Clinical and Cost-Effectiveness of Nicotine Replacement Therapy for New Licensed Indications and Combination Therapy: A Summary of Best Evidence

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

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About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service’s Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG).

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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Warning

This is a confidential document.  
Do not quote without first seeking permission of NICE and ARIF.

The information in this report is primarily designed to give approved readers a starting point to consider research evidence in a particular area. Readers should not use the comments made in isolation and should have read the literature suggested. This report stems from a specific request for information, as such utilisation of the report outside of this context should not be undertaken. Readers should also be aware that more appropriate reviews or information might have become available since this report was compiled.
Executive Summary

Background
In 2005 the Healthcare Regulatory Authority (MHRA) undertook a review of the indications for nicotine replacement therapy (NRT). The MHRA reviewed licensing arrangements for NRT with regard to the wider access to NRT products across the following groups; adolescents, pregnant women, breastfeeding women, cardiovascular disease, and the use of combination NRT. The National Institute for Health and Clinical Excellence (NICE), as part of a wider programme of work on smoking and the NHS in England and Wales, commissioned this report to identify the best evidence on the clinical and cost effectiveness of NRT for each of the licences.

Methods
Searches were conducted in key databases such as MEDLINE, EMBASE and the Cochrane Library for evidence relating to the clinical and cost-effectiveness for each of the aims of this report. The main questions addressed in this report were;

- What evidence was cited by the MHRA when reporting the licensing of the specific use of NRT?
- What additional evidence is there of a similar or higher methodological quality than that cited by the MHRA?
- What ongoing research is there?
- What economic evidence is there?
- What are the economic considerations for the specific use of NRT?

Results

Adolescents
Two studies were identified in the MHRA documentation which concluded that there was evidence of efficacy and no indication that NRT if used in this population would raise specific safety issues. A Cochrane review (including one extra study) and two further studies were identified for the current report. These studies do raise some additional questions about whether there is a balance of evidence in favour of NRT being effective to the same degree in adolescents as it is in adults. These studies do not however raise any new safety concerns.

Pregnant Women
The MHRA considered evidence from several studies, of which two placebo-controlled RCTs were identified that investigated NRT patch use in pregnant women. The findings indicated no benefit of NRT with counselling over counselling alone. Although there are a number of short-term utilisation (hours, days) studies of nicotine patch or gum on biomarkers in mother and child and a small pilot RCT, questions regarding the efficacy and safety of NRT in pregnancy still exist. An ongoing UK based RCT may address some of these uncertainties.
**Breastfeeding**
The MHRA did not identify any studies on the effectiveness and safety of NRT in breastfeeding. One small 'before and after' study was identified for this report. In the absence of more evidence to address the issues surrounding infant safety and given the benefits to mother and baby of not smoking, the recommendation of the MHRA on minimising nicotine dose to the infant via careful scheduling of NRT usage does seem a sensible approach if NRT is used by these women.

**Cardiovascular Disease**
The primary concern is safety in this group. MHRA recommendation is based on a large population-based study considering the risk of acute MI, stroke and death associated with the use of NRT. We identified one systematic review based on a series of reviews by the Cochrane Tobacco Addiction Review Group. Overall the results of these trials confirm that although there may be some cardiovascular risk associated with NRT this is substantially lower than the risk of continuing to smoke.

**Combination NRT + NRT**
The MHRA reviewed the evidence on the combination use of NRT, as product information warned against the concurrent use of more than one product. The review recommended that these warnings against combined use be removed based on the findings of five RCTs and a systematic review. We identified another good quality RCT on the use of patch with nasal spray NRT. The results of this trial are comparable to the other trials combining patch and gum or inhaler considered by the MHRA.

**Combination NRT + Bupropion**
The combination of NRT with bupropion was not covered in the MHRA report. NICE guidance was issued in 2002 and recommends the use of bupropion in smokers over the age of 18. The NICE guidance states there is currently insufficient evidence to recommend a combination therapy of NRT with bupropion. This was based on the evidence of one trial.
We identified three new trials, two of which agree with the NICE guidance. The third trial does suggest an advantage in early term twelve week quit rate with the use of combination bupropion and inhaler delivered NRT.

**Economic analysis**
It was not possible to undertake any *de novo* modelling within the resources available for this report. Searches for existing models did not identify any models for adolescents, pregnancy, breastfeeding, cardiovascular disease or combination NRT. Issues surrounding the cost-effectiveness of NRT for these conditions are discussed, as is a cost-effectiveness model of the combination NRT + bupropion which was identified.

**Conclusion**
The current evidence supports the majority of the conclusions of the MHRA report. There are issues that cannot be adequately addressed with the current evidence base, such as the safety and use of NRT during pregnancy and breastfeeding, as such there is a need for more robust primary research and regular review of the evidence base of the clinical and cost-effectiveness of NRT use.
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1. **Aims**

- To identify the best evidence on the clinical and cost-effectiveness of NRT for smoking cessation in:
  - Adolescents
  - Breast Feeding
  - Pregnancy
  - Cardiovascular disease

- To identify the best evidence on the clinical and cost-effectiveness of
  - Combined NRTs (i.e. NRT+NRT)
  - Combined NRT/bupropion therapy

for smoking cessation.

2. **Background**

In 2005 an Expert Working Group of the Committee for Safety of Medicines/Commission on Human Medicines of the Medicines and Healthcare Regulatory Authority (MHRA) undertook a review of the indications for nicotine replacement therapy. The result of this review was a change to the licensing arrangements for NRT to provide wider access to, and more consistency across, NRT products. The key changes to the licensing were:

1. All forms of NRT can be used in smokers aged 12-17 years
2. NRT can be used by pregnant smokers
3. NRT can be used by breast feeding smokers
4. All forms of NRT can be used by patients with cardiovascular disease
5. More than one form of NRT can be used concurrently
6. NRT can be used in those smokers who are unable to quit abruptly with NRT but want to cut down smoking frequency as a prelude to quitting (e.g. Cut Down to Quit)

The National Institute for Health and Clinical Excellence (NICE), as part of a wider programme of work on smoking and the NHS in England and Wales, commissioned this report to identify the best evidence on the clinical and cost effectiveness of NRT of each of the licence changes 1-5 above. It also commissioned a similar assessment on the evidence on the combined use of NRT and bupropion (Zyban®; GSK).

The use of NRT for reducing smoking frequency as a prelude to quitting (point 6 above) is the subject of full health technology assessment being conducted for NICE by the National Coordinating Centre for Health Technology Assessment and the West Midlands Health Technology Assessment Collaboration. As such this indication does not constitute part of this report.
3. Methods

3.1 Searches

Specific searches of electronic bibliographic databases were undertaken to identify the evidence relating to the clinical and cost-effectiveness for each of the aims of this report.

For each aim searches were conducted in
- The Cochrane Library (2006 Issue 3)
- MEDLINE (Ovid - 1966 to August Week 2 2006)
- EMBASE (Ovid - 1980 to 2006 Week 32)

Generic searches were also conducted for cost effectiveness information to cover all aims in:
- OHE HEED (August 2006)
- MEDLINE (see above)

Searches for ongoing studies were conducted in the National Research Register.

Where possible search strategies employed both MeSH and text terms appropriate to the specific aim and where appropriate terms to limit searches to the most robust study designs (e.g. systematic reviews and controlled trials) were utilised. Although English language terms were utilised, no language restrictions were applied to searches.

Full search strategies are detailed in Appendix 1. All searches were carried out by an information specialist.

All search results were entered in to an aim specific reference management database (Reference Manager, version 11, ISI); a process which automatically removed most duplicate entries. The databases are available on request.

3.2 Identification of relevant studies

Each database was scanned by a research analyst for relevant studies. The algorithm for this process was based on the following:

- Was the study on NRT?
- Was the study on the relevant population/combination?
- For clinical effectiveness –
  - Was the study a systematic review?
  - Was the study an RCT (if a systematic review was identified only more recent RCTs were sought)?
If no RCTs were identified what was the best study design available (in order: controlled trials, cohort studies, before and after studies/case series)?

- For cost-effectiveness –
  - Was the study an economic evaluation/economic model?

All decisions were made by a single research analyst.

Hard copies of all relevant articles were obtained. Part translations of articles not in English were undertaken to aid determination of the relevancy.

Articles and studies which were relevant to a specific aim but not considered to be the best study design available were utilised where necessary to inform background and discussion sections of this report.

### 3.3 Critical appraisal

The methodological strengths and weakness of studies identified through the above process were identified using established quality assessment processes.²

For clinical effectiveness this was undertaken by a research analyst. For cost-effectiveness this was undertaken by a health economist.

### 3.4 Analysis/Reporting

For clinical effectiveness evidence, the findings under each aim are reported using the following framework:

- What evidence was cited by the MHRA when reporting the licensing of the specific use of NRT?¹
- What additional evidence is there of a similar or higher methodological quality than that cited by the MHRA?
- What ongoing research is there?

Where the MHRA had not addressed the specific use of NRT the best available evidence was reported.

Tables detailing characteristics, methodological quality and results of the studies were produced and commented upon.

For economic evidence:

- What economic evidence is there?
- What are the economic considerations for the specific use of NRT?
4. Results

4.1 Clinical Effectiveness

4.1.1 Adolescents

Many adult smokers start their habit in adolescence. The most recent figures for England suggest that 1% of 11 year olds smoke regularly, a figure which rises to 23% of 15 year olds. These levels appear to be similar in other developed countries. Although most of the focus in tobacco control in younger people has been on the prevention of smoking, there are a number of reasons why smoking cessation should also be pursued. Firstly many adolescents who have started smoking want to give up and have made attempts to do so. Second there may be a relationship between the age at which smoking habits are established and ability to give up. In either event, assisting smoking cessation in adolescence would seem additional goal. The important outstanding question is whether the effectiveness of successful approaches in adults, such as nicotine replacement therapy can be generalised to younger people.

4.1.1.1 MHRA Clinical Effectiveness Evidence

The MHRA identified just two studies providing evidence on effectiveness of NRT in adolescence (see Table 1, Table 2 and Table 3).

The first study by Smith et al was not an RCT and followed 22 girls given NRT for a period of 6 months. Although the claimed smoking rates for the participants fell, the numbers confirmed as not smoking never exceeded 5, and at 3 and 6 months was just 1 non-smoker (4.5% 95% CI 0.1 to 22.8%).

Moolchan et al was a double-blind RCT which compared three arms: NRT patch + placebo gum (N=34) vs NRT gum + placebo patch (N=46) vs placebo patch and placebo gum (N=40). The treatment phase was 12 weeks and all groups had cognitive behavioural therapy. Unfortunately information about method of randomisation and allocation concealment was unclear. However apart from this it was a well conducted study with results analysed on an intention to treat basis. The participants, mostly white and female, had an average age of 15 years, had started smoking at 11 years and had smoked daily for a mean of 2.65 years, with current smoking levels of 19 cigarettes per day. The proportions abstinent at 3 months after completion of treatment were 18%, 7% and 3% in the patch, gum and placebo groups respectively. The odds ratio (OR) for cessation for NRT patch relative to placebo was 8.4 (95% CI 0.95 to 73.3); in other words the likelihood of quitting was over 8 times more in the NRT group than the placebo group although the certainty about the true value was low as indicated by the wide confidence intervals which included 1.0, the value indicating no difference; for gum the OR was 2.7, again with wide confidence intervals including 1.0, no difference (95% CI 0.27 to 27.3).
There were more adverse events in the NRT groups. However these differences were only statistically significant for pruritus (itching), erythema (reddening of the skin) and shoulder or arm pain for the NRT patch. For gum only the differences in pruritus (itching), sore throat and hiccups could not be accounted for by chance alone. The paper claims the adverse events were similar to those experienced in adults.

