predictors of the glucuronidation ratio: African American ethnicity sum of all urinary nicotine equivalents (nicotine, cotinine, trans-3 hydroxycotinine).

Study quality comments

Blood for genotyping was obtained from 32 participants.

Overall Quality Score: +

Moolchan MT et al, 2005. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. The Journal of Pediatrics 2005; 115: e407-44.

Design

Double blind, randomised trial

Participants

n= 120. 72% white, 70% female, age 15.2 ± 1.33 years. Smokers (18.8 ± 8.56 CPD). 75% of participants had at least 1 current psychiatric diagnosis.

Interventions / comparators

Three arms:

1. Nicotine patch (21 mg) + placebo gum
2. Nicotine gum (2 mg if smoking ≤ 24 CPD, 4mg if smoking > 24CPD) + placebo patch
3. Placebo gum + placebo patch

Abstinence assessed by self report and verified by exhaled carbon monoxide levels.
Safety assessed by adverse event reports

Smoking behaviour / co-interventions

Participants were encouraged to stop smoking. Self reported CPD was recorded throughout the study.

Pharmacokinetic outcomes

Safety Outcomes

Adverse events:

	Patch	**Gum**	**Placebo**
Pruritus	44*	61*	25
Erythema	49*	39	23
Headache	24	26	36
Fatigue	15	20	32
Viral infection	14	30	19
Insomnia	13	17	13
Cough	9	15	8
Nausea	10	10	11
Jaw pain	10	12	8
Anxiety	6	13	7
Sore throat	3	18*	3
Hiccups	4	14	4
Dyspepsia	4	10	8
Shoulder or arm pain	15*	0	3
Dizziness	3	3	9
Congestion	3	3	4
Oedema	4	2	4
Constipatio	3	0	0
Diarrhoea	0	0	2

There was a mean reduction in self reported smoking (CPD) for all three groups (gum, patch and placebo) and this exceeded 80% reduction in each case. The authors suggest that the pattern of adverse events reported in this trial was similar to those reported in adult trials
Although the degree of reduction achieved by study participants (means exceeding 80% for all three groups), neither biomarker of smoke exposure (CO or saliva thiocyanate) declined during the trial. The authors suggest compensatory smoking may have occurred.
The nicotine patch and gum were well tolerated in this population. Adverse events profile was consistent

with those seen in previous studies with adults.

Study quality comments

Small percentage of applicants were actually enrolled.
Study designed to consider concurrent NRT gum and patch use. Reduction in numbers of cigarettes smoked per day was recorded.
A large percentage of participants had a concurrent psychiatric illness.
Overall Quality Score: ++

Smith TA et al, 1996. Nicotine Patch Therapy in Adolescent Smokers. Pediatrics 1996; 98: 659.

Design

Non-randomised, open label trial

Participants

n= 22. Smokers (>20CPD). Ages 13 to 17 years.

Interventions / comparators

Nicotine patch (21 mg/day for 6 weeks followed by 11 mg/day for 2 weeks)

Smoking behaviour / co-interventions

At study outset participants smoked a mean of 21.9 cigarettes per day. During administration of NRT, the mean number of cigarettes smoked per day ranged from 1.3 to 2.2.

Safety Outcomes

Fifteen subjects (68%) experienced a skin reaction (erythema, oedema or vesicle formation); this was compared to a similar study in adults where 64% (58 of 90) subjects reported a skin reaction over the 8 week course of treatment. Other common symptoms reported by the adolescents included headache (41%), nausea and vomiting (41%), tiredness (41%), dizziness (27%) and arm pain (23%). None of these episodes were of greater than moderate intensity; none were serious or life-threatening. Authors conclude the nicotine patch therapy is safe and well tolerated in these subjects.

Study quality comments

Trial recruited from public schools.

Adverse events and numbers of cigarettes smoked were recorded in diary.

Overall Quality Score: +

Hurt RD et al. Nicotine Patch Therapy in 101 Adolescent Smokers. Arch Pediatr Adolesc Med 2000; 154: 31-37.

Design

Non randomised open label trial

Participants

n= 101, adolescents (aged 13 to 17). Smokers (at least 10 cigarettes per day).

Interventions / comparators

Nicotine patch 15 mg/16 hr.
Six weeks of therapy with weekly visits.
Adverse events recorded.

Smoking behaviour / co-interventions

Cessation study, participants motivated to quit.

Pharmacokinetic outcomes

Not reported.

Safety Outcomes

87 subjects reported experiencing at least 1 adverse event during 6 weeks of treatment. Upper respiratory tract infections (44%), headache (43%), nausea and vomiting (13%), skin reactions (12%) and sleep disturbance (10%) were the most commonly reported adverse events

Study quality comments

Subjects given a diary to record number of cigarettes smoked and withdrawal symptoms experienced.
Subjects instructed in the use of the NRT patch.
Community based study with regular visits.
Sample size calculated to demonstrate an abstinence rate ranging from 5 to 30%.
Intent to treat analysis performed.
Subjects were motivated to stop smoking.
Overall Quality Score: +

Rubinstein ML et al, 2008. A randomised trial of nicotine nasal spray in adolescent smokers

Design

Randomised open label trial

Participants

n= 40. Adolescents (age 15 to 18). Smokers (5 or more CPD)

Interventions / comparators

- No intervention
- NRT nasal spray

Both groups received weekly counselling.

Smoking behaviour / co-interventions

Abstinence verified by expired air CO and salivary cotinine.

Pharmacokinetic outcomes

None given

Safety Outcomes

57% of participants stopped using the spray after only one week.
During the first week of use, only 26% of those assigned to NRT spray used it every day. Median use was 1.14 sprays/day (range 0.14 to 3.00 sprays)
Subjects who used NRT nasal spray did not have different scores on the withdrawal scale from those who had counselling alone (8.84 vs 9.58; p= 0.26).
Of the group using the spray 38.9% were of the opinion that the spray had lots of side effects. The most common adverse effect was nasal irritation (34.8%), followed by complaints about taste and smell (13%). Nasal burning was the most common complaint and was the reason given for poor adherence.

Study quality comments

Subjects randomised to use the nasal spray were given training on proper usage.
Adverse events reported at each weekly visit. Subjects were questioned regarding attitudes to the spray and adverse effects experienced.
Small trial.
Method of randomisation was described.
Subjects were motivated to quit smoking.
Overall Quality Score: ++

Molander L et al, 2001. Pharmacokinetics of nicotine in healthy elderly people.

Design

Pharmacokinetic study.

Participants

n= 40. Elderly (65-76 years) n=20, Adult (22-43 years) n=20. All subjects healthy. 35 subjects were smokers, 4 users of wet snuff and 1 subject used both cigarettes and snuff.

Interventions / comparators

Intravenous dose of nicotine: 0.028 mg/kg body weight given over 10 minutes.
Regular bloods taken for measurement of nicotine from immediately before the dose until 23 hours after the start of infusion.
Heart rate and Blood pressure (systolic and diastolic) were also recorded.

Smoking behaviour / co-interventions

Abstinence required for 36 hours before commencing the study. Confirmed by CO measurement.

Pharmacokinetic outcomes

Following an intravenous infusion of 0.028 mg/kg of nicotine over 10 minutes, the clearance of nicotine was significantly reduced by approximately 25% in elderly (65 to 76 years) subjects compared with younger (22 to 43 years) adults (14.9 ± 4.1 L/kg vs 19.3 ± 4.1 L/kg; p =0.0002). The maximal nicotine concentration was higher in the elderly subjects (16.8 ± 7.8 ng/ml vs 10.4 ± 3.5 ng/ml). Despite this, the maximal heart rate increase was significantly lower in elderly subjects than younger adults (15 ± 6 bpm vs 21 ± 8 bpm, p = 0.0062) and there were no differences in the systolic and diastolic blood pressure responses between the two groups.

Safety Outcomes

The maximal heart rate increase was significantly (p = 0.0062) lower in elderly subjects than younger adults (15 ± 6 bpm vs 21 ± 8 bpm) and there were no differences in the systolic and diastolic blood pressure responses between the two groups.
There were no differences in the adverse events experienced by the subjects, either in terms of the type of event or severity:
35 subjects reported 68 adverse events (16 elderly and 19 adult subjects reported 31 and 37 adverse events respectively).
Almost all subjects experienced local symptoms such as pain or numbness at the infusion site.
There were 14 reports of dizziness (6 elderly, 8 adults), 4 reports of dry mouth (3 elderly and 1 adult), 3 reports of nausea (1 elderly and 2 adults).

Study quality comments

Overall Quality Score: +

Stapleton JA, 2008. varenicline in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness. Addiction 2008; 103: 146-154.

Design

Before and after study

Participants

n=412. Smokers making a quit attempt. 111 (27%) reported that they were receiving treatment for mental illness

Interventions / comparators

6 weeks treatment with either:

- Nicotine replacement therapy (choice of product) (n= 204)
- Varenicline (n= 208)

Two groups of patients were studied; one before the introduction of varenicline and one after.
Verified abstinence, withdrawal, incidence of adverse drug reaction, cost per patient treated and cost per successful short term quitter were measured.

Smoking behaviour / co-interventions

Cessation study.

Pharmacokinetic outcomes

Not provided.

Safety Outcomes

Odds ratio for smoking cessation verified by CO assessment (varenicline:NRT) 20.6 (95% CI 0.93-4.55)

Higher incidence of adverse reactions among subjects taking varenicline than those taking NRT. Skin irritation was the only reaction having a higher incidence in those using NRT. The authors report a similar incidence of adverse events for NRT and varenicline groups but did not analyse the frequency of adverse events in the NRT treated subjects with and without mental illness.

Incidence of adverse events in patients trated with NRT % [n]

Symptom	Incidence (% out of 204)	n
Nausea	1.0	2
Disturbed sleep	6.4	13
Vivid dreams	4.4	9
Drowsiness	1.5	3
Constipation	1.5	3
Headache	2.5	5
Dyspepsia	2.0	4
Dry mouth	1.5	3
Bad taste	0.5	1
Low mood/depression	1.0	2
Diarrhoea	0.5	1
Disorientation/confusion	0.5	1
Skin irritation	6.9	14
Anxiety/panic	0.5	1

Study quality comments

No randomisation; subjects selected their own treatment based on preference.
Cohorts selected around the introduction of varenicline. Subjects who chose NRT after the introduction of varenicline were excluded from the study.

Overall Quality Score: -

Dalack GW, 1999. Nicotine Withdrawal and Psychiatric Symptoms in cigarette Smokers with Schizophrenia. Neuropsychopharmacology 1999; 21: 195-202.

Design

Randomised, double blind, balanced crossover study

Participants

n=19. Middle aged (40 ± 5 years) male veterans with diagnosis of schizophrenia (74%) or schizoaffective disorder (26%). 75% were on typical antipsychotic medication. All smokers (average 29.4 ± 18.7 CPD).

Interventions / comparators

- Nicotine patch (22 mg/day)
- Placebo patch

Psychiatric symptoms and medication side effects were assessed using Brief Psychiatric rating Scale (BPRS) and Schedule for the Assessment of negative Symptoms (SANS)

Smoking behaviour / co-interventions

1 day of ad libitum smoking
3 days of abstinence while wearing 22 mg/day NRT patch OR placebo patch.
Each subject completed each patch condition on consecutive weeks.

Safety Outcomes

Despite physiological evidence for withdrawal, mild increases in reported subjective withdrawal symptoms did not reach statistical significance in either condition. Measures in neuroleptic-induced parkinsonism did not change during smoking abstinence. The study did not detect any exacerbation of psychiatric symptoms when assessed using the Brief Psychiatric Rating Scale (BPRS) score or the Scale for the Assessment of Negative Symptoms (SANS) score. Abnormal Involuntary Movement Score (AIMS) decreased by as much as 35% with placebo patch treatment and with active patch treatment AIMS score increased by 17%. The authors conclude that abnormal voluntary movements were not significantly affected during treated and untreated smoking abstinence.

Study quality comments

Study was completed in stable outpatients. Authors note that acutely ill patients may respond differently.
Short period of abstinence (3 days)
Subjects admitted to a clinical research period for two 4 day stays.
Overall Quality Score: ++

17 Appendix 10 - Swedish snus in Nordic countries: patterns of use, pharmacokinetics and safety

17.1 Background to the work on Swedish snus

The Programme Development Group (PDG) for the NICE public health guidance in development on tobacco harm reduction (THR) met on 18.10.2011 and considered the review of pharmacokinetics, risk and safety of nicotine replacement therapy (NRT) presented by Cedar. The safety data on NRT was cited from randomised trials of THR with a maximum follow up period of 24 months (Batra et al. 2005 [+]; Bolliger et al. 2000 [++];Carpenter et al. 2003 [+]; Carpenter et al. 2004 [++]; Etter et al. 2002 [++]; Haustein et al. 2004 [+]; Joseph et al. 2008 [+]; Kralikova et al. 2009 [+]; Rennard et al. 2006 [++]; Wennike et al. 2003) [+]) and from the lung health study, where the maximum exposure to NRT recorded was 5 years (Murray et al. 1996 [+], Murray et al. 2009 [+]).

The PDG concluded that the evidence presented to date does not answer the question of whether it is safe to use medicinal NRT indefinitely (e.g. as a life-long strategy), the concern being whether nicotine itself causes harm after long term exposure. The PDG noted that in Sweden many people are exposed to nicotine by using snus, a type of moist, oral tobacco. The smokeless tobacco industry attributes low smoking-related mortality rates that are observed for Sweden to the fact that Swedish men in particular tend to use snus as an alternative to smoking cigarettes (ESTOC, 2012). The implication is that Swedish snus may be, relatively speaking, a 'cleaner' source of nicotine than other forms of tobacco. Some public health academics have stated that although the use of snus is not hazard-free, it is less harmful than cigarette smoking (Britton & Edwards, 2008). The PDG requested a review of the safety of long term exposure to nicotine from snus, as a surrogate for long term exposure to NRT.

17.2 Swedish snus

Snus is a form of moist, oral tobacco, manufactured in Sweden and used predominantly in Sweden and some other Scandinavian countries. The company Swedish Match produces almost all (>99%) of the snus produced in Sweden (Broadstock, 2007 [+]) and snus is sold under many different brand names, either as loose weight in boxes, or in small 'tea-bag'-like sachets representing the standard portion for use (SCENIHR, 2008 [+]). Snus users place either a small, 1-2g pinch of loose snus or a 0.5-1g sachet between the upper lip and the gum (Idris et al. 1998 cited by Broadstock 2007 [+]), and a typical snus user may keep snus in the mouth for 11-14 hours per day (SCENIHR, 2008 [+]).

Swedish snus is generally regarded as a unique product, distinct from other forms of smokeless tobacco, including American oral moist snuff, even though American oral moist snuff often has Nordic-sounding brand names e.g. Skoal, Copenhagen. Since 1983, Swedish snus has a different manufacturing and storage process than other forms of oral moist tobacco, including:

- heat treatment to kill microorganisms
- no sugar content
- refrigerated storage (RCP 2007, Broadstock, 2007 [+]).

The process is thought to contribute, in part at least, to the lower levels of toxins that are present in Swedish snus compared to other smokeless tobacco forms (Hatsukami et al. 2004; Nilsson 1998; Ramstrom 2000; cited by Broadstock 2007 [+]). An important group of toxins are the tobacco-specific nitrosamines (TSNA), particularly NNN and NNK, which are thought to be important carcinogens (International Agency for Research on Cancer 1985 cited by Broadstock 2007 [+]). In Sweden, TSNA levels in snus have decreased 85 per cent since the 1980s; a survey of Swedish snus in 2002 indicated a mean level of the total TSNA content of 1.0 µg/g (n = 27 samples) (Osterdahl et al. 2004, cited by Broadstock 2007 [+]). Recently snus was investigated as a smoking cessation intervention in a randomised trial comparing regular snus with placebo snus (Fagerstrom et al. 2011). Cessation rates were generally low, however the ethically approved trial reflects the widely held view that snus is inherently safer than cigarette smoking.

17.3 Legal status of snus

Snus falls under the following definition in the EU Tobacco Products Directive:

"'Tobacco for oral use' means all products for oral use, except those intended to be smoked or chewed, made wholly or partly of tobacco, in powder or in particulate form or in any combination of those forms, particularly those presented in sachet portions or porous sachets, or in a form resembling a food product"

Source: DIRECTIVE 2001/37/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 June 2001

Sale of oral moist snuff including snus is banned in the European Union (EU) since 1992 with the exception of member state Sweden, which successfully sought exemption from the ban due to an established culture of use in men (McNeill et al. 2006, cited by Broadstock 2007 [+]). Snus is permitted in Norway, which is outside of the EU, but is not permitted in Finland or Denmark (EU states). Snus use is relatively low in Denmark and Finland, although snus may be purchased tax

free and imported on Ferries to Finland (Vainio and Weiderpass 2003, cited by Broadstock 2007 [+]).

18 Methods – Swedish snus

18.1 Research question

The research question and study inclusion criteria are defined as follows:

Population Scandinavian populations (predominantly Swedish, Norweigan) who use snus (smokers, ex-smokers, those who never smoked)
Intervention Snus, defined as moist snuff (ground tobacco) taken orally and held in the mouth between cheek and gum. Snus is generally pre-packaged into small paper or cloth packets. Excluded are tobacco-based, chewed products used in the UK by the South Asian population (e.g. Gutkha, Pan).
Comparator Any comparator
Outcomes Pharmacokinetic profile of nictotine from the snus administration route Profile of snus use: demographics, consumption patterns Safety outcomes: • Incidence of cancer in snus users • Incidence of cardiovascular disease in snus users • Psychological outcomes in snus users Where possible, report outcomes by subgroups for age, gender, socioeconomic group or other salient factor.
Study design The following study designs will be sought: • Randomised controlled trials • Large, epidemiological studies (e.g. cohort studies, large case series) • Pharmacokinetic studies

18.2 Identification of evidence

Relevant literature was sought using the Medline, Embase, Psychinfo and Cochrane Library databases. An example search strategy is provided in Section 23. In addition the following websites were searched:

- Norwegian Institute of Public Health
- Swedish National Institute of Public Health.

Study records were retrieved and kept in a Reference Manager v12 database. After removal of duplicate records there were 790 potentially relevant studies.

Due to the limited time scale of this review, a pragmatic approach is required. Recent, well conducted systematic reviews were sought as a starting point, and a PDG member recommended a report on smokeless tobacco, written in 2008 by the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, 2008 [+]). The SCENIHR report represents a major piece of work, is comprehensive and is heavily cited in this review.

