



Rapid review for NICE: long term use of non-tobacco nicotine containing products in individuals who have quit smoking abruptly

Produced by

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5

November 2021: NICE guidelines PH45 (June 2013) PH48 (November 2013) have been updated and replaced by NG209.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.



Cardiff Institute of Society and Health
Athrofa y Gymdeithas ac Iechyd Caerdydd

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EXECUTIVE SUMMARY

1. INTRODUCTION

1.1. Background

NICE requested a further evidence review to accompany a series of reviews to support the development of tobacco harm reduction (THR) guidance. This rapid review investigated the long term use of non-tobacco nicotine containing products (NCPs) in individuals who have attempted to quit smoking abruptly rather than via THR approaches. Long term use of nicotine replacement therapy (NRT) has previously been identified as a potential issue in treating nicotine addiction in smokers (Hughes, 1998; RCP, 2000).

For the purposes of this review 'non-tobacco nicotine containing products' were defined as NRT and 'electronic nicotine delivery systems' (sometimes known as 'electronic cigarettes' or 'e-cigarettes') and topical gels. NRT is available in the following formulations: chewing gum, transdermal patches, inhalers, microtabs, mouth/nasal sprays and lozenges.

Evidence for individuals who used NCPs long term following THR approaches (cut down to quit or long term harm reduction) would have been identified in the two previous THR effectiveness reviews.

It was agreed that a *full systematic review* was not required but that the SURE team would examine studies that were identified through searching for the four THR reviews for any data on long term NCP use following an attempt of abrupt cessation; as well as employing snowballing techniques to identify other relevant studies concerned with the long term use of NCPs that were not identified in the production of the THR reviews.

1.2. Aim of the review

To identify and summarise evidence relating to the long term use of NCPs at or longer than 12 months among abrupt quitters.

1.3. Research questions

Information was collected on the following:

1. Length of time of using NCP
2. Pattern of NCP use i.e. type of NCP, amount, frequency, reason for use
3. Demographics of long term users e.g. gender, ethnicity, social determinants
4. Predictors of long term use
5. Purchase patterns

2. METHODS

A rapid review of evidence relating to long term use of nicotine containing products amongst abrupt quitters was carried out. A search was conducted of the Reference Manager databases constructed from the comprehensive literature searches carried out for the reviews of the effectiveness of tobacco harm reduction approaches and the barriers and facilitators to their implementation (which included smoking cessation search terms), as well as the database for the review of the safety, risk and

pharmacokinetics profiles of tobacco harm reduction technologies. The original search from which the Reference Manager databases were constructed included a wide range of databases and web sites to identify a wide range of publications, including grey literature. Searches were limited to studies published in the English language between 1990 and 2012. Additional snowballing techniques were carried out to ensure relevant publications had been identified. All populations, except pregnant women, of all ages were included.

Interventions, longitudinal and cross-sectional studies were included that examined:

- Long term use, of 12 months or longer, in those attempting to quit smoking abruptly
- Purchase patterns, e.g. information relating to over the counter and online purchases

Study selection was carried out by a single reviewer, with exclusions at the full text screening stage being verified by a second reviewer. Quality assessment and data extraction was carried out by one reviewer and checked by a second.

A narrative summary of the evidence was carried out; this was supported by evidence statements.

3. RESULTS

A total of 18 papers comprising 15 studies were included in the review. See Table 1 (pp. 14-16) for a brief summary of the studies. Full details are provided in the Evidence Tables (Appendix A).

Overall, the quality of the 15 included studies varied. Whilst the three RCTs (**Blondal 1999 ++**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Sutherland 1992 ++**) were all assessed as being of high quality, only four of the remaining studies, two prospective cohort studies (**Hajek 2007 +**, **Schneider 2003 +**) and two of the eight cross-sectional surveys (**Etter 2009 +**, **Etter 2011 +**), were rated as moderate quality.

Three studies were from the UK (**Hajek 2007 +**, **Shetty 2010 –**, **Sutherland 1992 ++**) and these were in specific populations with **Shetty 2010 –** having a small sample size. Two studies were conducted in Europe (**Blondal 1999 ++**, **Schneider 2003 +**). Seven studies were conducted in Canada and the USA (**Foulds 2011 –**, **Hatsukami 1993 –**, **Hughes 2004 –**, **Johnson 1991 & 1992 –**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Shiffman 2003 –**). Three were internet surveys (**Etter 2009 +**, **Etter 2011 +**, **Heavner 2010 –**) conducted in English with **Etter 2011 +** also in French.

Of the 15 studies, 5 were in a community setting (**Blondal 1999 ++**, **Hatsukami 1993 –**, **Hughes 2004 –**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Shiffman 2003 –**). **Foulds 2011 –** at an electronic cigarette enthusiast meeting, **Etter 2009 +**, **Etter 2011 +**, **Heavner 2010 –** were internet surveys, **Hajek 2007 +**, **Schneider 2003 +** and **Sutherland 1992 ++** in a smoker's clinic or smoking cessation unit, **Johnson 1991 –** and **Johnson 1992 –** within a health maintenance organization and **Shetty 2010 –** was conducted in a medium secure hospital..

4. EVIDENCE STATEMENTS

4.1. Long term NRT use

Three studies collected data on a range of NRT products (**Hajek 2007 +**, **Shetty 2010 –**, **Shiffman 2003 –**). Six studies examined nicotine gum (**Etter 2009 +**, **Hatsukami 1993 –**, **Hughes 2004 –**, **Johnson 1991 –**, **Johnson 1992 –**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995]). Two

explored the effect of nicotine nasal spray (**Schneider 2003 +, Sutherland 1992 ++**). One (**Blondal 1999 ++**) looked at the effect of nicotine patch with nicotine nasal spray.

Evidence Statements:

- 4.1** There is moderate evidence of long term (12 months) NRT use in a small number of people who had quit smoking. The evidence is provided by three RCTs (**Blondal 1999 ++, LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Sutherland 1992 ++**), two prospective cohort studies (**Hajek 2007 +, Schneider 2003 +**) and one UBA (**Hatsukami 1993 –**). This extended use is beyond the length of time that is recommended, treatment is usually between eight and 12 weeks before the dose is reduced and eventually stopped. From the studies that provided 12-month follow-up data, 7% (range 3-11%) of individuals who had quit smoking were still using NRT. This evidence is for nasal spray (**Blondal 1999 ++, Sutherland 1992 ++, Schneider 2003 +**), nicotine gum (**LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Hatsukami 1993 –**) and a range of NRT products (**Hajek 2007 +**).
- 4.2** There is moderate evidence that most long term (≥ 12 months) use of nicotine gum or spray is within recommended dosage limits. The evidence is provided by two RCTs (**Blondal 1999 ++, LHS++** [Bjornson-Benson 1993; Murray 1996]), one prospective cohort study (**Schneider 2003 +**) and two cross-sectional surveys (**Hughes 2004 –, Johnson 1991 –**). For this dosage evidence participants in **Blondal 1999 ++, LHS++** [Bjornson-Benson 1993; Murray 1996] and **Schneider 2003 +** had quit smoking but the smoking status was not reported for participants in **Hughes 2004 –** and **Johnson 1991 –**.
- 4.3** There is moderate evidence from two studies that nicotine dependence at baseline is a predictor of long term NRT use at 12 months (**LHS ++** [Bjornson-Benson 1993], **Hajek 2007 +**). The data was from participants who had all quit smoking.

This evidence is directly applicable to people in the UK who attempt to quit smoking abruptly. Of the studies that reported NRT use at 12 months in former smokers, two studies were conducted in the UK (**Hajek 2007 +, Sutherland 1992 ++**) and three were conducted in community settings (**Blondal 1999 ++, Hatsukami 1993 –**), **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995].

4.2. Electronic cigarettes

Three studies explored the use of electronic cigarettes (**Etter 2011 +, Foulds 2011 –, Heavner 2010 –**).

Evidence Statements:

- 4.4** There is no evidence of e-cigarette use for periods of 12 months or longer in individuals who quit smoking abruptly and insufficient evidence of the pattern of use.
- 4.5** There is weak evidence from three cross-sectional surveys, possibly of e-cigarette enthusiasts, (**Etter 2011 +, Foulds 2011 –, Heavner 2010 –**), that e-cigarettes are used for 12 months or longer though only **Heavner 2010 –** states that some individuals have completely replaced cigarettes with e-cigarettes. There was no evidence related to the dosage used by long term e-cigarette users.

4.6 No evidence was identified on predictors or purchase patterns of e-cigarette use.

The evidence is only partially applicable to people in the UK who quit smoking abruptly. This is because e-cigarettes are not licensed for smoking cessation. However the evidence does indicate that e-cigarettes are used in the UK (**Etter 2011 +, Heavner 2010 –**) though it does not indicate if any of the e-cigarette users quit smoking abruptly. Also the evidence is provided by three cross-sectional surveys (**Etter 2011 +, Etter 2011 +, Foulds 2011 –, Heavner 2010 –Heavner 2010 –**) in which participants were possibly e-cigarette enthusiasts, particularly **Foulds 2011 –**.

5. DISCUSSION

A variety of settings, interventions and outcomes were studied, which together with a lack of high quality studies specifically investigating the long term use of nicotine containing products (NCPs) beyond 12 months in former smokers made it difficult to summarise the evidence relating to long term use of NCPs. Also some studies reported data related to NRT purchases or prescription refills rather than on actual use of NRT. The motivation of participants across the studies varied and in many cases was not reported.

Of the 15 included studies, ten had a primary focus on the use of NCPs (**Etter 2009 +, Etter 2011 +, Foulds 2011 –, Hajek 2007 +, Heavner 2010 –, Hughes 2004 –, Johnson 1991 –, Johnson 1992 –, Shetty 2010 –, Shiffman 2003 –**). Of these studies only **Hajek 2007 +** had 12 month follow-up data specifically concerned with long term NRT use in former smokers and provided details of the NRT provision but no information related to dose or amount. **Hajek 2007 +** was a prospective cohort study, **Shetty 2010 –** was an uncontrolled before and after and the others were cross-sectional surveys (**Etter 2009 +, Etter 2011 +, Foulds 2011 –, Heavner 2010 –, Hughes 2004 –, Johnson 1991 –, Johnson 1992 –, Shiffman 2003 –**).

Overall there were three studies graded as high quality ++ (**Blondal 1999 ++, LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Sutherland 1992**). Only three studies were conducted in the UK, **Hajek 2007 +, Shetty 2010 –** and **Sutherland 1992 ++**. **Hajek 2007 +** and **Sutherland 1992 ++** were conducted in a smokers' clinic and **Shetty 2010 –** within a medium secure hospital.

This rapid review provides evidence that some smokers who quit smoking continue to use NRT products beyond the recommended period though overall this use is within recommended dosage limits. The evidence also suggests that baseline nicotine dependence is a predictor of long term NRT use.

The evidence identified indicates that some users of e-cigarettes do use them for 12 months or longer but it is not clear if all users of e-cigarettes use them as a complete replacement for cigarettes.

ABBREVIATIONS

BMI	Body mass index
BNF	British National Formulary
C	Control group
CI	Confidence interval
CO	Carbon monoxide
CPD	Cigarettes per day
CSS	Cross-sectional survey
E-cigarette	Electronic cigarette
FTND	Fagerstrom Test of Nicotine Dependence
HMO	Health maintenance organization
I	Intervention group
ITT	Intention to treat
LHS	Lung Health Study
MANOVA	Multiple analysis of variance
MHRA	Medicines and Healthcare products Regulatory Agency
NCP	Nicotine containing product
NICE	National Institute for Health and Clinical Excellence
NRT	Nicotine replacement therapy
OR	Odds ratio
OTC	Over the counter
PC	Prospective cohort
RCP	Royal College of Physicians
RCT	Randomised controlled trial
SI	Special intervention
THR	Tobacco harm reduction
UBA	Uncontrolled before and after study

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3. Demographics of long term users e.g. gender, ethnicity, social determinants
4. Predictors of long term use
5. Purchase patterns

2. METHODS

2.1. Literature search

A search was conducted of the Reference Manager databases constructed from the comprehensive literature searches for all three reviews on effectiveness of tobacco harm reduction approaches and the barriers and facilitators to their implementation (which included smoking cessation search terms), as well as the database for the review: safety, risk and pharmacokinetics profiles of tobacco harm reduction technologies (Jones, 2011).¹ The search string sets listed below were combined with 'AND' and used to search within title, abstract and keywords (Reference Manager automatically searches for plurals). To be consistent with the three previous reviews, research conducted from 1990 was considered.

NCP terms:

{nicotine patch} OR {nicotine gum} OR {nicotine inhaler} OR {nicotine therapy} OR {nicotine replace} OR {nicotine lozenge} OR {nicotine tablet} OR {nicotine microtab} OR {nicotine nasal spray} OR {nicotine spray} OR {nicotine delivery} OR {nicotine gel} OR {nicotine pastille} OR {NRT} OR {e-cig} OR {electronic cigarette} OR {ecig} OR {Intellcig} OR {vaping} OR {vaporiser} OR {vaporizer} OR {cigarette substitut} OR {THR product} OR {nicotine containing product} OR {NCP} OR {Nicorette} OR {Nicorette} OR {Nicotinell} OR {Niconil} OR {NiQuitin} OR {Polacrilex} OR {Habitrol} OR {Nicabate} OR {NicoDerm} OR {Nicotex} OR {Nicotrol} OR {ProStep} OR {Quickmist} OR {Stoppers} OR {Commit lozenge} OR {nicotine pharmacotherapy} OR {Stubit} OR {super-25}

Long term use terms:

{long term use} OR {continued use} OR {continuous use} OR {extended use} OR {ever use} OR {longer duration} OR {usage pattern} OR {persistent use} OR {12 month} OR {18 month} OR {24 month} OR {36 month} OR {12-month} OR {18-month} OR {24-month} OR {36-month} OR {year} OR {pattern of use} OR {purchase pattern}

2.1.1. Additional searches

The first authors of the included publications of the three THR reviews were contacted in February 2012 to request information on additional published studies.

The reference lists of all the included publications were checked for additional studies.

Publications from large scale smoking cessation studies and long term observational studies on smoking behaviours e.g. Lung Health Study (LHS), Smoking Toolkit study, ITC Four Country Survey were identified and considered for inclusion.

Alerts received from ASH Scotland and Global link were screened and a request was posted to Global link for information relevant to this review. *Note:* These alerts identify all types of publication, including grey literature.

The contents pages of the 'top' journals for the three previous reviews as well as for this current review (i.e. the journals that contain the greatest number of papers that meet inclusion criteria) were hand searched from September 2011 to March 2012. These journals were: *Addiction*; *Addictive Behaviors*; *Nicotine & Tobacco Research*; *Preventive Medicine and Tobacco Control*.

¹ The original search from which the Reference Manager databases were constructed included 48 databases and web sites to identify a wide range of publications, including grey literature. Searches were for studies published in the English language between 1990 and 2011. Update searches were conducted in November 2011 and January 2012.

2.2. Inclusion and exclusion criteria

<p><i>Inclusion:</i></p> <ul style="list-style-type: none"> • Long term use (≥ 12 months) in those attempting to quit abruptly • Published intervention, longitudinal and cross-sectional studies • Purchase patterns i.e. information relating to OTC and online purchases 	<p><i>Exclusion:</i></p> <ul style="list-style-type: none"> • Adverse effects (covered by Review 1) • Addiction • Interventions to aid NCP reduction or cessation • Long term use of NCP when used in combination with other smoking cessation preparations e.g. Varenicline or Bupropion or with alternative or complementary therapies e.g. hypnotherapy or acupuncture. • Use in pregnant women
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Where interventions of interest were compared to or used in combination with excluded interventions, studies were only included if the data for the interventions of interest could be disaggregated. Where disaggregation was not possible they were excluded.

2.3. Study selection

Publications that were identified by title as being clearly irrelevant were excluded. Titles and abstracts were screened by HM using the inclusion/exclusion parameters, if in doubt the publication was included. Only publications that explicitly stated in the abstract that they were concerned with long term use or contained other relevant information of interest or stated that had follow-up data of 12 months or longer were retained for full text screening. If an abstract only stated follow-up data at 12 months without data concerned with long term use or other relevant information of interest then it was excluded. Publications were also retained which had been identified for the previous three reviews as containing long term use data. Full publication screening was undertaken by HM and exclusions were checked by FM. Publications excluded at full text were retained with reasons for exclusion.

2.4. Quality assessment

Quality assessment was conducted by each data extractor (FM, HM, AW or SW) and checked by another member of the review team using the GATE checklists for quantitative studies [NICE 2009]. Any disagreement was resolved by discussion. The review team assessed each study's internal and external validity; where external validity measured how far the findings of the study might be generalised beyond the participants to a wider population from which the participants were drawn (e.g. from one community setting in the US to all US communities) but not to other populations. Given the inherent problems of bias and confounding associated with the design of cross sectional surveys, these studies were rated only as + or – and summary scores only are presented. All ratings are included in the evidence tables. In addition, Appendix B and C provide a summary of the quality ratings for each element of the included studies that were assessed.

2.5. Applicability to the UK

Based on advice from members of the Expert Advisory Group for the previous three reviews, it was agreed that research from settings where the smoking reduction and cessation programmes are

sufficiently similar to those in the UK (including Spain, Norway, Denmark, Australia and New Zealand) would be assessed as having high applicability to the UK.