Overall the findings from these two studies do indeed provide support for the MHRA’s stated view that “there was evidence of efficacy and no indication that NRT used in this population would raise specific safety issues ….” It must be appreciated that the study by Smith et al is a minor contributor, so essentially the specific evidence base relied on by the MHRA is limited to one relatively small RCT.
### Table 1 Adolescents: MHRA Identified Trials: Trial Characteristics

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
<th>N (location; centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al 1996*</td>
<td>Case-series; not RCT</td>
<td></td>
<td></td>
<td>Not appraised in detail</td>
<td></td>
</tr>
</tbody>
</table>
| Moolchan et al 2005* | Three arms: 1. Nicotine patches * 21 or 14 mg for 12 weeks + placebo gum N=34  
2. Nicotine gum * 2 or 4 mg as required for 12 weeks + placebo patch N=46  
3. Placebo patch + placebo gum for 12 weeks N=40  
All participants received a 45 minute cognitive behavioural therapy session by a trained social worker at the end of each of the 11 treatment sessions over the 12 week treatment period.  
* GlaxoSmithKline | N=120  
120 participants drawn from 1347 adolescents responding to advertisements  
329 of these were eligible at a phone screen  
Only 159 consented to the study  
39 of these were ineligible, predominantly because psychiatric problems (n=22)  
Characteristics of included patients (approximate averages of the values for each of the three treatment arms)  
Mean age c 15 years  
% female c 70%  
% white c 72%  
Mean FTND score c 7.0  
Mean CPD 19  
Mean age started smoking c 11 years  
Mean years smoked daily c 2.65  
75% of included participants had at least 1 current psychiatric diagnosis particularly oppositional defiant and conduct disorder  
All participants wanted to quit and were able to discuss this with their parent/guardian | Primary: smoke exposure (saliva thiocyanate concentrations)  
Other:  
□ Smoking cessation (point prevalence and prolonged abstinence)  
□ Self reported smoking rates (CPD)  
□ Adverse events (open questions and questionnaires of specific events) | Smoking cessation point prevalence based on self report that not smoking during 7 days prior to visit + expired air CO 0f < 6ppm  
Smoking cessation prolonged abstinence based on point prevalence abstinence based throughout the trial |
### Table 2 Adolescents: MHRA Identified Trials: Trial Quality

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Randomisation and concealment</th>
<th>Blinding</th>
<th>Duration, missing data and loss to follow-up</th>
<th>ITT analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al 1996⁴</td>
<td>Case-series; not RCT</td>
<td>Not appraised in detail</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moolchan et al 2005³</td>
<td>RCT – double blind</td>
<td>Stated to be double-blind</td>
<td>Study completion rates: 1. NRT patch 18/34, 53% 2. NRT gum 19/46, 41% 3. Control 16/40, 40%</td>
<td>ITT principle adopted All losses or non-attendance considered to indicate that participant had smoked of birth weight.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unclear</td>
<td>No further details</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"... Adolescents were randomized to 1 of 3 groups according to an algorithm held by the National Institute on Drug Abuse pharmacy, with true replacement of trial-noncompleters."

### Table 3 Adolescents: MHRA Identified Trials: Trial Results (main)

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Smoking cessation</th>
<th>Safety</th>
<th>Other</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al 1996⁴</td>
<td></td>
<td></td>
<td></td>
<td>Not appraised in detail</td>
</tr>
<tr>
<td>Moolchan et al 2005³</td>
<td>Prolonged abstinence at 3 months post end of treatment: 1. Patch 6/34, 17.7% 2. Gum 3/46, 6.5% 3. Control 1/40, 2.5%</td>
<td>Adverse events: 19 events reported. Patch – 3 events statistically significantly greater for patch relative to control: pruritus; erythema; shoulder or arm pain Gum – 3 events statistically significantly greater for gum relative to control: pruritus; sore throat; hiccups</td>
<td>Compliance: high 1. Patch 78.4% 2. Gum 82.8% 3. Control 80.9%</td>
<td>Changes in CPD, CO levels and saliva thiocyanate values between baseline and end of treatment highly affected by losses to follow-up; &lt;50% of randomised patients included.</td>
</tr>
</tbody>
</table>

Odds ratios:
- Patch vs control OR 8.36 (95% CI 0.95 to 73.3)
- Gum vs control OR 2.72 (95% CI 0.27 to 27.3)
4.1.1.2 Other Evidence

In general our further searches confirmed the paucity of research evidence.

There was a highly up to date Cochrane review, “Tobacco cessation interventions for young people” published in the Cochrane Library 2006, Issue 4 (i.e. after the end of the search and identified by chance). This addressed not just the effectiveness of NRT but other interventions too, such as the effectiveness of psychosocial interventions. The review was systematic in approach.

There were two included RCTs in the Cochrane review targeting pharmacological interventions: Moolchan et al (see above) and Killen et al. However, the latter apparent additional study relative to those identified by the MHRA, although an RCT, in fact addressed the effectiveness of bupropion SR, the comparison being between NRT patch + bupropion and NRT patch + placebo. This study is thus not considered further. Concerning the results of the study by Moolchan et al, the Cochrane review’s interpretation is possibly more cautious than the MHRA, its conclusion with respect to NRT being, “Medications such as nicotine replacement and bupropion have not been sufficiently tested in adolescents”.

Our own wider searches identified two other RCTs potentially relevant to the effectiveness of NRT (see Table 4, Table 5 and Table 6).

- Hanson et al. This was a double-blind placebo controlled RCT of NRT patch in 100 adolescents with an average age of 17 years and an average cigarette consumption of 16 per day. The treatment phase was 10 weeks and all groups had cognitive behavioural therapy. There were no details about how randomisation was achieved, although there was good balance in the baseline characteristics between the two trial groups. The study was excluded from the Cochrane review on the grounds that the quit rate was only measured up to 10 weeks, at the end of the treatment period. However, given that early reporting of results is likely to bias in favour of NRT, it may be useful to note that Hanson found virtually no differences in quit rates between NRT and placebo. The only significant difference in any of the 15 groups of adverse events considered was an excess of headaches in the placebo group [56% in NRT vs 76% in placebo].

- Stotts et al. This was a further RCT of NRT + behavioural intervention (N=98) vs placebo + behavioural intervention (N=100) vs usual care alone (N=105) for spit tobacco addiction. No mention of this was study was made in the Cochrane review, which may be because spit tobacco use was not considered to meet the inclusion criteria. However, the study did seem sufficiently relevant to be worthy of mention in the context of this report. The RCT was relatively large with 303 randomised between each of the three trial groups. Randomisation was clearly described and allocation appeared to be concealed. Although there were high losses to follow-up, an intention-to-treat analysis strategy was used assuming that those lost to follow-up had relapsed. The study showed that although the behavioural intervention appeared to improve spit tobacco quit rates at 1 year relative to usual care, the addition of NRT provided no further benefit. There were no differences between all tobacco quit rates. The study claimed no serious adverse events among patch users.
We have been alerted to a third RCT additional to the MHRA studies, published since completion of the search but prior to finalisation of the report. As indicated in Table 4, Table 5 and Table 6, this was a well conducted RCT comparing active NRT patch with placebo patch, both arms receiving behavioural counselling. Consistent with the other additional studies was both the very low completion rates of treatment and the absence of difference in quit rates between the trial arms.

In conclusion, concerning other evidence not available to the MHRA report, it does appear that there is additional RCT evidence of relevance. These three studies taken together do raise some additional questions about whether there is truly a balance of evidence in favour of NRT being effective to the same degree in adolescents as it is in adults. These studies do not however raise any new safety concerns.
### Table 4 Adolescents: Additional Identified Trials: Trial Characteristics

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanson et al 2003</td>
<td>Two arms:</td>
<td>N=100</td>
<td>Primary outcomes: nicotine withdrawal &amp; salivary cotinine levels</td>
<td>Other:</td>
</tr>
<tr>
<td>RCT – double-blind</td>
<td>1. Nicotine patches *</td>
<td>Eligibility criteria:</td>
<td></td>
<td>▪ Smoking cessation*; 7 day point prevalence</td>
</tr>
<tr>
<td></td>
<td>For ≥15 CPD 21mg (6w) then 14mg (2w) then 7mg (2w)</td>
<td>1. Smoked 10 CPD for at least 6 months</td>
<td></td>
<td>▪ Smoking cessation*; 30 day point prevalence</td>
</tr>
<tr>
<td></td>
<td>For 10-14 CPD 14mg (6w) then 7mg (4w)</td>
<td>2. Did not use any other tobacco products more than once per week</td>
<td></td>
<td>▪ Adverse events (15 groups)</td>
</tr>
<tr>
<td></td>
<td>N=50</td>
<td>3. Were motivated to quit smoking (≥7 on 10 point scale)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Placebo patches *</td>
<td>4. Not currently using NRT</td>
<td></td>
<td>*Cessation defined as no reported cigarettes during period AND expired air CO ≤ 5ppm</td>
</tr>
<tr>
<td></td>
<td>N=50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All participants received 10-15 minute cognitive behavioural at the end of each of the weekly treatment sessions over the 10 week treatment period. Also received contingency management procedure (financial incentives for achieving expired air CO readings &lt; 8 ppm) – probably to each trial arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>223 of 375 who phoned clinic met eligibility criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Characteristics of included adolescents:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Mean age 17 years</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>% female 67%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>% white 87%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean CPD 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age started smoking 12 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stotts et al 2003</td>
<td>Three arms:</td>
<td>N=303</td>
<td>Primary outcomes: smoking cessation*; 30 day point prevalence at 1 year</td>
<td>*Cessation defined as no reported cigarettes during period AND no cotinine in their saliva samples</td>
</tr>
<tr>
<td>RCT</td>
<td>1. Nicotine patches (6 weeks) + behavioural intervention classes (6 * 50 minutes) N=98</td>
<td>Eligibility criteria:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Placebo patches (6 weeks) + behavioural intervention (BI) classes (6 * 50 minutes) N=100</td>
<td>1. Males aged 14-19</td>
<td></td>
<td></td>
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<td></td>
<td>3. Usual care, 5-10 minute counselling followed by a phone call 2 weeks later N=105</td>
<td>2. Reported regular use of spit tobacco and for the previous year</td>
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<td></td>
<td></td>
<td>3. Wanted to quit</td>
<td></td>
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<td></td>
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<td>Of those randomised only the following numbers received intervention:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1. NRT patches + BI, 57 of 98</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Placebo patches + BI, 54 of 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Usual care, 55 of 105</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Characteristics of included adolescents (approximate average across three trial arms):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age 17 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>% female 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>% white 93%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c 73% smoked cigarettes as well as using spit tobacco</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial ID</td>
<td>Intervention and control</td>
<td>N (location; centres)</td>
<td>Patients</td>
<td>Outcomes</td>
</tr>
<tr>
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<tr>
<td></td>
<td>Patch schedule: 15mg (2 weeks) then 10mg (2 weeks) then 5 mg (2 weeks)</td>
<td>145 volunteered for screening (trials nested within a survey of 264 young people)</td>
<td>Characteristics of included adolescents (approximate average across three trial arms): Mean age 15 years % female 60%</td>
<td></td>
</tr>
<tr>
<td>Trial ID</td>
<td>Randomisation and concealment</td>
<td>Blinding</td>
<td>Duration, missing data and loss to follow-up</td>
<td>ITT analysis</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hanson et al 2003&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Unclear “At the prequit visit participants were randomly assigned in a double-blind manner to receive either the active nicotine patch or the control”</td>
<td>Stated to be double-blind Active and placebo patches stated to be identical in appearance</td>
<td>NRT patch: 25/50, 50% completed treatment Placebo patch: 28/50, 56% completed treatment</td>
<td>ITT model used where drop-outs were considered to be smokers</td>
</tr>
<tr>
<td>Stotts et al 2003&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Randomisation described in detail Sequence was random Allocation was concealed Allocation between active and placebo probably blind Allocation between patch arms and usual care unlikely to be blind</td>
<td>Allocation between active and placebo probably blind Allocation between patch arms and usual care unlikely to be blind</td>
<td>NRT patch + BI: 33/98, 34% completed treatment Placebo patch + BI: 40/10, 40% completed treatment Usual care: 25/105 completed “treatment”</td>
<td>ITT model used where drop-outs were considered to be smokers</td>
</tr>
<tr>
<td>Roddy et al 2006&lt;sup&gt;c&lt;/sup&gt;</td>
<td>“… and were randomised using computer generated randomisation codes in batches of 10 to either active or placebo nicotine patches.” Sequence random; however allocation concealment unclear</td>
<td>Although not stated to be double-blind, probably was Special effort to ensure active and placebo patches were identical “The researchers delivering NRT and counselling were blind to the allocation of subjects”</td>
<td>Completed 6 week treatment: 1. NRT patch + BC 3/49, 6% 2. Placebo patch + BC 5/49, 10%</td>
<td>ITT analysis used; losses to follow-up assumed to be non responders</td>
</tr>
</tbody>
</table>