Additional studies were included to provide evidence against the research question. Evidence from the following published sources informs this review:

- Two systematic reviews that provide detailed coverage of smokeless tobacco, with good coverage of Swedish snus (Broadstock (2007) [+], SCENIHR (2008 [+]). Whilst the SCENIHR review has broader coverage, there is a high degree of overlap in terms of the primary studies included in the two reviews.
- Three systematic reviews which provide pooled estimates of risk for cancer or cardiovascular events, based on meta-analyses (Boffetta et al. (2008) [+], Boffetta & Straif (2009) [+], Lee & Hamling (2009a) [+]). These again are based largely on the same body of data as the two reviews above.
- One cohort study, recently published and therefore not included in any of the systematic reviews, that investigates the risk of bowel cancers (Nordenvall et al. 2011 [+]).
- Two cohort studies investigating the risk of diabetes or weight gain, that were not included in the systematic reviews (Eliasson et al. 2004) [+], Hansson et al. 2011) [+]).
- Two randomised crossover studies investigating the pharmacokinetics of nicotine from snus (Kotlyar et al. 2007 [+], Lunell & Curvall 2011 [+]).
- Two observational studies providing further information on patterns of use of tobacco in Sweden, over time (Engstrom et al. 2010 [-], Tillgren et al. 1996 [-]).

The studies listed above have been critically appraised for quality using the checklists in the NICE CPHE methods document (NICE, 2009). The study quality assessment is summarised in Section 24. The primary studies included in the systematic reviews and meta-analyses met inclusion criteria specified by the respective authors, who also critically examined the validity of the results Broadstock (2007) [+] and SCENIHR (2008) [+]. For this reason, this review does not critically appraise the primary studies included in the systematic reviews or apply a quality score [++, +, -], but presents an overview of the primary studies in Section 25.

19 Profile of use of Swedish snus

Data for this section drawn from the SCENIHR (2008) [+] review is shown in Section 26.

19.1 Sweden

Snus has been used in Sweden for almost 200 years, but by the 1960s cigarettes were more popular and snus was generally used by elderly men (SCENIHR 2008 [+]). In the early 1980s the snus manufacturer Tobaksbolaget (now Swedish Match) modified its product as described above and launched a marketing strategy directed at health conscious young men (SCENIHR 2008 [+]). The 1980s saw the beginning of a rise of snus use in men, coinciding with a rapid reduction in smoking in men. In women the decline in smoking was less profound than in men, though since 1996, the rate of decline in smoking in men has lessened, resulting in a similar rate of decline in men and women (SCENIHR 2008 [+]). Snus use has remained rare in women throughout; data from 2006 indicate that snus use in women remains substantially lower in Swedish women (4%) than in Swedish men (21%), although in Northern Sweden, where snus is more popular, use in women may be as high as 10% (SCENIHR 2008 [+]).

In Sweden snus is associated strongly with younger men irrespective of educational status and is more popular in young men than is smoking: in the 18-39 age group, 20% of men with a university degree use snus daily and 32% of those without a university degree. Respective percentages for smoking are 6% and 14% (Upmark 2003, in SCENIHR 2008 [+]). For men with no university degree, it is only in the age group 40-49 and above that smoking rates begin to be higher than the rate of using snus, and for men with a university degree, in the age group 60-69 and above (Upmark 2003, in SCENIHR 2008 [+]).

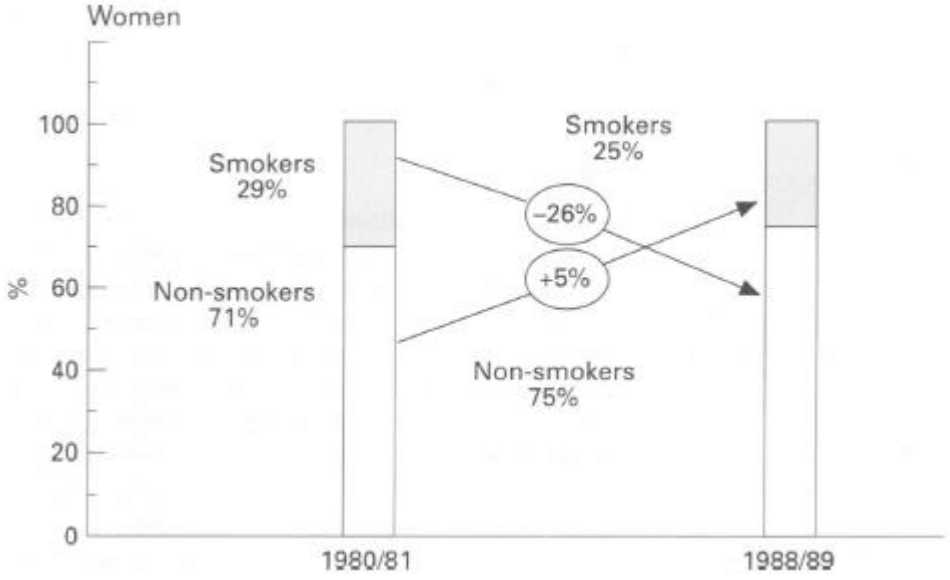
Snus use is more popular in men born in Sweden (including those born to immigrant parents) than in men born abroad (Statistics Sweden 2007 in SCENIHR 2008 [+]).

19.1.1 Patterns of tobacco use over time in Sweden

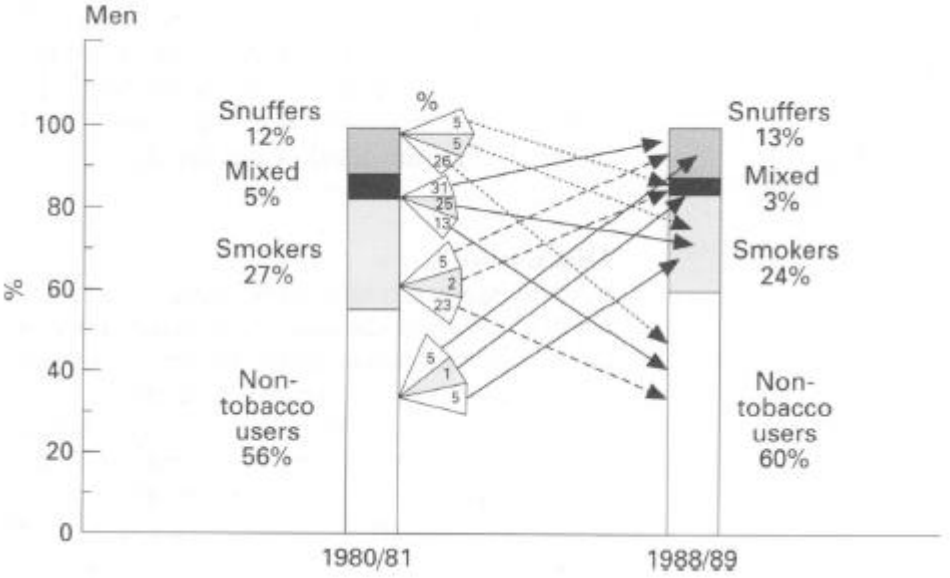
The figures below show changes in tobacco usage during the 1980s based on data from Statistics Sweden's surveys of living conditions in 1980-1 and 1988-9 (Tillgren et al. 1996 [-]). In women, 26% quit smoking and 5% started smoking, while in men 23% quit smoking and 26% quit using snus (Tillgren et al. 1996 [-]). In the men, 5% of the snus users began to smoke instead, while approximately 5% of smokers, became exclusive snus users and 2% of smokers became dual smokers / snus users (Tillgren et al. 1996 [-]). Of the men who had not previously used tobacco, 5% began smoking or using snuff (Tillgren et al. 1996 [-]). The proportion of men who both smoked

and used snuff dropped from 5% in 1980-1 to 3% in 1988-9 (Tillgren et al. 1996 [-]). The data from this study do not suggest that Swedish women start using other tobacco products as substitutes after they give up smoking.

Percentage of daily smokers and non-smokers among women in a sample (n=2578) of the Swedish population in 1980-1 and 1988-9. Reproduced from Tillgren et al. (1996) with permission from the BMJ Publishing Group, copyright license no 2878831086303



Percentages of daily snus users, smokers and non-tobacco users among men in a sample (n=2383) of the Swedish population in 1980-1 and 1988-9. Reproduced from Tillgren et al. (1996) with permission from the BMJ Publishing Group, copyright license no 2878831086303



19.2 Norway

Swedish snus is used substantially in Norway and mainly in men, though not to the same extent as in Sweden: data from 2006 indicate that 11% of Norwegian men use snus daily, compared with only 0.4% of Norwegian women (Statistics Norway 2007 in SCENIHR, 2008 [+]).

In Norway between 1973 and 1998 men had higher smoking rates than women, though since 1998 the smoking rate has been approximately equal and declining at an equal rate to 24% of men and women in 2006, which is higher than respective rates in Sweden (Statistics Norway 2007 in SCENIHR, 2008 [+]). Smoking is roughly equal between sexes for all age groups in Norway, with highest rates in Norwegians of age 35-64 (Statistics Norway 2007 in SCENIHR, 2008 [+]).

As in Swedish men, the trend in Norwegian men since 1980 is for smoking to decline and snus use to increase in all age groups, with the highest rates of snus use observed in Norwegian men of age range 16-34 (based on 2006 data). In contrast to Sweden, in no age group of Norwegian men does the prevalence of snus use exceed that of smoking (Statistics Norway 2007 in SCENIHR, 2008 [+]).

19.3 Finland

Despite being banned, snus is used predominantly in younger males (age 15-44 years) with the highest use (5.3%) observed in males of age 25-34 years (National Public Health Institute 2005 in SCENIHR 2008 [+]).

19.4 Denmark

In Denmark snus is not a significant source of nicotine (SCENIHR 2008 [+]).

20 Pharmacokinetics of nicotine from snus

Cigarette smoke is a potent means by which nicotine can rapidly enter the body. Ten minutes of cigarette smoking has been shown to generate an arterial blood Cmax of 38-40 ng/ml nicotine and a venous blood C_{max} of 17-19 ng/ml in a T_{max} of 11-12 minutes (Gourlay & Benowitz 1997).

SCENIHR (2008) [+] describes the pharmacokinetics of nicotine from snus based upon numerous primary studies (Benowitz 1988a, Benowitz et al. 1988b, Benowitz 1999 Fant et al. 1999, Fant et al. 2000, Fant & Fant 2005, Holm et al. 1992, Russell et al. 1983, Stratton et al. 2001 in SCENIHR 2008 [+]) and concludes as follows:

- Nicotine is a weak base and more readily crosses biological membranes at higher pH. Snus is buffered to alkaline pH to facilitate absorption of nicotine through the oral mucosa.

- Nicotine from snus that is swallowed with saliva will be absorbed from the small intestine but is subject to first pass metabolism by the liver, so not all swallowed nicotine reaches the general circulation.
- Buccal absorption of nicotine from snus is rapid and becomes maximal at 30 minutes, but absorption is less rapid than from cigarette smoke. The maximal plasma nicotine concentration (C_{max}) is higher for cigarettes compared to snus, but the C_{max} value of snus is higher than that of nicotine replacement products.
- Blood levels of nicotine fall more slowly after removing the snus compared to putting out a cigarette. This is presumably due to absorption of nicotine that has been swallowed and also nicotine remaining in the oral mucosa.
- The absorbed dose of nicotine has been found to be at least twice as great from American smokeless tobacco compared to cigarettes, with estimated absorbed doses of nicotine of 1.8, 3.6 and 4.5 mg from cigarette, snuff and chewing tobacco respectively (Benowitz et al. 1988b in SCENIHR 2008, [+]).
- When moist snuff is used throughout the day, venous blood nicotine concentrations are similar to those seen with cigarette smoking. There is considerable individual variation in the amount of nicotine absorbed from smokeless tobacco.

Two additional studies that were not included in the SCENIHR review are presented here.

In a 3-way crossover randomised trial, Lunell & Curvall (2011) [+] compared pharmacokinetics and subjective effects following 30 minutes' use of two brands of Swedish snus and 4mg medicinal nicotine gum, in 14 regular cigarette smokers. Plasma nicotine was sampled frequently up until 8h following dose. The pharmacokinetic data are summarised in the table below.

Table: summary of pharmacokinetic data from Lunell & Curvall (2011) [+]

Product	**C_{max} (ng/ml)**	**T_{max} (min)**	**AUC_{∞} (ng min/ml)**
Snus 1	14.8	37.1	3,062
Snus 2	13.7	37.1	2,829
Gum	12.8	46.1	3,190

The results concur with SCENIHR (2008) [+] in that the snus yields a greater maximum plasma concentration (C_{max}) and in a shorter time (T_{max}), compared to the medicinal nicotine gum. The AUC for the nicotine gum, representing total bioavailability, is greater, reflecting slower absorption (Lunell & Curvall 2011) [+]. In the same study, participants reported (subjectively, on a visual-analogue scale) a stronger 'head rush' in the first 30 minutes following snus use, compared to gum use. Subjectively assessed cravings for cigarettes in the first 30 minutes saw a similar reduction for snus and medicinal gum (Lunell & Curvall 2011) [+].

A similar study was performed by Kotlyar et al. (2007) [+], comparing American moist snuff (Copenhagen) with 4mg medicinal nicotine gum in a randomised crossover study design. Use of the American product may have limited applicability to Swedish snus. 10 male subjects (who had used Copenhagen snus for at least a year) used the products for 30 minutes at a time and blood was sampled immediately before, and at 1, 5, 10, 15, 20, 25, 30, 45, 60, 75 and 90 min after product placement. Pharmacokinetic data are shown below.

Table: summary of pharmacokinetic data from Kotlyar et al. (2007) [+]

	C_{max} (ng/ml)	**T_{max} (min)**	**$AUC_{0–90}$ (ng x min/ml)**
Copenhagen moist snuff	16.1	27-33 (all products)	1038
Commit medicinal 4mg gum	7.3	27-33 (all products)	467

Compared to the Swedish snus data presented by Lunell & Curvall 2011) [+], the American moist snuff reaches a higher maximum concentration of nicotine and sooner. However, the precise manner of use by the user may play a part, since the Swedish subjects in Lunell & Curvall 2011) [+], although smokers, were naïve to snus.

Conclusion – pharmacokinetics of snus

Evidence from pharmacokinetic studies indicates that ten minutes of cigarette smoking can generate an arterial blood C_{max} of 38-40 ng/ml nicotine and a venous blood C_{max} of 17-19 ng/ml in a T_{max} of 11-12 minutes. Absorption of nicotine from snus is primarily through the oral mucosa and can produce a venous blood C_{max} of 14ng/ml in a T_{max} of 30-37 minutes. Therefore the pharmacokinetic profile of nicotine from snus appears to reflect less rapid absorption compared to cigarettes, with a lower maximum blood concentration.

21 Safety outcomes for Swedish snus

21.1 Cancer

21.1.1 Association between snus and cancer

The systematic review by Broadstock (2007) [+] concluded that based on six population-based case control studies, there is no evidence for a strong association between snus and oral, neck and gastro-intestinal cancers. However Broadstock (2007) [+] also stated that estimates reported in the studies lacked precision and the possibility of risks associated with snus should not be ruled out.

In contrast the SCENIHR review (2008) [+] concluded that there is sufficient evidence that the use of a wide variety of smokeless tobacco products causes cancer in humans, with the pancreas identified as a main target organ. It should be noted that in reaching this conclusion, SCENIHR considered smokeless tobacco products from outside of the Nordic countries, and states that the risk varies widely in different smokeless tobacco products (SCENIHR 2008 [+]).

Some risk estimates for different types of cancer in the primary studies of Nordic populations included in either review (Broadstock 2007 [+] and SCENIHR 2008 [+]) suggest that there may be a statistically significantly raised risk of certain cancers through the use of Swedish snus.

- The cohort study by Boffetta et al. (2005) found that adjusted for age and smoking, the RR of pancreatic cancer (ever use of snus versus never use of snus) was 1.67 (95% CI 1.12-2.50).
- The cohort study by Zendehdel et al. (2008) found an elevated risk of oesophageal squamous cell carcinoma in snus users: RR (ever use versus never use of snus) 3.5 (95% CI 1.6-7.6), although this result was not controlled for alcohol intake. The risk of pancreatic cancer was also raised: RR (ever snus use versus never used tobacco) 2.0 (95% CI 1.2-3.3), RR (current use versus never used tobacco) 2.1 (95% CI 1.2-3.6). There was a dose-response effect with RR (>10g/day versus ≤10g/day) 2.1 (95% CI 1.1-3.8).
- A case control study by Lewin et al. 1998 found a RR of squamous cell head/neck cancer (ex snus users versus never tobacco users) to be 10.5 (95% CI 1.4-117.8). This estimate, though statistically significant, is imprecise because there were only 9 cases of cancer and 10 referents. The study did not detect elevated risks for other cancer subtypes.
- A case-control study by Lagergren et al. (2000) used multivariate analyses controlled for numerous potential confounders including smoking and alcohol use. In general the study

did not detect elevated risks of oesophageal / gastric cardia cancer but found the RR oesophageal squamous cell carcinoma (>25 years snus use versus ≤ 25 years use) to be 2.8 (95% CI 1.4-5.4).

- Luo et al. (2007) found RR for pancreatic cancer (current snus use versus no tobacco use) 2.1 (95% CI 1.2-3.6) and RR (ever snus use versus no tobacco use) 2.0 (95% CI 1.2-3.3). There was also a dose-response effect for using >10g snus per day: RR 2.1 (95% CI 1.1-3.8).
- Roosaar et al. (2008) found an elevated risk of pancreatic cancer associated with snus use: RR (ever daily snus use versus never snus use) 3.1 (95% CI 1.5-6.6), adjusted for alcohol use and smoking.

Two systematic reviews (Boffetta et al. 2009 [+] and Lee and Hamling 2009a [+]) have conducted meta-analyses of the risks of cancer associated with using Swedish snus, drawn largely from the same evidence base as Broadstock (2007) [+] and SCENIHR (2008) [+]. Relevant results for the Nordic countries are summarised in the table below.