2.6. Data extraction

Data were extracted by a member of the review team (FM, HM, AW or SW) and checked by another, in accordance with Appendix K of the NICE Public Health Methods Manual. These are presented in the Evidence Tables with study characteristics, quality scores and outcome measures reported by the authors (with associated 95% confidence intervals (CI) and p-values where available).

2.7. Data synthesis

The key findings of evidence have been summarised in concise narrative summaries and are supported by evidence tables (Appendix A).

The strength of evidence assessment in the evidence statements is based on the most recent GRADE guidance (Guyatt 2011). The definitions used are broadly defined as follows with potential for moving up or down a grade as summarised in the guidance (Guyatt 2011):

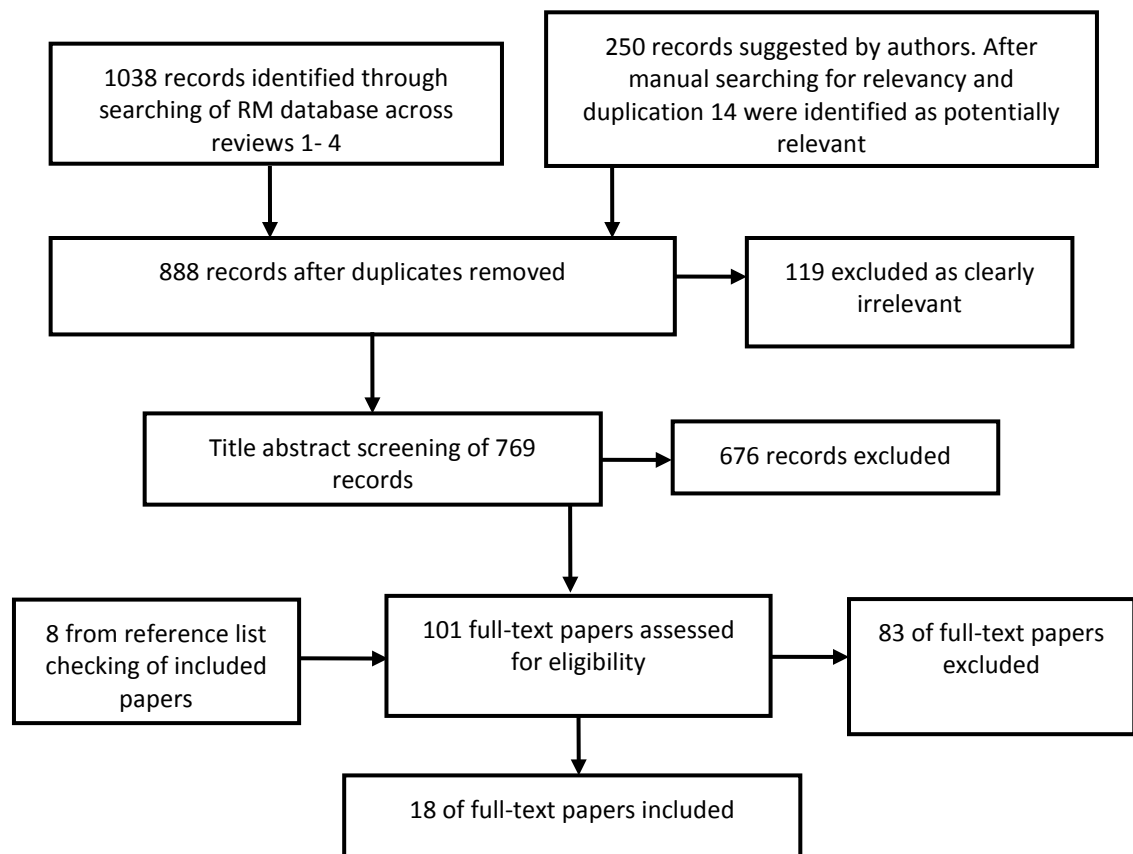
GRADE low, very low quality	=	weak evidence (e.g. before and after studies graded –)
GRADE moderate quality	=	moderate evidence (e.g. RCTs/quasi RCTs graded +)
GRADE high quality	=	strong evidence (e.g. RCTs graded ++)

3. RESULTS

3.1. Search Results

The search methods identified 888 citations of which 119 were excluded by title as clearly irrelevant. Of the remaining 769 citations that were screened by title and abstract 676 were excluded and 93 were considered for full text screening. An additional 8 publications were identified from reference list checking of included papers. A total of 101 papers were screened in full text which resulted in the exclusion of 83 and the inclusion of 18 papers. A full list of excluded papers for this review, with reasons for exclusion, is provided in Appendix F.

A total of 18 papers were included in the review, comprising of 15 studies. See Table 1 (pp. 10-12) for a brief summary of the studies. Full details are provided in the Evidence Tables (Appendix A).



3.2. Quality and applicability of studies

Overall, the quality of the 15 included studies varied. Whilst the three RCTs (**Blondal 1999 ++**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Sutherland 1992 ++**) were all assessed as being of high quality, only four of the remaining studies, two prospective cohort studies (**Hajek 2007 +**, **Schneider 2003 +**) and two of the eight cross-sectional surveys (**Etter 2009 +**, **Etter 2011 +**), were rated as moderate quality.

Three studies were from the UK (**Hajek 2007 +**, **Shetty 2010 –**, **Sutherland 1992 ++**) and these were in specific populations with **Shetty 2010 –** having a small sample size. Two studies were conducted in Europe (**Blondal 1999 ++**, **Schneider 2003 +**). Seven studies were conducted in Canada and the USA (**Foulds 2011 –**, **Hatsukami 1993 –**, **Hughes 2004 –**, **Johnson 1991 & 1992 –**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Shiffman 2003 –**). Three were internet surveys (**Etter 2009 +**, **Etter 2011 +**, **Heavner 2010 –**) conducted in English with **Etter 2011 +** also in French.

Of the 15 studies, 5 were in a community setting (**Blondal 1999 ++**, **Hatsukami 1993 –**, **Hughes 2004 –**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Shiffman 2003 –**). **Foulds 2011 –** at an electronic cigarette enthusiast meeting, **Etter 2009 +**, **Etter 2011 +**, **Heavner 2010 –** were internet surveys, **Hajek 2007 +**, **Schneider 2003 +** and **Sutherland 1992 ++** in a smoker's clinic or smoking cessation unit, **Johnson 1991 –** and **Johnson 1992 –** within a health maintenance organization and **Shetty 2010 –** was conducted in a medium secure hospital.

3.3. Outcomes

Data were extracted for all NCP use of 12 months or longer related to length of time used, type of NCP, amount, frequency, reason for use, demographics of long term users, predictors of long term use and purchase patterns of long term users.

Table 1: Brief summary of included studies

* Studies are complex and this table can only give a flavour of each intervention. See Appendix A for more detailed summaries.

Author and Year	Location and setting ²	Population	Study outline	Internal validity ³
Blondal 1999 RCT	Iceland + Community	237 adults 1% attrition	Nicotine patch for 5 months (tapering from 15 mg for 3 months, 10 mg at month 4 to 5 mg at month 5) with nicotine nasal spray (0.5mg/nostiril) for 1 year. CO verified abstinence to 12 months and 5 years. Participants likely to motivated to quit since responders to adverts in local papers and on television.	++ High quality study other than self-reported outcomes only for NRT use (though would be difficult to confirm). Two authors were employed by, and one consulted for, Pharmacia and Upjohn. Pharmacia and Upjohn measured the cotinine concentrations but the trial is described as double blind.
Etter 2009 Cross-sectional survey	Internet + English survey on a Swiss website	526 adults	Questionnaire in English on the StopTabac.ch web site with a link from other smoking cessation web sites. After 30 days, NRT gum users who agreed and indicated an email address received a message asking whether they were still using NRT, their length of NRT use and their level of craving for NRT gum. Participants were self selected visitors to tobacco cessation web site.	+ Self-selected sample. Unlikely to be representative of all gum users. Self-reported data. Mean duration of gum use was more than 2 years but authors described long term use as > 3 months. No separate data for 12 months plus. Authors received financial support from Pfizer and Novartis, gum producers.
Etter 2011 Cross-sectional survey	Internet – Website available in English and French languages	3,587 adults	Survey assessed the profile, utilization patterns, satisfaction and perceived effects among users of electronic cigarettes. Motivation of participants not reported.	+ Predominantly self-selected users of web sites dedicated to e-cigs. Self-reported data.
Foulds 2011 Cross-sectional survey	USA – Meeting of e-cigarette enthusiasts	104 adults	Cross-sectional survey aimed to identify the e-cig products used by experienced e-cig users, their pattern of e-cig use and the impact on tobacco use. Motivated e-cigarette users.	– Self-selecting sample of e-cig users so potential for bias. Small sample so not likely to be representative.

² The symbols (++ + –) in this column refer to the external validity; where ++ indicates an intervention that is applicable to all members of the population for which the study was designed. As external validity decreases, it is measured by + and then –.

³ The symbols in this column provide a summary rating for quality; where ++ indicates that the study has been conducted so as to minimise risk of bias. As quality decreases/risk of bias increases, it is measured by + and then –.

Hajek 2007 Prospective cohort	UK ++ Smokers' clinic	1,518 adults	NRT prescription for attendees to a smokers' clinic. 3-month programme of treatment combined medication (with advice to use for ≤3 months) and behavioural support (UK Stop Smoking Service). Until April 2001 NRT was sold to participants for ≤one year at a cost of \$17 ⁴ per week. From April 2001 prescription was free for ≤one year contingent on continuing abstinence (free prescription for circa 70% of participants and \$11 per week for others). Follow-up to 12 months. Participants likely to be motivated since attendees at a cessation clinic.	+ Self-report only, small sample for assessing effect of cost. No data on consumption of NRT.
Hatsukami 1992 Uncontrolled before and after	USA + Community	71 adults 11% attrition	Use of 2mg gum for 1 or 3 month, attendance at weekly individual sessions. Each participant provided \$50 deposit to be returned if they were abstinent at end of treatment. Participants in 1-month group who complied with study procedures paid \$50; those in 3-month group paid \$150. Follow-up to 12 months. Participants motivated to quit.	- Small sample and no biochemical verification at follow-up. Lack of control. 3 month group had more frequent contact than the 1 month group.
Heavner 2010 Cross-sectional survey	Internet - Respondents predominantly from USA and Europe	270 adults	Survey assessed e-cigarette users' patterns of cigarette and e-cigarette usage and smoking cessation attempts, and compared health status and smoking-attributable symptoms between people who completely switched from smoking to e-cigarettes, and those who supplemented cigarette smoking with e-cigarette usage. Highly motivated e-cigarette users.	- Highly motivated and passionate e-cigarette users, likely leading to a biased sample. Some of the questions were imprecise and some answers difficult to interpret. Self-report only. One author is Director of E Cigarette Direct, who initiated and conducted the research.
Hughes 2004 Cross-sectional survey	USA ++ Community	Study 1: 266 adults Study 2: 100 adults	Survey to estimate the misuse of and dependence on over-the-counter nicotine gum in a volunteer sample, including patterns of use. Mixed motivations.	- Volunteer samples, so results may not be applicable (often have higher prevalence and more severe forms of a disorder than population-based samples). Single cross-sectional surveys tending to oversample those with chronic conditions. Possible recruitment bias toward those addicted to NRT.
Johnson 1991 Cross-sectional survey	USA/Canada + Health Maintenance Organisation	1,970 adults	Cross-sectional survey to describe the extent of nicotine chewing gum use among health maintenance organization members, the characteristics of prescribers and users, and the patterns of gum use over a two-year period.	- No data provided on actual number of users and length of continuous use or how many users and gum dose. No data collected on smoking behaviour.
Johnson 1992	USA/Canada +	612 gum users	Cross-sectional survey to assess nicotine gum use when prescribed in a	- Random sampling and high response rate but

⁴ Note: amounts in US\$ because paper published in US-based journal

Cross-sectional survey	Health Maintenance Organisation	86.4% response rate	non-research, routine outpatient setting including patterns of use. Motivation of participants not reported.	caveats associated with cross-sectional survey
Lung Health Study: Bjornson-Benson 1993; Murray 1996; Nides 1995 RCT	USA/Canada ++ Community	5,887 adults 10% attrition of SI group	Special intervention with either bronchodilator (SI-A) or placebo (SI-P) inhaler plus a multisession behavioural program. Additionally, smoking cessation maintenance activities, 4-monthly scheduled clinic visits plus 2mg/piece nicotine gum after quitting. Follow-up to five years. Participants were willing to consider cessation.	++ Self-report of gum use. Large study with specific objective of evaluating the efficacy of early intervention for chronic obstructive pulmonary disease among cigarette smokers who have mild to moderate impairment in pulmonary function. Long term use of NRT was not a primary focus, so difficult to extract specific data.
Schneider 2003 Prospective cohort	Switzerland + Hospital based smoking cessation unit	92 adults 11% attrition	Nicotine nasal spray provided for up to 18 months. Usage measured by MDILog device attached to spray. Self-reported continuous abstinence validated by expired CO measured up to 24 months. Highly motivated participants.	+ Small sample
Shetty 2010 Uncontrolled before and after	UK + Medium secure hospital	50 male adults	Retrospective review of the effect of a trust wide smoke-free policy on changes in behaviour, incidents and prescribing. Motivation of participants not reported.	- Small sample, retrospective analysis, smoking practices outside of hospital would have been useful.
Shiffman 2003 Cross-sectional survey	USA + Community	2,960 households	Cross-sectional survey to estimate the incidence of persistent use of OTC nicotine gum and patch for periods of >3 months, ≥ 6 months, ≥ 12 months and ≥ 24 months. No information on motivation of participants.	- No actual use data collected i.e. NRT products may be purchased but not used. Household data rather than individual. No data on smoking status or behaviour. No data on physician consultations. Purchase patterns may shift with time as OTC NRT becomes more established.
Sutherland 1992/ Stapleton 1998 RCT	UK ++ Hospital smokers' clinic	227 adults 4.5% attrition	Nicotine nasal spray 1mg/dose with maximum 5 doses/hour and 40 doses/day. Recommended duration of use = 3 months. No formal dose reduction regimen. Biochemically validated complete abstinence measured up to 12 months. Participants were motivated to stop smoking.	++ Well conducted study

4. FINDINGS

Three studies collected data on a range of NRT products (**Hajek 2007 +**, **Shetty 2010 –**, **Shiffman 2003 –**). Six studies examined nicotine gum (**Etter 2009 +**, **Hatsukami 1993 –**, **Hughes 2004 –**, **Johnson 1991 –**, **Johnson 1992 –**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995]). Two explored the effect of nicotine nasal spray (**Schneider 2003 +**, **Sutherland 1992 ++**). One (**Blondal 1999 ++**) looked at the effect of nicotine patch with nicotine nasal spray. Three studies explored the use of electronic cigarettes (**Etter 2011 +**, **Foulds 2011 –**, **Heavner 2010 –**). Ten of the included studies (**Etter 2009 +**, **Etter 2011 +**, **Foulds 2011 –**, **Hajek 2007 +**, **Heavner 2010 –**, **Hughes 2004 –**, **Johnson 1991 –**, **Johnson 1992 –**, **Shetty 2010 –**, **Shiffman 2003 –**) specifically explored the use of NRT products or electronic cigarettes with the remainder providing usage data as additional information to their primary outcomes of interest.

4.1. Nicotine Gum

Study Background

Etter 2009 + (cross-sectional survey) assessed the use of and dependence on nicotine gum in former smokers and compared short-term users (3 months or less) to long-term users (greater than 3 months). The survey was conducted with a self-selected sample which might not be representative of all users. Information was not provided regarding the manner in which gum was obtained. Of those using gum for greater than 3 months 82.8% (250/302) agreed to the statement “because I am addicted to the nicotine gum” as being either very or extremely true. Those using gum for greater than 3 months were using a median nicotine dose of 24mg/day.

Hajek 2007 + (prospective cohort) assessed the effect of long-term use of different NRT products in smokers attending routine smoking cessation treatment and examined the effect of NRT cost on its long term use. Participants were allowed to select their preferred NRT product and advised to use it in accordance with the manufacturer's instructions for up to 3 months. Information regarding the dose and amount of NRT that was used was not provided. They were seen weekly over 6 weeks with the last session scheduled at 4 weeks after their quit date. Patients continued to receive NRT as needed via their doctors or pharmacists, collecting prescription forms at the clinic, or buying NRT over-the-counter. The clinic treatment was free though the NRT products had varying levels of cost. Until April 2001, NRT was sold to participants for up to 1 year at a cost of \$17 per 1-week supply (during this time participants receiving free prescriptions were entitled to one or four weeks free NRT). From April 2001 NRT was provided ‘on prescription’ for up to 1 year, contingent on remaining abstinent from smoking. Approximately 70% of clinic patients were entitled to receive NRT free of charge, while the rest paid a prescription charge of US \$11 for each 1-week supply (amounts in US\$ because paper published in US-based journal).