<sup>a</sup> RCT – double-blind

<sup>b</sup> RCT

<sup>c</sup> RCT – double-blind
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Smoking cessation</th>
<th>Safety</th>
<th>Other</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanson et al 2003³</td>
<td>Smoking cessation trials: 30 day point prevalence at 10 weeks (end of treatment)</td>
<td>Safety</td>
<td>Other</td>
<td>Comments</td>
</tr>
<tr>
<td></td>
<td>NRT patch: 10/50, 20%</td>
<td>One statistically significant difference out of 15</td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Placebo patch: 9/50, 18%</td>
<td>groups.</td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>P for difference: 1.0</td>
<td></td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td>Stotts et al 2003³</td>
<td>All tobacco, 30 day point prevalence at 1 year</td>
<td>Safety</td>
<td>Other</td>
<td>Comments</td>
</tr>
<tr>
<td></td>
<td>NRT patch + BI: 6/98, 6%</td>
<td>Brief comments about absence of severe adverse events, but not quantified</td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Placebo patch + BI: 13/100, 13%</td>
<td></td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Usual care: 8/105, 8%</td>
<td></td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Spit tobacco, 30 day point prevalence at 1 year</td>
<td></td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>NRT patch + BI: 17/98, 17%</td>
<td></td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Placebo patch + BI: 25/100, 25%</td>
<td></td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Usual care: 12/105, 11%</td>
<td></td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td>Roddy et al 2006⁷⁰</td>
<td>Carbon monoxide validated quit rates (point prevalence) at 13 weeks (7 weeks post treatment)</td>
<td>Safety</td>
<td>Other</td>
<td>Comments</td>
</tr>
<tr>
<td></td>
<td>NRT patch + BC 0</td>
<td>Adverse events (no in active trial arm vs no in placebo):</td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Placebo patch + BC 0</td>
<td>• Itching 16 vs 7</td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Carbon monoxide validated quit rates (point prevalence) at 4 weeks</td>
<td>• Rash 6 vs 3</td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>NRT patch + BC 5/49, 10%</td>
<td>• Pain or tingling at patch site 6 vs 4</td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td>Placebo patch + BC 4/49, 8%</td>
<td>• Dizziness/nausea/headache 2 vs 3</td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No tests of statistical significance provided</td>
<td></td>
<td>34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)</td>
</tr>
</tbody>
</table>
4.1.2 Pregnant Women

Smoking in pregnancy can cause many adverse outcomes including miscarriage, premature birth, still birth and low-weight babies. There is also the possibility of post natal outcomes such as elevated risk of sudden infant death and neonatal mortality.

Whilst being pregnant acts as motivation for one third of smokers to quit, it is estimated that over a quarter of pregnant women in the UK still smoke.\textsuperscript{11} Many who do quit smoking during pregnancy return to smoking after giving birth.

In pregnancy nicotine is metabolised more rapidly with clearance rates of nicotine and cotinine from plasma being greatly increased.\textsuperscript{12} This could lead to those who continue to smoke elevating consumption to compensate and thus potentially increasing any harm to the foetus.\textsuperscript{13}

Reducing cigarette consumption during pregnancy is a key public health aim as indicated in the Government White Paper on Tobacco.\textsuperscript{14}

4.1.2.1 MHRA Clinical Effectiveness Evidence

The MHRA considered evidence from several studies. Two were randomised controlled trials; Wisborg et al (2000)\textsuperscript{15} and Kapur et al(2001).\textsuperscript{16} A third trial, Hegaard et al (2003),\textsuperscript{17} cannot provide evidence on the clinical effectiveness of NRT in pregnancy as the design of the study was a comparison of a multimodal intervention for smoking cessation with usual care and not an NRT regimen compared to usual care/other care. Furthermore, several elements of the methodology of the study do not address confounding/bias by motivation to quit.

Other studies referred to by the MHRA were on the metabolism of nicotine and cotinine during pregnancy and not about the clinical effectiveness of NRT in pregnancy\textsuperscript{12} or were narrative reviews and editorials.\textsuperscript{13,18}

The characteristics, methodological quality and results of the two randomised controlled trials can be found in Table 7, Table 8 and Table 9 respectively. Both studies randomised pregnant women to receive either NRT patch or placebo patch.

One of the trials, Kapur et al,\textsuperscript{16} had a small sample size and was of short duration of follow-up and the women who took part in this study tended to be heavy smokers. Compliance was poor and enrolment was terminated early due to the apparent case of foetal distress in a woman randomised to receive placebo (the distress subsided on recommencement of smoking). Whilst a well conducted study, due to the factors above it cannot contribute much to our knowledge of NRT in pregnancy.