Table: meta-analyses of risk of cancer associated with snus in Nordic countries (comparison of analyses from Bofetta et al. (2008) [+] and Lee and Hamling (2009a) [+]

Cancer type	Pooled estimate of RR (95% CI) reported in Bofetta et al. (2008) [1]	Pooled estimate of RR/OR (95% CI) reported in Lee and Hamling (2009a)		
		Overall data[2]	Smoking adjusted[3]	Never smokers[4]
Oral	1.0 (0.7-1.3)	0.97 (0.68-1.37) [5]	0.97 (0.68-1.37) [5]	1.01 (0.71-1.45) [5]
Oesophageal	1.6 (1.1-2.4)	1.10 (0.92-1.33)	1.10 (0.92-1.33)	1.92 (1.00-3.68)
Pancreatic	1.8 (1.3-2.5)	1.20 (0.66-2.20)	1.20 (0.66-2.20)	1.61 (0.77-3.34)
Lung	0.8 (0.6-1.0)	0.71 (0.66-0.76)	0.71 (0.66-0.76)	0.82 (0.52-1.28)

[1] Based on studies that controlled for confounding factors including tobacco smoking
[2] Not restricted on smoking status or on adjustment for smoking
[3] Restricted to estimates for the whole population (adjusted for smoking) or never smokers
[4] Restricted to never smokers only
[5] Stated as oropharyngeal cancer in Lee and Hamling (2009a)

The results of the two papers differ substantially with regard to oesophageal cancer and pancreatic cancer, where analyses by Boffetta et al. (2009) [+] are suggestive of increased risk associated with snus use. In contrast Lee and Hamling (2009a) [+] found no statistically significant association between snus and any type of cancer, based on Scandinavian primary studies, although the ratio value of 1.92 (95% CI 1.00-3.68) is of borderline statistical significance.

In the table above, some of the results from Lee and Hamling (2009a) suggest that snus is protective for lung cancer, including when the effect of smoking is taken into account, but not when analysis is restricted to never smokers. There is no obvious biological explanation why snus should be protective with regard to lung cancer when analysis is adjusted for the effects of smoking.

In response to the differences in findings between the two meta-analysis papers, Lee and Hamling (2009b) provide a discussion of the methodological differences in the two publications. These are stated as:

- Differences in use of RRs as reported in primary studies, versus using other data in the primary publication to calculate RRs
- Differences in which primary studies to include for meta-analysis
- Classifications of snus use (ever, current, unspecified)
- Classifications of smoker status (some studies presented aggregated data for smokers/non smokers combined; also depending on pipe & cigar smoking)
- Classifications of cancer subtypes (e.g. oral versus oropharyngeal cancer)

In general, Lee and Hamling (2009a) provide a more detailed description of their methods than do Boffetta et al. (2008). On the other hand Lee and Hamling's (2009a) work was funded by the European Smokeless Tobacco Council, an organisation with an interest in promoting snus.

Additional study, published subsequent to the systematic reviews and meta-analyses

In a recent publication Nordenvall et al. (2011) [+] presented an analysis of the Swedish construction workers cohort study, which investigated the relationship between smoking and using snus with cancer of the colon, rectum and anus in 343,822 with mean of 24 years of follow up (8,208,741 person-years in total). In exclusive snus users the RR (95% CI) of cancer of the colon, rectum and anus was 1.08 [0.91-1.29], 1.05 [0.85-1.31] and 0.61 [0.07-5.07], respectively.

Table: association between tobacco and colorectal cancer, from Nordenvall et al. (2011) [+]

	Colon	Rectum	Anus
No tobacco (referrant)	1	1	1
Pure smoker	1.08 [0.99-1.19]	1.16 [1.04-1.30]	2.41 [1.06-5.48]
Pure snus user	1.08 [0.91-1.29]	1.05 [0.85-1.31]	0.61 [0.07-5.07]
Dual smoker/snus user	1.17 [1.04-1.32]	1.21 [1.05-1.39]	3.48 [1.40-8.64]

21.1.2 Risk in the context of cancer disease burden

The table below shows the incidence of selected sites of cancer in Sweden in 2010 (Socialstyrelsen, 2011 [+]).

Table: new cases of cancer (selected sites) in Sweden in 2010 (Socialstyrelsen, 2011 [+])

ICD-7 code	Site	Males		Females		Total n
		n	%	n	%	
140-209	All cancer sites	29047	100	26295	100	55342
141	Tongue	119	0.4	95	0.4	214
142	Salivary glands	53	0.2	58	0.2	111
143	Floor of mouth	38	0.1	20	0.1	58
144	Mouth, other parts unspecified	87	0.3	78	0.3	165
145	Mesopharynx	150	0.5	64	0.2	214
146	Nasopharynx	24	0.1	15	0.1	39
147	Hypopharynx	43	0.1	18	0.1	61
148	Pharynx, part unspecified	5	0	1	0	6
141-148	Total oropharyngeal	519	1.7	349	1.4	868
150	Oesophagus	293	1.0	95	0.4	388
157	Pancreas	500	1.7	466	1.8	966
162	Trachea, bronchus, lung and pleura, primary	1942	6.7	1755	6.7	3697

The data show that in 2010 in Sweden there were 868 incident cases of oropharyngeal cancer, 388 incident cases of oesophageal cancer and 966 incident cases of pancreatic cancer.

Boffetta et al. (2008) [+] calculated the attributable fractions to snus (a function of the RR and exposed population) of rates of oesophageal cancer for Denmark, Norway, Swedish men and Swedish women as 2.1%, 3.5%, 10.7% and 0.6%, respectively. Respective values for pancreatic cancer are 2.7%, 4.6%, 13.8% and 0.8%.

The attributable fraction to snus of oesophageal cancer in men Sweden is therefore likely to translate to approximately 31 cases per year: 0.107 x 293 = 31 cases.

The attributable fraction to snus of pancreatic cancer in men Sweden is therefore likely to translate to approximately 69 cases per year: 0.138 x 500 = 69 cases.

Smoking tobacco accounts for around 80% of cases of lung cancer in men (Cancer Research UK, 2012, Nordlund, 1998). If we apply this proportion to the 2010 incidence of lung cancer in men in Sweden, then we would expect smoking to cause 0.8 x 1942 = 1554 cases of lung cancer per year.

It therefore appears that the increased RR for oesophageal and pancreatic cancer translate into modest proportions of those cancers caused by snus, and that the absolute numbers of cases are substantially lower than cases of lung cancer that we would expect to see from smoking.

21.1.3 Cancer risk in smokers

In a cohort study by Zendehdel et al. (2008) odds ratios in 'ever' cigarette smokers relative to 'never' tobacco users (adjusted for age and BMI and excluding 'ever' snus users) were 2.6 (95%CI 1.5-4.3) for oesophageal adenocarcinoma, 4.5 (95%CI 2.6-7.8) for oesophageal squamous cell carcinoma, 1.7 (95%CI 1.2-2.5) for cardia stomach cancer and 1.3 (95%CI1.1-1.5) for non cardia stomach cancer. A dose response was strongly evident for oesophageal cancer where 'ever' smokers of more than 20 cigarettes/day had OR 4.7 (95%CI2.5-9.0) for oesophageal adenocarcinoma and 11.2 (95%CI 6.2-20.2) for oesophageal squamous cell carcinoma.

In the population-based case-control study by Ye et al. (1999) current smokers, relative to never smokers, had greater odds (adjusted for snus use) of cardia stomach cancer (OR 1.7, 95% CI 1.0-3.1, i.e. of borderline statistical significance), intestinal type distal stomach cancer (OR 1.8, 95% CI 1.2-2.7) and diffuse type distal stomach cancer (OR 2.2, 95% CI 1.4-3.5). In another analysis for either kind of gastric cancer, current smokers who had never used snus had OR 2.0 (95% CI 1.3-2.9) relative to never tobacco users.

In the population-based case-control study by Lagergren et al. (2000) current smokers, relative to never smokers, were at increased risk of gastric cardia adenocarcinoma (OR 4.5, 95% CI 2.9-7.1) and oesophageal squamous cell carcinoma (OR 9.3 95% CI 5.1-17.0), in a multivariate analysis adjusted for snus use.

In a cohort study by Roosaar et al. (2008), 'ever' daily smokers, relative to 'never' daily smokers, were at increased odds of any cancer (OR 1.26, 95%CI 1.13-1.40) and smoking related cancer (OR 2.2, 95%CI 1.8-2.7), in analyses adjusted for snus use.

In the population-based case-control study by Lewin et al. (1998) current smokers, relative to never smokers had OR (cases:controls) 8.4 (95% CI 2.5-12.2) for squamous cell carcinoma of the oral cavity, pharynx, larynx and oesophagus combined. When current smoking was accompanied by high alcohol intake (>20g/day) the OR for current smokers was 22.1 (95% CI 13.0-37.8).

In a population-based case-control study by Rosenquist et al. (2005), relative to never smokers and with adjustment for alcohol use, smokers of 11-20 cigarettes per day were at increased odds of oral and oropharyngeal squamous cell carcinoma (OR 2.4, 95% CI 1.3-4.1) as were those who smoked >20 cigarettes per day (OR 2.8, 95% CI 1.3-6.1).

In a population-based case-control study by Schildt et al. (1998), current smokers were at greater odds relative to never smokers for oral cancer (OR 1.8, 95% CI 1.1-2.7) in a univariate analysis.

In the cohort study by Nordenvall et al. (2011) [+] smokers were at increased risk of rectal (RR 1.16, 95% CI 1.04-1.30) and anal (RR 2.41, 95% CI 1.06-5.48) cancer, relative to non-tobacco users.

21.1.4 Cancer risk in dual smokers/snus users

In the Cohort study by Bofetta et al. (2005) the odds ratio for pancreatic cancer in current smokers who had ever used snus (relative to never tobacco users) was 1.86 (95%CI 1.13-3.05) and for lung cancer, it was 0.68 (95%CI 0.51-0.90).

In the cohort study by Luo et al. (2007) current smokers, relative to never tobacco users, were at increased odds of oral cancer (OR 2.5, 95%CI 1.7-3.50, lung cancer (OR 10.2, 95%CI 8.6-12.2) and pancreatic cancer (OR 3.5, 95%CI 2.6-4.6). In these analyses 31% of participants were ever users of snus and 26% current users. Respective odds ratios for ex-smokers were 1.1 (95%CI 0.8-1.7) for oral cancer, 2.6 (95%CI2.2-3.2) for lung cancer and 1.8 (95%CI1.3-2.4) for lung cancer.

In a cohort study by Zendehdel et al. (2008) odds ratios in 'ever' cigarette smokers who used snus relative to 'ever' smokers who never used snus (adjusted for age and BMI) were 0.9 (95%CI 0.7-1.3) for cardia stomach cancer and 1.0 (95%CI 0.9-1.2) for non cardia stomach cancer, suggesting that for stomach cancer the adverse impact of snus among smokers is not large.

In the cohort study by Nordenvall et al. (2011) [+] dual smokers / snus users were at increased risk of colon (RR 1.17, 95% CI 1.04-1.30) rectal (RR 1.21, 95% CI 1.05-1.39) and anal (RR 3.48, 95% CI 0.40-8.64) cancer, relative to non-tobacco users.

21.1.5 Cancer risk in smokers who "switch to snus"

In the Cohort study by Bofetta et al. (2005) the odds ratio for pancreatic cancer in former smokers who had ever used snus (relative to never tobacco users) was 1.37 (95%CI 0.59-3.17) and for lung cancer, it was 0.64 (95%CI 0.24-1.68).

In the population-based case-control study by Ye et al. (1999), former smokers who had ever used snus, relative to never tobacco users, had OR for gastric cancer 1.2 (95% CI 0.8-1.9), in an analysis adjusted for age, BMI, socioeconomic status and alcohol use.

In the population-based case-control study by Lewin et al. (1998) former smokers who were active snus users were not at greater risk of oral cancer than 'never' tobacco users (OR 0.6, 95% CI 0.3-1.3).

21.1.6 Conclusion – cancer

Evidence statement 7a Conclusion - cancer

Several case-control and cohort studies have found statistically significantly increased risks of cancer associated with using snus, after taking account of the risk associated with smoking. The most frequently reported association is for pancreatic cancer, where the risk due to snus appears to be approximately doubled (OR 1.8, 95% CI 1.3-2.5, Boffetta et al. (2008) [+]), and with a dose-response apparent for using more than 10g of snus per day. Other cancer types where increased risk has been demonstrated are oesophageal cancer (OR 1.6, 95% CI 1.1-2.4 Boffetta et al. (2008) [+]), and possibly squamous cell head/neck cancer (OR 10.5, 95% CI 1.4-117.8). The latter value is subject to doubt due to high imprecision of the estimate. In addition increased risks of cancer associated with snus were not consistently evident in two published meta-analyses.

The exact duration of exposure to snus in primary studies that demonstrate an increased risk of cancer is often difficult to determine, however data from Roosaar et al (2008) [+] suggest, by some extrapolation, that 60% of the cohort of men were using snus for 1-6 hours per day over a period of 20 years. Similarly Lewin et al. (1998) [+] dichotomised duration of exposure to snus as greater than, or less than 30 years, and greater than, or less than 125kg consumed, suggesting lengthy exposure.

Evidence statement 7b Risk of cancer associated with snus in the context of burden of disease

The attributable fraction of oesophageal cancer reported to arise from snus in Swedish men is 10.7% (Boffetta et al. 2008 [+]). By applying this percentage to oesophageal cancer incidence for Swedish men in 2010, this appears to represent approximately 31 cases per annum in Swedish men. By the same extrapolation the corresponding value for pancreatic cancer is 69 cases per year. Assuming that cigarette smoking casuses 80% of cases of lung cancer in men (Cancer Research UK, 2012), this would represent over 1500 cases of lung cancer in Sweden per year.

It should be noted that snus contains some levels of known carcinogens, whereas pharmaceutical nicotine is not regarded as a carcinogen.

Evidence statement 7c Smokers

The risks of cancers that are attributed to snus tend to be substantially lower than those that are attributed to smoking. Relative to non-tobacco users, the data reviewed here consistently suggest that smokers are at increased risk of cancer, and specifically cancer of the lung, oesophagus, oropharynx, rectum and anus. Odds ratios and risk ratios tend to be higher than those seen for snus and often a dose-response effect is reported e.g. for oesophageal cancer, Zendehdel et al.

(2008) reported OR 11.2 (95% 6.2-20.2) relative to non-tobacco users, in smokers of 20 or more cigarettes per day.

Evidence statement 7d Dual smokers / snus users

The picture regarding dual smokers / snus users is complicated by poorly applicable data (e.g. cohorts where only a proportion of subjects analysed used snus, or 'current smokers who had ever used snus'). Another drawback of data on dual smokers / snus users is that the intensity of cigarette use (cigarettes/day), relative to snus use, is not known. Another drawback is that many cohort studies attributed tobacco status at baseline and assumed no change in habit in subsequent analyses. Also in many studies analysis of different strata of tobacco users results in small subgroups and low event rates.

Therefore we cannot comment to what degree snus has replaced cigarettes in this subgroup. Nevertheless it appears that the risk of cancer in dual smokers / snus users exceeds the risk of cancer that is attributed to snus alone. Data reviewed here suggest that dual smokers / snus users are at increased risk of lung cancer, pancreatic cancer, oral cancer and cancer of the colon, rectum and anus. The odds ratio for lung cancer reported by Luo et al. (2007) in current smokers relative to never tobacco users where approximately one quarter of smokers were current snus users was 10.2 (95% CI 8.6-12.2); a large proportion of this risk may arise from smoking, rather than snus.

Evidence statement 7e Smokers who switched to snus

There appear to be scant data on smokers who switched to snus, although there appears to be no demonstrated increased risk of cancer, relative to never tobacco users, in former smokers who ever used snus. It is likely that better data exists for ex-smokers in general i.e. from populations outside of Sweden.

21.2 Cardiovascular disease

21.2.1 Association between snus and cardiovascular disease

The systematic review by Broadstock (2007) [+] concluded that an increased risk of death from stroke and MI associated with snus use in non smokers cannot be excluded. This was on the basis of six primary case-control or cohort studies (Huhtasaari et al. 1992, Bolinder et al. 1994, Huhtasaari et al. 1999, Asplund et al. 2003, Hergens et al. 2005, Johansson et al. 2005). Five of these six studies found no significantly increased prevalence of cardiovascular disease for snus users compared with no tobacco use. However, the primary study by Bolinder et al. (1994), a large cohort study of construction workers recruited in the early 1970s found a 40 per cent increased

risk of death from cerebrovascular and cardiovascular disease in snus users compared with no tobacco use. These risks were greater in men aged 35-54 years than for those aged 55 years and over. Broadstock (2007) [+] reports that the excess risks found in the construction worker study may be associated with population and exposure characteristics specific to the cohort, and findings may be less applicable to snus products currently on the market.

Based on broadly the same primary studies as Broadstock (2007) [+], SCENIHR (2008) [+] concluded that there is evidence for an increased risk of fatal myocardial infarction among smokeless tobacco products users (2008).

Bofetta and Straif (2009) [+] performed a systematic review and meta-analysis of cardiovascular effects of smokeless tobacco, and reported a subset of results restricted to data on Swedish snus in never smokers, summarised in the table below.

Table: meta-analyses of risk of cardiovascular disease associated with snus in never smokers in Sweden, from Boffetta and Straif (2009) [+]

Outcome	RR (95% CI)
Any myocardial infarction	0.87 (0.75-1.02)
Fatal myocardial infarction	1.27 (1.07-1.52)
Any stroke	1.02 (0.93-1.13)
Fatal stroke	1.25 (0.91-1.70)

The results provide evidence that use of Swedish snus is not associated with increased incidence of myocardial infarction or stroke in never smokers, but is associated with increased likelihood of fatality due to myocardial infarction.

21.2.2 Risk in the context of cardiovascular disease burden

In Sweden 33712 cases of acute MI were diagnosed in 2010 and the incidence in 2010 was 25 percent lower among both men and women compared to year 2001 (Sederholm-Lawesson, 2012 [+]). The MI incidence was three times higher in men than in women in Sweden in 2010 (Sederholm Lawesson, 2012 [+]). In 2010 in Sweden case fatality within 28 days following MI was 27% in men and 31%, in women (Sederholm Lawesson, 2012 [+]). The source of these data is the Myocardial infarction database for Sweden 1987 – 2010, held by the National Board of Health and Welfare (Socialstyrelsen).

Bofetta and Straif (2009) [+] report the attributable fraction (a function of the RR and exposed population) to snus for fatal myocardial infarction in Sweden in the year 2001 as 5.6% (346 deaths) and for fatal stroke as 5.4 % (220 deaths).