Hatsukami 1993 – (uncontrolled before and after) examined whether longer duration of nicotine gum use in smokers promoted dependence on nicotine gum. Of the 128 participants entering the study only 71 complied with all study procedures and were successful at quitting smoking. Participants were randomly assigned to use 2mg nicotine gum for either one month or three months. Participants’ motivation to quit smoking was self-rated as seven or greater on a 10-point scale. Gum was provided free of charge and participants were required to attend weekly individual sessions while being treated with nicotine gum. Participants had to provide a \$50 deposit to be returned if they had quit smoking at the end of treatment. Those in the one month group who complied with study procedures were paid \$50 and those in the three month group \$150.

Hughes 2004 – (cross-sectional survey) estimated the misuse of and dependence on OTC nicotine gum in a volunteer sample in two separate studies. The recruitment strategy of both may have resulted in a biased sample. For study 1 most participants were recruited via newspaper ads indicating that current nicotine gum users were sought for a telephone survey and would be reimbursed with \$25 for their time. Study 2 also recruited via newspaper ads stating “Are you addicted to nicotine gum? If so we would like to interview you as part of a university study. Reimbursement of \$25 for one telephone interview”. For both studies participants were required to have a history of smoking.

Johnson 1991 – and **Johnson 1992** – (both cross-sectional surveys) described the use of nicotine chewing gum among members of a health maintenance organization. **Johnson 1991** – only provided prescription data and did not provide data on smoking status, reason for use, nicotine dose or the manner in which gum was provided i.e. if encouraged by health professionals or individual choice. **Johnson 1992** – focussed on 498 nicotine gum users who reported being regular smokers of cigarettes during the previous 3 years. Many of the respondents (75%, numbers not provided) reported that they had initially requested nicotine gum from their physician, dentist or nurse, as opposed to having their provider encourage them to try the gum. The dose of the nicotine gum was not provided. Only 5% of gum users attended a structured behavioural treatment program while using the gum. Over half, 56.6% (282/498), of the gum users in the total sample reported that they had used nicotine gum to help them “cut down on the amount smoked each day”.

The primary objective of the **LHS ++** (RCT)[Bjornson-Benson 1993; Murray 1996; Nides 1995] was to evaluate the efficacy of early intervention for chronic obstructive pulmonary disease among cigarette smokers who have mild to moderate impairment in pulmonary outcomes and provided an opportunity to investigate other outcomes. Participants to the intervention group were offered, either on an individual or group basis, a 12 week stop-smoking program and were encouraged to use nicotine gum throughout the 12 week program. Nicotine gum (2mg dose) was provided free of charge at each meeting of the initial cessation program and then at two week intervals. Careful instruction was provided and the recommendation that 10-12 pieces of gum were used per day. Gum use was limited to 6 months; extended use was approved when necessary. A maintenance program, including various support activities, was also offered. The publications from the **LHS ++** included in this review focused on the following: patterns of nicotine-gum use and smoking cessation in the first year of the LHS (Bjornson-Benson 1993); cardiovascular conditions and other side effects associated with the use of 2mg nicotine polacrilex (Murray 1996); predictors of initial smoking cessation and relapse during the first 2 years of the LHS (Nides 1995).

Shiffman 2003 – (cross-sectional survey) estimated the incidence of persistent use of OTC nicotine gum and patch for periods up to and beyond 24 months. All OTC NRT purchases made by a panel of households were tracked. These included: doses of 2 and 4mg nicotine gum; 7, 11, 14, 15, 21 and 22mg patches; various flavours; colours and package sizes. Data was not collected regarding actual use, smoking behaviour or physician consultations.

Length of time of using gum

Although **Blondal 1999 ++** evaluated the efficacy of using a nicotine patch for five months with a nicotine nasal spray for one year it was observed that at five years, two of the 22 participants in

the intervention group (9.1%) were occasionally using nicotine chewing gum; their smoking status was not reported or how nicotine gum was obtained.

The **LHS ++** (Bjornson-Benson 1993) observed that at 12 months 33.6% of 1069 sustained non-smokers, 19.2% of 2071 continuing smokers and 54.5% of 595 intermittent smokers were using nicotine gum. Intermittent non-smokers (those that had a non-smoking status at the time of the follow-up visit but who reported a smoking pattern that included at least one month each of smoking and non-smoking in the eight months prior to the 12 month visit) were more likely to be using gum than any other group, $p < 0.001$.

LHS ++ [Murray 1996]) observed at five years that 14% of former smokers and 5% of participants who were unsuccessful at quitting smoking were using gum.

Hajek 2007 + reported that at 12 months 13% (10/76) of long term users of NRT who had quit smoking were using nicotine gum.

Hatsukami 1993 – identified that after 12 months since quitting smoking 8% (5/63) of participants reported regular gum use since the last follow-up with one participant still continuing to use gum.

Etter 2009 + reported that of former smokers responding to an internet survey, 57% (302/526) had used gum for more than three months with a median of 730 days of use.

In **Hughes 2004 –**, the first of two cross-sectional surveys (Study 1) reported that 46% (122/266) of the sample had used the gum for longer than the recommended three months. Among long term users (i.e. use of gum ≥ 90 days), the median number of days of use was 242 (25th-75th percentile 158-409). For the second cross-sectional survey (study 2), in which participants had self-reported addiction to nicotine gum, the median duration of gum use was 32 months (95% CI 15, 50) and 98% (98/100) of participants had used gum for at least 3 months. In study one 35% (CI 29%, 41%) of all gum users were smoking and using gum concurrently and in study two 12% (CI 6%, 23%) were concurrent gum and cigarette users.

Johnson 1991 – reported that of the 11% (216/1970) of nicotine gum users with four or more prescriptions, 90% (195/216) had periods of continuous use (218 periods in total). Of those continuous use periods, 30% (66/218) were longer than six months, with the longest period being 19 months. A period of continuous use was considered to be time between refills where gum could have been used at a consistent average daily dose (eight or more pieces of gum/day). Smoking status was not reported. In a similar study (**Johnson 1992 –**), 4.4% (19/428) of participants reported using gum for between one and two years and 2.8% (12/428) reported using gum for more than 2 years. The smoking status of these users was not reported though over half, 56.6% (282/498), of the gum users in the total sample reported that they had used nicotine gum to help them “cut down on the amount smoked each day”.

Pattern of long term gum use

Dosage:

The **LHS ++** [Bjornson-Benson 1993] observed at 12 months that sustained non-smokers were using an average of 8.2 pieces of nicotine gum per day (average total of 16.4mg nicotine/day). Average pieces of gum/day were significantly different for intermittent smokers and intermittent non-smokers, 7.5 (total of 15mg nicotine/day) and 9.7 (total of 19.4mg nicotine/day) respectively ($p < 0.001$). (Intermittent non-smokers had a non-smoking status at the time of the follow-up visit but overall reported a smoking pattern that included at least 1 month each of smoking and non-

smoking in the 8 months prior to the 12 month visit.) Additionally (**LHS ++** [Murray 1996]), among sustained non-smokers from the intervention groups, the level of gum use trended upwards over the course of the study (4-60 months) to 10 pieces per day (total of 20mg nicotine/day).

In the first cross-sectional survey (Study 1) in **Hughes 2004** –, the mean daily dose of nicotine obtained by long term users of gum (i.e. use of gum for at least 90 days) was 16mg/day. In Study 2, in which participants had self-reported addiction to nicotine gum, the mean daily dose of nicotine obtained by gum users was 30mg/day with the median duration of gum use being 32 months (95% CI 15, 50). In both studies not all gum users had quit smoking.

In **Johnson 1991** –, where gum was used for a period of 12-18 months, there were 10 periods of continuous use that involved less than eight pieces of gum per day (either less than 16 or 32mg/day assuming that either 2 or 4mg of nicotine/piece) and seven that involved eight or more pieces per day (at least 16 or 32mg/day assuming that either 2 or 4mg of nicotine /piece). For gum use over eighteen months, there were two periods of continuous use involving less than eight pieces of gum per day and four involving eight or more pieces per day. A period of continuous use was considered to be time between refills where gum could have been used at a consistent average daily dose (eight or more pieces of gum/day). The study identified that 0.3% of users consumed 50-99 boxes (one box=96 pieces of gum) over two years. Two users consumed more than 100 boxes (9600 pieces of gum) during this period, although it is not clear whether this was for personal use or if gum had been shared with another user. The dose of the gum used is not provided but assumed that either 2 or 4 mg/piece.

Reason for use:

At the time of the Study 1 survey in **Hughes 2004** –, most long-term users (i.e. use of gum for at least 90 days), 72% (CI 63%, 79%), were using gum to stop smoking or prevent relapse, 8% (CI 4%, 14%) for non-cessation reasons and 20% (CI 14%, 29%) spontaneously volunteered addiction to nicotine gum as the reason for their continued use. In the study 2 survey, in which participants had self-reported addiction to nicotine gum, a total of 92% (CI 87%,97%) of all users purchased gum initially to stop smoking or prevent relapse, 2% (CI 0%, 5%) to reduce smoking and 4% (CI 0%, 8%) to avoid restrictions. 65% (CI 55%, 74%) reported inability to control use, 75% (CI 66%, 84%) reported difficulty stopping, 61% (CI 46%, 76%) reported that stopping gum was extremely difficult, compared to 59% (44%, 74%) who reported that stopping cigarettes was extremely difficult. In both studies not all gum users had quit smoking.

Demographics of long term gum users

The **LHS ++** identified that at 12 months, of those who had quit smoking, women were more likely than men to use nicotine gum ($p<0.0001$) but no differences were found for the amount used (Bjornson-Benson 1993). Of sustained non-smokers at 24 months (numbers not provided), 28% of women and 19% of men reported current use of nicotine gum (Nides 1995).

The study 1 survey in **Hughes 2004** – identified that those who were older were more likely to be long term users ($p<.0001$).

Predictors related to long term gum use

The **LHS ++** [Bjornson-Benson 1993]) identified that for sustained non-smokers ($n=1069$) at 12 months, gum use was significantly associated with being female ($p=0.002$); having a lower body

mass index ($p=0.028$); previous history of gum use ($p=0.0001$) or quit attempts ($p=0.004$) and nicotine dependence (seven variables assessed with $p=0.0001-0.038$). Only nicotine dependence variables were associated with using more pieces per day.

The study 1 survey in **Hughes 2004** – identified that those who had smoked for longer more likely to be long term users ($p<.0001$).

Purchase patterns of long term gum users

Shiffman 2003 – reported that 1% (8/805) of households purchased gum for 12 months or more and 0.4% (3/805) for 24 months or more. In households with persistent gum purchase (allowing for a 1 month gap between purchases), 2.8% (23/805) purchased gum for 12 months or more and 1% (8/805) for 24 months or more. Only purchase data was collected.

4.2. Nicotine Patch

Study Background

Hajek 2007 + (prospective cohort) assessed the effect of long-term use of different NRT products in smokers attending routine smoking cessation treatment and examined the effect of NRT cost on its long term use. Participants were allowed to select their preferred NRT product and advised to use it in accordance with the manufacturer's instructions for up to 3 months. Information regarding the dose and amount of NRT that was used was not provided. They were seen weekly over 6 weeks with the last session scheduled at 4 weeks after their quit date. Patients continued to receive NRT as needed via their doctors or pharmacists, collecting prescription forms at the clinic, or buying NRT over-the-counter. The clinic treatment was free though the NRT products had varying levels of cost. Until April 2001, NRT was sold to participants for up to 1 year at a cost of \$17 per 1-week supply (during this time participants receiving free prescriptions were entitled to one or four weeks free NRT). From April 2001 NRT was provided 'on prescription' for up to 1 year, contingent on remaining abstinent from smoking. Approximately 70% of clinic patients were entitled to receive NRT free of charge, while the rest paid a prescription charge of US \$11 for each 1-week supply (amounts in US\$ because paper published in US-based journal).

Shiffman 2003 – (cross-sectional survey) estimated the incidence of persistent use of OTC nicotine gum and patch for periods up to and beyond 24 months. All OTC NRT purchases made by a panel of households were tracked. These included: doses of 2 and 4mg nicotine gum; 7, 11, 14, 15, 21 and 22mg patches; various flavours; colours and package sizes. Data was not collected regarding actual use, smoking behaviour or physician consultations.

Length of time of using patches

Hajek 2007 + reported that at 12 months 20% (15/76) of long term users of NRT who had quit smoking were using nicotine patches.

Pattern of long term patch use

No studies were identified that reported this data.

Demographics of long term patch users

No studies were identified that reported this data.

Predictors related to long term patch use

No studies were identified that reported this data.

Purchase patterns of long term patch users:

Shiffman 2003 – reported that 0.1% (2/2050) of households purchased patches for 12 months or longer and 0.05% (1/2050) for 24 months or longer. In households with persistent patch purchase (allowing for a one month gap) 0.4% (8/2050) purchased for 12 months or longer and 0.05% (1/2050) for 24 months or longer. Only purchase data was collected.

4.3. Nicotine Nasal Spray

Study Background

Blondal 1999 ++ (RCT) evaluated the efficacy of using a nicotine patch for five months with a nicotine nasal spray for one year allowing a more flexible method of nicotine delivery. Recruited smokers received a baseline assessment 3-6 weeks before they were required to stop smoking, followed by an instructional meeting. Participants attended four supportive group meetings at 1, 8, 15 and 22 days after stopping smoking. Nicotine patch was received for 5 months (tapering from 15mg for 3 months, 10mg at month 4 to 5mg at month 5) with nasal spray (0.5mg/nostiril) for 1 year.

Hajek 2007 + (prospective cohort) assessed the effect of long-term use of different NRT products in smokers attending routine smoking cessation treatment and examined the effect of NRT cost on its long term use. Participants were allowed to select their preferred NRT product and advised to use it in accordance with the manufacturer's instructions for up to 3 months. Information regarding the dose and amount of NRT that was used was not provided. They were seen weekly over 6 weeks with the last session scheduled at 4 weeks after their quit date. Patients continued to receive NRT as needed via their doctors or pharmacists, collecting prescription forms at the clinic, or buying NRT over-the-counter. The clinic treatment was free though the NRT products had varying levels of cost. Until April 2001, NRT was sold to participants for up to 1 year at a cost of \$17 per 1-week supply (during this time participants receiving free prescriptions were entitled to one or four weeks free NRT). From April 2001 NRT was provided 'on prescription' for up to 1 year, contingent on remaining abstinent from smoking. Approximately 70% of clinic patients were entitled to receive NRT free of charge, while the rest paid a prescription charge of US \$11 for each 1-week supply (amounts in US\$ because paper published in US-based journal).

Schneider 2003 + (prospective cohort) evaluated the efficacy of prolonged administration (18 months) of a nicotine nasal spray in a smoking cessation program and attempted to characterise the pattern of spray use with a specially developed electronic monitor in an effort to assess the factors associated with cessation success or failure. This was a small study sample of 92 participants referred to a smoking cessation unit. Spray use was allowed *ad libitum* for 18 months with the advice to use as often as necessary for the first 4-6 months followed by only for occasional help. Only usual smoking cessation counselling was offered except if requested by the participant or clinician. A dose of the nicotine nasal spray consisted of two puffs (0.5mg/nostiril) though as some participants only used one puff per dose analysis was done on number of puffs used.

Sutherland 1992 ++ (RCT) evaluated the efficacy of a nasal nicotine spray as an adjunct to group treatment for smoking cessation and the companion paper (Stapleton, 1998) reported on the long term follow up to estimate the impact of relapse after one year on effectiveness. A dose consisted of two sprays, one to each nostril (1mg of nicotine in total). Spray use was *ad libitum* but limited to 5 doses per hour (total of 5mg of nicotine) and 40 doses per day (40mg of nicotine in total). An instruction leaflet was provided and the recommended duration of use was 3 months. No formal dose reduction regimen was provided.

Length of time of using spray:

Blondal 1999 ++ evaluated the efficacy of using a nicotine patch for five months with a nicotine nasal spray for one year. At 12 months, 32 participants in the intervention group had ceased smoking, of these 13% (4/32) were still using the nasal spray. In the placebo group 13 participants had ceased smoking; none of these were using the placebo nasal spray.

Hajek 2007 + reported that at 12 months 23% (18/76) of long term users of NRT who had quit smoking were using spray.

Schneider 2003 + found that among former smokers 50% (8/16) at 12 months and 42% (5/12) at 18 months were still using a spray. Of the six participants considered partial successes (i.e. those who admitted occasional smoking but with a CO level less than 10 ppm and were willing to continue in the study) three were still using spray at 18 months.

Sutherland 1992 ++ reported that none of the control participants who had given up smoking used the spray beyond six months. However, in the intervention group 43% (13/30) of former smokers were still using the spray at 12 months. A follow-up paper (Stapleton 1998) reported that of 33 former smokers in the intervention group, 19 used the spray for one year and 14 for more than one year (range 1-39 weeks).

Pattern of long term spray use

Dosage:

Blondal 1999 ++ evaluated the efficacy of using a nicotine patch for 5 months with a nicotine nasal spray for 1 year. At 12 months 13% (4/32) of former smokers were using nasal spray with a mean of 22 self-reported 1mg doses per day (22mg/day). These four former smokers had higher cotinine levels than baseline (131% of mean blood cotinine concentration at baseline).