The other RCT, Wisborg et al,\textsuperscript{15} enrolled 250 women less than 22 weeks pregnant, who smoked at least 10 cigarettes per day to NRT patch (15mg [16hr/day] for 8 weeks then 10mg for 3 weeks) or placebo patch. Both groups received counselling on 4 occasions (baseline, 8 weeks, 11 weeks and 4 weeks prior to
delivery). Non-attendees at follow-up visits increased with study duration but were contacted by telephone for outcome data (Table 7). Methodological quality of the study appears to be relatively good and analysis for the most part was intention to treat with women who were lost to follow up categorised as being smokers rather than abstainers (Table 8). The findings of the study were that there were no significant differences in point prevalence abstinence between NRT and placebo at any time points in the study (Table 9). Four weeks before the due date 28% of the NRT women and 25% of the placebo receiving women were abstinent (non-smoking for the 7 days before assessment) (p=0.52). 21% of the NRT group and 19% of the placebo group had been continuously abstinent from the start of the study to this time point. One year after delivery continuous abstinence had reduced to 15% in the NRT group and 14% in the placebo group. Compliance was poor with less than 1 in 5 women using all patches (less than 1 in 10 for most types of patch), with compliance being lower in the placebo group. Outcomes relating to the foetus were limited to assessment of birth weight (women who has spontaneous abortions and twins were excluded from this analysis; there were no differences in the rates of these between treatment and placebo). There were statistically significant trends to lower mean birth weight and greater number of pre-term deliveries in the placebo group compared to the NRT group. There were no statistically significant differences in proportion of babies born weighing under 2500g and rate of pre-term deliveries between NRT and placebo treatment. Whilst adverse events are given for the study (skin irritation, headache, palpitations), these are not reported by treatment group. Therefore the findings of the RCT indicate no statistically significant benefit of NRT plus counselling over placebo plus counselling.
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
<th>N (location; centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisborg et al 2000&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Nicotine Patches*: 15mg (16hr/d) for 8 wks; 10mg (16hr/d) for 3 weeks</td>
<td>N= 124</td>
<td>Pregnant woman due to deliver at a single centre</td>
<td>Smoking status (self-reported abstinence of at least 7 days at each clinic session plus 3 months and 1 year post partum.</td>
<td>Non-attendees at follow-up visits were telephoned to determine outcome data. The proportion of non-attendees increased with length of study so that 31%, 44% and 53% of participants needed to be interviewed by telephone at the 2, 3, and 4&lt;sup&gt;th&lt;/sup&gt; follow up respectively. 7 women had spontaneous abortions and one who had twins were excluded from analysis of birth weight.</td>
</tr>
<tr>
<td>RCT – double blind</td>
<td>Placebo patches*: no details N=126</td>
<td>250 actually enrolled/randomised</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 centre (Denmark)</td>
<td>Less than 22 weeks pregnant</td>
<td></td>
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<tr>
<td></td>
<td>All women appeared to get smoking cessation counselling by a midwife on four independent occasions during pregnancy, and were supplied written material on smoking in pregnancy. First session was a baseline, one at 8 weeks, one at 11 weeks and the final session 4 weeks prior to delivery. * Pharmacia &amp; UpJohn</td>
<td></td>
<td>Other factors are given by treatment group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapur et al 2001&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Nicotine patches** 15mg (18hr/d) for 8 weeks, 10 mg for 2 weeks. N=17</td>
<td>N=30</td>
<td>Pregnant women 12-24 weeks gestation</td>
<td></td>
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<tr>
<td>RCT – double blind</td>
<td>Placebo patches**: <em>identical placebo patch</em> N=13</td>
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<tr>
<td></td>
<td>All women received counselling at baseline including information on how to use patches. Additional counselling was provided at each clinic visit (1, 4, 8 weeks). Weekly telephone support including encouragement and monitoring for adverse events was provided. **Pharmacia Inc</td>
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</tr>
<tr>
<td>Trial ID</td>
<td>Randomisation and concealment</td>
<td>Blinding</td>
<td>Duration, missing data and loss to follow-up</td>
<td>ITT analysis</td>
<td>Comments</td>
</tr>
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<td>------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wisborg et al 2000</td>
<td>Pre-generated randomisation list, blocks of size 6.</td>
<td>Placebo patches: no details given</td>
<td>11 weeks of treatment with follow up to 1 year post partum</td>
<td>Stated as ITT for smoking cessation</td>
<td>Sample size determined based on smoking cessation rate from study in non-pregnant population (80% power (alpha level 0.05) to detect a difference in smoking cessation of 20% in those given nicotine patches and 5% in those given placebo.</td>
</tr>
<tr>
<td>RCT – double blind</td>
<td>Treatment appears to be centrally assigned and the randomisation list concealed until end of data collection.</td>
<td>Stated that throughout the study the treatment status was not known by the women or the midwife who had contact with the women</td>
<td>Women who missed visits were automatically given a second appointment within 2 weeks and if failing to attend this they were followed up by telephone.</td>
<td>7 women had spontaneous abortions and one who had twins were excluded from analysis of birth weight.</td>
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<tr>
<td></td>
<td>Groups appear reasonably well balanced at baseline (no statistically significant difference)</td>
<td>44% of the treatment group correctly guessed they were receiving nicotine patches, whereas only 11% of the placebo group did. Suggesting that 81% of placebo group knew they were receiving the placebo. The effect of this is unknown.</td>
<td>9% (n=23), 13% (n=33) and 13% (n=33) of women had missing data about smoking at second, third and fourth follow-up visit. All were categorised as smokers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapur et al 2001</td>
<td>Unclear</td>
<td>“identical placebo patch”</td>
<td>8 weeks</td>
<td>No</td>
<td>No power calculation</td>
</tr>
<tr>
<td>RCT – double blind</td>
<td>Reference made to “opening the code” on patient experiencing a fetal adverse event (forceful movements) suggesting that there was some attempt at concealment.</td>
<td>No other details stated.</td>
<td>Unclear if those discontinuing the program were followed up. Number discontinuing was high in each group 10/17 in the nicotine group, 13/13 in the placebo arm.</td>
<td></td>
<td>Small numbers</td>
</tr>
<tr>
<td></td>
<td>Baseline characteristics supplied appear similar between groups.</td>
<td></td>
<td></td>
<td>Small numbers</td>
<td>Short follow up</td>
</tr>
<tr>
<td>Trial ID</td>
<td>Smoking cessation</td>
<td>Safety</td>
<td>Other</td>
<td>Comments</td>
<td></td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Wisborg et al</td>
<td>26% of all participants were non-smoking at fourth visit (4 weeks before due date).</td>
<td>Adverse events: 11 (5%) of the women did not use all their patches due to adverse events (skin irritation, headache). Other adverse events reported were palpitation (n=5, 2% of the study population) and nausea (n=2, 0.8%). The distribution of these events across intervention and placebo groups is unclear.</td>
<td>Compliance: low in both groups. Nicotine patch group: 17% used all 15mg patches, 11% all 10mg patches. Mean of 14 patches (0-77) were used Placebo patch group: 8% used all 15mg patches, 7% all 10mg patches. Mean of 7 patches (0-77) were used.</td>
<td>Adverse event data not fully reported. 7 women had spontaneous abortions and one who had twins were excluded from analysis of birth weight – these appear evenly distributed across treatment and placebo.</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>RCT – double blind</td>
<td>Birth weight (mean): Nicotine group = 3457g Placebo: 3271g, mean difference 186g 95CI 35-336g). In children born after 37 weeks the figures are 3539g vs 3381g (mean difference 157g 95CI 25, 291g)</td>
<td>Low birth weight (under 2500g): No-significant difference - nicotine group: 3% Placebo group 9% (RR: 0.4 CI 0.1, 1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28% of the nicotine patch group and 25% of the placebo were non-smoking at this time (p=0.52).</td>
<td></td>
<td>Pre-term delivery: nicotine group: no significant difference: 8%, placebo group 10% (RR 0.8 95%CI 0.4-1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21% of the nicotine group and 19% of the placebo group were continuously abstinent after the start of intervention to the fourth visit.</td>
<td></td>
<td>None</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Salivary cotinine levels were measured at all time points however there were considerable missing data at all but the first time point (up to 43%). which render findings unreliable.</td>
<td></td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapur et al 2001</td>
<td>Nicotine patch: 4/17 had quit smoking by 8th week, 10/17 had discontinued the program in the first week. 3/17 continued with the patches for 3 weeks</td>
<td>Enrolment terminated on safety grounds as the foetus of the last woman enrolled exhibited rapid and forceful movements three hours after the mothers’ last cigarette, necessitating a series of tests which proved normal. The movements subsided after the woman commenced smoking again. The code for this woman was broken to reveal that the she was receiving placebo. The investigators decided it was unethical to continue to randomise women to placebo</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
4.1.2.2 Other Evidence

No relevant systematic reviews were identified.

A good recent narrative review accurately summarises the information from the RCTs assessed by the MHRA (see Section 4.1.2.1).19

We identified only one other randomised study of NRT in pregnant women where smoking cessation or other woman/baby clinically relevant outcomes of long-term NRT use were measured.20 This was a pilot study conducted in Australia in 40 women randomised to nicotine patch plus counselling or just counselling. 15% of women using NRT had confirmed cessation in late pregnancy compared to zero in the non-NRT group. However, the study was not blinded and therefore this difference could be influenced by knowledge of receipt (or not) of NRT. Further details of this study are detailed in Table 10, Table 11 and Table 12, however the study does not add to the information identified by the MHRA. It was unclear whether this pilot study was being followed by a full trial.

Several other studies were identified which assessed short-term utilisation (hours, days) of nicotine patch or gum on biomarkers in mother and foetus21,22,23,24 or were of longer duration and measured clinically relevant outcomes but were uncontrolled and therefore likely not to be as strong evidence as that from the RCTs.25

Although the RCTs (Section 4.1.2.1) provide some evidence on the utilisation of NRT in pregnancy, the findings of these studies do not clearly show that NRT improves cessation rates, nor have harms to the foetus from NRT been adequately studied. There are a number of issues still to be addressed:

- The RCTs only used patch, and not other forms of NRT and therefore apart for very limited evidence from two of the short-term non-RCTs21,22 we can only hypothesise about the effectiveness and safety of gum and inhaler NRT.
- There is still limited evidence on the safety of NRT plus smoking as may occur during the early stages of quitting in some women.
- There is no evidence on what constitutes a ‘safe’ level of nicotine/cotinine for the foetus,
- The inertness of other components of the NRT to the foetus is unclear.
- With the availability of gum and inhaled NRT for cut down to quit, there will be concerns about the long-term use of these interventions. With regard to pregnancy this will be strongest in those women who struggle to reduce and quit and therefore might for a long period be subjecting their baby to greater nicotine and cotinine than just smoking alone, whilst the baby is also subjected to the other toxins associated with smoking.

Given all the above it is clear that many questions regarding the efficacy and safety of NRT in pregnancy still exist and this is confirmed by the fact that a double blind placebo controlled RCT of NRT in pregnancy is currently being undertaken in the UK. The aims of the study are:
• To compare at delivery: the effectiveness and cost effectiveness for achieving biochemically-validated smoking cessation of nicotine replacement therapy and placebo patches in pregnancy.

• To compare at two years after delivery: the effects of maternal nicotine replacement therapy and placebo patch use in pregnancy on behaviour and cognitive development in children.

Women 12-24 weeks gestation who smoke 10 or more cigarettes per day (confirmed by CO greater than 8ppm) are being randomised to either an eight week course of 15 mg/16 hour NRT transdermal patches or an identical placebo. This study is being coordinated by the Queen’s University Medical Centre in Nottingham and is funded by NHS Research and Development Health Technology Assessment Programme - HTA (UK). The trial is due to complete in early 2012.
### Table 10 Pregnancy: Additional Identified Trials: Trial Characteristics

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
<th>N (location; centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotham et al 2006</td>
<td>Nicotine Patches: 15mg (16hr/d) for up to 12 weeks + standard counselling (approx 5 min at start of study and approx 2 min at subsequent antenatal visits) N= 20</td>
<td>1 centre (Australia)</td>
<td>Pregnant woman due to deliver at a single centre ≥15 cigarettes/day (confirmed by CO &gt;8ppm) 12-28 weeks pregnant Interested in quitting</td>
<td>Smoking status (self-reported, breath CO. Cotinine in saliva) Recorded monthly with the primary outcome at the last prenatal visit. Secondary end points were 48hrs post delivery (breath CO) and 6 and 12 weeks post delivery (self reported smoking status only) No foetal/baby outcomes were measured.</td>
<td>1426 pregnant women screened. 367 were smokers of whom 133 met the smoking frequency criteria. Of these 40 were excluded as planned care did not allow sufficient contact, 21 were too far into pregnancy (more than 28 weeks) . 33 were not interested in the study and/or stopping smoking. One woman appears unaccounted for.</td>
</tr>
<tr>
<td>Hotham et al 2006 Pilot RCT – feasibility study.</td>
<td>Placebo*: standard counselling (as above) N=20</td>
<td>* investigators could not source any placebo patches</td>
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</tr>
</tbody>
</table>

### Table 11 Pregnancy: Additional Identified Trials: Trial Quality

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Randomisation and concealment</th>
<th>Blinding</th>
<th>Duration, missing data and loss to follow-up</th>
<th>ITT analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotham et al 2006</td>
<td>Sealed envelope system using computer generated numbers</td>
<td>None</td>
<td>Up to 12 weeks of patch with follow up to 3 months post partum</td>
<td>Stated as ITT</td>
<td>Pilot study with no sample size calculation, no blinding and a high withdrawal rate.</td>
</tr>
<tr>
<td>Hotham et al 2006 Pilot RCT – feasibility study.</td>
<td>No other details given</td>
<td></td>
<td>14 women withdrew from the study. 7 in each arm.</td>
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<td></td>
<td>Some baseline data on groups given but no statistical analysis presented. From this limited data the groups appear reasonably well balanced for the characteristics presented</td>
<td></td>
<td>Reasons for withdrawal included, decided they did not want to quit, or too hard to partake in study (9/14).</td>
<td></td>
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</tr>
<tr>
<td>Trial ID</td>
<td>Smoking cessation</td>
<td>Safety</td>
<td>Other</td>
<td>Comments</td>
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</tr>
<tr>
<td>Hotham et al 2006</td>
<td>Cessation:</td>
<td>5 women stopped patch due to adverse events. These included rashes, dead arm, felt ill/nauseous, increased morning sickness symptoms, exacerbation of existing depression. 2 of the 5 woman withdrew due to these adverse events.</td>
<td>Compliance: 25% of women (N=5) complied with patch protocol (12 week continuous use), most women used patches intermittently and 20% (4) used few or no patches.</td>
<td>No statistical analysis undertaken</td>
<td></td>
</tr>
<tr>
<td>Pilot RCT – feasability study.</td>
<td>Patch: 15% (self-reported and confirmed by cotinine analysis)</td>
<td>Reduction (50% reduction in cotinine level):</td>
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<td></td>
<td>Control: 0%</td>
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<tr>
<td></td>
<td>Reduction (50% reduction in cotinine level):</td>
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<td></td>
<td>Patch: 35% (7/20)</td>
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<td></td>
<td>Control: 25% (5/20)</td>
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</table>
4.1.3 Breastfeeding Women

Women who smoke after giving birth not only expose their baby to passive smoke but if they are breast feeding as well may expose their baby to water and fat soluble tobacco toxins and their metabolites. Only limited research has been undertaken on the nature and quantity of any toxins transmitted to the infant via breast milk. It is known that nicotine and cotinine are able to be transferred from mother to baby via breast milk and there might be some relationship between concentration of nicotine in breast milk and maternal smoking frequency. The half-life of nicotine in breast milk is similar to that of maternal serum. Smoking may also decrease maternal milk production.18,26 Thus to reduce passive smoke inhalation by the baby and toxin transmission via breast milk, mothers are advised not to smoke.