Taking a case fatality for MI of 29% (intermediate value based on the rates for men and women reported by Sederholm-Lawesson, (2012) [+], and the 2010 annual incidence of 33712 cases (Sederholm-Lawesson, 2012 [+]) this represents 9976 fatal cases of MI in Sweden in 2010:

29% x 33 712 = 9976 fatal cases of MI.

The 9976 fatalities per year due to MI (based on 2010 data) would arise from all MI risk factors, including smoking. The attributable fraction estimated by Bofetta and Straif (2009) [+] of 5.6% would represent 559 fatalities in 2010 (0.056 x 9976 = 559), which appears substantially smaller than the 9976 fatalities in total. Therefore the impact of increased fatal MI associated with snus in never smokers appears to be relatively small in the context of wider risk factors for fatal MI, which include smoking.

Bofetta and Straif (2009) [+] report the attributable fraction (a function of the RR and exposed population) to snus for fatal stroke as 5.4 % (220 deaths). This value is based on a relative risk that is not statistically significant (RR 1.25, 95% CI 0.91-1.70). The incidence rate of stroke in Sweden is summarised in the table below, based on World Health Organisation estimates (Truelsen et al. 2006 [+].

Stroke incidence (first stroke) in Sweden (per 100,000), from a World Health Organisation estimate based on papers published between January 1993 and June 2004 and reported in Truelsen et al. (2006) [+]

Age group	Men	Women	Total
25-34	8	6	14
35-44	16	13	29
45-54	122	65	187
55-64	294	164	458
65-74	841	535	1376
75-84	1579	1287	2866
85+	1943	1767	3710
Total	4803	3837	8640

The incidence data appear to relate to an incidence rate per annum. The Swedish Stroke Registry reports that Sweden has approximately 23,000 first strokes per annum (Riks-Stroke, 2011).

21.2.3 Cardiovascular disease in smokers

In the population-based case-control study by Huhtasaari et al. (1992) smokers were at increased odds, relative to non-tobacco users, of myocardial infarction (OR 1.87, 95% CI 1.40-2.48). Relative to snus users, smokers had OR 2.09 (95% CI 1.39-3.15).

In the cohort study by Bolinder et al. (1994), smokers of <15 cigarettes per day, relative to non-tobacco-users, were at increased risk of death due to cardiovascular disease (OR 1.8, 95% CI 1.6-2.0). Those who smoked 15 or more cigarettes per day had OR 1.9 (95% CI 1.7-2.2).

In the population-based case-control study by Huhtasaari et al. (1999) current smokers (who never used snus), relative to 'never' tobacco users had OR 3.65 (95% CI 2.67-4.99) for acute myocardial infarction.

A multivariate analysis that excluded snus users from the case controlled study by Asplund et al. (2003) found that regular smoking was not an independent predictor of stroke (OR 1.74, 95% CI 0.85-3.54) whereas elevated blood pressure was (OR 6.98, 95% CI 3.04-16.0). In a univariate analysis smoking was associated with smoking, relative to 'never tobacco use' (OR 1.86, 95% CI 1.13-3.05), although this analysis did not take account of other risk factors including snus use Asplund et al. (2003).

21.2.4 Cardiovascular disease in dual smokers/snus users

In the population-based case-control study by Huhtasaari et al. (1999) current smokers who also used snus (relative to 'never' tobacco users) had OR 2.66 (95% CI 1.24-5.71) for acute myocardial infarction. This estimate of risk does not look substantially different to the risk in smokers who never used snus from the same study, presented above.

In the population-based case-control study by Hergens et al. (2005) current smokers who were also current snus users were at increased risk of acute myocardial infarction relative to 'never tobacco users' (OR 2.3, 95% CI 1.6-3.4).

21.2.5 Cardiovascular disease in smokers who "switch to snus"

In the population-based case-control study by Hergens et al. (2005) former smokers who were current snus users, relative to 'never tobacco users' had greater risk of acute myocardial infarction (OR 1.6, 95% CI 1.1-2.2).

21.2.6 Conclusion – cardiovascular outcomes

Evidence statement 8a Conclusion – cardiovascular outcomes

Three well conducted systematic reviews of largely the same base of primary studies provide evidence that the use of Swedish snus is associated with greater likelihood of fatal myocardial infarction (OR 1.27, 95% CI 1.07-1.52, Boffetta and Straif 2009 [+]). The exact duration of exposure to snus in primary studies that demonstrate an increased risk of death due to cardiovascular disease is not reported. However Bolinder et al. (1994) [+] report that 87% of deaths due to cardiovascular disease were in snus users of >15 years duration, suggesting that exposure is lengthy.

SCENIHR (2008) [+] states that there is no change in resting blood pressure associated with chronic exposure to nicotine from smokeless tobacco products, but that there is experimental evidence that nicotine may affect lipid metabolism. Based on evidence presented here, it is not possible to rule out whether medicinal nicotine replacement therapy, if administered indefinitely, would produce similar long term cardiovascular effects to those of Swedish snus.

Evidence statement 8b Risk associated with snus in the context of burden of cardiovascular disease

Bofetta and Straif (2009) [+] report the attributable fraction (a function of the RR and exposed population) to snus for fatal myocardial infarction in Sweden in the year 2001 as 5.6% (346 deaths) and for fatal stroke as 5.4 % (220 deaths). This analysis estimates the harm arising from snus after taking account of the harm of smoking. Sweden has each year, approximately 33,000 cases of acute myocardial infarction and approximately 23,000 cases of first stroke.

Evidence statement 8c Smokers

Smokers are at substantially increased risk of myocardial infarction, compared to non-tobacco users, an odds ratio reported by Huhtasaari et al. (1999) was 3.65 (95% CI 2.67-4.99). Smokers are also at increased risk of myocardial infarction relative to exclusive snus users (OR 2.09, 95% CI 1.39-3.15, Huhtasaari et al. (1992).

Evidence statement 8d Dual smokers / snus users

Two studies have reported that current smokers who also use snus are at double or more odds of myocardial infarction relative to non-tobacco users: OR 2.66 (95% CI 1.24-5.71, Huhtasaari et al. 1999), OR 2.3 (95% CI 1.6-3.4, Hergens et al. 2005). These findings do not isolate separately the elements of risk that arise from smoking and from snus.

Evidence statement 8e Smokers who switch to snus

In the population-based case-control study by Hergens et al. (2005) former smokers who were current snus users, relative to 'never tobacco users' had greater risk of acute myocardial infarction (OR 1.6, 95% CI 1.1-2.2).

21.3 Diabetes and related conditions

SCENIHR (2008) [+] reviewed several Swedish primary studies exploring a causal relationship between snus and development of type-II diabetes. One study found a RR of diabetes arising from snus use to be 3.9 (95% CI 1.1-14.3) when restricted to non smokers (Persson et al. 2000 in SCENIHR (2008) [+]). A cohort study found that consumption of >4 cans/week of snus at baseline was associated with increased odds of metabolic syndrome at 10 years; OR 1.6 (95%CI 1.26-2.15), (Norberg et al. 2006 in SCENIHR 2008 [+]). SCENIHR (2008) [+] does not draw firm conclusions on the relationship between snus and diabetes due to limitations in the design of studies.

Two further studies that were not included in SCENIHR (2008) [+] are discussed here. Hansson et al. (2011) [+] investigated weight gain (≥ 5%) and tobacco use in a prospective cohort study of 9954 men in Stockholm County. Exclusive snus users were at modestly increased odds of weight gain (relative to no tobacco use) when assessed over a 7 year period (OR 1.31, 95% CI 1.04-1.65), with adjustment for age, baseline weight, alcohol, exercise, fruit and breakfast consumption. The OR for incident obesity during the study period was 1.93, 95% CI 1.13-3.30.

Smoking, relative to never using tobacco, was not statistically significantly associated with an increase in body weight ≥5% (OR 1.24, 95%CI 1.00-1.54) when adjusted for age, baseline weight, alcohol, exercise, fruit and breakfast consumption. Smoking plus using snus was associated with an increase in body weight ≥5% (OR 1.34, 95%CI 1.17-1.53) when adjusted for age, baseline weight, alcohol, exercise, fruit and breakfast consumption.

Another measure in this study was incident obesity (defined as BMI>30). Snus use, relative to never using tobacco was associated with incident obesity (OR 1.93, 95%CI 1.13-3.30) when adjusted for age, baseline weight, alcohol, exercise, fruit, breakfast. Current smoking, relative to never using tobacco, was not associated with incident obesity with adjustment for age, baseline weight, alcohol, exercise, fruit and breakfast (OR 1.31, 95%CI 0.78-2.22). Combined current smoking and snus use was also not associated with incident obesity with adjustment for age, baseline weight, alcohol, exercise, fruit and breakfast (OR 1.25, 95%CI 0.91-1.73).

An analysis of the incidence of diabetes in the MONICA study was performed by Eliasson et al. (2004) [+]. In an eight year study period there were no cases of diabetes in exclusive snus users,

based on case notes and oral glucose tolerance tests. Consistent exclusive smokers had OR 4.61 (95% CI 1.37-15.5), adjusting for age, follow up and annual percentage weight gain. The corresponding OR in ex snus users was 1.72 (95% CI 0.20-14.8) and in smokers who switched to snus, 3.25 (95% CI 0.78-13.6).

Conclusion – diabetes and related conditions

SCENIHR (2008) [+] reports that studies have suggested there is an increased risk of diabetes and the related metabolic syndrome associated with snus, but notes limitations in their designs. There is evidence from one cohort study that exclusive snus users may be at greater risk of obesity than non tobacco users, whereas another cohort study found no evidence of diabetes in snus users. The data on diabetes and related conditions presented here appear equivocal.

21.4 Oral lesions

SCENIHR (2008) [+] states that oral tobacco is associated with changes to the non-keratinised mucosa and gingival of the mouth at the site where a smokeless tobacco product is placed. In Scandinavia these are referred to as snus induced lesions (SILs), and use of this term does not rule out a risk of oral malignancy (SCENIHR 2008 [+]). SILs have been classified in four degrees of severity/progression, marked by increasing wrinkling, thickening and discolouration (Axel et al. 1976, in SCENIHR 2008 [+]). Amongst snus users, prevalence of SILs has been estimated at 94% (Axel 1976, in SCENIHR 2008 [+]) and at 80% (salonen et al. 1990, in SCENIHR 2008 [+]). Snus can also cause retractions of the gingiva, at a prevalence of 24% for loose snus and 3% for portion packed snus (Andersson and Axel 1989 in SCENIHR 2008 [+]).

Conclusion – oral lesions

There is good evidence that Swedish snus induced lesions are present on the oral mucosa of over 90% of snus users, and the pattern of progression of the lesions has been defined. Whether the lesions are at high risk of progressing to oral cancer is less clear.

21.5 Psychological outcomes

The SCENIHR report (2008) [+] does not discuss the relationship between tobacco and depressive illness, other than in the context of the addictive nature of tobacco and depressive mood as a symptom of nicotine withdrawal.

SCENIHR (2008) [+] states that in contrast with medicinal nicotine replacement therapy, there is clear evidence that smokeless tobacco can induce dependence, since users of smokeless tobacco develop cravings and nicotine withdrawal symptoms when attempting to abstain, and find it difficult to quit. SCENIHR (2008) [+] also states that the time course and symptoms of withdrawal from smokeless tobacco are generally similar to those of cigarette smokers although depressive symptoms and negative affect do not appear to be observed among abstinent smokeless tobacco product users.

One published paper by Edwards et al. (2011) presents data on the association between cigarette smoking or using snus, and major depression, derived from a sample of Swedish same sex twins (12,774 males and 15,249 females). Both cigarette smoking and using snus appear to be associated with increased odds of major depression. For snus, the OR [95% CI] for major depression was 1.28 [1.14-1.45] in males and 2.01 [1.52-2.66] in females. Likewise, in male snus users, medium and high levels of nicotine dependence were associated with major depression: OR [95% CI] 1.39 [1.17-1.66] for medium dependence and OR 1.71 [1.29-2.27] for high dependence. Conversely in females it was very low nicotine dependence that was associated with major depression (OR 2.42 [1.53-3.95]).

A caveat in discussing the data from Edwards et al. (2011) here is that the paper does not provide the original and full description on how the data were gathered, and does not permit a critical appraisal of the validity of the findings.

A cross sectional study (Engstrom et al. 2010 [-]) undertaken in Stockholm County, Sweden found that in men, there was no association between psychosocial distress and snus use: the odds ratio for snus use (psychosocial distress present:absent) was 0.96 (95% CI 0.83-1.10) whereas there were associations for smoking (OR 1.33 [95% CI 1.12-1.58]) and dual smoking/snus use (OR 1.68 [95% CI 1.28-2.20]). In women there was only an association between smoking and psychological distress (OR 1.54 [95% CI 1.37-1.73]).

Conclusion – psychological outcomes

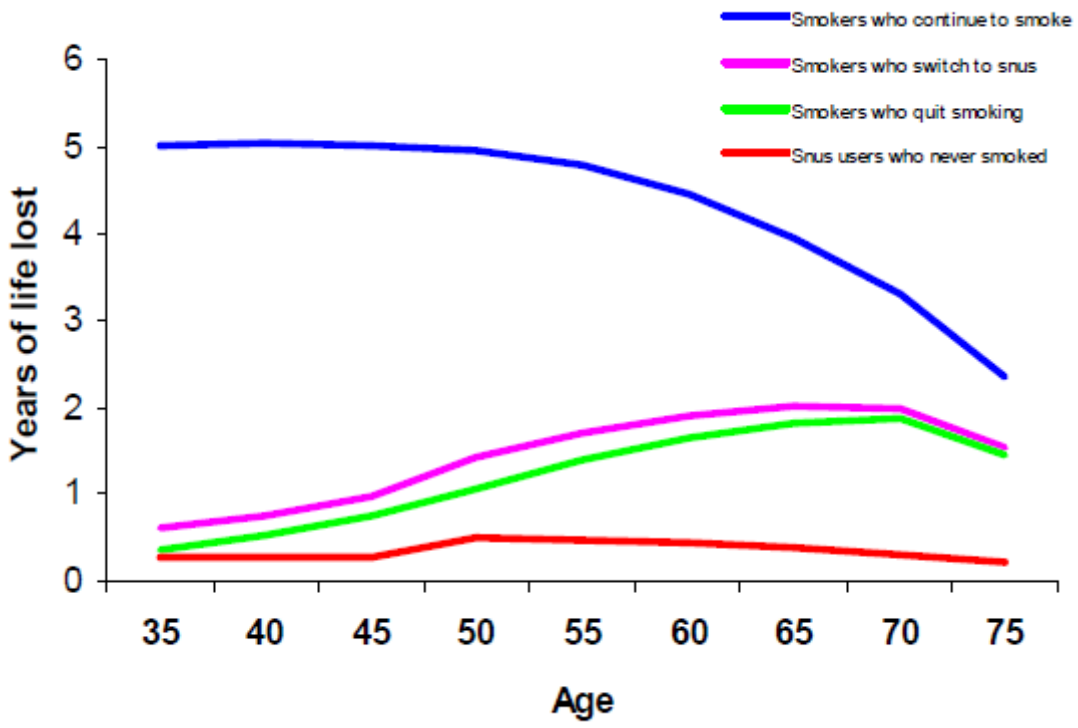
The nicotine in snus can induce dependence, since users of smokeless tobacco develop cravings and nicotine withdrawal symptoms when attempting to abstain. Nicotine withdrawal symptoms can include depressive mood. On the basis of one study Edwards et al. (2011), both cigarette smoking and using snus appear to be associated with increased odds of major depression. For snus, the OR [95% CI] for major depression was 1.28 [1.14-1.45] in males and 2.01 [1.52-2.66] in females. However these results are reported from a published summary and a full paper would need to be seen in order to comment on causation. A second study found no association between snus use and psychosocial distress in either men or women (Engstrom et al. 2010 [-]).

21.6 Estimated years of life lost in different tobacco subgroups

SCENIHR (2008) [+] report that the precise magnitude of health gains arising from choosing less harmful alternatives to smoking are difficult to quantify. SCENIHR (2008) [+] cite a modelling study

by Gartner et al. (2007) which reported estimated years of life lost in different groups based on tobacco habits. SCENIHR used data from Gartner et al. (2007) to produce the figure shown below.

Figure - Estimated years of life lost by male smokers, male smokers who quit smoking, male smokers who switch to snus, and male snus users. Produced by SCENIHR (2008) [+] on the basis of data from Gartner et al. (2007) [reproduced with permission from SCENIHR]



SCENIHR (2008) [+] report that the data suggest that the health benefit experienced by a smoker who switches to snus but would not otherwise have quit smoking is substantially greater than the risk of snus (compared to non-tobacco users). SCENIHR (2008) [+] conclude that according to Gartner's model, the overall population effect of snus is likely to be beneficial.

NRT should be an inherently safer option than Swedish snus because it does not contain the numerous potentially harmful constituents e.g. nitrosamines. The figure above does not show a profile for smokers who concurrently use snus. In terms of NRT, a safety issue to overcome is whether through smoking with concurrent NRT, any harm is likely to result from the maximum blood concentrations of nicotine achieved and also the potentially long term exposure to nicotine. Data from Swedish studies presented in this report appear to be based on long term exposure (i.e. decades). The same studies do not accurately estimate the volume of nicotine taken over time from cigarettes and snus combined. Studies of efficacy may inform the PDG whether NRT use with concurrent smoking leads to a reduced volume of smoking expressed as cigarettes per day.

22 References (Swedish snus)

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23 Example literature search strategy (Swedish snus)

The search strategy shown below was used for the Medline database, 1946 – 9th January 2011. The search strategy was adapted for Embase, Psychinfo and the Cochrane Library databases.

1. smokeless tobacco.mp. or exp Tobacco, Smokeless/

2. ((oral* or mouth* or buccal* or dip* or chew*) adj4 (tobacco or snus or snuff)).ti,ab.

3. (snus or snuff).ab,ti.