Schneider 2003 + that at 18 months one of the five former smokers still using the spray was using it above recommended levels (median of 94 puffs/day, approx. 47mg/day). Of the three users in the partial success group (i.e. those who admitted occasional smoking but with a CO level less than 10 ppm and were willing to continue in the study) still using the spray, one was using 1-15 puffs/day (0.5mg-7.5mg/day), a second 16-30 puffs/day (8mg-15mg/day) and the third more than 30 puffs/day (median 33 puffs/day, approx. 16.5mg/day). A dose of the nicotine nasal spray consisted of two puffs (0.5mg/nostril) though as some participants only used one puff per dose analysis was done on number of puffs used.

Demographics of long term spray users

No studies were identified that reported this data.

Predictors related to long term spray use

Schneider 2003 + identified that all participants using the nasal spray at 18 months had high craving scores (figures not provided) at the beginning of the study, and all but one still mentioned craving as a reason for continuing to use the spray. The smoking status of these participants was not clear.

Purchase patterns of long term spray users

No studies were identified that reported this data.

4.4. Other NRT products and non-specified NRT

Study Background

Hajek 2007 + (prospective cohort) assessed the effect of long-term use of different NRT products in smokers attending routine smoking cessation treatment and examined the effect of NRT cost on its long term use. Participants were allowed to select their preferred NRT product and advised to use it in accordance with the manufacturer's instructions for up to 3 months. Information regarding the dose and amount of NRT that was used was not provided. They were seen weekly over 6 weeks with the last session scheduled at 4 weeks after their quit date. Patients continued to receive NRT as needed via their doctors or pharmacists, collecting prescription forms at the clinic, or buying NRT over-the-counter. The clinic treatment was free though the NRT products had varying levels of cost. Until April 2001, NRT was sold to participants for up to 1 year at a cost of \$17 per 1-week supply (during this time participants receiving free prescriptions were entitled to one or four weeks free NRT). From April 2001 NRT was provided 'on prescription' for up to 1 year, contingent on remaining abstinent from smoking. Approximately 70% of clinic patients were entitled to receive NRT free of charge, while the rest paid a prescription charge of US \$11 for each 1-week supply (amounts in US\$ because paper published in US-based journal).

Shetty 2010 – (uncontrolled before and after) considered the effect of a trust-wide smoke free policy on changes in behaviour, incidents and prescribing in a population of 50 male in-patients at a medium secure hospital. Specific details relating to the provision of NRT were not provided.

Length of time of using NRT product

Hajek 2007 + reported that only 5% of participants (76/1518) who had quit smoking were still using NRT products at 12 months.

Shetty 2010 – observed that at 12 months post-implementation of a smoke-free policy at a medium secure hospital 20% (10/50) of the participants were receiving NRT of whom four had received intermittent (not defined) NRT for longer than 12 months (specific details relating to the provision of NRT were not provided).

Pattern of long term NRT use

Hajek 2007 + reported that at 12 months, only 5% (76/1518) of participants who had quit smoking were still were using NRT with 23% (18/76) using spray, 20% (15/76) patches, 13% (10/76) gum, 24% (18) sublingual tablets, 5% (4) lozenges and 15% (11) an inhalator.

Demographics of long term NRT users

Hajek 2007 + identified that participants who had quit smoking and were long term (12 months) NRT users were less likely to have completed education to age 16 compared to those who were not using NRT, OR 0.66 (95% CI 0.36, 1.21), $p < 0.05$.

Predictors related to long term NRT use

Hajek 2007 + observed that having a higher Fagerström Test of Nicotine Dependence (FTND) score (OR 1.20, 95% CI 1.03, 1.40; $p = 0.02$) and smoking for withdrawal relief (OR 1.95, 1.06 to 3.60; $p = 0.03$) predicted long term (12 months) NRT use among those who remained cigarette-free. FTND mean score for former smokers using NRT at 12 months was 5.6 (SD =2.1) compared to 4.7 (SD 2.1) for those not using NRT. Previous NRT use, smoking to help concentrate, smoking for weight control, educational status and employment were not significant.

Purchase patterns of long term NRT users

Hajek 2007 + found that there was no significant difference in long term (12 month) NRT use between people entitled to free prescriptions and those who paid for their prescriptions. However, there was only a small sample (76) in which to assess the effect of cost.

4.5. Summary of long term NRT use

There was considerable variation in the evidence identified in terms of study design, study objectives, participant populations and outcomes. Therefore a statistical analysis and synthesis of the findings was not appropriate. A narrative summary of the findings is provided together with tabulation of mean percentage use of NRT at 12 months among former smokers who had quit smoking abruptly.

NRT use at 12 months among former smokers who had quit smoking abruptly

The evidence indicates that there are small numbers of individuals who use NRT products over an extended period of time. Most of the studies identified looked at 12-month usage of gum or spray. Though **Schneider 2003 +** reported spray use at 18 months and both **Blondal 1999 ++** and **LHS ++** [Murray 1996] reported gum use at five years in small numbers of participants. From the studies that provided 12-month follow-up data, 7% (range 3-11%) of individuals who had quit smoking were still using NRT, see Table 2.

Table 2: Mean percent of former smokers using NRT at 12 months who quit smoking abruptly

NRT Use at 12 months among former smokers who quit abruptly					
Study	NRT Product	Total number of participants provided with NRT	Number of participants at 12 months who had quit smoking abruptly	Number of participants who had quit smoking abruptly and were using NRT at 12 months	% of participants who had quit smoking abruptly and were using NRT at 12 months
Blondal 1999 ++	Spray	118	32	4	3

Hajek 2007 +	Range of products	1518	Not stated	76	5
Hatsukami 1993 –	Gum	71	63	5	7
LHS ++ [Bjornson-Benson 1993; Murray 1996; Nides 1995]	Gum	3923	1069	359	9
Schneider 2003 +	Spray	92	16	8	9
Sutherland 1992 ++	Spray	116	30	13	11
Mean % using NRT (range)					7 (3-11)

Patterns of long term NRT use

Dosage:

Evidence related to amount of NRT used long term was provided for the use of gum (**LHS ++** [Bjornson-Benson 1993; Murray 1996], **Hughes 2004 –**, **Johnson 1991 –**) and spray (**Blondal 1999 ++**, **Schneider 2003 +**).

LHS ++ [Bjornson-Benson 1993] reported that former smokers who were using nicotine gum at 12 months were using an average of 8.2 pieces of gum/day (16.4mg/day).

Hughes 2004 – presented two studies. In study 1 the mean daily dose of nicotine obtained by long term users of gum (i.e. use of gum for at least 90 days) was 16mg/day. In Study 2, in which participants had self-reported addiction to nicotine gum, the mean daily dose of nicotine obtained by gum users was 30mg/day with the median duration of gum use being 32 months (95% CI 15, 50).

Johnson 1991 – provided data for gum consumption during continuous periods of use (a period of continuous use was considered to be time between refills where gum could have been used at a consistent average daily dose of eight or more pieces of gum/day, either more than 16 or 32mg/day assuming that either 2 or 4mg of nicotine /piece) and reported seven periods of continuous use of between 12-18 months with consumption of eight or more pieces of gum per day. The study also found that six users consumed 50-99 boxes (4,800-9504 pieces) over two years and one user may have consumed more than 100 boxes over 2 years. However, it is not clear whether this was for personal use or if gum had been shared with another user.

Blondal 1999 ++ reported that former smokers using a 1mg dose spray at 12 months reported using a mean of 22 doses per day (22mg/day).

Schneider 2003 + indicated that at 18 months one of the five former smokers still using spray was using spray above recommended levels (median of 94 sprays/day, approx. 47mg/day).

The evidence indicates that most long term users of gum and spray are not using them above recommended levels; although they may be using products longer than is recommended. The British National Formulary (accessed on line: 4 April 2012) recommends that the maximum dose for gum is 15 pieces of 4mg/piece per day (60mg/day) and for nasal spray 64 sprays/day (0.5mg/spray) equivalent to 32mg/day (0.5mg/spray). However it is recommended that users should reduce the dose at three months for gum and eight weeks for spray.

Product choice:

Only **Hajek 2007 +** provided evidence on the type of NRT product chosen by long term users who had quit smoking. This study indicated spray to be the product selected most often.

Reason for use:

Only **Hughes 2004 –**, who explored gum use, provided information of the reasons behind individuals' long term (at least 90 days) use of NRT although the sample sizes were small. The study found most individuals (72%) used gum to stop smoking or prevent relapse.

Demographics of long term NRT use

There was limited information on the demographics of long term NCP users. The **LHS ++** [Bjornson-Benson 1993] identified, of those who had quit smoking, that women were more likely than men to use gum long term (12 months).

Hajek 2007 + reported that of those who had quit smoking and were long term (12 months) NRT users were less likely to have completed education to age 16 compared to those who did not use NRT long term.

Hughes 2004 – observed that those who were older were more likely to be long term users (at least 90 days).

Predictors related to long term NRT use

Evidence for predictors of long term use was limited. The **LHS ++** [Bjornson-Benson 1993] identified that being female ($p=0.002$), having a lower BMI ($p=0.028$), previous history of gum use ($p=0.0001$) or quit attempts ($p=0.004$) and nicotine dependence variables (seven variables assessed with $p=0.0001-0.038$) were significantly associated with gum use at 12 months.

Hajek 2007 + also observed that nicotine dependence as defined by the FTND score was associated with long term NRT use (OR 1.20, 95% CI 1.03, 1.40; $p=0.02$) as well as smoking for withdrawal relief. FTND mean score for former smokers using NRT at 12 months was 5.6 (SD =2.1) compared to 4.7 (SD 2.1) for former smokers at 12 months not using NRT.

Schneider 2003 + reported that all participants using spray at 18 months had higher craving scores at baseline.

Hughes 2004 – observed that those who had smoked for a longer period were more likely to be long term users (at least 90 days).

Purchase patterns of long term NRT users

There was little evidence regarding purchase patterns of long term users.

Shiffman 2003 – reported that 0.1% (2/2050) of households purchased patches for 12 months or longer and 0.05% (1/2050) for 24 months or longer. In households with persistent patch purchase (allowing for a one month gap between purchases) 0.4% (8/2050) purchased for 12 months or longer and 0.05% (1/2050) for 24 months or longer.

Hajek 2007 + found no significant difference in long term (12 months) NRT use between people entitled to free prescriptions and those who paid for their prescriptions though there were only a small number of long term users ($n=76$) in which to assess an effect of cost.

Evidence Statements:

- 4.1** There is moderate evidence of long term (12 months) NRT use in a small number of people who had quit smoking. The evidence is provided by three RCTs (**Blondal 1999 ++, LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Sutherland 1992 ++**), two prospective cohort studies (**Hajek 2007 +, Schneider 2003 +**) and one UBA (**Hatsukami 1993 –**). This extended use is beyond the length of time that is recommended, treatment is usually between eight and 12 weeks before the dose is reduced and eventually stopped. From the studies that provided 12-month follow-up data, 7% (range 3-11%) of individuals who had quit smoking were still using NRT. This evidence is for nasal spray (**Blondal 1999 ++, Sutherland 1992 ++, Schneider 2003 +**), nicotine gum (**LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Hatsukami 1993 –**) and a range of NRT products (**Hajek 2007 +**).
- 4.2** There is moderate evidence that most long term (≥ 12 months) use of nicotine gum or spray is within recommended dosage limits. The evidence is provided by two RCTs (**Blondal 1999 ++, LHS++** [Bjornson-Benson 1993; Murray 1996]), one prospective cohort study (**Schneider 2003 +**) and two cross-sectional surveys (**Hughes 2004 –, Johnson 1991 –**). For this dosage evidence participants in **Blondal 1999 ++, LHS++** [Bjornson-Benson 1993; Murray 1996] and **Schneider 2003 +** had quit smoking but the smoking status was not reported for participants in **Hughes 2004 –** and **Johnson 1991 –**.
- 4.3** There is moderate evidence from two studies that nicotine dependence at baseline is a predictor of long term NRT use at 12 months (**LHS ++** [Bjornson-Benson 1993], **Hajek 2007 +**). The data was from participants who had all quit smoking.

This evidence is directly applicable to people in the UK who attempt to quit smoking abruptly. Of the studies that reported NRT use at 12 months in former smokers, two studies were conducted in the UK (**Hajek 2007 +, Sutherland 1992 ++**) and three were conducted in community settings (**Blondal 1999 ++, Hatsukami 1993 –**), **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995].

4.6. Electronic cigarettes (e-cigarettes)

Study Background

Etter 2011 + (cross-sectional survey) assessed the profile, utilisation patterns, satisfaction and perceived effects among users of e-cigarettes. The data is self-reported and likely to be a highly enthusiastic sample of e-cigarette users. The sample included current and former smokers.

Foulds 2011 – (cross-sectional survey) identified the electronic cigarette products used by experienced e-cigarette users, their pattern of e-cigarette use and the impact on tobacco use. The participants were a group of highly motivated and enthusiastic e-cigarette users. Of the 104 respondents 88% (91/104) described themselves as ex-cigarette smokers and 13% (13/104) reported making greater than 10% of their income from the e-cigarette business. Comparisons were made between users of less than a year (short term users) and users of a year or more (long term users).

Heavner 2010 – (cross-sectional survey) described e-cigarette users' patterns of cigarette and e-cigarette usage and smoking cessation attempts and compared health status and smoking

attributable symptoms between people who completely switched from smoking to e-cigarettes, and those who supplemented cigarette smoking with e-cigarette usage. The data was self-reported and participants were likely to be highly enthusiastic e-cigarette users. One author is Director of E Cigarette Direct, who initiated and conducted the research.

The two internet surveys involved a self-selected sample and as electronic cigarettes are subject to varying levels of country specific regulation and legislation it is likely that the samples are biased. For **Etter 2011 +** the country distribution of respondents was as follows: 62% USA; 14% France; 6% UK; 4% Switzerland; 3% Canada; 11% other countries and for **Heavner 2010** – nearly 75% resided in the USA and 17% in the UK.

Length of time of using e-cigarettes

Etter 2011 + reported that 15% (434/2899) of respondents had used e-cigarettes for more than one year. Smoking status of these users was not provided.

Foulds 2011 – found that 54% (56/104) of respondents had been using e-cigarettes for at least one year. Smoking status of these users was not provided.

Heavner 2010 – identified that 3% (9/303) of respondents had been using e-cigarettes for longer than 13 months; 2% (5/303) for 13-18 months; 0.3% (1/303) for 19-24 months and 1% (3/303) for more than 24 months. Smoking status was not reported.

Pattern of e-cigarette use

Foulds 2011 – found that long term users typically used slightly lower nicotine strength liquid than short term users.

Heavner 2010 – reported that seven respondents who had been using e-cigarettes for longer than 12 months had used them as a complete replacement for cigarettes. Of 142 people who indicated that pharmaceutical products (i.e. nicotine gum or patches) did not help them to stop smoking, 84% (119) used e-cigarettes as a complete replacement for cigarettes. Data was not presented separately for those using e-cigarettes for more than 12 months.

Demographics of long term e-cigarette users

Foulds 2011 – reported that demographic characteristics did not differ significantly between long and short term users.

Heavner 2010 – observed that on average, respondents who lived in Europe had used e-cigarettes for longer than respondents in the US (this may be partly attributed to varying levels and timing of country specific regulation and legislation) though were less likely to use e-cigarettes as a complete replacement for cigarettes.

Predictors related to long term e-cigarette use

No studies were identified that reported this data.

Purchase patterns of long term e-cigarette users

No studies were identified that reported this data.

Evidence Statements:

- 4.4** There is no evidence of e-cigarette use for periods of 12 months or longer in individuals who quit smoking abruptly and insufficient evidence of the pattern of use.
- 4.5** There is weak evidence from three cross-sectional surveys, possibly of e-cigarette enthusiasts, (**Etter 2011 +**, **Foulds 2011 –**, **Heavner 2010 –**) that e-cigarettes are used for 12 months or longer though only **Heavner 2010 –** states that some individuals have completely replaced cigarettes with e-cigarettes. There was no evidence related to the dosage used by long term e-cigarette users.
- 4.6** No evidence was identified on predictors or purchase patterns of e-cigarette use.

The evidence is only partially applicable to people in the UK who quit smoking abruptly. This is because e-cigarettes are not licensed for smoking cessation however the evidence does indicate that e-cigarettes are used in the UK (**Etter 2011 +**, **Heavner 2010 –**) though it does not indicate if any of the e-cigarette users quit smoking abruptly. Also the evidence is provided by three cross-sectional surveys (**Etter 2011 +**, **Etter 2011 +**, **Foulds 2011 –**, **Heavner 2010 –**, **Heavner 2010 –**) in which participants were possibly e-cigarette enthusiasts particularly **Foulds 2011 –**.

5. DISCUSSION

A variety of settings, interventions and outcomes were studied, which together with a lack of high quality studies specifically investigating the long term use of nicotine containing products (NCPs) beyond 12 months in former smokers made it difficult to summarise the evidence relating to long term use of NCPs. Also some studies reported data related to NRT purchases or prescription refills rather than on actual use of NRT. The motivation of participants across the studies varied and in many cases was not reported.