4.1.3.1 MHRA Clinical Effectiveness Evidence

The MHRA did not identify any studies on the effectiveness and safety of NRT in breast feeding. The MHRA document does contain a consensus that:

...there was limited clinical data available on the use of NRT in...breast-feeding women but also that concerns about the potential adverse effects of nicotine on...the new-born were often theoretical whereas the danger of continuing to smoke were well established and considerably more damaging to mother and baby.

The Working Group advised that...lactation should not be a contraindication to the use of NRT...

...product information should advise that slow-release 24-hour patches should not be used in ...lactation to avoid administration of nicotine overnight.

For breast-feeding mothers intermittent NRT products will allow the time between NRT use and feeding to be as long as possible.

4.1.3.2 Other Evidence

No systematic reviews were found.

Only one relevant primary study was identified. This was a before and after study assessing the effect of NRT patches on nicotine and cotinine concentration in breast milk of mothers who smoked.27

The characteristics of this study are detailed in Table 13. Twenty-five women were initially enrolled in the study and they smoked an average of 17 cigarettes per day and had been smoking for a mean of 15.5 years. Nicotine and cotinine levels in breast milk were measured at baseline whilst still smoking and whilst stabilised on 21mg/day patch for weeks 1-6, 14mg/day patch in weeks 7 and 8, and 7mg/d patch in weeks 9 and 10. Other outcomes were infant dose of nicotine and cotinine determined by estimation of baby milk intake, and carbon monoxide confirmed smoking status of the mother.

Details of the methodological quality of the study are detailed in Table 14. There are uncertainties around how the sample of mothers was chosen and what criteria if any needed to be met before they were enrolled as these are not detailed in the study report. Of the 25 mothers enrolled initially, only 15 completed the study.
and were analysed (for some outcomes even less were analysed i.e. plasma nicotine concentration). Four mothers withdrew prior to patch wearing as they had begun to artificially feed their babies. The reasons for non-completion in the other mothers were related to personal issues or baby health concerns and needs. However, one woman was excluded from the analysis as she continued to smoke. Therefore it appears that the 15 mothers analysed were all abstainers (or very occasionally had a single cigarette; n=4, CO less than 10ppm, except for a single reading in one mother). Thus the findings of the study predominantly relate to the use of patch wearing and not patch wearing whilst smoking or reducing smoking. This study therefore does not give reliable information about the quit rate in breastfeeding women.

Assessment of the main outcomes of the study – nicotine/cotinine levels in breast milk, smoking – whilst not completely free from subjective influences were probably objective enough.

The findings of the study are detailed in Table 15. Nicotine and cotinine in breast milk whilst using a 21mg/day patch are of a similar order of magnitude to when smoking approximately 17 cigarettes per day. Exact data are not explicitly stated although from the graphs presented nicotine concentration is approximately 200µg/L (95%CI 160-245) and cotinine 55 µg/L (95%CI45-60) of breast milk when smoking an average of 17 cigarettes per day. The use of 14mg/day and 7mg/day patches significantly reduced nicotine levels to approximately 2/3 and 1/3 of the level found when smoking an average of 17 cigarettes per day, and to 3/4 and 1/2 in the case of cotinine. When infant dose of nicotine equivalents was calculated a similar statistically significant reduction was found with the 14mg/day and 7 mg/day patch compared to smoking.

The study does report on the volume of breast milk consumed during each smoking/patch regimen however as the infants will be developing and growing it is difficult to assess whether there are any regime-related changes to this volume due to the nature of the study design.

No other clinically relevant outcomes were reported.

Although this study provides some evidence on the utilisation of NRT in breastfeeding there are a number of issues still to be addressed:

- The study only used patch, and not other forms of NRT and thus we can only hypothesise about what the effects of gum and inhaler and their more variable delivery of nicotine to the mother has on the concentrations in breast milk.
- The study only assesses effects of NRT patch use compared to smoking. There is still no evidence on NRT plus smoking as may occur during the early stages of quitting.
- There is no evidence on what constitutes a ‘safe’ level of nicotine/cotinine in breast milk or infant plasma.
- The inertness of other components of the NRT to the infant and their concentration in breast milk are unclear.
- With the availability of gum and inhaled NRT for cut down to quit, there will be concerns about the long-term use of these interventions. With regard to breastfeeding this will be strongest in those women who struggle to reduce and quit and therefore might for a long period be subjecting their
baby to greater nicotine and cotinine via breast milk than just smoking alone, whilst the baby is also subjected to the other toxins associated with smoking.

In the absence of more evidence to address these issues and given the benefits to mother and baby of not smoking, the recommendation of the MHRA (Section 4.1.3.1) particularly the emphasis on minimising nicotine dose to the infant via careful scheduling of NRT usage does seem a sensible approach.
Table 13 Breastfeeding: Study characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Intervention and control</th>
<th>N (location; number of centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ilett et al 2003</td>
<td>Smoking at baseline - 21mg/day patch* weeks 1-6 - 14mg/day patch* weeks 7 &amp; 8 - 7mg/day patch* weeks 9 &amp; 10 - wean off patches around week 11</td>
<td>N=25 (? 1 centre, Western Australia)</td>
<td>Breastfeeding mothers who smoked Mean Age: 32 (range: 21-36) Cigarettes: 17/day (95% CI: 13.7-20.3) Time Smoked: 15.5 years (95% CI: 13.2-17.7) Fagerström Score: 6.3 (95% CI: 5.7-6.9) Infants** Age: median 4.8 months (range: 2.5-21) Birth weight: mean 3.4 kg (range: 2.6-4.1) Denver Development ratio: mean 1.0 (range: 0.8-1.2) Sex (M:F): 8:7 ** data only for mothers analysed</td>
<td>Nicotine and Cotinine levels in breast milk samples collected from both breasts at each feed on the day before a clinic visit. Clinic visits were at the start of the study, after stabilisation on a patch regimen for at least one week and at the end of the study. Infant milk intake (baby weight pre/post feeding) Infant dose of nicotine and cotinine Smoking status of mother Carbon monoxide testing of mother (abstinence not clearly defined – assumed to be &gt;10 ppm)) Nicotine and cotinine in plasma of mother and baby whilst on the highest dose patch.</td>
<td>One low smoking mother (6/d) had a different NRT regimen: w1-6 14mg/d, w7&amp;8-7mg/d then no NRT. Only 15 mothers included in analysis. Stated characteristics of these women appear similar to the whole population.</td>
</tr>
<tr>
<td>Study ID</td>
<td>Is the study based on a representative sample selected from a relevant population?</td>
<td>Are the criteria for inclusion explicit?</td>
<td>Were the characteristic of the mothers and babies similar at time of enrolment?</td>
<td>What were the follow up rates and was follow-up long enough for important events to occur?</td>
<td>Were outcomes assessed using objective criteria or was blinding used?</td>
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<tr>
<td>Ilett et al 2003</td>
<td>No</td>
<td>Unclear</td>
<td>There was a fairly wide range of ages of the babies of the mothers whose data was analysed.</td>
<td>Follow-up was only long enough to determine the nicotine/cotinine load on the baby on one day at each patch dose.</td>
<td>Mothers were aware of the nature of the study.</td>
</tr>
<tr>
<td>Before and After Study</td>
<td>It is unclear how the mothers were identified and recruited.</td>
<td>No</td>
<td>It is assumed that they were mothers who smoked and were breastfeeding their baby.</td>
<td>15 mothers completed the study.</td>
<td>Mothers were not blinded and knew which patch strength they were receiving.</td>
</tr>
<tr>
<td></td>
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<td>4 dropped out before the study commenced (3 had begun artificial feeding, 1 for personal reasons)</td>
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<td></td>
<td>5 withdrew after the start of the study (2 for personal reasons, 1 due to poor milk expression, 1 for reasons regarding baby health and use of NRT, 1 woman continued to smoke)</td>
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<td>One woman was enrolled twice but dropped out twice (data from the second enrolment was used for 21mg/d and 14 mg/d analysis).</td>
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</tbody>
</table>
Table 15 Breastfeeding: Results

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Smoking cessation</th>
<th>Safety</th>
<th>Other</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ilett et al 2003</td>
<td>All mothers included in the analysis (N=15) appeared for the most part to be abstinent from smoking whilst using the patch. 4/15 mothers had an 'occasional' cigarette whilst using patches. Only one CO reading in one mother exceeded 10ppm. Nicotine and cotinine levels in breast milk using a 21mg/d patch are of a similar order of magnitude to when smoking about 17 cigarettes/day. Using 14 and 7 mg/d patch significantly reduces the nicotine (approx. 1/3 and 2/3) and cotinine (approx. 1/4 and 1/2) content of breast milk compared to smoking an average of 17 cigarettes/day. Infant dose of nicotine and cotinine are similar with 21mg/d patch and smoking an average of 17 cigarettes per day, but infant dose is much lower on 14mg/d and 7 mg/d patch. Nicotine equivalents are statistically lower with 14 and 7 mg/d patch compared to smoking. Plasma results are only available for 9 mother/infants and therefore are not reported in this table.</td>
<td>No significant difference in milk intake by the baby between smoking and any of the patch regimens.</td>
<td>Some outcomes are not reported for all 15 mother/babies analysed. Mothers were predominantly abstinent whilst outcomes were being measured in the patch using phases of the study.</td>
<td></td>
</tr>
</tbody>
</table>
4.1.4 Cardiovascular disease

Smoking is a major risk factor for cardiovascular disease. A reduction in the risk of coronary artery disease (CAD) following quitting smoking has been shown for patients with existing heart disease, especially following myocardial infarction (MI). Studies have shown reductions in 5 year mortality rates of 8-15% in quitters compared to smokers.28

Smoking is thought to increase cardiovascular risk via at least 4 mechanisms: promotion of thrombosis; inflammatory effects and progression of atherosclerosis; reduction of oxygen delivery through inhalation of carbon monoxide, and haemodynamic effects of nicotine.