4. ((original or portion or strong or white or extra or Al Capone or bat or Below zero or Blue Ocean or Camel or Catch or Chaini or Khaini or Chess or Crushed ice or Ettan or General or Goteborgs or Rape or Gotland or Annis or Gallaher or Gellivare or Gotlandskt or Julesnus or Granit or Gringo or Grovsnus or Gustavus or Fiedler or Jagarpris or Jakobsonns or Kaliber or Kardus or Carneval or Knekt or Knok or Knox or Kronan or LD or Landstroms or Lundgren or Lucky or strike or Marlboro or Mega or Metropol or Pole or Mocca or Montecristo or Nordstrammen or Northener or Oden* or Offroad or Olde Viking or Oliver Twist or Onico or Phantom or Piccanell or Prince or Probe or Whiskey or Rallarsnus or Roda or Romeo or Julieta or Roots or Skruf or Snusab or Snusfabrik or Taboca or Thunder or Tre Ankare) adj2 (snus or snuff or tobacco)).ti,ab.

5. 1 or 2 or 3 or 4

6. (Swede* or Swedish or Norway or Norwegian* or Nordic or norsk or Denmark or Danish or Dane or Finland or Finnish or Iceland*or Scandinavian).ab,ti.

7. exp Sweden/ or exp Norway/ or exp Denmark/ or exp Finland/ or exp Iceland/

8. 6 or 7

9. 5 and 8

24 Study quality assessment (studies of Swedish snus)

Study

Broadstock, M. (2007) Systematic review of the health effects of modified smokeless tobacco products. New Zealand Health Technology Assessment. Available at: http://nzhta.chmeds.ac.nz/publications/smokeless_tobacco.pdf

Design

Systematic review of 16 primary studies. Aim: to systematically identify and appraise international epidemiological evidence relating to the major health effects, for reduced harm, of using modified smokeless tobacco products compared with conventional combustible tobacco products; the safety of using modified smokeless tobacco products compared with not using any form of tobacco is also considered.

Participants

Primary study inclusion criteria:

- English language
- Reduced toxicity smokeless tobacco (principally Swedish snus)
- Of design: case-control, cohort, all or none, systematic review
- >100 participants
- Reporting outcomes: cancer, cardiovascular disease, other diseases

Interventions / comparators

- Snus versus smoked tobacco
- Snus versus no tobacco exposure

Smoking behaviour / co-interventions

Interpretation of primary study results takes account of exposure to potential confounders: smoking, alcohol, exercise.

Safety Outcomes

Key findings and conclusions (Broadstock, 2007)

- Six case-control studies suggest that use of Swedish snus, compared with no tobacco use, is not associated with increased rates of oral, neck and gastro-intestinal cancers, although larger studies are required to increase the precision of risk estimates.
- Five of six case-control/cohort studies of risks of cardiovascular disease in male Swedish snus users found no increased risk compared with no tobacco use. One large cohort study of Swedish construction workers recruited in the early 1970s found a 40% increased risk of death from cardiovascular disease in snus users compared to non-tobacco users, and higher risks in middle aged men. This finding may have limited applicability to snus products available today, but should not be ruled out. Further research is required with better controlling of confounders.
- In a large cohort study of construction workers there was no increased mortality from all cancers associated with snus use, but there was a 40% increased risk for all cause mortality. No association was found between snus use and inflammatory bowel disease, diabetes and malignant lymphomas.
- The review did not include studies of the addiction potential of snus or oral mucosal changes, lesions or gingival effects.

Studies included in Broadstock (2007) review

1. Hansson, L. E., Baron, J., Nyren, O., Bergstrom, R., Wolk, A., & Adami, H. O. (1994). Tobacco, alcohol and the risk of gastric cancer. A population-based case-control study in Sweden. International Journal of Cancer, 57, 26-31.
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12. Johansson, S. E., Sundquist, K., Qvist, J., & Sundquist, J. (2005). Smokeless tobacco and coronary heart disease: A 12-year follow-up study. European Journal of Cardiovascular Prevention & Rehabilitation, 12, 387-392.
13. Persson, P. G., Hellers, G., & Ahlbom, A. (1993). Use of oral moist snuff and inflammatory bowel disease. International Journal of Epidemiology, 22, 1101-1103.
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16. Roth, H. D., Roth, A. B., & Liu, X. (2005). Health risks of smoking compared to Swedish snus. Inhalation Toxicology, 17, 741-748.
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Study quality comments

Highly methodologically sound. Clear research question defined. Literature search strategy described in full and reproducible. Study selection process described. Study quality was assessed using stated validity criteria, and results presented with full description of strengths and weaknesses.

Overall Quality Score: [+]

Study

European Commission Scientific Committee of Emerging and Newly Identified Health Risks (SCENIHR) (2008). Health Effects of Smokeless Tobacco Products. Available at: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_013.pdf

Design

European Commission report prepared by an expert committee. Aim: to review the scientific basis for a regulatory framework for smokeless tobacco. Research questions:
1. What are the adverse health effects of smokeless tobacco products?
2. What is the addiction potential of smokeless tobacco products?
3. Does the available data support the claim that smokeless tobacco may constitute a smoking cessation aid comparable to pharmaceutical nicotine replacement products?
4. What is the impact of smokeless tobacco use on subsequent initiation of smoking?
5. Is it possible to extrapolate the information on the patterns of smokeless tobacco use, smoking cessation and initiation from countries where oral tobacco is available to EU countries where oral tobacco is not available?

Participants

Numerous primary studies of smokeless tobacco

Interventions / comparators

Smokeless tobacco.
Smoking.

Smoking behaviour / co-interventions

N/A

Pharmacokinetic outcomes

Smokeless tobacco delivers quantities of nicotine comparable to those typically absorbed from cigarette smoking, although delivery of nicotine from STP lacks the high initial concentration and speed of delivery that results from inhalation of tobacco smoke, and may therefore have relatively less addiction potential than cigarettes. Nicotine levels obtained from STP are generally higher than those typically obtained from nicotine replacement therapy, which is considered to have a low addiction potential.

Safety Outcomes

Conclusion: cardiovascular outcomes

Human experimental studies show that smokeless tobacco use leads to short term increases in blood pressure and heart rate. Snus use may cause endothelial dysfunction; other moist snuff products have not been studied.

Conclusion: cancer

There is sufficient evidence that the use of a wide variety of STP causes cancer in humans. The pancreas has been identified as a main target organ in two Scandinavian cohort studies.

The published studies also support a causal role of STP in oesophageal cancer. Four out of six studies were from Northern Europe. Tobacco smoking and alcohol drinking was controlled in several of the studies and a causal association is further supported by positive exposure response data.

In five Swedish or Scandinavian studies, an increased risk of oral cancer has not been proven in snus users, however a recent cohort study from Sweden reported a statistically significant three-fold increase of combined oral and pharyngeal cancer, adjusted for tobacco smoking and alcohol drinking. Results among never smokers were similar. Also, in one study from Sweden among users of moist snuff, an increased overall risk of head and neck cancer was not detected. However, an increased risk was observed among a small subgroup of never-smokers.

Diabetes

The acute effects of Swedish moist snuff on insulin sensitivity were investigated in a randomised treatment

study of 7 healthy smokers (4 females and 3 males, mean age 31 11 years) with the normoglycaemic clamp technique (Attvall et al. 1993). Measurements 12 were performed while either smoking one filtered cigarette (1.2 mg nicotine) per hour, one sachet of snus (1 mg nicotine) per hour or after 2 days of total tobacco abstinence. The steady-state plasma nicotine levels were similar during smoking and use of snus. The insulin and glucose levels were also similar during all three sessions. Smoking, but not use of snus, impaired insulin action, mainly due to a lower peripheral glucose uptake.

Addiction potential

In contrast with NRT, there is clear evidence that smokeless tobacco can induce dependence, since users of smokeless tobacco develop cravings and nicotine withdrawal symptoms when attempting to abstain, and find it difficult to quit. The time course and symptoms of withdrawal from smokeless tobacco are generally similar to those of cigarette smokers although depressive symptoms and negative affect do not appear to be observed among abstinent STP users.

- There is sufficient evidence that the use of a wide variety of STP causes cancer in humans. The pancreas has been identified as a main target organ in two Scandinavian cohort studies.
- In Sweden, the evidence for an increased risk of oral cancer in users of oral tobacco is less clear**.** In one study from Sweden among users of moist snuff, an increased risk of head and neck cancer has been found among never-smokers. A recent cohort study from Sweden reported a statistically significant three-fold increase of oral and pharyngeal cancer, adjusted for tobacco smoking and alcohol drinking.
- It appears that the use of smokeless tobacco increases the risk of death after myocardial infarction, but that it does not increase the risk of myocardial infarction.
- The Swedish data do not support the hypothesis that smokeless tobacco (i.e. Swedish snus) is a gateway to future smoking. The marked social, cultural and product differences between North America and Europe suggest caution in translating findings across countries, also within Europe.

Study quality comments

Overall Quality Score: [+]

The methodology section describes the following activities:

- Reference to an International Agency for Research on Cancer monograph
- Public call for relevant articles in English-language, peer reviewed scientific journals
- Focus on epidemiologic, experimental (human and animal) and cell culture studies
- Evaluation of positive and negative studies
- Critical appraisal, including exploring uncertainty, confounding, bias, chance findings, strength of associations, exposure, dose-response and general validity.

Study

Boffetta, P., Hecht, S., Gray, N., Gupta, P. & Straif, K. (2008) Smokeless tobacco and cancer. Lancet Oncology, 9: 667-675.

Design

Systematic review and meta-analysis

Participants

6 relevant studies of snus conducted in Sweden / Norway– considerable overlap with reviews by Broadstock (2007) and SCENIHR (2008)

Interventions / comparators

Smokeless tobacco (American and Scandinavian). Data presented here are Scandinavian.

Smoking behaviour / co-interventions

Many participants in the primary cohort / case-control studies were smokers – smoking was controlled for in multivariate analyses.

Safety Outcomes

RR (snus:no snus), controlling for smoking

Cancer type	Pooled estimate of RR (95% CI)	p heterogeneity (individual studies)	p heterogeneity (geographical regions)
Oral	1.0 (0.7-1.3)	0.4	0.01
Oesophageal	1.6 (1.1-2.4)	0.08	0.8
Pancreatic	1.8 (1.3-2.5)	0.6	0.5
Lung	0.8 (0.6-1.0)	1.0	0.02

Study quality comments

Overall Quality Score: [+]

Search strategy and study selection criteria described in brief.
No details provided of methods employed for meta-analysis.
The authors included only studies that controlled for confounding factors, including smoking.
There was little evidence of heterogeneity in individual studies, but there was evidence of heterogeneity across different geographical regions.
Funding source not reported. Authors state no conflict of interest.

Meta-analyses uses data from 6 primary Nordic studies:

- Lewin et al. (1998)
- Schildt et al. (1998)
- Lagergren et al. (2000)
- Boffetta et al. (2005)
- Luo et al. (2007)
- Zendehdel et al. (2008)

Study

Boffetta, P. & Straif, K. (2009) Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. BMJ, 339: b3060.

Design

Systematic review & meta-analysis

Participants

8 primary cohort or case-control studies are included.

Interventions / comparators

Exposure is snus and outcomes are myocardial infarction, stroke and death due to myocardial infarction and stroke.

Smoking behaviour / co-interventions

The meta-analysis was restricted to samples of never smokers only

Safety Outcomes

Meta-analyses of risk of cardiovascular disease associated with snus in never smokers in Sweden

Outcome	RR (95% CI)
Any myocardial infarction	0.87 (0.75-1.02)
Fatal myocardial infarction	1.27 (1.07-1.52)
Any stroke	1.02 (0.93-1.13)
Fatal stroke	1.25 (0.91-1.70)

Study quality comments

Overall Quality Score: [+]

Scant details provided on methods used for the meta-analysis – random effects model used, and a test performed for statistical heterogeneity.

Basic literature search performed in Pubmed based on MeSH terms.

Study

Lee, P. N. & Hamling, J. (2009) Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. BMC Medicine, 7: 36.

Design

Systematic review & meta analysis. Aim: to review epidemiological evidence in Western countries relating smokeless tobacco to cancer and to quantify risks.

Participants

Study inclusion criteria:

- published in a peer reviewed journal (or the results publicly available)
- epidemiological study in humans, of cohort or case-control design
- study location specified
- any form of cancer as the outcome
- chewing tobacco, oral snuff or unspecified smokeless tobacco as the exposure.

Study exclusion criteria:

- conducted in an Asian or African population
- no control group
- inappropriate design (case report, qualitative study or review/meta analysis).

Interventions / comparators

Exposure: smokeless tobacco. Outcome: cancer (odds ratios for different cancer types)
Literature search: MEDLINE search conducted in May 2008 of "cancer" AND ("smokeless tobacco" OR "chewing tobacco" OR "snuff" OR "snus"), supplemented by citations in recent reviews and in the papers obtained.

Smoking behaviour / co-interventions

The confounding role of smoking is handled in two ways:

1. by using primary data already adjusted for smoking in multivariate analyses
2. by restricting analyses to lifelong non smokers only

Safety Outcomes

RR/OR for cancer based on studies of snus in Scandinavia

Cancer type	**Pooled estimate of RR/OR**		
	Overall data [1]	**Smoking adjusted [2]**	**Never smokers [3]**
Oropharyngeal	0.97 (0.68-1.37) [5]	0.97 (0.68-1.37) [5]	1.01 (0.71-1.45) [5]
Oesophageal	1.10 (0.92-1.33)	1.10 (0.92-1.33)	1.92 (1.00-3.68)
Pancreatic	1.20 (0.66-2.20)	1.20 (0.66-2.20)	1.61 (0.77-3.34)
Lung	0.71 (0.66-0.76)	0.71 (0.66-0.76)	0.82 (0.52-1.28)
Any cancer	1.03 (0.91-1.16)	1.03 (0.91-1.16)	1.10 (0.94-1.29)

[1] Not restricted on smoking status or on adjustment for smoking
[2] Restricted to estimates for the whole population (adjusted for smoking) or never smokers
[3] Restricted to never smokers only
The study found no statistically significant association between snus use and any type of cancer.

Study quality comments

Overall Quality Score: [+]

Very good description of all methods provided.
Statistical heterogeneity was tested for, and outlying data removed.
Meta-regression analysis was performed to investigate to what degree the estimates in primary studies vary by various factors, including region, period, study design, publication before/after 1990, smoking adjustment, alcohol adjustment.

Study

Hansson, J., Galanti, M. R., Magnusson, C. & Hergens, M. P. (2011) Weight gain and incident obesity among male snus users. BMC Public Health, 11: 371.

Design

Prospective cohort study

Participants

9954 men (5422 never smokers, 4532 ever smokers) from an original sample of 50,000 Stockholm county residents, aged 18-84 years.

Interventions / comparators

Two surveys were conducted, in 2002 and in 2007.
Subjects were categorised into 10 mutually exclusive groups according to tobacco use:

- No tobacco use
- Daily snus
    - Stable current snus use
    - Stable former snus use
    - Quit snus during follow up
    - Began snus during follow up
- Daily smoking
    - Stable current smoker
    - Stable former smoker
    - Quit smoking during follow up
    - Began smoking during follow up
- Other, including combined snus/smoking

18% of respondents reported snus use at baseline (n=1793), of these 839 were never smokers. At follow up 445 were still exclusive snus users.
Respondents reported their height, weight, exercise level, alcohol consumption, educational level, frequency of eating breakfast, fruit consumption.

Safety Outcomes

OR for increase in body weight ≥5% with never tobacco users as referent group:
OR (stable daily current **snus** use versus never tobacco use): 1.39 (95%CI 1.12-1.73) adjusted for age. OR 1.41 (95%CI 1.13-1.75), adjusted for age and baseline weight. OR 1.31 (95%CI 1.04-1.65) adjusted for age, baseline weight, alcohol, exercise, fruit, breakfast.

OR (stable daily current **smoking** versus never tobacco use): 1.52 (95%CI1.25-1.84) adjusted for age. OR 1.50 (95%CI 1.24-1.82), adjusted for age and baseline weight. OR 1.24 (95%CI 1.00-1.54) adjusted for age, baseline weight, alcohol, exercise, fruit, breakfast.

OR (**smoking plus snus** versus never tobacco use): 1.46 (95%CI 1.29-1.64) adjusted for age. OR 1.50 (95%CI 1.33-1.69), adjusted for age and baseline weight. OR 1.34 (95%CI 1.17-1.53) adjusted for age, baseline weight, alcohol, exercise, fruit, breakfast.

OR (stable daily current **snus** use versus never tobacco use): 1.39 (95%CI 1.12-1.73) adjusted for age. OR 1.41 (95%CI 1.13-1.75), adjusted for age and baseline weight. OR 1.31 (95%CI 1.04-1.65) adjusted for age, baseline weight, alcohol, exercise, fruit, breakfast.

OR for incident obesity during follow up (BMI ≥30) with never tobacco users as referent group:
OR (stable daily current **snus** use versus never tobacco use): 1.68 (95%CI 1.03-2.72) adjusted for age. OR 1.77 (95%CI 1.06-2.95), adjusted for age and baseline weight. OR 1.93 (95%CI 1.13-3.30) adjusted for age, baseline weight, alcohol, exercise, fruit, breakfast.

OR (stable daily current **smoking** use versus never tobacco use): 1.46 (95%CI 0.94-2.26) adjusted for age.

OR 1.71 (95%CI 1.07-2.72), adjusted for age and baseline weight. OR 1.31 (95%CI 0.78-2.22) adjusted for age, baseline weight, alcohol, exercise, fruit, breakfast.

OR (stable daily current **smoking plus snus** use versus never tobacco use): 1.61 (95%CI 1.22-2.12) adjusted for age. OR 1.44 (95%CI 1.08-1.92), adjusted for age and baseline weight. OR 1.25 (95%CI 0.91-1.73) adjusted for age, baseline weight, alcohol, exercise, fruit, breakfast.

Authors conclude that snus use is moderately associated with weight gain and obesity.

Study quality comments

Overall Quality Score: [+]

Authors note that BMI does not report the proportion of fat/muscle in the body. The study relies on self-report of outcomes and has a low participation rate at baseline. As there was a detectable weight gain in response to smoking cessation, this suggests no bias as a result of different response rates in tobacco habit subgroups.

Study

Eliasson, M., Asplund, K., Nasic, S. & Rodu, B. (2004) Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: the northern Sweden MONICA study. Journal of Internal Medicine, 256: 101-110.

Design

Cohort study. Aim: to investigate the effects of smoking and snus on type II diabetes.

Participants

3384 men aged 25-74 years and free from diabetes at baseline, randomly drawn from the WHO MONICA study in Sweden: four population based surveys conducted in the years 1986, 1990, 1994 and 1999.