Of the 15 included studies, ten had a primary focus on the use of NCPs (**Etter 2009 +**, **Etter 2011 +**, **Foulds 2011 –**, **Hajek 2007 +**, **Heavner 2010 –**, **Hughes 2004 –**, **Johnson 1991 –**, **Johnson 1992 –**, **Shetty 2010 –**, **Shiffman 2003 –**). Of these studies only **Hajek 2007 +** had 12 month follow-up data specifically concerned with long term NRT use in former smokers and provided details of the NRT provision but no information related to dose or amount. **Hajek 2007 +** was a prospective cohort study, **Shetty 2010 –** was an uncontrolled before and after and the others were cross-sectional surveys (**Etter 2009 +**, **Etter 2011 +**, **Foulds 2011 –**, **Heavner 2010 –**, **Hughes 2004 –**, **Johnson 1991 –**, **Johnson 1992 –**, **Shiffman 2003 –**).

Overall there were three studies graded as high quality ++ (**Blondal 1999 ++**, **LHS ++** [Bjornson-Benson 1993; Murray 1996; Nides 1995], **Sutherland 1992**). Only three studies were conducted in the UK, **Hajek 2007 +**, **Shetty 2010 –** and **Sutherland 1992 ++**. **Hajek 2007 +** and **Sutherland 1992 ++** were conducted in a smokers' clinic and **Shetty 2010 –** within a medium secure hospital.

This rapid review provides evidence that some smokers who quit smoking continue to use NRT products beyond the recommended period though overall this use is within recommended dosage limits. The evidence also suggests that baseline nicotine dependence is a predictor of long term NRT use.

The evidence identified indicates that some users of e-cigarettes do use them for 12 months or longer but it is not clear if all users of e-cigarettes use them as a complete replacement for cigarettes.

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APPENDIX A – INCLUDED STUDIES - EVIDENCE TABLES

<p>First author and year: Blondal 1999</p> <p>Aim of study: To evaluate the efficacy of using a nicotine patch for 5 months with a nicotine nasal spray for 1 year.</p> <p>Study Design : RCT</p> <p>Quality score: ++</p> <p>External validity score: +</p>	<p>Setting: Community; Reykjavik, Iceland</p> <p>Participants: Smokers aged 22-66 years; 67% female; 17% with history of treatment for alcoholism</p> <p>Inclusion: Aged 21-69 years; Smokers of at least one cpd for ≥ 3 years.</p> <p>Exclusion: History of recent myocardial infarction; severe nasal allergy; skin disease; smokeless tobacco users; alcohol misusers; pregnant or breast feeding.</p> <p>Motivation of participants: Probably motivated to quit since responders to adverts in local papers and on television.</p>	<p>Method of allocation: Computer generated randomisation</p> <p>Intervention(s): Nicotine patch for 5 months (tapering from 15 mg for 3 months, 10 mg at month 4 to 5 mg at month 5) with nicotine nasal spray (0.5mg/dose/nostril) for 1 year</p> <p>Control: Nicotine patch for 5 months (as above) with placebo nasal spray for 1 year.</p> <p>Both groups received support.</p> <p>Sample sizes: 237 with I: 118, C: 119</p> <p>Baseline comparisons: Similar</p> <p>Study power: Numbers estimated for 90% power and a 5% significance level.</p> <p>Intervention delivery: Smoking clinic staff.</p>	<p>Primary outcomes: Sustained smoking abstinence (CO verified as <10 ppm). Blood cotinine also measured.</p> <p>Secondary outcomes: None</p> <p>Follow-up periods: 6 weeks; 3,6 and 12 months; 6 years</p> <p>Method of analysis: Chi squared statistic for proportions of abstainers at each time point. Kaplan-Meier method for measuring abstinence over time. Parametric t-tests for continuous variables with normal distributions and Mann-Whitney rank tests for non-normal distributions.</p>	<p>Length of time of using NCP and/or prevalence of use: At 12 months 32 participants in the intervention group were abstainers of which 13% were using nasal spray with mean of 22 (SD 9) self-reported 1mg doses per day. In the placebo group there were 13 abstainers, none of whom were using the placebo nasal spray.</p> <p>At 12 months 4 abstainers in the intervention group who were still using the nicotine nasal spray after 12 months had higher cotinine levels than baseline (mean 131% compared to baseline). Of these one relapsed during the 2nd year, two during 3rd year and the 4th remained abstinent throughout the study.</p> <p>At 5 years 2 of 22 participants in the intervention group (9.1%) were using nicotine chewing gum occasionally.</p> <p>Pattern of NCP use: None</p> <p>Demographics of long term NCP users: None</p> <p>Predictors related to long term NCP use: None</p> <p>Purchase patterns: None</p> <p>Attrition: 99% completed follow ups</p>	<p>Limitations (author): None</p> <p>Limitations (review team): High quality study other than self-reported outcomes only for NRT use (though would be difficult to confirm). Two authors were employed by, and one consulted for, Pharmacia and Upjohn. Pharmacia and Upjohn measured the cotinine concentrations but the trial is described as double blind.</p> <p>Evidence gaps: None</p> <p>Funding sources: Pharmacia and Upjohn</p> <p>Applicable to UK? The support provided may be different in Iceland</p>
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<p>First author and year: Etter 2009</p> <p>Aim of study: To assess use of, and dependence, on nicotine gum in former smokers.</p> <p>Study Design : Cross-sectional survey</p> <p>Quality score: +</p> <p>External validity score: +</p>	<p>Setting: Community. Internet survey 'survey for users of nicotine chewing gums'.</p> <p>Participants: 526 daily users of nicotine gum. For users of gum > 3 months 36.8% men, median age 47 years, median income 82.8% of national average; median days since quitting smoking 960.</p> <p>Inclusion: Nicotine gum users; assumption of smoking abstinence</p> <p>Exclusion: None</p> <p>Motivation of participants: Self-selected visitors to tobacco cessation web site.</p>	<p>Sample sizes: 526</p> <p>How were the data collected:</p> <ul style="list-style-type: none"> • What method(s): Self-initiated completion of internet survey in English on the StopTabac.ch web site with a link from other smoking cessation web sites. After 30 days, participants who agreed and indicated an email address received a message asking whether they were still using NRT and their level of craving for NRT gum. • By whom: University researchers • What setting(s): Community. Internet survey of users of nicotine gum • When: Nov 2004-Oct 2007 	<p>Primary outcomes: Numerous characteristics of participants, their NRT gum use, nicotine dependence, cigarette dependence and cigarette craving.</p> <p>Method of analysis: T tests to compare means, Mann-Whitney U tests to compare medians, chi square tests to compare proportions and linear regression models to test associations between continuous variables.</p>	<p>Length of time of using NCP and/or prevalence of use: Of respondents 302 had used gum for > 3 months. Median days use for smokers using NRT for > 3 months = 730 days. 60.1% of users for >3 months answered that stopping all NRTS would be 'difficult' or 'impossible'. 49.5% of these users rated their addiction to gum as similar to, or stronger than their former addiction to cigarettes.</p> <p>Pattern of NCP use: None</p> <p>Demographics of long term NCP users: None</p> <p>Predictors related to long term NCP use: None</p> <p>Purchase patterns: None</p>	<p>Limitations (author): Survey likely to attract users with concerns about long term gum use.</p> <p>Limitations (review team): Self-selected sample. Unlikely to be representative of all gum users. Self-reported data. Mean duration of gum use was more than 2 years but authors described long term use as > 3 months. No separate data for 12 months plus. Authors received financial support from Pfizer and Novartis, gum producers.</p> <p>Evidence gaps: Studies to examine prevalence of dependence among NRT users</p> <p>Funding sources: None. University of Geneva received financial support from Pfizer and Novartis, producers of NRT products, to develop online smoking cessation programs for NRT users under the supervision of JFE</p> <p>Applicable to UK? Quite likely relevant to internet site users with concerns about NRT addiction.</p>
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<p>First author and year: Etter 2011</p> <p>Aim of study: To assess the profile, utilization patterns, satisfaction and perceived effects among users of electronic cigarettes.</p> <p>Study Design : Cross-sectional survey</p> <p>Quality score: +</p> <p>External validity score: -</p>	<p>Setting: Community. Internet survey. Country distribution of respondents: 62% USA; 14% France; 6% UK; 4% Switzerland; 3% Canada; 11% other countries.</p> <p>Participants: 3,587; 70% former smokers; 61% men; mean age 41 years; household income 27.% below average, 30.9% average, 36.4% above average; median duration of e-cigarette use 3 months.</p> <p>Inclusion: >18 years; current, past or never user of e-cigs</p> <p>Exclusion: None</p> <p>Motivation of participants: Not provided</p>	<p>Sample sizes: 3,587</p> <p>How were the data collected:</p> <ul style="list-style-type: none"> • What method(s): Self-initiated completion of internet survey in English & French on web sites and online discussion forums dedicated to e-cigarettes & smoking cessation. • By whom: University researchers • What setting(s): Community. Internet survey of users of e-cigarettes • When: March-Oct 2010 	<p>Primary outcomes: Participant characteristics, utilization and satisfaction with e-cig use; reasons for use, for stopping use and withdrawal symptoms; comparisons (current/former smokers, forum vs web site respondents).</p> <p>Method of analysis: Analysis of variance (ANOVA) to compare means; Mann-Whitney U tests for medians, chi square tests for proportions. Linear regressions (95% CI) to test associations between continuous variables.</p>	<p>Length of time of using NCP and/or prevalence of use: 15% (434/2899) of the sample had used e-cigs for more than 1 year.</p> <p>Pattern of NCP use: None</p> <p>Demographics of long term NCP users: None</p> <p>Predictors related to long term NCP use: None</p> <p>Purchase patterns: None</p>	<p>Limitations (author): Predominantly self-selected users of web sites dedicated to e-cigs.</p> <p>Limitations (review team): Self-reported data. Likely to be highly enthusiastic sample.</p> <p>Evidence gaps: Need to address the safety and efficacy of the products.</p> <p>Funding sources: Not stated.</p> <p>Applicable to UK? Quite possibly (for e-cig enthusiasts)</p>
<p>First author and year: Foulds 2011</p> <p>Aim of study: To identify the e-cig products used by experienced e-cig users, their pattern of e-cig use and the impact on tobacco use</p> <p>Study Design : Cross-sectional survey</p> <p>Quality score: -</p> <p>External validity score: -</p>	<p>Setting: Meeting of e-cigarette enthusiasts; Philadelphia, USA</p> <p>Participants: E-cigarette users attending a meeting of electronic cigarette enthusiasts; 74% male; 88% white; 40% with college degree; mean age 34; 77% employed full-time</p> <p>Inclusion: E-cigarette users</p> <p>Exclusion: Not provided</p> <p>Motivation of participants:</p>	<p>Sample sizes: 104 responses from e-cigarette users from 110 questionnaires (94.5%), 48 short term users (<12 months) and 56 long term (1 year or more)</p> <ul style="list-style-type: none"> • What method(s): Questionnaire handed out at a meeting of e-cigarette enthusiasts. • By whom: University researchers • What setting(s): Meeting (Philly Vapefest) 	<p>Primary outcomes: E-cig use history, tobacco use history, beliefs about e-cigs</p> <p>Method of analysis: Descriptive statistics plus statistical comparisons (chi-squared, independent t-test, Mann-Whitney U test) between long and short term users</p>	<p>Length of time of using NCP and/or prevalence of use: 56 (54%) respondents had been using e-cigs for at least a year.</p> <p>Pattern of NCP use: None</p> <p>Demographics of long term NCP users: Demographic characteristics did not differ significantly between long and short term users. Long term users did typically use slightly lower nicotine strength liquid than short term users.</p> <p>Predictors related to long term NCP use:</p>	<p>Limitations (author): None reported</p> <p>Limitations (review team): Group of highly motivated and enthusiastic e-cigarette users and may not be generalisable outside this group. 13% of respondents making > 10% of their income from e-cigarette business.</p> <p>Evidence gaps: Urgent need to establish a safety profile for e-cigarettes and, if acceptable, to assess</p>

	Motivated e-cigarette users	2011) • When: 2011		None Purchase patterns: None	efficacy in appropriately designed clinical trials Funding sources: No information provided. Lead author has worked as paid consultant for manufacturers of smoking cessation aids. Applicable to UK? Yes but only to a sample of people with the same characteristics of those in this study.
<p>First author and year: Hajek 2007</p> <p>Aim of study: To assess the effect of long-term use of different nicotine replacement treatment products in smokers attending routine smoking cessation treatment and to examine the effect of nicotine replacement treatment cost on its long-term use.</p> <p>Study Design : Prospective cohort</p> <p>Quality score: +</p> <p>External validity score: ++</p>	<p>Setting: Smoker's clinic in East London, between January 2000 & November 2002</p> <p>Participants: Consecutive participants using NRT treatment who set a quit date. Mean age 48 (SD 14); mean CPD 23 (SD 10); 56% female, 31% in paid employment; 60% completed education to 16 years.</p> <p>Inclusion: Participants using NRT who had set a quit date at the clinic.</p> <p>Exclusion: None</p> <p>Motivation of participants: Smoking cessation clinic attendees.</p>	<p>Method of allocation: Not applicable</p> <p>Intervention(s): NRT prescription for attendees to a smokers' clinic and follow up at 12 months. 3-month programme of treatment at the clinic combines medication (with advice to use for up to 3 months) and behavioural support (the UK Stop Smoking Service). Until April 2001 NRT was sold to participants for up to one year at a cost of \$17 per week. From April 2001 prescription was free for up to one year contingent on continuing abstinence (with free prescription for circa 70% of participants and \$11 per week for others).</p> <p>Control: Not applicable</p> <p>Sample sizes:</p>	<p>Primary outcomes: Demographic and smoking characteristics, test of nicotine dependence, motives for smoking and expired CO. Duration of NRT use at 12 month follow up.</p> <p>Secondary outcomes: None</p> <p>Follow-up periods: 12 months</p> <p>Method of analysis: Analysis of variance to explore correlation of demographic variables with smoking characteristics (1-year abstainers still using NRT, 1-year abstainers not using NRT and 1-year smokers). Chi squared, univariate ANOVA and logistic regression to assess predictors of long-term NRT use.</p>	<p>Length of time of using NCP and/or prevalence of use: 76 of 1,518 participants (5%) were using NRT at 12 months after their quit date. All had been continuously abstinent.</p> <p>Pattern of NCP use: Of all long term users(n=76) 20% used the transdermal patch, 24% sublingual tablet, 5% lozenge, 15% inhalator, 13% chewing gum and 24% nasal spray.</p> <p>Demographics of long term NCP users: Long term abstinent NRT users were less likely to complete education to age 16 compared to NRT free status abstainers OR 0.66 (95% CI 0.36, 1.21), p<0.05.</p> <p>Predictors related to long term NCP use: Two factors predicted long term NRT use among continuous abstainers: higher Fagerström Test of Nicotine Dependence (OR 1.20, 95% CI 1.03, 1.40) p=0.02 and smoking for</p>	<p>Limitations (author): No data on the consumption of NRT or self-reported reasons for long term use. Small sample (76) in which to assess an effect of cost.</p> <p>Limitations (review team): Self-report only.</p> <p>Evidence gaps: Examine consumption patterns and reasons for long term use. Re-examination of licencing restrictions.</p> <p>Funding sources: Not stated</p> <p>Applicable to UK? Yes, London based study. Authors noted that the sample were typical of smokers seeking treatment in the UK</p>

		1,518 Baseline comparisons: Not applicable Study power: Not reported Intervention delivery: Smokers clinic personnel		withdrawal relief (OR 1.95, 1.06 to 3.60) p=0.03. Previous NRT use, smoking to help concentrate, smoking for weight control, educational status and employment were not significant. Purchase patterns: There was no significant difference in long-term NRT use between people entitled to free prescriptions and those who paid for their prescriptions. Attrition: ITT used.	
First author and year: Hatsukami 1993 Aim of study: To examine if longer duration on nicotine gum promoted dependence on nicotine gum Study Design : Uncontrolled before and after Quality score: - External validity score: +	Setting: Recruited from community (USA) and conducted in research laboratory Participants: 71; 51% male; mean age 38.3 (SD 9.3) Inclusion: Smoke at least 1 pack/day; no use of other tobacco products; no previous use of nicotine gum; motivation to quit smoking; fulfil DSM-III-R criteria for a history of nicotine withdrawal; not undergoing treatment for any psychiatric disorder; not abusing alcohol or drugs; no current use of psychoactive medications; no medical contraindications to nicotine gum use. Exclusion: Present or planned pregnancy Motivation of participants:	Method of allocation: Not provided Intervention(s): Use of 2mg gum for 1 or 3 months, attendance at weekly individual sessions. Each participant provided a \$50 deposit to be returned if they were abstinent from smoking at the end of treatment. Participants in the 1-month group who complied with study procedures (were paid \$50; those in the 3-month group were paid \$150. Control: No control group. Sample sizes: 1 month group: 33; 3 month group: 38 Baseline comparisons: No significant difference between groups or between those who did or did not	Primary outcomes: Weekly smoking status with biochemical verification and withdrawal symptoms, gum use Follow-up periods: 1, 6 and 12 month Method of analysis: Chi-square, t-tests and analysis of variance	Length of time of using NCP and/or prevalence of use: At 12 months 5/63 participants reported regular gum use since last follow-up at 6 months post-cessation. Pattern of NCP use: At the 12 month 15 participants had discontinued gum were smoking again, 4 participants had discontinued gum and were abstinent and 1 participant was still using gum and was abstinent from smoking. Demographics of long term NCP users: No details Predictors related to long term NCP use: No details Purchase patterns: No details Attrition: 63/71 (88.7%) contacted at all three	Limitations (author): Small sample and no biochemical verification at follow-up. Lack of placebo. The 3 month group had more frequent contact than the 1 month group. Lack of information on whether groups were comparable in degree of cigarette withdrawal symptoms. Limitations (review team): Lack of detail on source population Evidence gaps: None stated. Funding sources: National Institute on Drug Abuse. Marion Merrell Dow research Institute provided the nicotine gum. Applicable to UK? Yes