Since the introduction of nicotine replacement, some concerns have been raised about potential cardiovascular side effects from nicotine and the suitability of NRT for cardiovascular patients. However, it has been pointed out that NRT replicates only one of the mechanisms of cardiovascular damage associated with smoking, that this is considered the least important mechanism of harm and that the concentration of nicotine in the blood produced by NRT is typically lower than that produced by smoking. Therefore, whilst NRT may not be entirely risk free for people with stable cardiovascular disease it is likely to be preferable to continuing smoking for those individuals who find it difficult to stop.

Recently, the MHRA reviewed the evidence and supported revisions of the product information as follows:

- in stable cardiovascular disease, NRT presents a lesser hazard than continuing to smoke;
- dependent smokers hospitalised with a recent myocardial infarct, severe dysrhythmia or recent cerebrovascular accident and/or who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, NRT may be considered but as data on safety in this group are limited, initiation should be under medical supervision.

4.1.4.1 MHRA Clinical Effectiveness Evidence

The main concern for the MHRA in considering this amendment to the licence was the safety of NRT in this population. An important element of the evidence considered was a large population-based study considering the risk of acute MI, stroke and death associated with the use of NRT published by Hubbard et al in 200.29 Information was collected on 33,247 individuals who had been prescribed NRT, of whom 861 had had a myocardial infarction and 506 a stroke. The study found that there had been a progressive increase in the incidence of first myocardial infarction in the 56 days leading up to the first NRT prescription, which is probably related to the reasons for NRT being instituted. Incidence fell following prescription of NRT and in particular was not increased in the first 8 weeks after NRT was started. The results were similar for second myocardial infarction and stroke, and for subgroups of people with pre-existing angina and hypertension. There were 960 deaths in the cohort over a mean follow up period of 2.6 years after starting NRT, with no
evidence of an increased mortality in the first 8 weeks after the NRT prescription (incidence ratio 0.86, 95% CI 0.60 to 1.23).

The figures below, reproduced from Hubbard et al, shows the pattern of MI and stroke respectively in the weeks before and after NRT prescription for this large cohort.

The MHRA utilised the results of several clinical studies and reviews, including three randomised controlled trials and a large population-based study. The RCTs are summarised in Table 16, Table 17 and Table 18 below.

Only one of these trials is really of adequate size to detect important differences in safety and this trial recruited an almost exclusively male population (8 women of 548 participants). The other two trials recruited 156 and 106 patients respectively. All trials were of fairly short duration, with the largest study also having the longest duration (10 weeks). The trials were all of moderately good quality; the poorest quality trial was Tzivona et al. Of greatest concern in this trial is the failure to report the method of randomisation and concealment of allocation. There were some substantial imbalances at baseline in this trial, particularly with respect to cardiovascular fitness, with the placebo group being considerably less healthy on average. While these sorts of imbalances will happen purely by chance from time to time, the fairly extreme differences add to concerns about the quality of randomisation in this trial. The analyses presented in the paper do not
account for baseline imbalances in the characteristics being measured and so the results should be interpreted with caution.

Overall the results of these trials confirm the results of larger population based studies and clinical expectation; that although there may be some cardiovascular risk associated with NRT this is substantially lower than the risk of continuing to smoke. Cardiovascular event rates in the NRT arms were not higher, and were in some cases lower, than those in the placebo arms of these trials.
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
<th>N (location; centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joseph, 1996&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Patches&lt;sup&gt;*&lt;/sup&gt; (21mg/day for 6 wks, 14mg/day for 2 wks, 7mg/day for 2 wks)&lt;sup&gt;**&lt;/sup&gt; Placebo patches</td>
<td>548&lt;sup&gt;‡&lt;/sup&gt; (USA; 10)</td>
<td>Age ≥45 ≥15 cigarettes/day with ≥2 previous attempts to quit and CO≥8ppm History of MI, CABS, angioplasty, stenosis ≥50% in at least one major artery or a clinical history of angina, CHF, cor pulmonale, arrhythmia, peripheral vascular disease or cerebrovascular disease No unstable angina, MI, CABS, angioplasty, hospitalisation for arrhythmia within 2 weeks of randomisation No prior continuous use of transdermal nicotine for &gt;48 hours, unwillingness to stop current use of tobacco products or nicotine gum, unstable psychiatric illness or disorder involving use of alcohol or controlled substances, history of severe dermatitis, pregnancy</td>
<td>Patient diaries (smoking and symptoms) Expired CO Mortality MI Cardiac arrest Hospital admissions and outpatient visits Side effects</td>
<td>Only 8 female subjects (most were veterans)</td>
</tr>
<tr>
<td>STNPCAD, 1994&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Patches&lt;sup&gt;‡&lt;/sup&gt; (14mg/day)&lt;sup&gt;**&lt;/sup&gt; + weekly group counselling Placebo patches (&lt;1mg/day) + weekly group counselling</td>
<td>Patches: 77 (78&lt;sup&gt;‡&lt;/sup&gt;) Placebo: 79 (78&lt;sup&gt;‡&lt;/sup&gt;) Total: 156&lt;sup&gt;‡&lt;/sup&gt; (155&lt;sup&gt;‡&lt;/sup&gt;) (USA; 4)</td>
<td>CAD, defined as coronary angiography showing ≥60% obstruction of ≥1 major artery or primary branches, or documented MI, or clinical history typical of angina pectoris with exercise treadmill test or nuclear scan consistent with myocardial ischaemia, or prior CABS or angioplasty Age 21-70 ≥20 cigarettes/day and Fagerström score ≥7 Expired CO ≥10ppm above ambient levels at screening No acute MI within 3 months of study entry, unstable angina, vasospastic conditions, symptomatic valvular heart disease, uncontrolled CHF, serious ventricular arrhythmias, ≥2nd degree atrioventricular block, IDDM, active peptic ulcer or any contra-indication to use of transdermal systems</td>
<td>Smoking diary Weekly expired CO Cardiac symptom diary Withdrawal symptom diary 12-lead ECG 24 hour ambulatory ECG monitoring (AEM) in one centre only Blood pressure Heart rate Body weight Plasma nicotine and cotinine</td>
<td></td>
</tr>
<tr>
<td>Trial ID</td>
<td>Intervention and control</td>
<td>Patients</td>
<td>Outcomes</td>
<td>Comments</td>
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<tr>
<td>Tzivoni, 1998&lt;sup&gt;38&lt;/sup&gt;</td>
<td>28/day smokers: Nicotine patches 20cm&lt;sup&gt;2&lt;/sup&gt; (14mg/24hr) +SCP&lt;sup&gt;*&lt;/sup&gt;  “Placebo” low dose nicotine patches 20cm&lt;sup&gt;2&lt;/sup&gt; (2g/24hr) +SCP&lt;sup&gt;**&lt;/sup&gt;</td>
<td>CAD (angiographic evidence, stable angina pectoris with positive exercise test or previous MI) Age 30-75 Nicotine dependent (≥15 cigarettes/day for ≥ 5 years and Fagerström score ≥5) Wishing to stop smoking No MI, coronary artery bypass surgery, coronary angioplasty or stroke within 3 months prior to screening ≤12 ischaemic episodes during 48 hour ambulatory ECG monitoring Blood pressure ≤110mmHg (diastolic) and ≤200mmHG (systolic) No reduced LVF or clinical signs of heart failure, complex ventricular arrhythmias or episodes of supraventricular tachycardia of &gt;60 seconds duration</td>
<td>48 hour ambulatory ECG monitoring (AEM) Smoking diary Carbon monoxide testing (abstinence defined as &lt;12ppm) Symptoms Skin tolerability</td>
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<td></td>
<td>&lt;20/day smokers: Nicotine patches 30cm&lt;sup&gt;2&lt;/sup&gt; (21mg/24hr) +SCP&lt;sup&gt;<strong>&lt;/sup&gt;  “Placebo” low dose nicotine patches 30cm&lt;sup&gt;2&lt;/sup&gt; (3g/24hr) +SCP&lt;sup&gt;</strong>&lt;/sup&gt;</td>
<td>81 in higher dose group (Israel; 2 centres)</td>
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<td>Nicotinell  weekly group smoking cessation programme</td>
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<td></td>
<td></td>
<td>Patches: 52 Placebo: 54 Total: 106</td>
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<tr>
<td>Trial ID</td>
<td>Randomisation and concealment</td>
<td>Blinding</td>
<td>Duration, missing data and loss to follow-up</td>
<td>ITT analysis</td>
<td>Comments</td>
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<tr>
<td>Joseph, 1996</td>
<td>Pre-generated randomisation list, blocks of size 10. Treatment appears to be centrally assigned, but no clear statement given</td>
<td>Placebo patches identical in smell and appearance – no further details given</td>
<td>10 weeks</td>
<td>Yes</td>
<td>Sample size determined based on safety endpoints (90% power to detect an increase of 10% from a baseline of 15% in rate of adverse events)</td>
</tr>
<tr>
<td>STNPCAD, 1994</td>
<td>Central randomisation, list in blocks of 4, separate list for each centre but not otherwise stratified</td>
<td>Placebo patches contained very low dose nicotine to give identical colour and odour</td>
<td>5 weeks</td>
<td>Withdrawals treated as “failures” for smoking cessation ECG performed immediately after withdrawal for safety endpoints One participant excluded from efficacy due to randomisation as a couple, with one set of data “selected” for exclusion during randomisation</td>
<td>Sample size calculation based on cessation rates in previous studies of nicotine gum; no consideration of power for safety outcomes</td>
</tr>
<tr>
<td>Tzivoni, 1998</td>
<td>No description</td>
<td>Placebo patches contained very low dose nicotine to give identical colour and odour</td>
<td>2 weeks</td>
<td>Not clear (“The data on all patients who were randomised to treatment and received at least one dose of study medication were analysed. A total of 106 patients were included in the analysis.”) Numbers randomised match numbers analysed, but definition is not ITT.</td>
<td>Small study; no sample size calculation. Analysis does not use baseline values. Of some concern as there were some baseline differences which may affect interpretation of the results</td>
</tr>
<tr>
<td>Trial ID</td>
<td>Smoking cessation</td>
<td>Safety</td>
<td>Other</td>
<td>Comments</td>
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<td>------------------</td>
<td>------------------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Joseph, 1996³⁰</td>
<td><strong>CO confirmed cessation at 14 weeks:</strong> 21% on patches vs 9% on placebo (p=0.001)</td>
<td><strong>Deaths:</strong> 1 on patches vs 6 on placebo (p=0.07)</td>
<td></td>
<td>Most consistent only for patients continuing on treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>CO confirmed cessation at 24 weeks:</strong> 14% on patches vs 11% on placebo (p=0.67)</td>
<td><strong>Death or MI, cardiac arrest, admission for angina, arrhythmia or CHF:</strong> 5.4% vs 7.9% (p=0.23 inc deaths)</td>
<td></td>
<td>Fewest events in non-smokers on placebo, but no evidence that patches cause more events than smoking</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other admissions:</strong> 11.9% vs 9.7% (p=0.37)</td>
<td><strong>Weight:</strong> +1.4kg on patches, +0.3kg on placebo (p=0.001)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>All:</strong> 16.3% vs 16.2% (p=0.97)</td>
<td><strong>Blood pressure/pulse:</strong> negligible changes in both groups</td>
<td></td>
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<tr>
<td></td>
<td>Results similar when considered only for patients continuing on treatment</td>
<td></td>
<td><strong>Sleep disturbance, skin reactions and GI distress:</strong> similar in both groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STNPCAD, 1994⁷¹</td>
<td><strong>Required increased dose patches:</strong> 19 (26%) on patches vs 40 (51%) on placebo</td>
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<tr>
<td></td>
<td>Smoking cessation (from diaries confirmed by CO):</td>
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<tr>
<td></td>
<td>36% on patches vs 22% on placebo (p&lt;0.05). Much higher cessation rates in one centre but no centre-treatment interaction found; this centre had more patients with advanced NYHA class and performed 24 hour ECG monitoring</td>
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<tr>
<td></td>
<td><strong>Mean withdrawal symptom scores:</strong> 1.8 on patches vs 2.2 on placebo (p&lt;0.05)</td>
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</tr>
<tr>
<td>Tzivoni, 1998⁸⁶</td>
<td><strong>Patient reported smoking cessation:</strong> 14/52 (27%) on patches vs 7/54 (13%) on placebo</td>
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<td></td>
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<tr>
<td></td>
<td>Mean cigarettes smoked: 7.7/day vs 3.1/day</td>
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<tr>
<td></td>
<td><strong>CO at 12pm:</strong> 38/52 (73%) vs 28/54 (52%)</td>
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</tbody>
</table>