Interventions / comparators

Questionnaire responses categorised participants as smoker (ex, current, never), snus user (ex, current, never) and also snus (<2, 2-3, >3 boxes/week). Also data was collected for known cases of diabetes (from case records), and oral glucose tolerance test (OGTT) was employed in 513 randomly selected men, to detect undiagnosed impaired glucose tolerance.
Other data collected were for weight, height, waist circumference, physical activity and alcohol consumption.

Safety Outcomes

127 men developed known diabetes during follow up. There were no cases of diabetes in exclusive snus users.

OR for incident **known diabetes** (adjusted for age, follow up and annual % weight gain), with never tobacco users as referent group:
Consistent exclusive smokers: 4.61 (95%CI 1.37-15.5)
Ex snus users: 1.72 (95% CI 0.20-14.8)
Smokers who switched to snus: 3.25 (95% CI 0.78-13.6)

There was no statistically significant association (OR) between any tobacco use category and blood test determined diabetes (including impaired glucose tolerance to detect insidious disease) in the 513 men who received OGTT.

Study quality comments

Overall Quality Score: [+]

Tobacco exposure status was verified with a blood test for nicotine and cotinine in a subgroup of 321 subjects. For the remainder, tobacco group relies on self report.
The study is limited by low rates of diabetes. Possibly more cases of insidious disease may have been detected if the whole 'undiagnosed sample' had undergone OGTT.

Study

Nordenvall, C., Nilsson, P. J., Ye, W. & Nyren, O. (2011) Smoking, snus use and risk of right- and left-sided colon, rectal and anal cancer: a 37-year follow-up study International Journal of Cancer, 128: 157-165.

Design

Cohort study – Swedish construction workers study. Aim: to investigate the relationship between smoking, snus and cancer of the colon, rectum and anus

Participants

Analytic sample was 343,822 men with no history of cancer, drawn from a construction worker cohort who attended health check ups between 1971 and 1992.

Interventions / comparators

Cancer cases were identified from the Swedish National Cancer Institute based on ICD codes. Follow-up was defined as first visit to diagnosis of cancer, death, emigration or December 31 2007.

Smoking behaviour / co-interventions

Snus exposure variable was dichotomous, smoking exposure variable was categorical.

Safety Outcomes

Follow up had mean 24 years and comprised 8,208,741 person-years in total.

Table: RR [95% CI] of colon, rectum and anus cancer (adjusted for age and BMI)

	Colon	Rectum	Anus
No tobacco (referrant)	1	1	1
Pure smoker	1.08 [0.99-1.19]	1.16 [1.04-1.30]	2.41 [1.06-5.48]
Pure snus user	1.08 [0.91-1.29]	1.05 [0.85-1.31]	0.61 [0.07-5.07]
Dual smoker/snus user	1.17 [1.04-1.32]	1.21 [1.05-1.39]	3.48 [1.40-8.64]

Study quality comments

Overall Quality Score: [+]

Tobacco exposure was determined on the basis of the first visit only.

Cox proportional hazard models of exposure and outcome were adjusted for age, BMI.

Analyses are performed based on exposure as reported at first visit and also with exposure continued through follow-up (on the assumption that tobacco habits did not change).

A sensitivity analysis was performed excluding participants in the 1971-1975 period, where misclassification of tobacco status was possible – the sensitivity analysis showed that the primary analysis was robust.

Kotlyar, Mendoza-Baumgart & Li . Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge . Tobacco Control 16[2], 138-142. 2007.

Design

Randomised crossover study (5 arms, testing 5 different products)

Participants

n=10 American moist snuff (Copenhagen) users of >1year duration. Average use was 2.4 cans per week and an average 8.1 dips/day. All subjects were male. Average age 30.9 years (range 20 to 49).

Interventions / comparators

The following nicotine containing products were evaluated:

- Ariva (smokeless tobacco lozenge)
- Copenhagen (moist snuff)
- Stonewall (smokeless tobacco lozenge)
- Revel (smokeless tobacco packet)
- Commit (4 mg medicinal nicotine lozenge)

Of these, only data for Commit & Copenhagen are presented here.
Nicotine concentrations were obtained during product use and for 1 hour after use. Subjective measurements of withdrawal, craving and drug effects/ liking were also made.
Subjects placed the assigned product between their cheek and gum for 30 min after which the product was removed and subjects rinsed their mouth with water. Blood was drawn immediately before and at 1, 5, 10, 15, 20, 25, 30, 45, 60, 75 and 90 min after product placement.

Smoking behaviour / co-interventions

All had used Copenhagen smokeless tobacco daily for at least 1 year.
12 hour pre-session abstinence was required. A further 2 hr period of abstinence prior to investigations.

Pharmacokinetic outcomes

PK parameters (95% CI)

	Cmax (ng/ml)	**Tmax (min)**	**AUC0–90 (ng x min/ml)**
Copenhagen moist snuff	16.1	27-33 (all products)	1038
Commit medicinal 4mg gum	7.3	27-33 (all products)	467

The paper does not provide mean nicotine concentrations at the different sampling times.
Tmax for Commit not provided, although the paper states that for those three products for which nicotine concentration increased significantly above baseline (Commit lozenges and two other smokeless tobacco products), the Cmax was observed at an average of 27 to 33 minutes after starting product use.

Safety Outcomes

Subjects were asked if they experienced any bad effects, felt alert, relaxed, light-headed/dizzy, drowsy, energetic, jittery or had any tremor. There were no specific concerns documented for Commit but it was stated that the results for Copenhagen ST showed a higher score regarding experiencing a fast/pounding heart.

Study quality comments

One subject completed only one laboratory session and was excluded from the analysis.
12 hour abstinence was required, paper does not mention whether this was verified.
Study quality score [+]

Study

Lunell, E. & Curvall, M. (2011) Nicotine delivery and subjective effects of Swedish portion snus compared with 4 mg nicotine polacrilex chewing gum. Nicotine & Tobacco Research, 13: 573-578.

Design

3-way crossover randomised trial. Aim: to compare the nicotine delivery of two brands of Swedish snus and with medicinal 4mg nicotine polacrinex gum.

Participants

15 regular cigarette smokers, 9 males/6 females, who had never used snus or nicotine gum.
Age: 19–49 years of age, participated in the study.
One subject was excluded from statistical analysis due to baseline nicotine plasma concentration exceeding 4 ng/ml. Consequently, analytic sample = 14 subjects.

Interventions / comparators

Subjects underwent 3 procedures in randomised order (washout 6 days):

1. Snus 1: 'General Onyx Portion', 1g, containing 9.9mg nicotine
2. Snus2: 'General Portion', 1g, containing 8.7mg nicotine
3. 4mg gum

Each product was taken for 30 minutes: snus held in upper gingival sulcus and gum chewed once every 2 seconds for 30 minutes with metronome. Beverages were prohibited.
Baseline and residual nicotine content was measured by gas chromatography to determine released nicotine.
Venous blood samples (5 ml) were collected at the following time points: before (0), 2, 4, 8, 16, 24, 30, 45, 60 min, 1.5, 2, 4, 6, and 8 hr after administration of each preparation.

Smoking behaviour / co-interventions

Existing smoking habit 15.3 ± 4.9 cigarettes/day since 14.3 ± 10.5 years. (Fagerström Tolerance Questionnaire score of 4.1 ± 1.8). Subjects were fasting and abstinent overnight (12 hr) from cigarette smoking. Baseline levels of exhaled carbon monoxide up to 11 ppm were considered compatible with abstinence.

Pharmacokinetic outcomes

Baseline nicotine content	Residual nicotine	Nicotine release
Snus 1: 9.92mg Snus 2: 8.65mg Gum: 3.80 mg	Snus 1: 7.80 mg Snus 2: 6.47 mg Gum: 1.24 mg	Snus 1: 2.12mg Snus 2: 2.18mg Gum: 2.56mg

The extracted amount of nicotine from the gum was significantly larger than that from Snus 1 ($p = .0072$) as well as Snus 2 ($p = .0408$).

Product	Cmax (ng/ml)	Tmax (min)	AUC∞ (ng min/ml)
Snus 1	14.8	37.1	3,062
Snus 2	13.7	37.1	2,829
Gum	12.8	46.1	3,190

Heart rate increase at 20 minutes (beats/min):
Snus 1: 9.3
Snus 2: 8.9
Gum: 9.9

VAS subjective results (0 = not at all, 100 = extreme)

Product	VAS score: head rush (5min)	VAS score: craving to smoke (30

		min)
Snus 1:	38.4	21.5
Snus 2:	30.9	22.5
Gum:	22.8	26.3

The difference for head rush between Snus 1 and Gum was statistically significant at 20 min (p = .0312).

The salivation score was visibly higher (based on published graphic) for gum than for snus.

Safety Outcomes

Burning was common for all three products. No subject withdrew due to adverse events.

Study quality comments

Overall Quality Score: [+]

Sample size calculation described. Crossover design and randomisation sequence fully explained. No blinding of participants feasible; no blinding of assessors of outcomes described.

Study

Engstrom, K., Magnusson, C. & Galanti, M. R. (2010) Socio-demographic, lifestyle and health characteristics among snus users and dual tobacco users in Stockholm County, Sweden. 128. BMC Public Health, 10: 619.

Design

Cross-sectional survey

Participants

34,707 responders to a questionnaire survey issued in 2006 to randomly selected residents of Stockholm County, Sweden.

Interventions / comparators

Participants were invited to complete a questionnaire by paper / internet form, containing questions on:

- socio-demographic factors
- health parameters
- physical activity
- lifestyle factors.

The majority of items were validated instruments.

Smoking behaviour / co-interventions

Tobacco behaviour is the outcome of interest

Outcomes

17.0% of males were exclusive daily snus users, and 2.4% reported combined daily use of snus and cigarettes. 11.3% were daily exclusive smokers. Daily smoking was more prevalent among women (15.2%) than men. Total tobacco use was higher among men (30.7%) than among women (18.8%).

The prevalence of exclusive snus use was highest in the youngest age categories (below age 35), with ORs declining steadily with increasing age. In contrast, the highest prevalence of smoking was seen in middle age, while the prevalence of dual tobacco use showed two age-related peaks, in age 18-24 and 45-54, for both men and women.

With high educational level as the reference subgroup in men, ORs for exclusive snus (OR Low:High 1.49 [95% CI 1.26-1.77]), exclusive smoking (OR Low:High 2.36 [95%CI 1.92-2.91]) and dual use (OR Low:High 2.45 [95%CI 1.68-3.58]) were elevated in low and intermediate education groups. In women similar and stronger effects were seen for smoking (OR Low:High 3.23 [95%CI 2.72-3.84]) whereas the effects for snus were weaker or non significant for snus.

In men snus use was more common in low, intermediate or high income groups with very high income as the reference group. There was no increased OR for the very low income group. In women and in contrast to men, there were no significant associations between snus use and income.

In men there were few associations between snus use and occupational class, whereas unskilled, skilled and self employment was associated with smoking relative to high level clerk. In women smoking was more likely in all occupation groups than high level clerk.

Psychological outcomes

The odds of smoking were weakly higher in men with psychological distress relative to those without (OR 1.33 [95%CI 1.12-1.58]. The same association was observed for dual use (OR 1.68 [95% CI 1.28-2.20]) but not exclusive snus (OR 0.96 [95% CI 0.83-1.10]). In women only smoking was associated with psychological distress (OR 1.54 [95%CI 1.37-1.73]).

Table: cross-sectional odds ratios of current daily tobacco use versus non-use in relation to socio-demographic factors (reproduced with permission from the publisher – open access, online journal)

Characteristic	Males			Females		
	Snus use OR[2] (95% CI)	Smoking OR[3] (95% CI)	Dual use OR (95% CI)	Snus use OR[2] (95% CI)	Smoking OR[3] (95% CI)	Dual use OR (95% CI)
Age, years						
18-24	Ref	Ref	Ref	Ref	Ref	Ref
25-34	0.92 (0.74-1.14)	1.26 (0.90-1.76)	0.64 (0.41-1.01)	0.63 (0.43-0.92)	0.58 (0.47-0.71)	0.66 (0.27-1.63)
35-44	0.85 (0.69-1.06)	1.47 (1.06-2.02)	0.82 (0.54-1.25)	0.72 (0.50-1.04)	0.63 (0.51-0.77)	0.66 (0.27-1.60)
45-54	0.58 (0.46-0.72)	2.00 (1.46-2.74)	0.94 (0.62-1.42)	0.59 (0.40-0.86)	1.02 (0.84-1.24)	1.26 (0.55-2.91)
55-64	0.31 (0.25-0.39)	2.06 (1.51-2.81)	0.61 (0.40-0.94)	0.22 (0.15-0.35)	0.86 (0.71-1.05)	0.80 (0.34-1.92)
65-74	0.18 (0.14-0.24)	1.50 (1.07-2.11)	0.35 (0.21-0.60)	0.14 (0.08-0.25)	0.68 (0.55-0.86)	0.07 (0.01-0.57)
75+	0.07 (0.05-0.11)	0.67 (0.43-1.03)	0.02 (0.00-0.16)	0.02 (0.00-0.12)	0.33 (0.24-0.45)	[4]
Education						
Low	1.49 (1.26-1.77)	2.36 (1.92-2.91)	2.45 (1.68-3.58)	1.07 (0.73-1.55)	3.23 (2.72-3.84)	3.51 (1.68-7.34)
Intermediate	1.60 (1.41-1.81)	1.66 (1.39-1.98)	1.97 (1.43-2.70)	1.49 (1.17-1.89)	2.12 (1.84-2.46)	2.03 (1.10-3.75)
High	Ref	Ref	Ref	Ref	Ref	Ref
Disposable income						
Very low	0.98 (0.82-1.16)	1.40 (1.14-1.72)	1.28 (0.88-1.86)	1.16 (0.82-1.64)	1.35 (1.12-1.62)	1.16 (0.51-2.62)
Low	1.25 (1.06-1.47)	1.15 (0.93-1.42)	1.20 (0.83-1.75)	1.28 (0.92-1.78)	1.14 (0.96-1.37)	0.84 (0.36-1.98)
Intermediate	1.25 (1.07-1.46)	0.77 (0.62-0.96)	0.99 (0.68-1.44)	1.29 (0.94-1.78)	0.99 (0.82-1.18)	0.69 (0.29-1.63)
High	1.24 (1.06-1.43)	0.97 (0.79-1.18)	1.07 (0.75-1.54)	1.17 (0.84-1.62)	0.95 (0.79-1.13)	1.99 (1.00-3.96)
Very high	Ref	Ref	Ref	Ref	Ref	Ref
Occupational class						
Unskilled worker	1.02 (0.85-1.23)	2.42 (1.90-3.10)	1.95 (1.25-3.04)	1.35 (0.92-1.96)	2.08 (1.66-2.60)	1.28 (0.51-3.22)
Skilled worker	1.40 (1.17-1.68)	2.04 (1.59-2.63)	2.94 (1.92-4.52)	1.30 (0.87-1.94)	2.28 (1.80-2.88)	1.56 (0.60-4.08)
Low-level clerk	1.14 (0.94-1.40)	1.28 (0.95-1.72)	1.10 (0.63-1.90)	1.00 (0.70-1.43)	1.67 (1.34-2.07)	1.19 (0.50-2.85)
Middle level clerk	1.06 (0.91-1.24)	1.12 (0.88-1.41)	1.18 (0.77-1.79)	1.27 (0.94-1.73)	1.41 (1.15-1.73)	1.15 (0.52-2.54)
High level clerk	Ref	Ref	Ref	Ref	Ref	Ref
Self-employed	1.09 (0.90-1.31)	1.48 (1.15-1.92)	1.32 (0.82-2.13)	1.02 (0.63-1.63)	1.45 (1.11-1.91)	1.09 (0.35-3.41)

[1] Adjusted for age, occupational class, disposable income and education, when applicable. [2] Further adjusted for past smoking. [3] Further adjusted for past snus use. [4] Model not converging due to small numbers.

Study quality comments

Overall Quality Score: [-]

Response rate = 61%. Non responders included a higher proportion of men, people of age <45y, foreign-born, single or separated, unemployed and in the lowest quartile of income.

The study is limited by its cross-sectional design.

Study

Tillgren, P., Haglund, B. J. A., Lundberg, M. & Romelsjo, A. (1996) The sociodemographic pattern of tobacco cessation in the 1980s: Results from a panel study of living condition surveys in Sweden 328. Journal of Epidemiology and Community Health.50 (6) pp 625-630

Design

Observational study – sample of the population surveyed at two time points: 1980-1 and 1988-9. Aim: to analyse the determinants of tobacco cessation in the 1980s in Sweden.

Participants

A sample of 5104 subjects who completed two surveys in 1980-1 and 1988-9:

- Daily smokers (men and women): n = 1546
- Men who used snus: n = 418
- Men use use snus and smoke: n=129

The sample was drawn from the Statistics Sweden's surveys of living conditions.
1980-81 survey: n = 14 964, 86% participation rate
1988-89 survey: n = 13 295, 79% participation rate

Interventions / comparators

Determinant variables analysed were age, education, marital status, socioeconomic status, social network, and physical activity.