	Motivated to quit	complete treatment. Study power: No details Intervention delivery: Researchers		follow-up periods.	
<p>First author and year: Heavner 2010</p> <p>Aim of study: To describe e-cigarette users' patterns of cigarette and e-cigarette usage and smoking cessation attempts and to compare health status and smoking-attributable symptoms between people who completely switched from smoking to e-cigarettes, and those who supplemented cigarette smoking with e-cigarette usage.</p> <p>Study Design : Cross-sectional survey</p> <p>Quality score: -</p> <p>External validity score: -</p>	<p>Setting: Community. Internet survey in English with links from the E Cigarette Direct website, various blogs and online forums. Nearly 75% resided in the USA and 17% in the UK.</p> <p>Participants: Convenience sample enrolled from E Cigarette Direct consumers, website visitors and users of an e-cigarette forum. 72% from the USA, 21% from Europe. 55% aged 31-50 and 32% > 50 years old.</p> <p>Inclusion: None</p> <p>Exclusion: None</p> <p>Motivation of participants: Mixed, but a majority who tried to quit smoking and failed, but then succeeded by switching to e-cigarettes.</p>	<p>Sample sizes: 303 (270 excluding possible duplicates)</p> <p>How were the data collected:</p> <ul style="list-style-type: none"> • What method(s): Completion of internet survey • By whom: Director of E Cigarette Direct, who initiated and conducted the research and analysis carried out by independent university researchers • What setting(s): Community. Internet survey. • When: May-June 2009 	<p>Primary outcomes: Patterns of use and health status.</p> <p>Method of analysis: Frequencies of all variables – univariate and bivariate analyses - (no confidence limits reported) and summary of freehand comments.</p>	<p>Length of time of using NCP and/or prevalence of use: Only 9/303 respondents (3% of the sample) had been using e-cigarettes for 13+ months, 2% (5/303) for 13-18 months, 0.3% (1/303) for 19-24 months and 1%(3/303) > 24 months.</p> <p>Pattern of NCP use: Of respondents 7 had been using e-cigarettes for >12 months as a complete replacement for cigarettes. 119 (84%) respondents who indicated that pharmaceutical aids did not help them to stop smoking used e-cigarettes as a complete replacement for cigarettes. Data not presented separately for those using e-cigarettes >12 months.</p> <p>Demographics of long term NCP users: On average, respondents who lived in Europe had used e-cigarettes for longer than respondents in the US, but were less likely to use e-cigarettes as a complete replacement for cigarettes.</p> <p>Predictors related to long term NCP use: None</p> <p>Purchase patterns: None</p>	<p>Limitations (author): Highly motivated and passionate e-cigarette users. Noted that some of the questions were imprecise and some answers difficult to interpret (e.g. users who reported better health might describing the benefits of reduced smoking overall or ease of smoking withdrawal symptoms in smoke-free situations).</p> <p>Limitations (review team): Self-report only. Likely to be a highly biased sample so difficult to make any conclusions about general patterns of e-cigarette use. One author is Director of E Cigarette Direct, who initiated and conducted the research.</p> <p>Evidence gaps: Future surveys should ask respondents to indicate the number of cigarettes that they smoked (per day) before using e-cigarettes and the number that they smoked after starting to</p>

					<p>use e-cigarettes, as well as when and where they smoke and use e-cigarettes.</p> <p>Funding sources: Not stated</p> <p>Applicable to UK? Possibly to highly motivated users but no licensed products in the UK as yet.</p>
<p>First author and year: Hughes 2004</p> <p>Aim of study: To estimate the misuse of and dependence on over-the-counter nicotine gum in a volunteer sample</p> <p>Study Design : Two cross-sectional telephone surveys</p> <p>Quality score: -</p> <p>External validity score: ++</p>	<p>Setting: Community. North-eastern states in the USA</p> <p>Participants: Study 1: 266 participants; 62% women; mean age 46; mean CPD when last smoked 21 Study 2: 100 participants; 59% women; mean age 50; mean CPD when last smoked 30</p> <p>Inclusion: Study 1: Age 18 years or older, smoked daily in the past, used at least one piece of nicotine gum on at least two of the last four days Study 2: Believed they were addicted to nicotine gum, currently used nicotine gum at least once per week, used gum for at least one month and used at least two pieces of gum in the past four days, age 18 years or older, smoked in the past.</p> <p>Exclusion: None</p> <p>Motivation of participants:</p>	<p>Sample sizes: Study 1: 266 participants Study 2: 100 participants</p> <p>How were the data collected: • What method(s): Telephone interview</p> <p>• By whom: Not stated</p> <p>• What setting(s): Community</p> <p>• When: Study 1: 1997 Study 2: 2000</p>	<p>Primary outcomes: Study 1: Gum use, reasons for nicotine gum use, concurrent gum and cigarette use. Long term use was considered to be ≥ 90 days. Study 2: Gum use, dependence</p> <p>Method of analysis: Descriptive statistics. Logistic regression in study 1 to determine whether selected variables predicted initial purchase of the gum to reduce vs. stop smoking, long vs. short term use of the gum, and addiction as a reason for continuing use of the gum.</p>	<p>Length of time of using NCP and/or prevalence of use: Study 1: 46% of the sample had used the gum for longer than the recommended three months. Among the long term users, the median number of days of use was 242 (25th - 75th percentile 158-409), and the mean number of milligrams of nicotine per day from gum was 16 (SD=11). Study 2: the median duration of gum use was 32 months (95% CI=15-50). A total of 98% (CI=96%-100%) of participants had used gum for at least 3 months. The mean daily dose of nicotine at the time of the interview was 30mg/day (SD=20).</p> <p>Pattern of NCP use: Study 1: at the time of the survey most long-term users were using gum to stop smoking or prevent relapse (72%) and only 8% for non-cessation reason. 20% spontaneously volunteered addiction as the reason for their continued use. Study 2: at the time of the survey 12% were concurrent gum and cigarette users. A total of 92% (CI</p>	<p>Limitations (author): Volunteer samples so results may not be applicable to national samples. Single cross-sectional surveys which tend to oversample those with chronic conditions. Possible bias in the recruitment strategy towards those who were addicted to NRT. Volunteer samples often have a higher prevalence of and more severe forms of a disorder than population based samples.</p> <p>Limitations (review team): Small samples and self-report</p> <p>Evidence gaps: Explore post-relapse concurrent use of NRT and cigarettes.</p> <p>Funding sources: Grants from Pharmacia (Pfizer), SmithKline Beecham, the National Institute on Drug Abuse,</p>

	Mixed			<p>87%,97%) purchased gum initially to stop smoking or prevent relapse, 2% (CI 0%, 5%) to reduce smoking and 4% (CI 0%, 8%) to avoid restrictions. 65% (CI 55%, 74%) reported inability to control use, 75% (CI 66%, 84%) reported difficulty stopping, 61% (CI 46%, 76%) reported that stopping gum was extremely difficult, compared to 59% (44%, 74%) who reported that stopping cigarettes was extremely difficult.</p> <p>Demographics of long term NCP users: Study 1: Those who were older were more likely to be long term users (p<.0001).</p> <p>Predictors related to long term NCP use: Study 1: Those who had smoked longer were more likely to be long term users (p<.0001).</p> <p>Purchase patterns: None</p>	<p>and Institutional Training Grant.</p> <p>The first author had several competing interests.</p> <p>Applicable to UK? Yes</p>
<p>First author and year: Johnson 1991</p> <p>Aim of study: To describe the extent of nicotine chewing gum use among health maintenance organization members, the characteristics of prescribers and users, and the patterns of gum use over a two-year period.</p> <p>Study Design :</p>	<p>Setting: Health Maintenance Organization, Kaiser Permanente (KP), USA and Canada</p> <p>Participants: 1970 KP members between 1 July 1987 and 30 June 1989 (4505 prescriptions for nicotine gum). 56.3% female; 86.1% aged 25-64.</p> <p>Inclusion: KP members</p> <p>Exclusion:</p>	<p>Method of allocation: Not applicable</p> <p>Intervention(s): Nicotine gum prescription</p> <p>Control: Not applicable</p> <p>Sample sizes: 1970 KP members who received 4505 prescriptions for nicotine gum dispensed from outpatient pharmacies</p> <p>Baseline comparisons: Not applicable</p>	<p>Primary outcomes: Extent of nicotine gum use, users, use and charges by prepaid drug benefit, prescribers, patterns of use, average daily dosage and duration of use.</p> <p>Follow-up periods: Not applicable</p> <p>Method of analysis: Chi-square tests with Yates' correction for categorical data and t-tests for continuous data.</p>	<p>Length of time of using NCP and/or prevalence of use: 11% (216/1970) of users with four or more prescriptions, 90% (195/216) had periods of continuous use which resulted in a total of 218 periods. 30% of continuous use periods >6 months, with longest period being 19 months. [Period of continuous use = time between refills where gum could have been used at a consistent average daily dose (≥8 pieces of gum)]</p> <p>Pattern of NCP use: 6/1970 users consumed 50-99 boxes</p>	<p>Limitations (author): None</p> <p>Limitations (review team): No data provided on actual number of users and length of continuous use or how many users and gum dose. No data collected on smoking behaviour.</p> <p>Evidence gaps: Use of gum in relation to past smoking history and current smoking status of users. Also in relation to</p>

<p>Cross-sectional survey</p> <p>Quality score: -</p> <p>External validity score: +</p>	<p>None stated</p> <p>Motivation of participants: Not provided</p>	<p>Study power: Not applicable</p> <p>Intervention delivery: Not applicable</p>		<p>(box = 96 pieces) over two years. 2/1970 consumed ≥100 boxes, not stated if for personal use or if shared.</p> <p>Continuous use of 12-18 months: 10 periods involved <8 pieces/day and 7 periods involved ≥8 pieces/day.</p> <p>≥ 18 months 2 periods involved <8 pieces/day and 4 periods involved ≥8 pieces/day.</p> <p>Demographics of long term NCP users: None</p> <p>Predictors related to long term NCP use: None</p> <p>Purchase patterns: None</p>	<p>their knowledge and attitudes about nicotine gum and potential adverse effects. Funding sources: Not provided</p> <p>Applicable to UK? Yes</p>
<p>First author and year: Johnson 1992</p> <p>Aim of study: To assess nicotine gum use when prescribed in a non-research, routine outpatient setting.</p> <p>Study Design : Cross-sectional survey</p> <p>Quality score: -</p> <p>External validity score: +</p>	<p>Setting: Health Maintenance Organization, Kaiser Permanente (KP), USA & Canada</p> <p>Participants: KP members who were recipients of nicotine gum prescriptions from outpatient pharmacies between 1 July 1987 and 1 Jan 1989. Regular smokers of cigarettes during last 3 years. Median age 45 years (range 15-78); 54.6% female.</p> <p>Inclusion: Recipient of prescription for nicotine gum.</p> <p>Exclusion: No address within KP</p>	<p>Sample sizes: 612/1224 gum users selected. 529 contacted and 498 completed questionnaires.</p> <p>How were the data collected:</p> <ul style="list-style-type: none"> • What method(s): Questionnaires. Where these were not returned, recipients contacted by phone and questionnaire completed as a phone interview. • By whom: Not stated • What setting(s): Community. • When: Jan-April 1990. 	<p>Primary outcomes: Smoking history and nicotine gum use.</p> <p>Method of analysis: Descriptive only – numbers and percentages of respondents.</p>	<p>Length of time of using NCP and/or prevalence of use: Of 428 participants 4.4% reported using nicotine gum between 1-2 years and 2.8% reported use for >2 years.</p> <p>Pattern of NCP use: None</p> <p>Demographics of long term NCP users: None</p> <p>Predictors related to long term NCP use: None</p> <p>Purchase patterns: None</p>	<p>Limitations (author): None</p> <p>Limitations (review team): None</p> <p>Evidence gaps: None stated</p> <p>Funding sources: Not provided</p> <p>Applicable to UK? Yes</p>

	<p>membership file; KP employees; participants in ongoing smoking cessation studies</p> <p>Motivation of participants: Not provided</p>				
<p>First author and year: Lung Health Study (LHS): Bjornson-Benson 1993; Murray 1996; Nides 1995 [Background information from Buist 1993; Connett 1993; O’Hara 1993;] Aim of study: To evaluate the efficacy of early intervention for chronic obstructive pulmonary disease among cigarette smokers who have mild to moderate impairment in pulmonary function. Study Design : RCT Quality score: ++ External validity score: ++</p>	<p>Setting: USA and Canada – community-based Participants: 5887 recruited from local worksites and shopping malls; 63% male; average age 48 yrs (97% white; 63% males. Inclusion: Cigarette smokers, aged 35-60; mild to moderate airflow obstruction Exclusion: Health conditions likely to affect lung function; unable to participate in a 5-year follow-up. Motivation of participants: Willingness to consider smoking cessation</p>	<p>Method of allocation: Computer generated randomisation schedule Intervention(s): Special intervention with either bronchodilator (SI-A) or placebo (SI-P) inhaler plus a multisession behavioural program., Additionally, smoking cessation maintenance activities, 4-monthly scheduled clinic visits plus 2mg/piece nicotine gum after quitting. Control: Usual care (UC) Sample sizes: 73,694 screened 5887 eligible: SI=3923, UC=1962. Baseline comparisons: Only minor difference between SI and UC groups. Significant differences between men and women on most variables. Study power: The power for detecting a 7.5ml/year effect of the combined smoking intervention and bronchodilator programs (UC</p>	<p>Primary outcomes: Rate of decline (in ml/year) of FEV₁ Secondary outcomes: Mean absolute decline in FEV₁ from baseline to 5th annual visit; rates of decline and absolute decline in other pulmonary function parameters; mortality; morbidity Follow-up periods: 4 monthly up to 5 years. Method of analysis: Self-report together and/or with statistical analysis</p>	<p>Length of time of using NCP and/or prevalence of use: At 5 years 14% of ex-smokers were using nicotine gum and 5% of participants unsuccessful at quitting smoking were using gum. Total number of ex-smokers and smokers not provided (Murray 1996). At 12 months 33.6% of 1069 sustained non-smokers, 19.2% of 2071 continuing smokers and 54.5% of 595 intermittent smokers were using nicotine gum. Intermittent non-smokers, those that had a non-smoking status at the time of the follow-up visit but overall reported a smoking pattern that included at least 1 month each of smoking and non-smoking in the 8 months prior to the 12 month visit, were more likely to be using gum than any other group, p<0.001 (Bjornson-Benson 1993). Pattern of NCP use: At 12 months sustained non-smokers were using nicotine gum at an average of 8.2 pieces/day. Average pieces of gum/day were significantly different for intermittent smokers and intermittent non-smokers, 7.5 and 9.7 respectively, p<0.001 (Bjornson=Benson 1993) Among ex-smokers from the</p>	<p>Limitations (author): SI participants provided with free nicotine gum; likely that they used more as a consequence and would have been encouraged to use the gum. Limitations (review team): Self-report of gum use. Large study with a specific primary outcome of interest. Long term use of NRT was not a primary focus so difficult to extract specific data. Evidence gaps: Long term users should be closely monitored. Smoking cessation programmes should emphasize techniques for coping with discontinuing the use of nicotine replacement. Funding sources: National Heart, Lung and Blood Institute, NIH Applicable to UK? Yes</p>

		<p>vs SI-A) is approximately 0.94</p> <p>Intervention delivery: Range of health professional & researchers</p>		<p>intervention groups the level of gum use trended upwards over the course of the study (4-60 months) from 8 to 10 pieces/day. The level of use by smokers ranged between 6 and 7 pieces/day (Murray 1996)</p> <p>Demographics of long term NCP users: Of sustained quitters at 12 months women were more likely than men to use nicotine gum ($p < 0.0001$) but no gender differences for amount used (Bjornson=Benson 1993). Of sustained quitters at 24 months 28% of women and 19% of men reported current use of nicotine gum (Nides 1995).</p> <p>Predictors related to long term NCP use: Among sustained non-smokers ($n=1069$) at 12 months, gum use significantly associated with being female; lower BMI; smoking history (gum use & quit attempts), nicotine dependence. Only nicotine dependence variables associated with using more pieces per day (Bjornson=Benson 1993).</p> <p>Purchase patterns: No information</p> <p>Attrition: 90% (3523/3923) of SI group had complete annual 5-year follow-up data.</p>	
<p>First author and year: Schneider 2003</p> <p>Aim of study: To evaluate the</p>	<p>Setting: Hospital based smoking cessation unit, Switzerland.</p> <p>Participants:</p>	<p>Method of allocation: Not applicable.</p> <p>Intervention(s): Nicotine nasal spray provided</p>	<p>Primary outcomes: Self-reported continuous abstinence validated by expired CO. Participants admitting</p>	<p>Length of time of using NCP and/or prevalence of use: At 18 months 5/12 abstainers still using spray.</p>	<p>Limitations (author): Small study size.</p> <p>Limitations (review team): Small study size</p>