**Safety:**

- **Deaths:** 1 on patches vs 6 on placebo (p=0.07)
- **Death or MI, cardiac arrest, admission for angina, arrhythmia or CHF:** 5.4% vs 7.9% (p=0.23 inc deaths)
- **Other admissions:** 11.9% vs 9.7% (p=0.37)
- **All:** 16.3% vs 16.2% (p=0.97)

**Other:**

- **Weight:** +1.4kg on patches, +0.3kg on placebo (p=0.001)
- **Blood pressure/pulse:** negligible changes in both groups
- **Sleep disturbance, skin reactions and GI distress:** similar in both groups

**Comments:**

- Compliance >90% for both groups (determined by number of patches returned at follow-up)
- Mean weight: “virtually unchanged”, +0.1kg vs –0.9kg (groups not clear)
- CO testing only done at end of 2 week study period - the much higher percentages of non-smokers according to CO than patient reported suggested that participants “gave up” shortly prior to the final follow-up tests

**Adverse effects:**

- 50% reported AEs in each group. Those on patches reported more transient itching at the patch site (36% vs 9%). Those on placebo reported more dizziness, insomnia, diarrhoea, body aches, nervousness and angina. Local erythema occurred in 20% of patients on patches but required no treatment

- 11 withdrawals for adverse events, 3 on patches (nausea, palpitations and malaise; severe chest pain; severe nausea) and 8 on placebo (increased angina intensity; hospitalisation for chest pain and bypass surgery; new ischaemic electrocardiographic changes; increased angina; hospitalised for severe nicotine withdrawal symptoms; parasthesia, dizziness, dyspnoea, palpitations; rash; 2 minute syncopal episode)
4.1.4.2 Other Evidence

We did not identify any RCTs which had not been considered by the MHRA.

We identified one systematic review by Wiggers et al\textsuperscript{32} based on a series of reviews by the Cochrane Tobacco Addiction Review Group. This review identified only two studies considering the effectiveness of NRT in cardiovascular patients, one of which (Joseph et al, 1996)\textsuperscript{30} is reported above. The second study included in this review was a small trial of 85 hospital inpatients by Campbell et al,\textsuperscript{33} this trial was not considered for inclusion in this report due to the inpatient population.
4.1.5 Combination Therapy NRT + NRT

Until recently, NRT product information warned against the concurrent use of more than one product. However, whilst nicotine patches appear to be effective at maintaining a background level of nicotine and maybe more effective overall than other “on demand” delivery systems, such as gum, inhalers and nasal spray, there may be advantages to combined use of patches with an “on demand” product to satisfy intermittent cravings.

The MHRA Working Group recently reviewed the evidence on the combination of different NRT products and recommended that these warnings against combined use be removed to allow smokers to identify and use the combination most appropriate for them.

4.1.5.1 MHRA Clinical Effectiveness Evidence

The MHRA considered the results of 5 RCTs in their report. Two of these investigated the use of patches and gum,34,35 two the use of patches and inhalers36,37 and one the use of patches combined with nasal spray.38

Details of the studies can be found in Table 19, Table 20 and Table 21.

Four of the five trials had treatment periods of 3-9 months and all had follow-up at one year. Overall trial quality was good with reasonably large sample sizes (range 237-446), adequate methods of randomisation and allocation concealment (where reported) and use of intention-to-treat analysis.

All five trials reported a trend towards improved efficacy for the combined NRT strategies. Early differences in success rates were statistically significant in all trials, although success rates in all groups declined over time and few statistically significant differences were reported at one year although differences in quit rates persisted in all trials.

One systematic (Cochrane) review by Silagy et al39 was considered by the MHRA. This review was well conducted and included 7 comparisons of combination NRT+NRT of various types. The included trials are discussed in more detail elsewhere in this report. The combined OR for smoking cessation was 1.42 (1.14, 1.76), suggesting a benefit for combination compared to single treatment approaches, but as the authors note there is substantial clinical heterogeneity in terms of the forms of NRT combined and which single treatments were used as the comparator.
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
<th>N (location; centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blondal, 1997</td>
<td>Patch (15mg) + nasal spray Patch + placebo spray</td>
<td>237 total (Iceland; 1)</td>
<td>Patients</td>
<td>Sustained abstinence at 1 year</td>
<td>Abstract only</td>
</tr>
<tr>
<td>Bohadana, 2000</td>
<td>Patch (15mg/day) + inhaler (10mg capsules, 6-12 capsules/day) ** Placebo patch + inhaler</td>
<td>400 (France; 3 workplaces)</td>
<td>Age 18-70 ≥10 cigarettes/day and expired CO≥10ppm One or more previous attempts to quit and willing to stop smoking No MI within 3 months, unstable angina, severe cardiac arrhythmia, serious renal, pulmonary, endocrine or neurological disorders, pregnancy or breastfeeding or use of any form of tobacco or nicotine substitution Subjects using any smoking cessation program within 6 months, alcoholics or illegal drug users and those with dermatological diseases also excluded</td>
<td>Smoking status at 3 months Continuous abstinence (self-reported non-smoking weeks 2-52 and expired CO&lt;10ppm at each follow-up) Expired CO Weight Craving and withdrawal symptoms Pulmonary symptoms and lung function AEs</td>
<td></td>
</tr>
<tr>
<td>Kornitzer, 1995</td>
<td>Patch* + gum Patch + placebo gum Placebo patch + placebo gum ** 15mg/day for 12 wks, 10mg/day for 6 wks, 5mg/day for 6 weeks</td>
<td>374 (149+150+75 on placebo) (Belgium; 3 workplaces)</td>
<td>Workplace recruitment (white collar) Age ≥20 ≥10 cigarettes/day and having smoked for at least 3 years No severe and/or symptomatic cardiac disease, pregnancy, breastfeeding, regular psychotropic medication, abuse of alcohol or other drugs, generalised chronic dermatological disorders or active peptic ulcer, use of any form of smokeless tobacco or current involvement in smoking cessation program</td>
<td>Smoking cessation, patient reported and CO measurement Abstinence defined as no smoking after week 1 and CO&lt;10ppm at all follow-up after week 1 Cotinine testing at weeks 1, 18 and 24 Compliance AEs</td>
<td></td>
</tr>
<tr>
<td>Puska, 1995</td>
<td>Patch* + gum Nicorette,15mg/day for 12 weeks, 10mg/day for 3 weeks, 5mg/day for 3 weeks *2mg/piece, encouraged to use at least 4 pieces a day for up to 12 months, with withdrawal encouraged after 6 months</td>
<td>300 (Finland; 10)</td>
<td>Age 20-65 ≥10 cigarettes/day, smoker for 3 years or more and wishing to stop smoking No recent MI, pregnancy, breastfeeding, regular psychotropic medication, use of smokeless tobacco, generalised dermatological disorder, active peptic ulcer, active temporomandibular joint disease, or currently on a smoking cessation programme</td>
<td>Smoking status Expired CO Abstinence defined as no smoking after week 1 with CO&lt;10ppm Diary on gum use AEs</td>
<td></td>
</tr>
<tr>
<td>Trial ID</td>
<td>Intervention and control</td>
<td>N (location; centres)</td>
<td>Patients</td>
<td>Outcomes</td>
<td>Comments</td>
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</tbody>
</table>
| Tonnesen, 2000   | Patch (15mg/day)"  Inhaler (10mg per container", 4-12 container/day used hourly)  Patch (15mg/day) + inhaler  Low dose (placebo) patch (5mg/day)  Nicorette  5mg available from 10mg/container | 446 (Denmark; 1)      | Recruited from attendees at a lung clinic  
≥10 cigarettes/day  Age 20-70  Willing to quit smoking and use NRT  No suspicion of lung cancer, tuberculosis, senility, pregnancy or lactation | Smoking cessation (confirmed by CO and cotinine if possible) assessed at follow-up and 1 year  Sustained abstinence (no smoking after week 2 and CO<10ppm at all visits)  Abstinence with slips (abstinence with smoking on two occasions with up to 10 cigarettes consumed, CO<10ppm at all visits)  Nicotine dependency (Fagerström score) |
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Randomisation and concealment</th>
<th>Blinding</th>
<th>Duration, missing data and loss to follow-up</th>
<th>ITT analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blondal, 1997</td>
<td>Computer generated code, dispensed by pharmacy (from Silagy et al)</td>
<td>Double blind (no details) (from Silagy et al)</td>
<td>Treatment recommended for 3 months; follow-up at one year and up to 6 years</td>
<td>Abstract only</td>
<td></td>
</tr>
<tr>
<td>Bohadana, 2000</td>
<td>Sealed envelopes held by hospital pharmacy</td>
<td>Double blind up to 6 weeks, single blind from week 6-12 and open thereafter</td>
<td>6 weeks (+6 weeks with both groups on placebo) and one year follow-up</td>
<td>Yes; non-attendees defined as relapers</td>
<td>Sample size seems optimistic; 80% power to detect at least 15% difference at 1 year based on observed success rates of 40% vs 55%</td>
</tr>
<tr>
<td>Kornitzer, 1995</td>
<td>Computer-generated list, sealed code envelopes helped by PI for emergency unblinding (not required) – no other details given</td>
<td>Identical placebos used – placebo gum designed to taste similar</td>
<td>24 weeks with follow-up at one year</td>
<td>Yes; withdrawals and loss to follow-up counted as treatment failures</td>
<td></td>
</tr>
<tr>
<td>Puska, 1995</td>
<td>No information given</td>
<td>&quot;strictly double blind&quot;; no further information</td>
<td>24 weeks and one year follow-up</td>
<td>Yes; loss to follow-up regarded as treatment failure, withdrawals from treatment continued on follow-up</td>
<td></td>
</tr>
<tr>
<td>Tonnesen, 2000</td>
<td>No description</td>
<td>None (open label)</td>
<td>3-9 months treatment and follow-up at one year</td>
<td>Yes (non-attenders counted as treatment failures)</td>
<td></td>
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</table>
Table 21 Combination NRT+NRT: MHRA Identified Trials - Trial Results