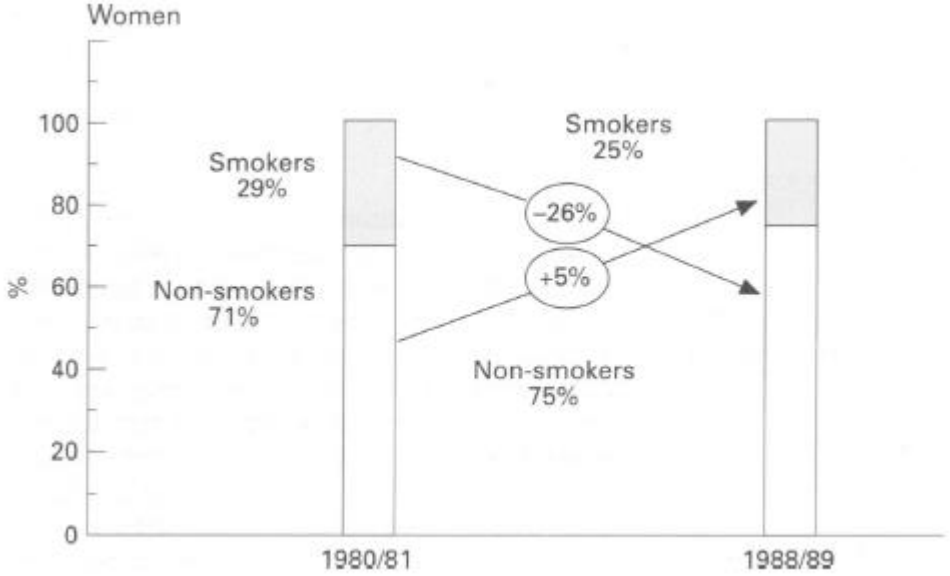
Smoking behaviour / co-interventions

Smoking behaviour is the outcome of interest

Results

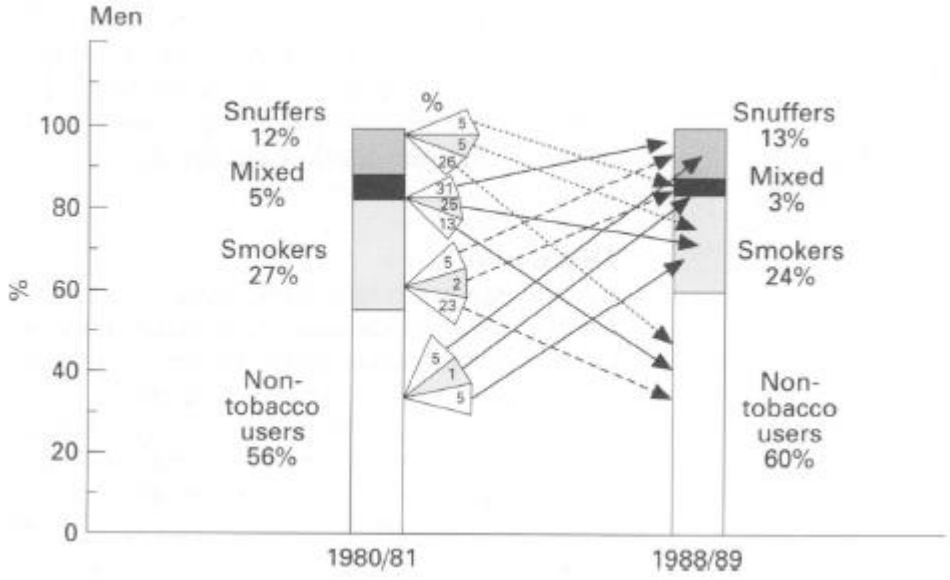
Changes in tobacco habits over time:

Percentage of daily smokers and non-smokers among women in a sample (n=2578) of the Swedish population in 1980-1 and 1988-9. Reproduced from Tillgren et al. (1996) with permission from the BMJ Publishing Group, copyright license no 2878831086303



Percentages of daily snus users, smokers and non-tobacco users among men in a sample (n=2383) of the Swedish population in 1980-1 and 1988-9. Reproduced from Tillgren et al. (1996) with permission from

the BMJ Publishing Group, copyright license no 2878831086303



Among the men, 26% of the daily snuff users had quit, while 5% took up smoking. Of the men who had previously smoked, 5% began using snuff instead. Of the men who had previously not used any tobacco, the same fraction 5% took up snuff. The data do not suggest that women start using other tobacco products as substitutes after they give up smoking.

Univariate analysis
There was no association between remaining a smoker and age or socioeconomic group in either men or women.
Unmarried men were more likely to remain a smoker with borderline statistical significance (OR unmarried:married 1.4 [95%CI 1.0-2.0]).
Women with low or intermediate educational level were more likely to remain smokers compared to those with high education (OR low:high 3.1 [95%CI 1.8-5.2], OR intermediate:high 2.2 [95%CI 1.3-3.7]).
Men with low social network were more likely to remain smokers with borderline statistical significance (OR low:high 1.6 [95%CI 1.0-2.5]).
Women with low level of physical exercise were more likely to remain smokers with borderline statistical significance (OR low:high 1.4 [95%CI 1.0-1.9).

In men and in women there were associations between remaining a smoker and a) years of smoking, b) daily consumption of cigarettes:
OR men, 20+years of smoking:0-6years = 2.3 [95%CI 1.4-3.6]
OR women, 20+years of smoking:0-6years = 2.4 [95%CI 1.5-3.8]

OR men, 21+ cigs/day:0-7 cigs/day = 2.7 [9%%CI 1.4-5.4]

Univariate analysis in men only re: snus
There was no association between remaining a snus user with age, education, marital status, socioeconomic group, social network or physical exercise.

Multivariate analysis
Age was associated with remaining a smoker only in the age group 25-44 (relative to 45+) in both men and women:
Men OR 2.1 [95%CI 1.1-3.7]
Women OR 2.3 [95%CI 1.2-4.4]

Unmarried status in men was associated with remaining a smoker:
OR 2.1 [95%CI 1.2-3.6]

Years of smoking was more strongly associated with remaining a smoker in men than in women:
OR men, 20+years:0-6years = 4.7 [95%CI 2.0-10.8]
OR women, 20+years:0-6years = 2.5 [95%CI 1.1-5.5]

Cigarettes/day	OR [95%CI] Men	OR [95%CI] Women
1-10	1	1
11-20	2.2 [1.5-3.4]	3.3 [2.1-5.0]
20+	2.8 [1.4-5.7]	3.1 [0.6-15.4] (not statistically significant)

Study quality comments

Snus use in women was not assessed in the 1980-1 sample.
Determinant variables (marital status) were assumed not to change between assessments
The multivariate model was subject to partial responses and therefore selection of a smaller sample.
Smoking & snus status were not biochemically assayed.

Overall Quality Score: -

25 Studies of Swedish snus included in published systematic reviews

Main primary study findings for cancer outcomes presented by two systematic reviews: Broadstock (2007) [+] and SCENIHR (2008) [+]

Study	Design	Population	Extent of exposure to nicotine	Main results
Boffetta 2005	Cohort study with nested case-control study	Norway 10,136 men enrolled in Norway since 1966 & followed up through 2001	Assessment was made at baseline as follows: Regular current users: n=1,999 (19.7%) Regular former users: n=1,216 (12%) Never, or occasional users: n=6,921 (n=68.3%) No assessment was made at any subsequent follow-up point.	Oral/pharyngeal cancer (adjusted for age and smoking) RR (ever use vs never use of snus) 1.10 (95% CI: 0.50-2.41). Oesophageal cancer RR (ever use vs never use of snus) 1.4 (95% CI: 0.61–3.24) Pancreatic cancer RR (ever use vs never use of snus) 1.67 (95% CI: 1.12–2.50). Stomach cancer RR (ever use vs never use of snus) 1.11 (95% CI 0.83-1.48) Lung cancer: RR (ever use vs never use of snus) 0.80 (95%CI 0.61-1.05) Kidney cancer RR (ever use vs never use of snus) 0.72 (95% CI 0.44-1.18) Bladder cancer RR (ever use vs never use of snus) 0.83 (95% CI 0.62-1.11)

<table>
<tr><th>Study</th><th>Design</th><th>Population</th><th>Extent of exposure to nicotine</th><th>Main results</th></tr>
<tr>
<td>Roosaar 2006</td>
<td>Long term follow up study of</td>
<td>Sweden

1,115 snus users with snus-induced lesions (SILs).</td>
<td>
<table>
<tr><th></th><th>1973-74</th><th>re-examined 1993-1995</th></tr>
<tr><td>N</td><td>1115</td><td>183</td></tr>
<tr><td>Snus hours/day</td><td></td><td></td></tr>
<tr><td>0</td><td>8%</td><td>5%</td></tr>
<tr><td>1-6</td><td>60%</td><td>63%</td></tr>
<tr><td>7-15</td><td>26%</td><td>25%</td></tr>
<tr><td>16-24</td><td>3%</td><td>1%</td></tr>
<tr><td>missing</td><td>4%</td><td>5%</td></tr>
</table>
Data in the table suggest that c60% participants assessed at both time points may have used snus for 1-6 hours/day for 20 years.
</td>
<td>3 cases of oral cancer were registered yielding a standardized incidence ratio of 2.3 (95% CI: 0.5-6.7). None of the cancers developed at the site of snus application or SIL. Two of the 3 individuals with cancer were concomitant daily smokers. The authors concluded that while the incidence of oral cancer in this cohort of individuals with SILs tended to be higher than expected, cancers did not occur at the site of the lesion observed in the distant past.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>Population</th><th>Extent of exposure to nicotine</th><th>Main results</th></tr>
<tr><td>Luo 2007</td><td>Retrospective cohort study of construction workers</td><td>Sweden

279 897 men recruited from 1969 through 1992</td><td>Exposure data was determined at the first visit only: snus user: (ever, current, never) and volume (grams per day <10g or ≥10g).</td><td>RR cancer by snus use (95% CI):
<table>
<tr><th>Tobacco use</th><th>Oral cancer</th><th>Lung cancer</th><th>Pancreatic cancer</th></tr>
<tr><td>Never</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Ever snus</td><td>0.8 [0.4-1.7]</td><td>0.8 [0.5-1.3]</td><td>2.0 [1.2-2.3]</td></tr>
<tr><td>Ex snus</td><td>0.7 [0.1-5.0]</td><td>0.9 [0.3-3.0]</td><td>1.4 [0.4-5.9]</td></tr>
<tr><td>Current snus</td><td>0.9 [0.4-1.8]</td><td>0.8 [0.4-1.3]</td><td>2.1 [1.2-3.6]</td></tr>
<tr><td><10 g/day</td><td>0.7 [0.2-2.8]</td><td>1.0 [0.5-2.1]</td><td>1.9 [0.8-4.3]</td></tr>
<tr><td>≥10 g/day</td><td>0.9 [0.4-2.0]</td><td>0.7 [0.4-1.3]</td><td>2.1 [1.1-3.8]</td></tr>
</table>
Results are for never smokers.</td></tr>
</table>

Study	Design	Population	Extent of exposure to nicotine	Main results
Zendehdel et al (2008)	Cohort study of construction workers	Sweden Sample drawn from same cohort as that of Luo 2007, above 343,822 male construction workers followed up for cancer incidence from 1971 up to 2004	Exposure data was determined at the first visit only: snus user: (ever, current, never) and volume (grams per day <10g or ≥10g).	Among never smoking snuff users excess risks for oesophageal squamous cell carcinoma (10 exposed cases, RR (ever use vs never use of snus) 3.5, 95% CI 1.6-7.6) and noncardia stomach cancer (68 exposed cases, RR = 1.4, 95% CI 1.1-1.9). The results are not adjusted for alcohol consumption. However, this cannot explain the elevated risks. No increase in risk was observed for adenocarcinoma of the oesophagus and cardia stomach cancer. RR for pancreatic cancer (snus use vs never use of any tobacco) in ever, current and former snus users were 2.0 (95% CI: 1.2-3.3), 2.1 (95% CI: 1.2-3.6), and 1.4 (95% CI: 0.4-5.9), respectively. The trend by amount of snus consumed/day was statistically significant (>10g/day RR 2.1 (95% CI: 1.1-3.8)).
Roosaar (2008)	Cohort study	Sweden 9,976 men, who participated in a population-based survey in 1973-74, followed up until January 31, 2002.	Exposure to snus was categorized at entry to the cohort in 1973-74 as never versus ever (daily).	RRs adjusted for smoking and alcohol drinking and area of residence. Oral / pharyngeal cancer (ever users vs never users of snus, 11 exposed cases, HRR 3.1, 95% CI 1.5-6.6) Among never smokers the RR of oral /pharyngeal cancer was 2.3 (5 exposed cases, 95% CI 0.7-8.3).

Study	Design	Population	Extent of exposure to nicotine	Main results
Sundstrom et al. (1982) (Axéll et al. 1978)	Case series	Sweden 23 cases of oral cancers in snuff dipping Swedish males, age range 52-93 years, mean age 76 years.		All cancers were in the anterior vestibulum where snuff was usually deposited and retained. Nine of these patients also had second primary tumours, oral or in other sites. The 23 cases were retrieved from material collected in a 10 year register study for the years 1962-1971 and where 33 cases were found in a localisation making an association with the placement of snuff. On the other hand, another 39 cases in the same localisation were registered in which no tobacco habit was registered. These latter cases were not analysed histopathologically. A calculated risk for the development of a snuff induced cancer was 1 case per year in 200,000 users of snuff (Axéll et al. 1978).
Hirsch et al. (2002)	Case series	Sweden 8 oral cancer cases (squamous cell carcinoma) in Swedish snuff-dippers. Seven of this series were elderly male and had used snuff for longer than 20 years.		The cancers developed exactly at the location where the snuff was placed mostly on the upper vestibulum. All were pathologically confirmed as squamous cell carcinomas.

Study	Design	Population	Extent of exposure to nicotine	Main results
Hansson et al. (1994)	Population based case control study	Sweden Individuals aged 40-79 years living in five counties of Sweden from February 1989 through January 1992. Cases (n=338) were diagnosed with histologically confirmed gastric cancer identified from regional hospital departments and national cancer registries. Controls (n=679) were drawn by random sampling from population registers, stratified by age and gender.	Study does not describe length of exposure to snus, nor the number of snus users.	Gastric cancer OR (snus users vs never tobacco users, adjusting for age, gender, SES, vegetable intake, and other tobacco use) = 0.70 95% CI, 0.47- 1.06). Cardia cancer, the RR for (current snus use vs never tobacco user) 0.5 (95% CI: 0.2–1.1). Cardia cancer RR (former use vs never use) 0.8 (95% CI: 0.3–1.9). Intestinal distal stomach cancer RR for (current use vs never use) 0.8 (95% CI: 0.5–1.3). Diffuse distal stomach cancer RR 0.6 (95% 4 CI: 0.3–1.2). After restriction to never smokers and after combining 5 all sites, the RR for ever using snus vs never using snus was 0.5 (95% CI: 0.2–1.2).

Study	Design	Population	Extent of exposure to nicotine	Main results
Ye et al. (1999)	Population based case control study	Sweden Individuals aged 40-79 years living in five counties of Sweden, drawn from the same population as in Hansson et al. (1994), above. Cases (n=514) diagnosed with gastric cancer were identified from regional hospital departments, /cancer registries. Controls (n=1,164) were drawn by random sampling, of approximately two controls per case, from population registers and frequency matched by age and gender.	Dose-response with regard to snus use and gastric cancer is examined by assessing duration of use (1-10, 11-30 and ≥31y) and no. of times/day (≤5, >5).	multivariate analysis adjusted for age, residence area, BMI, and SES, OR gastric/cardia cancer: (exclusive snus vs never tobacco) = 0.5 95% CI, 0.2-1.2) based on 47 snuff users.

Study	Design	Population	Extent of exposure to nicotine	Main results
Lewin et al. (1998)	Population-based case control study	Sweden Males aged 40-79 years recruited during the years 1988-1990. Cases (n=605) were identified from diagnoses and registrations at cancer registries. Controls (n=756) drawn by random sampling from population registrations, stratified by region and age.	Exposure to snus was assessed by estimating lifetime weight of snus consumed, based on 1 packet = 50g. Relative risks (cases:controls) of oral cancer were assessed in subgroups for age at start (<25y and ≥25y), duration of use (<30y and ≥30y), total consumption (<125kg and ≥125kg) and intensity of use (≤50g/week and >50g/week).	RR squamous cell head and neck cancer (current snus user vs never tobacco user3.3 (95% CI, 0.8-12.0), and RR for 'ex-snus-users' 10.5 (95% CI, 1.4-117.8). RR squamous cell head and neck cancer (current snus user vs never snus-users' adjusting for alcohol and smoking) (RR=1.0, 95% CI 0.6-1.6). RR squamous cell head and neck cancer (ex snus user vs never snus-users' (RR=1.2, 95% CI, 0.7-1.9). However, the reference group of never snus-users for these analyses included smokers, which may have lead to an underestimate of risk for snus use. Higher intensity of snus use (>50g per week) was associated with moderately, but not significantly, higher risk for oral cavity cancer (RR=1.7, 95% CI, 0.8-3.9), and for oesophageal cancer (RR=1.9, 95% CI, 0.8-3.9). However, it was not clear whether these risk estimates were adjusted for smoking.
Schildt et al. (1998)	Population-based case control study	Sweden Cases: 354 people (117 females, 237 males, mean age 70 years) diagnosed with squamous cell oral cancer between 1980 and 1989. Controls: drawn from the National Population Registry, matched for age, sex, county of residence and vital status.	Exposure to snus was assessed by estimating lifetime weight of snus consumed, based on 1 quid of snus = 1g of tobacco. The median weight of tobacco consumed in the control group was 156kg, corresponding to two packets (100g) per day over 30 years. Dose-response to snus for oral cancers was assessed in cases comparing low level use (≤156kg) and high level use (>156kg) with no use of snus.	Univariate analysis: oral squamous cell carcinoma (exclusive snus users vs never use of tobacco) (OR = 0.7, 95% CI, 0.4-1.2). Multivariate analyses (controlling for alcohol and smoking) did not differ substantially from univariate findings. Lip cancer (ex snuff users vs never use of tobacco) OR = 1.8, 95% CI 0.9-3.7) Higher levels of consumption of snus and brand of snus used were not associated with increased risk.

Study	Design	Population	Extent of exposure to nicotine	Main results
Lagergren et al. (2000)	Population based case-control study	Sweden Residents of Sweden from 1995-1997, aged under 80 years. Cases (n=618) were all newly diagnosed with gastric cardia adenocarcinoma (AC) (n=262), oesophageal AC (n=189), and half the cases of oesophageal squamous cell carcinoma (SCC) (n=262) born on even dates and identified from Swedish hospital departments / cancer registries. Controls (n=1,164) were drawn by random sampling of population registers, stratified by age and gender, by frequency matching.	Exposure to snus is analysed as: duration of use (1-10, 11-25, >25y) and intensity of use (1-14, 15-35, >35 quids/wk).	Multivariate analysis adjusted for age, gender, other tobacco smoking, alcohol use, educational level, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake, and physical activity. Oesophageal AC. (ever snus use vs never snus use) OR = 1.2 95% CI 0.7-2.0) Gastric cardia AC. (ever snus use vs never snus use) OR = 1.2 95% CI 0.8-1.8 Oesophageal SCC. (ever snus use vs never snus use) OR = 1.4 95% CI 0.9-2.3 Oesophageal AC (>25 years of snus use), OR = 1.9 (95% CI: 0.9–4.0) Oesophageal SCC (>25 years of snus use), RR 2.8 (95% CI: 1.4–5.4)

Study	Design	Population	Extent of exposure to nicotine	Main results
Rosenquist et al. (2005)	Population based case control study	Sweden 132 cases of oropharangeal SCC (41 females, 91 males) diagnosed in two regional hospitals 320 controls (105 females, 215 males) were drawn by stratified random sampling of three controls per case from the Swedish Population Registry and matched for age, sex, and county of residence. Recruitment took place between September 2000 and January 2004.	In both univariate and multivariate analyses, snus users were not at increased odds of oropharangeal squamous cell carcinoma compared to those who had never used snus. This was observed for duration of use <30y and >30y, exposure time <10h/day and > 10 h/day and consumption of <14g/day and >14g/day.	Multivariate analysis adjusting for alcohol and smoking: OOSCC: current snus-users vs never use OR = 1.1 95% CI, 0.5-2.5 OOSCC: ex-snus users vs never use OR = 0.3 95% CI, 0.1-0.9 OOSCC ever use of snus vs never use OR 0.7 (95% CI: 0.3-1.3). There was also no increased risk for users of fermented snus, which included users who later used non-fermented snus, or for users for more than 10 hours per day, or for users reporting at least 30 years of use. For higher levels of consumption of >14 g/day, OOSCC OR = 1.7 95% CI, 0.5-5.7.