<p>efficacy of prolonged administration (18 months) of a nicotine nasal spray in a smoking cessation program and to attempt to characterize the pattern of use of the nasal spray with a specially developed electronic monitor in an effort to assess the factors associated with cessation success or failure.</p> <p>Study Design : Prospective cohort</p> <p>Quality score: +</p> <p>External validity score: +</p>	<p>92 participants referred to SC unit Oct 1996 to April 1997 or recruited via advert in hospital. Male: 49; average age 40 (range 22-65); education 18 yrs range 14-28.</p> <p>Inclusion: 18 yrs plus, smoke at least 15 cigarettes/day, have smoked for more than 5 yrs, highly motivated to stop smoking</p> <p>Exclusion: History of myocardial infarction in preceding 3 months, pregnancy or breast-feeding, use of any form of smokeless tobacco or other NRT.</p> <p>Motivation of participants: Highly motivated to stop smoking.</p>	<p>for up to 18 months. Usage measured by MDILog device attached to spray</p> <p>Control: Not applicable</p> <p>Sample sizes: Eligible: 94 Enrolled 92</p> <p>Baseline comparisons: Not applicable</p> <p>Study power: The 95% confidence interval obtained was 20% rather than the planned 15%.</p> <p>Intervention delivery: Hospital smoking cessation unit</p>	<p>occasional smoking but with a CO level less than 10 ppm and willing to continue categorised as partial successes.</p> <p>Secondary outcomes: Nicotine nasal spray use</p> <p>Follow-up periods: Week 2; months 1, 2, 3, 4, 6, 9, 12, 15, 18, 21 and 24.</p> <p>Method of analysis: Consumption of the spray characterised by median values. Fisher's exact test for discrete variables and Mann-Whitney test for continuous variables. Findings were considered statistically significant if p<0.05. Demographic, pre-treatment, and intra-treatment characteristics examined using logistic regression models, presented as odds ratios with corresponding confidence intervals. [Participants relapsing during study considered failures in the analysis. Six participants admitting occasional smoking but with CO <10ppm and willing to continue categorized as partial successes.]</p>	<p>At 18 months 3/6 in partial success group still using spray. At 12 months 8/16 abstainers still using spray</p> <p>Pattern of NCP use: At 18 months 1/5 abstainers was using the spray above recommended levels (median of 94puffs/day). Of the 3 users in the partial success group still using the nasal spray, one was using 1-15puffs/day, another was using 16-30 puffs/day and the last more than 30 puffs/day (median 33 puffs/day).</p> <p>Demographics of long term NCP users: None</p> <p>Predictors related to long term NCP use: All participants using the nasal spray at 18 months had high craving scores at study start, and all except one still mentioned craving as a reason for continuing to use the spray.</p> <p>Purchase patterns: None</p> <p>Attrition: 89% follow-up at 24 months</p>	<p>Evidence gaps: None stated.</p> <p>Funding sources: Pharmacia Upjohn. AARDEX Ltd supplied MDILog units</p> <p>Applicable to UK? Yes</p>
<p>First author and year: Shetty 2010</p> <p>Aim of study: The effect of a trust-wide smoke-free policy on changes in behaviour, incidents and prescribing.</p>	<p>Setting: Medium secure hospital, UK</p> <p>Participants: 50 male in-patients</p> <p>Inclusion: Smokers prior to implementation of policy</p> <p>Exclusion:</p>	<p>Method of allocation: Not applicable</p> <p>Intervention(s): Introduction of a smoke free policy. Before introduction, interventions included smoking cessation group and individual sessions; NRT</p>	<p>Primary outcomes: Focused on rates of smoking, incidents of smoking-related verbal and physical aggression, use of as and when needed tranquillising medication, clozapine serum levels and use of NRT.</p>	<p>Length of time of using NCP and/or prevalence of use: 10/50 (20%) participants receiving NRT 12 months post-implementation, of whom four had received intermittent NRT for >12 months.</p> <p>Pattern of NCP use:</p>	<p>Limitations (author): None</p> <p>Limitations (review team): Small sample, retrospective analysis, smoking practices outside of hospital would have been useful.</p> <p>Evidence gaps:</p>

<p>Study Design : Retrospective before and after analysis</p> <p>Quality score: –</p> <p>External validity score: +</p>	<p>Non-smokers prior to implementation of policy</p> <p>Motivation of participants: Not provided</p>	<p>provision; staff training; engagement with patients through posters, individual and group discussion and patient advocates.</p> <p>Control: Not applicable</p> <p>Sample sizes: 56 in-patients of whom 50 were smokers</p> <p>How were the data collected:</p> <ul style="list-style-type: none"> • What method(s): Review of clinical records, primary healthcare records and incident reports. • By whom: Authors who are Trust staff. • What setting(s): Community. • When: Ban introduced in March 2007. 	<p>Follow-up periods: 12 month post-implementation</p> <p>Method of analysis: Mann-Whitney <i>U</i> test for before and after differences. $P < 0.05$ considered significant.</p>	<p>None</p> <p>Demographics of long term NCP users: None</p> <p>Predictors related to long term NCP use: None</p> <p>Purchase patterns: None</p> <p>Attrition: Not applicable</p>	<p>Evaluation of long term impact of smoking ban and post-hospital smoking behaviour of patients,</p> <p>Funding sources: No details</p> <p>Applicable to UK? Yes</p>
<p>First author and year: Shiffman 2003</p> <p>Aim of study: To estimate the incidence of persistent use of OTC nicotine gum and patch for periods of >3 months, ≥ 6 months, ≥ 12 months and ≥ 24 months.</p> <p>Study Design : Cross-sectional survey (Jan 1997-March 2000)</p> <p>Quality score:</p>	<p>Setting: Community, USA</p> <p>Participants: 2960 households that purchased NRT</p> <p>Characteristics of patch and gum purchasers, average household size =2.6 (P) 2.5 (G); median household income \$42500 (P) \$47500 (G); white 93.1% (P) 94.6% (G); married 64.9% (P) 62.0% (G) employed 79.8% (P) 79.0 (G) any college education 73.8% (P) 80.0% (G).</p>	<p>Sample sizes: 2960 householders with 2050 purchasing patch and 805 purchasing gum, 165 purchased both.</p> <p>How were the data collected:</p> <ul style="list-style-type: none"> • What method(s): Analysis of purchase data provided by AC Nielsen. No data collected on use of NRT or smoking status were collected. • By whom: 	<p>Primary outcomes: Persistent purchase</p> <p>Method of analysis: Duration of continuous purchase of gum and of patch was calculated for each household. Because some observations were censored (3.9% patch; 5.6% gum) continuous use rates were estimated in two ways. First, incidence of persistent purchase evaluated by random selection of a single observation per household and estimating the incidence of persistent use.</p>	<p>Length of time of using NCP and/or prevalence of use: No data on actual use.</p> <p>Pattern of NCP use: No data on actual use.</p> <p>Demographics of long term NCP users: No data on actual use.</p> <p>Predictors related to long term NCP use: No data on actual use.</p> <p>Purchase patterns: 0.05% of households purchased patch and 0.4% of household</p>	<p>Limitations (author): No actual use data collected. NRT products could have been purchased and not scanned. Household rather than individual data. No data on smoking status or behaviour. No data on physician consultations. Purchase patterns may shift with time as OTC NRT becomes more established.</p> <p>Limitations (review team):</p>

<p>- External validity score: +</p>	<p>Inclusion: Householders whose scanner data included an NRT product during the sampling period.</p> <p>Exclusion: Householders where duration of NRT purchase was unknown due to entry or exit from panel.</p> <p>Motivation of participants: No information</p>	<p>Researchers</p> <ul style="list-style-type: none"> • What setting(s): Community. • When: Jan 1997-March 2000. 	<p>Second survival curves were constructed, in which the denominator of households “at risk” was adjusted for censoring. The curves show the probability of continuous purchase at each month, for households under observation, with the time point of 24 months representing the probability of continuous use for 24 months or more.</p>	<p>purchased gum for ≥24 months. 0.1% of households purchased patch and 1.0% of household purchased gum for ≥12 months.</p> <p>Persistent purchase (allowing for a 1 month gap between purchases): 0.05% of households purchased patch and 1.0% of household purchased gum for ≥24 months. 0.4% of households purchased patch and 2.8% of household purchased gum for ≥12 months.</p> <p>Attrition: Not applicable</p>	<p>As above</p> <p>Evidence gaps: None.</p> <p>Funding sources: GlaxoSmithKline Consumer Healthcare (GSK) Shiffman and Pillitteri consultants to GSK for smoking cessation. Shiffman has an interest in a new NRT product. Hughes: honoraria, consultancy or research grants from Bioscience Communications, BL Seamon, Edelman Public Relations, Genatics, Maine Medical Center, Pacific Pharmaceuticals, Pfizer Inc, Pharmacia, Pinney Associates, Sanofi Pharmaceuticals. Burton: GSK employee.</p> <p>Applicable to UK? Yes</p>
<p>First author and year: Sutherland 1992 Stapleton 1998</p> <p>Aim of study: Efficacy and safety of a nasal nicotine spray as an adjunct to group treatment for stopping smoking</p> <p>Study Design : RCT</p> <p>Quality score: ++</p>	<p>Setting: Maudsley Hospital smokers clinic, London, UK</p> <p>Participants: 227 current daily smokers. female - C=65.8%, I=62.9%; non-manual occupation – C=70.3%, I=71.6%</p> <p>Inclusion: Current daily smokers; 18-68 years; good health; motivated to stop smoking; willing to adhere to the trial protocol.</p>	<p>Method of allocation: Drawing of lots.</p> <p>Intervention(s): Nicotine nasal spray 1mg/dose with max. 5 doses/ hour and 40 doses/day. Recommended duration of use=3 months. No formal dose reduction regimen.</p> <p>Control: Placebo spray containing black pepper oleo resin.</p> <p>Sample sizes:</p>	<p>Primary outcomes: Biochemically validated complete abstinence</p> <p>Secondary outcomes: Mood disturbance, cravings for cigarettes, withdrawal, side effects and positive effects</p> <p>Follow-up periods: 2, 3, 6, 9, and 12 months</p> <p>Method of analysis: Difference between C & I groups assessed by chi square, relapse by log rank test. Logistic</p>	<p>Length of time of using NCP and/or prevalence of use: None of the abstinent control participants used the spray beyond 6 months, 13/30 abstainers in the intervention group were still using the spray at 12 months (11% of total intervention group).</p> <p><u>Conflicting numbers from Stapleton:</u> Of those remaining abstinent (n=33) in the intervention group, 19 used the spray for 1 year and 14 for < 1 year (range 1-39 weeks). There was no difference in relapse after 1 year</p>	<p>Limitations (author): None</p> <p>Limitations (review team): None</p> <p>Evidence gaps: Investigation of limiting duration of spray use on therapeutic effect.</p> <p>Funding sources: MRC and Imperial Cancer Research Fund. Kabi Pharmacia Therapeutics AB supplied nasal sprays.</p>

<p>External validity score: ++</p>	<p>Exclusion: History of cardiovascular disease, hypertension, diabetes, severe allergy; current use of psychotropic medication; use of nicotine gum in the past year; current abuse of alcohol or other drugs; pregnancy</p> <p>Motivation of participants: Motivated to stop smoking</p>	<p>Eligible: 274 I=116; C=111. Long term follow-up - 47 sustained abstinence for 1 year (I=33, C=14)</p> <p>Baseline comparisons: No noted differences on demographic or smoking characteristics.</p> <p>Study power: Sample size > 200 required to detect as significant the difference between an abstinence rate of 30% for the active group and one of 15% for the placebo group, with 80% power and $\alpha = 0.05$. Estimates of abstinence based on results of NRT gum trial conducted in the same clinic. To allow for effect of having to assign couples or friends to the same spray (to preserve blinding), minimum sample size set at 220 since 20% of the sample was expected to fall into this category.</p> <p>Intervention delivery: Via hospital smokers clinic</p>	<p>regression and analysis of variance for effect of variables and differences between groups.</p>	<p>in the nicotine group between those who used the spray for 1 year and those who stopped earlier (Difference: 5% (95% CI -33%, 43%).</p> <p>Pattern of NCP use: None</p> <p>Demographics of long term NCP users: None</p> <p>Predictors related to long term NCP use: None</p> <p>Purchase patterns: None</p> <p>Attrition: Follow-up at all points: I = 96%; C = 95%.</p>	<p>Applicable to UK? Yes</p>
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APPENDIX B: SUMMARY OF QUALITY APPRAISAL – INTERVENTION STUDIES Key to headings (brief summary from Appendix F, NICE 2009): 1.1 Source population described; 1.2 Eligible population representative of source ; 1.3 Selected population representative of eligible; 2.1 Population described; 2.2 Intervention/comparison described; 2.3 Allocation concealed; 2.4 Blinded; 2.5 Exposure adequate; 2.6 Contamination low; 2.7 Other interventions similar in groups; 2.8 All participants accounted for; 2.9 Setting reflects UK practice; 2.10 Intervention reflects UK practice; 3.1 Reliable outcomes; 3.2 Complete outcomes; 3.3 Important outcomes assessed; 3.4 Relevant outcomes; 3.5 Similar follow up times; 3.6 Meaningful follow up; 4.1 Groups similar at baseline; 4.2 ITT used; 4.3 Sufficient power; 4.4 Estimates of effect size given; 4.5 Appropriate analysis; 4.6 Precision; 5.1 Internally valid; 5.2 Externally valid; ++ Minimal bias; +Bias unclear; - Risk of bias; nr Not reported; na Not applicable

Author Year	Study design	Population			Method of allocation to intervention (or comparison)										Outcomes						Analyses						Summary		
		1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5	4.6	5.1	5.2	
Blondal 1999	RCT	+	nr	nr	++	++	++	++	+	++	++	++	+	+	+	++	++	++	++	++	++	++	++	++	++	++	++	++	+
Hatsukami 1993	UBA	-	+	+	nr	-	nr	nr	++	+	-	++	+	+	+	-	++	++	++	++	-	-	nr	-	+	-	-	+	
LHS [Bjornson-Benson 1993; Murray 1996; Nides 1995]	RCT	++	++	++	++	++	++	++	-	++	++	++	++	+	++	++	++	++	++	++	+	++	++	+	++	+	++	++	
Shetty 2010	UBA	+	+	+	na	+	na	na	na	na	na	++	++	++	++	++	+	++	na	++	na	nr	nr	nr	+	nr	-	+	
Sutherland 1992 (and Stapleton 1998)	RCT	+	+	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	+	++	++	++	++	++	++	++

APPENDIX C: SUMMARY OF QUALITY APPRAISAL – CORRELATION STUDIES Key to headings (brief summary from Appendix G, NICE 2009): 1.1 Source population described; 1.2 Eligible population representative of source ; 1.3 Selected population representative of eligible; 2.1 selection bias minimised; 2.2 explanatory variables based on sound theoretical basis; 2.3 contamination acceptably low; 2.4 confounding factors identified and controlled; 2.5 setting applicable to the UK; 3.1 Reliable outcomes; 3.2 Complete outcomes; 3.3 Important outcomes assessed; 3.4 Relevant outcomes; 3.5 Similar follow up times; 3.6 Meaningful follow up; 4.1 Groups similar at baseline; 4.1 study sufficiently powered to detect an effect; multiple explanatory variables considered in the analyses; analytical methods appropriate; precision of association given or calculable; 5.1 Internally valid; 5.2 Externally valid. ++ Minimal bias; +Bias unclear; - Risk of bias; nr Not reported; na Not applicable

Author/ Year	Study design	Population			Method of selection of exposure/comparison group					Outcomes					Analyses				Summary		
		1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	3.1	3.2	3.3	3.4	3.5	4.1	4.2	4.3	4.4	5.1	5.2	
Etter 2009	CSS																			+	+
Etter 2011	CSS																			+	-
Foulds 2011	CSS																			-	-
Hajek 2007	PC	++	++	++	++	nr	na	+	++	+	++	++	na	++	nr	++	++	++	++	+	++
Heavner 2010	CSS																			-	-
Hughes 2004	CSS																			-	++
Johnson 1991	CSS																			-	+
Johnson 1992	CSS																			-	+
Schneider 2003	PC	+	+	++	+	nr	na	++	+	++	++	++	na	++	+	++	++	++	++	+	+
Shiffman 2003	CSS																			-	+

APPENDIX D: REVIEW TEAM

Staff/Resource Description	Role
Ms Fiona Morgan, SURE, Cardiff University	Searching, study selection, quality assessment, data extraction and report writing.
Dr Helen Morgan, SURE, Cardiff University	Project management, searching, study selection, quality assessment, data extraction, narrative synthesis and report writing
Dr Alison Weightman, SURE, Cardiff University	Project Director. Quality assessment, data extraction and report writing.
Dr Sarah Whitehead, CISHE, Cardiff University	Study selection, quality assessment, data extraction and report writing.