Main primary study findings for cardiovascular outcomes presented by two systematic reviews: Broadstock (2007) [+] and SCENIHR (2008) [+]

Study	Design	Population	Extent of exposure to nicotine	Main results
Huhtasaari et al. (1992)	Population based case control study (WHO MONICA study)	Sweden Men aged 35-64 years old. Cases (n=585) with an acute myocardial infarction (MI) between April 1989 and April 1991 were identified from care providers, registers and death certificates. 21% of cases were deceased. Controls (n=589) were drawn from population records, group-matched by age and sex.	Length of exposure to snus was not assessed. Exposure to snus was categorised as: regular user (at least once daily), former user, non-user. The study's analyses excluded concomitant smokers/snus users.	MI: OR (exclusive snus vs never tobacco, age adjusted) = 0.89 95% CI, 0.62-1.29. The ORs were non-significant for both younger (35-54 years) and older (55-64 years) age groups. In analyses investigating a dose-response effect, there was no clear significant effect for snus use. In a logistic regression model for MI with smoking, snus, low level of education, and age as predictors, snus use was not significant. Other potential confounders were not adjusted for in analyses, including illicit drug use, nutrition, socioeconomic status, alcohol abuse, physical exercise, BMI, CVD history and some cardiovascular disease risk factors.

Study	Design	Population	Extent of exposure to nicotine	Main results
Bolinder et al. (1994)	Cohort study	Sweden Study base: 135,036 Swedish construction industry workers attending preventive health check-up clinics between 1971 and 1974. Sample: 1,672 people aged 35-54 years, and 1,734 aged 55-64 years who were users of snuff at study entry. Study excluded women and mixed tobacco users (snus & cigarettes).	87% of deaths due to cardiovascular disease were in snus users of >15 years duration. Study does not evaluate dose-response in snus users.	In men, compared with never tobacco users, age-adjusted relative risk was significantly increased for all cardiovascular disease mortality in exclusive snuff users (RR=1.4 95% CI 1.2-1.6). Risks were higher for men aged 35-54 years, RR=2.1 (95% CI 1.5-2.9), and for men aged 55 years and over, RR=1.1 (95% CI 1.0-1.4).
Huhtasaari et al. (1999)	Population based case control study (WHO MONICA study) but distinct from the earlier study by Huhtasaari (1992).	Men aged 25-64 years old (mean 55.6 years) living in northern Sweden between May 1991 and December 1993 inclusive. Cases (n=687) were those with first-time myocardial infarction (MI), fatal (death within 28 days) for 17 % of the sample. Cases were identified from general practitioners' reports, hospital discharge registers and screening of death certificates. Controls (n=687) were drawn from population records and matched for age, by date of birth, and place of living.	Length of exposure to snus was not assessed, although study reported the mean volume of snus consumption in snus users as 2 boxes/day (=100g/day, based on other studies) and median age of starting to use snus 31.5y (the age at which many participants gave up smoking). Dose-response effects from daily consumption of snuff were not investigated.	Univariate analysis: OR (1st MI, exclusive snus vs never used tobacco) = 0.96, 95% CI, 0.65-1.41). OR (1st MI, former snus vs never smoked) = 1.23 (95% CI, 0.54-2.82). Logistic regressions adjusted for various cardiovascular risk factors and social variables including hypertension, diabetes, high cholesterol, family history of early cardiac death, low level of education, and whether married/cohabitating. In a conditional logistic regression excluding smokers, the adjusted OR for acute MI in regular snuff users was 0.58 (95% CI, 0.35-0.94), an unexpected significant protective effect. Adjusted OR for fatal AMI 1.50 (95% CI, 0.45-5.03).

Study	Design	Population	Extent of exposure to nicotine	Main results
Asplund et al. (2003)	Nested case control study utilising WHO MONICA study and the Västerbotten Intervention Project (VIP).	Sweden Only men were considered. Cases (n=276) were first-ever events of stroke, fatal (death within 28 days) or non-fatal, identified from a population-based stroke register between 1985 and 2000. Controls (n=551), recruited two per case, were matched for sex, age, geographical area, year of baseline examination and cohort.	Length of exposure to snus was not assessed. For both cigarette smoking and snus, participants were categorised as present user, former user and never user. Dose-response effects were not investigated.	Compared with 'never tobacco users', univariate comparisons of risk for first stroke suggested no increased risk for exclusive snuff users who were never smokers (OR = 1.05 95% CI 0.37-2.94), or for current snuff users who did not currently smoke (OR = 1.16 95% CI, 0.60-2.22). Logistic regression analyses: independent variables included hypertension, diabetes, serum cholesterol levels, level of education, and marital status. Excluding smokers, the adjusted OR of regular snuff use for first stroke, both fatal and non-fatal, was 0.87 (95% CI 0.41-1.83). Other potential confounders including illicit drug use, nutrition, physical exercise, BMI, and alcohol abuse were not considered.

Study	Design	Population	Extent of exposure to nicotine	Main results
Hergens et al. (2005)	Population-based case-control study (SHEEP study)	Sweden The study base comprised men aged 45-70 years living in Stockholm in 1992-1993, and men aged 45-65 years living in Västernorrland County in 1993-1994. Cases (n=1,432) were first-ever events of acute myocardial infarction (AMI), fatal (death within 28 days) or non-fatal, identified from hospital departments, and registers. Controls (n=1,810) were randomly sampled from each study base after matching for age and hospital catchment area.	Length of exposure to snus was not assessed. Exposure to snus was categorised as: never used snuff, former snuff user, current snuff user. Exposure to cigarette smoke was categorised as: never smoked, former smoker, current smoker.	Compared with 'never tobacco users', OR for first MI for exclusive never smoking snuff users was 0.73 (95% CI, 0.35-1.5) Analyses limited to either non-fatal cases or fatal cases did not alter the results. The authors stated that adjusting odds ratios for various CVD risk factors including hypertension, diabetes, hyperlipidemia, overweight, physical inactivity and job strain had negligible effect on risk estimates. Other potential confounders including illicit drug use, nutrition, family history of cardiac disease, level of education, and alcohol abuse were not adjusted for.
Johansson et al. (2005)	Cohort study	Sweden 3,120 men aged 30-74 years randomly sampled from the Swedish population resident between 1988 and 1989. Respondents were followed up until the end of 2000, a mean time of 11.2 years, with regard to fatal and non-fatal coronary heart disease. They were identified from national hospital discharge and cause of death registries) The sample excluded people who indicated that their general health was bad or 'anywhere between good and bad' (n=907).	Length of exposure to snus was not assessed. Exposure to tobacco was categorised as: never smokers, former smokers, daily smokers, daily snuffers and never-smokers, daily snuffers who were former smokers, daily snuffers and smokers.	Cox regression models estimated the hazard ratios for fatal and non-fatal CHD, adjusted for age. In men, compared with non-smokers, the age adjusted hazard ratio for coronary heart disease was not significant for exclusive never smoking snuff users (HR=1.62 95% CI 0.70-3.75). Associations were decreased after adjustment for other explanatory variables including physical activity, BMI, diabetes, and hypertension (HR=1.41 95% CI 0.66-3.28). Including socioeconomic status in the model made no difference to results.

Main primary study findings for other health outcomes presented by a systematic review: Broadstock (2007) [+]

Study	Design	Population	Extent of exposure to nicotine	Main results
Bolinder et al. (1994)	Cohort study	Sweden Study base: 135,036 Swedish construction industry workers attending preventive health check-up clinics between 1971 and 1974. Sample: 1,672 people aged 35-54 years, and 1,734 aged 55-64 years who were users of snuff at study entry. Study excluded women and mixed tobacco users (snus & cigarettes).	87% of deaths due to cardiovascular disease were in snus users of >15 years duration. Study does not evaluate dose-response in snus users.	RR of mortality (all cause) was 1.4, 95% CI 1.3-1.8 for exclusive snus users compared to those who were never tobacco users, and a RR of mortality (all cancers) to be 1.1, 95% CI 0.9-1.4. Broadstock (2007) comments that the study was well conducted with high statistical power, but that Bolinder et al (1994) did not adjust for diet and alcohol intake and that the snus exposure was pre-1985 when the cleaner products became available.

Study	Design	Population	Extent of exposure to nicotine	Main results
Persson et al. (1993)	Population-based case-control study	Sweden Swedish men. Cases (n=145) were randomly selected from patients admitted to Hospital with diagnoses of Crohn's Disease and ulcerative colitis between 1980 and 1984. Controls (n=145) were selected from a register of residents aged between 15 and 79 years, stratified by age and gender.	Length of exposure to snus was not assessed. Snus exposure is categorised as 'never' or 'ever' used snus. Cigarette smoking is categorised as 'never', 'former' or 'current'.	RR estimates for Crohn's Disease were not significantly increased for snus users who had never smoked (adjusted RR = 0.9, 95% CI, 0.3-3.1). Similarly for ulcerative colitis, compared with non tobacco-users, relative risk estimates were not significantly increased for snuff users that had never smoked (adjusted RR = 1.1, 95% CI, 0.4-3.1). Broadstock (2007) reports that this study should be interpreted cautiously due to • small sample size for comparisons • low disease rates • lack of adjustment for potential confounders (socio-economic status, nutrition, or alcohol and illicit drug use) • Poor definition of tobacco use • Reliance on self-report of tobacco use five years earlier. *NB In the original paper by Persson et al. 1993 the RR of ulcerative colitis for all subjects who ever used snus (relative to 'never' users) is 2.2 (95%CI 1.1-4.4) when adjusted for the effect of smoking. The corresponding analysis for Crohn's disease gives RR 1.0 (95% CI 1.0-4.6).*

Study	Design	Population	Extent of exposure to nicotine	Main results
Eliasson et al. (2004)	Population based case control study (WHO MONICA study)	Sweden 2540 Swedish men selected randomly from population registers as part of the WHO MONICA study.	Length of exposure to snus was not assessed. Snus exposure is categorised as ever snus user, ex snus user, never snus user and smoker who switched to snus.	After average follow-up of 8.7 years, or 15,726 person years, 27 eligible participants developed diabetes mellitus. There were no cases of diabetes in 'exclusive snus users'. Compared with consistent non tobacco-users, the risk of PGT during follow-up was not increased for 'consistent tobacco users' (snus or cigarettes), but there was a nonsignificant trend for increased risk in 'ex-snus users' with 5 of 20 having PGT (OR 1.85, 95% CI 0.60-5.7). Broadstock (2007) reports that there was no significant risk of diabetes observed for snus users, and that the study is limited by low rates of diabetes and analysis in a young study population (below the diabetes prone age groups).
Fernberg et al. (2006)	population-based prospective cohort study	Sweden 335,612 male Swedish construction workers (i.e. the same cohort as in Bolinder et al. 1994). Cases of Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) were identified in the Swedish Cancer Registry, Migration Registry and Cause of Death Registry. Tobacco exposure was measured through self-administered questionnaires between 1971 and 1974, and personal interviews with a nurse from 1978 onwards. tobacco use status and duration were established at date	Length of exposure to snus is presented in one multivariate analysis, indication that exposure was over a long period of time: exposure of 1-30y and of >30y are analysed against never using snus.	Results were adjusted for age, tobacco use and BMI. After follow-up of, on average, 19.1 years, 1,309 people were diagnosed with NHL, and 205 with HD. Compared with 'never tobacco-users' at baseline, the adjusted risk of developing NHL during follow-up was not increased for 'exclusive snus users' (IRR 0.77, 95% CI 0.59-1.01), or for 'exclusive cigarette smokers' (IRR 1.00, 95% CI 0.86-1.16). Similarly, compared with never tobacco users, the risk of developing HD was not increased for exclusive snuff users (IRR 0.88, 95% CI 0.49-1.58), or for exclusive cigarette smokers (IRR 1.32, 95% CI 0.91-1.91). Compared with never tobacco users, men who had used snuff exclusively for more than 30 years were at a statistically significantly increased risk for developing HD, (IRR 3.78 95% CI 1.23-11.60) but not for developing NHL

Study	Design	Population	Extent of exposure to nicotine	Main results
		of entry, on the first visit, only. 12 per cent had ever used snuff and not smoked, and 30 per cent had ever smoked cigarettes exclusively.		(IRR 0.69, 95% CI 0.41-1.15). The finding of increased risk for HD was based on four cases of snus users. Linear dose-response relationships were not demonstrated for dose or years of smoking. Compared with never tobacco users, men who smoked 11-20 cigarettes per day at baseline were at increased risk for developing HD (IRR 1.73 95% CI 1.14-2.63). There was no change in risk for men who smoked fewer or more than this dose at baseline. Broadstock (2007) describes strengths of this study as large sample size and the prospective exposure data collection, but notes weaknesses as follows: • 25 per cent of workers did not attend follow-up appointments, based on Bolinder et al. (1994). • Self reporting of tobacco exposure was not verified. • Tobacco exposure defined only at baseline (which would not capture changes in patterns of use that were observed in subsequent years i.e. increased snus use, decreased cigarette smoking, and in the age groups where snus use is prevalent) , • Confounders not adjusted for include SES, education, indices of obesity, immunosuppressive status, immunosuppressive therapy, autoimmune diseases and Epstein-Barr infection. • Broadstock (2007) concludes that the prospective cohort study generally did not identify a relationship between snus or smoking and HD or NHL. The finding of an increased risk for developing HD in long-term snuff users, based on four cases, and exposure to products that may

Study	Design	Population	Extent of exposure to nicotine	Main results
				not be comparable to modern snus, is subject to the weaknesses noted above and may be a type I error.

26 Data on patterns of use of Swedish snus

Country	Time period	Gender	Age group	Socioeconomic factor	Prevalence (snus use)	Prevalence (smoking)	Source
Sweden	2003	M	18-39	High education	Daily: 20%	6%*[1]	Upmark 2003, in SCENIHR 2008
Sweden	2003	M	60-84	High education	Daily: 5%	10%*	Upmark 2003, in SCENIHR 2008
Sweden	2003	M	18-39	Low education	Daily: 32%	14%*	Upmark 2003, in SCENIHR 2008
Sweden	2003	M	60-84	Low education	Daily: 7%	17%*	Upmark 2003, in SCENIHR 2008
Sweden	2003	F	30-69	High education	4%	12%	Upmark 2003, in SCENIHR 2008
Sweden	2003	F	30-69	Low education	2%	25%	Upmark 2003, in SCENIHR 2008
Sweden	2005	M	12		Daily: 2%	3%	CAN 2006 in SCENIHR 2008
Sweden	2005	M	15		Daily: 12%	4%	CAN 2006 in SCENIHR 2008
Sweden	2005	M	16-24		Daily: 26%	7%	Statistics Sweden 2007 in SCENIHR 2008
Sweden	2005	M	25-34		Daily: 33%	10%	Statistics Sweden 2007 in SCENIHR 2008
Sweden	2005	M	35-44		Daily: 31%	13%	Statistics Sweden 2007 in SCENIHR 2008
Sweden	2005	M	45-54		Daily: 24%	17%	Statistics Sweden 2007 in SCENIHR 2008
Sweden	2005	M	55-64		Daily: 17%	22%	Statistics Sweden 2007 in SCENIHR 2008

[1] Values marked * are inferred visually from Figure 4b, p35, SCENIHR (2008).

Country	Time period	Gender	Age group	Socioeconomic factor	Prevalence (snus use)	Prevalence (smoking)	Source
Sweden	2005	M	65-74		Daily: 10%	10%	Statistics Sweden 2007 in SCENIHR 2008
Sweden	2005	M	16-84	Total population	26%		Statistics Sweden 2007 in SCENIHR 2008
Sweden	2005	M	16-84	Born abroad	14%		Statistics Sweden 2007 in SCENIHR 2008
Sweden	2005	M	16-84	Born in Sweden: immigrant parents	31%		Statistics Sweden 2007 in SCENIHR 2008
Sweden	2005	M	16-84	Born in Sweden to Swedish parents	27%		Statistics Sweden 2007 in SCENIHR 2008
Norway	2006	M	16-74		Daily: 11% Occasionally: 7%	24%	Statistics Norway 2007 in SCENIHR 2008
Norway	2006	F	16-74		<1%	24%	Statistics Norway 2007 in SCENIHR 2008
Norway	2006	M	16-24		17%	22%	Statistics Norway 2007 in SCENIHR 2008
Norway	2006	M	25-34		20%	22%	Statistics Norway 2007 in SCENIHR 2008
Norway	2006	M	35-44		11%	26%	Statistics Norway 2007 in SCENIHR 2008
Norway	2006	M	45-54		5%	29%	Statistics Norway 2007 in SCENIHR 2008
Norway	2006	M	55-64		3%	28%	Statistics Norway 2007 in SCENIHR 2008

Country	Time period	Gender	Age group	Socioeconomic factor	Prevalence (snus use)	Prevalence (smoking)	Source
Norway	2006	M	65-74		0%	17%	Statistics Norway 2007 in SCENIHR 2008
Norway	2004-2006	F	16-24		0.7%		Norwegian Directorate of Health and Social Affairs 2007 in SCENIHR 2008
Norway	2004-2006	F	25-34		0.5%		Norwegian Directorate of Health and Social Affairs 2007 in SCENIHR 2008
Norway	2004-2006	F	16-74		0.4%		Norwegian Directorate of Health and Social Affairs 2007 in SCENIHR 2008