APPENDIX E: LIST OF INCLUDED PAPERS

- Bjornson-Benson, W., Nides, M., Dolce, J., Rand, C., Lindgren, P., O'Hara, P., Buist, A.S., Bjornson-Benson, W., Nides, M., Dolce, J., Rand, C., Lindgren, P., O'Hara, P., & Buist, A.S. 1993. Nicotine gum use in the first year of the Lung Health Study. *Addictive Behaviors*, 18, (4) 491-502
- Blondal, T., Gudmundsson, L.J., Olafsdottir, I., Gustavsson, G., Westin, A., Blondal, T., Gudmundsson, L.J., Olafsdottir, I., Gustavsson, G., & Westin, A. 1999. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up.[Erratum appears in *BMJ* 1999 Mar 20;318(7186):764]. *BMJ*, 318, (7179) 285-288
- Etter, J.F. & Etter, J.F. 2009. Dependence on the nicotine gum in former smokers. *Addictive Behaviors*, 34, (3) 246-251
- Etter, J.F. & Bullen, C. 2011. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction*, 106, (11) 2017-2028
- Foulds, J., Veldheer, S., & Berg, A. 2011. Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. *International Journal of Clinical Practice*, 65, (10) 1037-42
- Hajek, P., McRobbie, H., & Gillison, F. 2007. Dependence potential of nicotine replacement treatments: Effects of product type, patient characteristics, and cost to user. *Preventive Medicine*, 44, (3) 230-234
- Hatsukami, D., Huber, M., Callies, A., Skoog, K., Hatsukami, D., Huber, M., Callies, A., & Skoog, K. 1993. Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology*, 111, (4) 449-456
- Heavner KK, Dunworth J, Bergen PL, Nissen CM, & Phillips CV 2010. Electronic cigarettes(e-cigarettes) as potential tobacco harm reduction products: Results of an online survey of e-cigarette users. *Tobacco Harm Reduction Year book 2010*
- Hughes, J.R., Pillitteri, J.L., Callas, P.W., Callahan, R., & Kenny, M. 2004. Misuse of and dependence on over-the-counter nicotine gum in a volunteer sample. *Nicotine & Tobacco Research*, 6, (1) 79-84
- Johnson, R.E., Hollis, J.F., Stevens, V.J., & Woodson, G.T. 1991. Patterns of nicotine gum use in a health maintenance organization. *DICP.*, 25, (7-8) 730-735
- Johnson, R.E., Stevens, V.J., Hollis, J.F., & Woodson, G.T. 1992. Nicotine chewing gum use in the outpatient care setting. *Journal of Family Practice*, 34, (1) 61-65
- Murray, R.P., Bailey, W.C., Daniels, K., Bjornson, W.M., Kurnow, K., Connett, J.E., Nides, M.A., & Kiley, J.P. 1996. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest*, 109, (2) 438-445
- Nides, M.A., Rakos, R.F., Gonzales, D., Murray, R.P., Tashkin, D.P., Bjornson-Benson, W.M., Lindgren, P., Connett, J.E., Nides, M.A., Rakos, R.F., Gonzales, D., Murray, R.P., Tashkin, D.P., Bjornson-Benson, W.M., Lindgren, P., & Connett, J.E. 1995. Predictors of initial smoking cessation and relapse through the first 2 years of the Lung Health Study. *Journal of Consulting & Clinical Psychology*, 63, (1) 60-69
- Schneider, M.P., van, M.G., Uldry, C., Huynh-Ba, M., Fallab Stubi, C.L., Iorillo, D., Burnier, M., Zellweger, J.P., Schneider, M.P., van Melle, G., Uldry, C., Huynh-Ba, M., Fallab Stubi, C.L., Iorillo, D., Burnier, M., & Zellweger, J.P. 2003. Electronic monitoring of long-term use of the nicotine nasal spray and predictors of success in a smoking cessation program. *Nicotine & Tobacco Research*, 5, (5) 719-727
- Shetty, A., Alex, R., & Bloye, D. 2010. The experience of a smoke-free policy in a medium secure hospital. *The Psychiatrist*, 34, (7) 287-289
- Shiffman, S., Hughes, J.R., Pillitteri, J.L., & Burton, S.L. 2003. Persistent use of nicotine replacement therapy: an analysis of actual purchase patterns in a population based sample. *Tobacco Control*, 12, (3) 310-316

Stapleton, J.A., Sutherland, G., Russell, M.A., Stapleton, J.A., Sutherland, G., & Russell, M.A. 1998. How much does relapse after one year erode effectiveness of smoking cessation treatments? Long-term follow up of randomised trial of nicotine nasal spray. *BMJ*, 316, (7134) 830-831

Sutherland, G., Stapleton, J.A., Russell, M.A., Jarvis, M.J., Hajek, P., Belcher, M., & Feyerabend, C. 1992. Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet*, 340, (8815) 324-329

APPENDIX F: EXCLUDED STUDIES WITH REASONS FOR EXCLUSION

References	Reason for exclusion
Agboola, S., McNeill, A., Coleman, T., Leonardi, B.J., Agboola, S., McNeill, A., Coleman, T., & Leonardi Bee, J. 2010. A systematic review of the effectiveness of smoking relapse prevention interventions for abstinent smokers. [Review]. <i>Addiction</i> , 105, (8) 1362-1380	No long term use data
Alberg, A.J., Patnaik, J.L., May, J.W., Hoffman, S.C., Gitchelle, J., Comstock, G.W., Helzlsouer, K.J., Alberg, A.J., Patnaik, J.L., May, J.W., Hoffman, S.C., Gitchelle, J., Comstock, G.W., & Helzlsouer, K.J. 2005. Nicotine replacement therapy use among a cohort of smokers. <i>Journal of Addictive Diseases</i> , 24, (1) 101-113	No long term use data
Anthonisen NR, F.A.U., Connett JE, F.A.U., Kiley JP, F.A.U., Altose MD, F.A.U., Bailey WC, F.A.U., Buist AS, F.A.U., Conway WA Jr FAU - Enright, Enright PL, F.A.U., Kanner RE, F.A.U., & O'Hara, P. 1994. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. <i>JAMA</i> , 272, (19) 1497-505	No long term use data
Anthonisen, N.R., Skeans, M.A., Wise, R.A., Manfreda, J., Kanner, R.E., Connett, J.E., Lung Health Study Research Group., Anthonisen, N.R., Skeans, M.A., Wise, R.A., Manfreda, J., Kanner, R.E., Connett, J.E., & Lung Health Study Research Group. 2005. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial.[Summary for patients in Ann Intern Med. 2005 Feb 15;142(4):112; PMID: 15710952]. <i>Annals of Internal Medicine</i> , 142, (4) 233-239	No long term use data
Balmford, J., Borland, R., Hammond, D., & Cummings, K.M. 2011. Adherence to and reasons for premature discontinuation from stop-smoking medications: Data from the ITC four-country survey. <i>Nicotine and Tobacco Research</i> , 13, (2) 94-102	No long term use data
Bansal, M.A., Cummings, K.M., Hyland, A., & Giovino, G.A. 2004. Stop-smoking medications: who uses them, who misuses them, and who is misinformed about them? <i>Nicotine Tob Res</i> , 6 Suppl 3, S303-S310 available from: PM:15799593	Population of smokers
Beard, E., Michie, S., Fidler, J., & West, R. (in press). Use of Nicotine Replacement Therapy in Situations Involving Temporary Abstinence From Smoking: A National Survey of English Smokers. <i>Addictive Behaviors</i> , http://dx.doi.org/10.1016/j.addbeh.2012.09.013 .	No long term use data
Beard, E., Vangeli, E., Michie, S., & West, R. (2012). The use of Nicotine Replacement Therapy for smoking reduction and temporary abstinence: An interview study. <i>Nicotine & Tobacco Research</i> , 14(7), 849-856	No long term use data
Bjornson, W., Rand, C., Connett, J.E., Lindgren, P., Nides, M., Pope, F., Buist, A.S., Hoppe-Ryan, C., O'Hara, P., Bjornson, W., Rand, C., Connett, J.E., Lindgren, P., Nides, M., Pope, F., Buist, A.S., Hoppe-Ryan, C., & O'Hara, P. 1995. Gender differences in smoking cessation after 3 years in the Lung Health Study. <i>American Journal of Public Health</i> , 85, (2) 223-230	No long term use data
Black A, Beard E, Brown J, Fidler J, & West R. 2012. Beliefs about the harms of long-term use of nicotine replacement therapy: perceptions of smokers in England. In press.	No long term use data

<p>Blondal, T. 1999. Correction: Nicotine nasal spray with nicotine patch for smoking cessation: Randomised trial with six year follow up (British Medical Journal (1999) 30 January (285-289). <i>British Medical Journal</i>, 318, (7186) 764</p>	<p>No relevant data</p>
<p>Botello-Harbaum, M., Schroeder, J.R., Collins, C.C., Moolchan, E.T., Botello-Harbaum, M., Schroeder, J.R., Collins, C.C., & Moolchan, E.T. 2010. Nicotine replacement therapy use among adolescent smokers seeking cessation treatment. <i>Ethnicity & Disease</i>, 20, (2) 180-184</p>	<p>No long term use data</p>
<p>Crealey, G.E., McElnay, J.C., Maguire, T.A., & O'Neill, C. 1998. Costs and effects associated with a community pharmacy-based smoking-cessation programme. <i>Pharmacoeconomics</i>, 14, (3) 323-333</p>	<p>No long term use data</p>
<p>Daughton, D.M., Fortmann, S.P., Glover, E.D., Hatsukami, D.K., Heatley, S.A., Lichtenstein, E., Repsher, L., Millatmal, T., Killen, J.D., Nowak, R.T., Ullrich, F., Patil, K.D., Rennard, S.I., Daughton, D.M., Fortmann, S.P., Glover, E.D., Hatsukami, D.K., Heatley, S.A., Lichtenstein, E., Repsher, L., Millatmal, T., Killen, J.D., Nowak, R.T., Ullrich, F., Patil, K.D., & Rennard, S.I. 1999. The smoking cessation efficacy of varying doses of nicotine patch delivery systems 4 to 5 years post-quit day. <i>Preventive Medicine</i>, 28, (2) 113-118</p>	<p>No long term use data</p>
<p>Edmunds, M., Conner, H., Jones, C., Gorayeb, R., Waranch, H.R., Edmunds, M., Conner, H., Jones, C., Gorayeb, R., & Waranch, H.R. 1991. Evaluation of a multicomponent group smoking cessation program. <i>Preventive Medicine</i>, 20, (3) 404-413</p>	<p>No long term use data</p>
<p>Eliasson, B., Taskinen, M.R., & Smith, U. 1996. Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. <i>Circulation</i>, 94, (5) 878-881</p>	<p>No long term use data</p>
<p>Emmons, K.M., Puleo, E., Mertens, A., Gritz, E.R., Diller, L., Li, F.P., Emmons, K.M., Puleo, E., Mertens, A., Gritz, E.R., Diller, L., & Li, F.P. 2009. Long-term smoking cessation outcomes among childhood cancer survivors in the Partnership for Health Study. <i>Journal of Clinical Oncology</i>, 27, (1) 52-60</p>	<p>No long term use data</p>
<p>Etter, J.F. & Etter, J.F. 2010. Electronic cigarettes: a survey of users. <i>BMC Public Health</i>, 10, 231</p>	<p>No long term use data</p>
<p>Fix, B.V., Hyland, A., Rivard, C., McNeill, A., Fong, G.T., Borland, R., Hammond, D., & Cummings, K.M. 2011. Usage Patterns of Stop Smoking Medications in Australia, Canada, the United Kingdom, and the United States: Findings from the 2006-2008 International Tobacco Control (ITC) Four Country Survey. <i>International Journal of Environmental Research and Public Health</i>, 8, (1) 222-233</p>	<p>No long term use data</p>
<p>Fowler, G. 1994. Randomised trial of nicotine patches in general practice: Results at one year. <i>British Medical Journal</i>, 308, (6942) 1476-1477</p>	<p>No long term use data</p>
<p>Fu, S.S., Sherman, S.E., Yano, E.M., van, R.M., Lanto, A.B., & Joseph, A.M. 2005. Ethnic disparities in the use of nicotine replacement therapy for smoking cessation in an equal access health care system. <i>American Journal of Health Promotion</i>, 20, (2) 108-116</p>	<p>No long term use data</p>
<p>Fu, S.S., Kodl, M.M., Joseph, A.M., Hatsukami, D.K., Johnson, E.O., Breslau, N., Wu, B., Bierut, L., Fu, S.S., Kodl, M.M., Joseph, A.M., Hatsukami, D.K., Johnson, E.O., Breslau, N., Wu, B., & Bierut, L. 2008. Racial/Ethnic disparities in the use of nicotine replacement therapy and quit ratios in lifetime smokers ages 25 to 44 years. <i>Cancer Epidemiology, Biomarkers & Prevention</i>, 17, (7) 1640-1647</p>	<p>No long term use data</p>

Garcia-Vera, M.P. & Garcia-Vera, M.P. 2004. Clinical utility of the combination of cognitive-behavioral techniques with nicotine patches as a smoking-cessation treatment: five-year results of the "Ex-Moker" program. <i>Journal of Substance Abuse Treatment</i> , 27, (4) 325-333	No long term use data
Gilpin, E.A., Messer, K., Pierce, J.P., Gilpin, E.A., Messer, K., & Pierce, J.P. 2006. Population effectiveness of pharmaceutical aids for smoking cessation: what is associated with increased success? <i>Nicotine & Tobacco Research</i> , 8, (5) 661-669	No long term use data
Glavas, D., Rumboldt, M., Rumboldt, Z., Glavas, D., Rumboldt, M., & Rumboldt, Z. 2003. Smoking cessation with nicotine replacement therapy among health care workers: randomized double-blind study. <i>Croatian Medical Journal</i> , 44, (2) 219-224	No long term use data
Grandes, G., Cortada, J.M., Arrazola, A., Laka, J.P., Grandes, G., Cortada, J.M., Arrazola, A., & Laka, J.P. 2003. Predictors of long-term outcome of a smoking cessation programme in primary care. <i>British Journal of General Practice</i> , 53, (487) 101-107	No long term use data
Hall, S.M., Humfleet, G.L., Munoz, R.F., Reus, V.I., Robbins, J.A., Prochaska, J.J., Hall, S.M., Humfleet, G.L., Munoz, R.F., Reus, V.I., Robbins, J.A., & Prochaska, J.J. 2009. Extended treatment of older cigarette smokers. <i>Addiction</i> , 104, (6) 1043-1052	No long term use data
Hammond, D., Reid, J.L., Driezen, P., Cummings, K.M., Borland, R., Fong, G.T., & McNeill, A. 2008. Smokers' use of nicotine replacement therapy for reasons other than stopping smoking: findings from the ITC Four Country Survey [corrected] [published erratum appears in ADDICTION 2008 Dec;103(12):2075]. <i>Addiction</i> , 103, (10) 1696-1703	No long term use data
Haug, N.A., Hall, S.M., Prochaska, J.J., Rosen, A.B., Tsoh, J.Y., Humfleet, G., Delucchi, K., Rossi, J.S., Redding, C.A., Eisendrath, S., Haug, N.A., Hall, S.M., Prochaska, J.J., Rosen, A.B., Tsoh, J.Y., Humfleet, G., Delucchi, K., Rossi, J.S., Redding, C.A., & Eisendrath, S. 2005. Acceptance of nicotine dependence treatment among currently depressed smokers. <i>Nicotine & Tobacco Research</i> , 7, (2) 217-224	No long term use data
Haynes, E.F. 2003. <i>Effectiveness of smoking cessation intervention supported by Medicaid in Ohio</i> . Ph.D. Ohio State University.	Not available – USA thesis
Herrera, N., Franco, R., Herrera, L., Partidas, A., Rolando, R., & Fagerström, K.O. 1995. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. <i>Chest</i> , 108, 447-451	No long term use data
Hsueh, K.C., Chen, C.Y., Yang, Y.H., Huang, C.L., Hsueh, K.C., Chen, C.Y., Yang, Y.H., & Huang, C.L. 2010. Smoking cessation program in outpatient clinics of Family Medicine Department in Taiwan: a longitudinal evaluation. <i>Evaluation & the Health Professions</i> , 33, (1) 12-25	No long term use data
Hubbard, R., Lewis, S., Smith, C., Godfrey, C., Smeeth, L., Farrington, P., & Britton, J. 2005. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. <i>Tobacco Control</i> , 14, (6) 416-421	No long term use data
Hughes, J.R., Gust, S.W., Keenan, R., Fenwick, J.W., Skoog, K., & Higgins, S.T. 1991. Long-term use of nicotine vs placebo gum. <i>Arch Intern Med.</i> , 151, (10) 1993-1998	No long term use data
Hughes J 1991, "Long-term use of nicotine replacement therapy," <i>In New developments in nicotine-delivery systems: Proceedings of a conference</i> ,	Conference proceeding. No extractable data.

Johns Hopkins University, September 24, 1990., Henningfield JE & M. L. Stitzer, eds., New York: Cortlandt Communications, pp. 63-70.	
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Hung, W.T., Dunlop, S.M., Perez, D., & Cotter, T. 2011. Use and perceived helpfulness of smoking cessation methods: results from a population survey of recent quitters. <i>BMC Public Health</i> , 11, 592	No long term use data
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