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Smoking cessation</th>
<th>Safety</th>
<th>Other</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blondal, 1997&lt;sup&gt;38&lt;/sup&gt;</td>
<td>&quot;significant increase in sustained abstinence at one year&quot; (reported by Silagy et al&lt;sup&gt;39&lt;/sup&gt;)</td>
<td>Withdrawal symptoms: significantly greater in placebo group at 1 week (p&lt;0.001)</td>
<td>Inhaler cartridges used in abstainers: 4.41 (patch+inhaler) vs 4.6 (placebo+inhaler) per day up to week 6; 3.75 vs 4.32 per day weeks 6-12</td>
<td>Abstract only</td>
</tr>
<tr>
<td>Bohadana, 2000&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Smoking cessation at 12 months: 19.5% (patch+inhaler) vs 14% (placebo+inhaler), p=0.14</td>
<td>craving symptoms: significantly greater in placebo group at 6 weeks (p=0.04)</td>
<td>Weight: +0.49kg (patch+inhaler) vs +0.99kg (placebo+inhaler) (p=0.01) at week 2; +4.22kg vs 3.96kg at 1 year (p=0.14)</td>
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<td></td>
<td>Smoking cessation at 6 weeks: 60.5% (patch+inhaler) vs 47.5% (placebo+inhaler), p=0.009</td>
<td>Respiration symptoms: decreased in both groups, slight improvements in pulmonary function</td>
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<td></td>
<td>Smoking cessation at 12 weeks: 42% (patch+inhaler) vs 31% (placebo+inhaler), p=0.02</td>
<td>Adverse events: rare and tolerable</td>
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<td></td>
<td>Time to relapse over 1 year: logrank test, p=0.04</td>
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<tr>
<td>Kornitzer, 1995&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Abstinence: 34.2% (patch+gum) vs 22.7% (patch) vs 17.3% (placebo) at week 12; 27.5% vs 15.3% vs 14.7% at 24 weeks; 18.1% vs 12.7% vs 13.3%</td>
<td>No severe dermatological reactions; no statistically significant differences for itching, erythema or edema</td>
<td>Gum consumption: no significant differences between groups</td>
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<td></td>
<td>OR (patch vs patch+gum): 1.72 (1.03, 2.94), p=0.039 at 12 weeks; 2.04 (1.14, 3.57), p=0.018 at 24 weeks; 1.47 (0.76, 2.78), p=0.125 at 52 weeks</td>
<td></td>
<td>Patch compliance: 52% daily use at 12 weeks, 41% at 24 weeks (no difference between groups)</td>
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</tr>
<tr>
<td>Puska, 1995&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Time to relapse: logrank p=0.04</td>
<td>Relatively few adverse events reported</td>
<td>Compliance: 70% (active patch) vs 58% (placebo patch) using patch ar 12 weeks</td>
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<tr>
<td></td>
<td>Abstinence at 12 weeks: 39.3 (patch+gum) vs 28.0 (gum only), p=0.038</td>
<td>Itching more common with active patch (29% vs 11%, p=0.001)</td>
<td>Gum use: average 4 pieces/day in both groups over first 3 months; slightly higher in gum only group; gum use reduced over 6-12 months</td>
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<td></td>
<td>Abstinence at 26 weeks: 27.3 (patch+gum) vs 20.7 (gum only), p=0.175</td>
<td>No other significant differences</td>
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<td></td>
<td>Abstinence at 52 weeks: 24.0 (patch+gum) vs 17.3 (gum only), p=0.154</td>
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<td>Cotinine: mean 147 vs 198 (p=0.035)</td>
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<tr>
<td>Tønnesen, 2000&lt;sup&gt;37&lt;/sup&gt;</td>
<td>12 month cessation: 6% (placebo) vs 16% (patch) vs 9% (inhalar) vs 11% (patch + inhaler)</td>
<td>No serious AEs reported</td>
<td>No significant differences in body weight, cotinine and lung function</td>
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<tr>
<td></td>
<td>12 month sustained abstinence: 1.8% vs 8.7% vs 5.1% vs 3.5%</td>
<td></td>
<td>Motivation, sex, age, baseline cigarette consumption, baseline CO, Fagerstrøm score significant predictors of outcome (and included in adjusted Cox model)</td>
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<tr>
<td></td>
<td>HR for relapse (adjusted Cox regression): 0.56 (patch), 0.76 (inhalar), 0.51 (inhalar + patch)</td>
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<tr>
<td></td>
<td>Patch vs placebo, p&lt;0.05</td>
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</table>
4.1.5.2 Other Evidence

We identified 3 further RCTs which were not explicitly mentioned in the MHRA report.\textsuperscript{40-42} These trials are summarised in Table 22, Table 23 and Table 24. One further RCT was identified but this was a crossover design with 4 treatment groups (using placebo or active patches, and placebo or active patches). The treatment period was only 3 days for each treatment assignment, with a 4 days washout period with smoking. A crossover design is of questionable value for answering pragmatic questions in this area and the results of this study are not interpretable in a useful way for this report.

All three of the other RCTs identified examined the use of nicotine nasal spray in combination with patches. Two of these were reported as abstracts only and we have very little information about the study designs or results. The large trial which has been fully reported Croghan et al,\textsuperscript{42} is of good quality and reports similar results to those trials investigating patches combined with gum or inhalers. The treatment period in this trial was only 6 weeks, with follow-up to 6 months. The results are comparable to the other trials combining patch and gum or inhaler reported above. The trial by Croghan et al was included in the systematic review by Silagy et al.\textsuperscript{39}
**Table 22 Combination NRT+NRT: Additional Identified Trials - Trial Characteristics**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
<th>N (location; centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croghan, 2003</td>
<td>Patch (15mg/day)</td>
<td>1384 (USA; several)</td>
<td>≥18</td>
<td>≥15 cigarettes/day for last year</td>
<td>Smoking cessation at end of study</td>
</tr>
<tr>
<td></td>
<td>Nasal spray (0.5mg/spray)</td>
<td></td>
<td></td>
<td>No general poor health or planning pregnancy, MI within 3 months, angina pectoris, serious cardiac arrhythmia, presence of psychiatric disorder, use of psychiatric drugs, chronic nasal disorders, allergies or sinusitis, pregnancy or breastfeeding, current use of tobacco products other than cigarettes, current use of NRT or other pharmacological smoking cessation treatment, use of IND within 30 days, history of skin allergies, or participation in smoking cessation programme within last 12 months</td>
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<tr>
<td></td>
<td>Patch + spray all for 6 weeks</td>
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<td></td>
<td>*Recommended dose of one puff/nostril as required, maximum 5 doses/hour or 40/day</td>
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<td>AEs</td>
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<tr>
<td>Landfeldt, 1998</td>
<td>Patch + nasal spray</td>
<td>101</td>
<td>≥20</td>
<td>≥7</td>
<td>Abstract only</td>
</tr>
<tr>
<td></td>
<td>Placebo patch + nasal spray</td>
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<tr>
<td>Sutherland, 1999</td>
<td>Nasal spray</td>
<td>380</td>
<td></td>
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<td>Abstract only</td>
</tr>
<tr>
<td></td>
<td>Patch</td>
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<td></td>
<td>Patch + nasal spray</td>
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<tr>
<td></td>
<td>Placebo</td>
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</table>

**Table 23 Combination NRT+NRT: Additional Identified Trials - Trial Quality**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Randomisation and concealment</th>
<th>Blinding</th>
<th>Duration, missing data and loss to follow-up</th>
<th>ITT analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croghan, 2003</td>
<td>Minimisation (factors: gender, cigarettes/day at baseline, total years smoking)</td>
<td>None</td>
<td>6 weeks with 6 month follow-up</td>
<td>Yes; non-attendees or loss to follow-up classified as treatment failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presumably central allocation (given that minimisation used)</td>
<td></td>
<td>34% completed study; 45% non-compliance; 4% loss to follow-up; 10% withdrawal of consent; &lt;3% unknown reason</td>
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<tr>
<td>Landfeldt, 1998</td>
<td></td>
<td></td>
<td>12 weeks + withdrawal period of 6 weeks</td>
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<td></td>
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<tr>
<td>Sutherland, 1999</td>
<td></td>
<td></td>
<td>4 weeks with follow-up at 8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial ID</td>
<td>Smoking cessation</td>
<td>Safety</td>
<td>Other</td>
<td>Comments</td>
<td></td>
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<tr>
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<td>--------------------------------------------------------</td>
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<tr>
<td>Croghan, 2003</td>
<td><strong>CO confirmed abstinence at 3 weeks</strong>: 25.5% (patch) vs 21.2% (spray) vs 34.4% (patch+spray), p=0.003 (patch vs patch+spray)<strong>&lt;br&gt;<strong>CO confirmed abstinence at 6 weeks</strong>: 20.7% (patch) vs 13.6% (spray) vs 27.1% (patch+spray), p=0.025 (patch vs patch+spray)</strong>&lt;br&gt;<strong>CO confirmed abstinence at 6 months</strong>: 7.8% (patch) vs 6.9% (spray) vs 9.1% (patch+spray), p=0.554 (patch vs patch+spray)**</td>
<td>Nasal spray associated with more burning in nose and throat (63% vs 12%), watery eyes (48% vs 14%), nose and throat irritation (53% vs 17%) and sneezing (49% vs 21%)&lt;br&gt;No other adverse events reported with high frequency&lt;br&gt;More withdrawals due to AEs on nasal spray (3% vs 1%)</td>
<td>No interactions found by race, gender, history of alcoholism or subclinical depressive symptoms</td>
<td>Sample size based data from previous studies and well reported</td>
<td></td>
</tr>
<tr>
<td>Landfeldt, 1998</td>
<td>Abstinence: overall 18% at 12 weeks&lt;br&gt;No differences between groups (no data reported)</td>
<td></td>
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</tr>
<tr>
<td>Sutherland, 1999</td>
<td>Spray+patch vs patch alone: OR=1.66 (0.96, 2.88) at 4 weeks&lt;br&gt; Spray+patch vs spray alone: OR=1.29 (0.78, 2.21) at 4 weeks</td>
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</tbody>
</table>
4.1.6 Combination therapy NRT + Bupropion (Zyban)

Bupropion (Zyban® GSK) is a slow release prescription only drug, licensed for use in smoking cessation with motivational support. NICE guidance was issued in 2002 and recommends the use of Bupropion in smokers over the age of 18.\textsuperscript{43} A dosage of 150mg for the first six days followed by two tablets per day for the following 6 to 8 weeks is recommended. The NICE guidance states there is currently insufficient evidence to recommend a combination therapy of NRT with Bupropion. This was based on the evidence of one trial available at the time by Jorenby et al 1999.\textsuperscript{44} The trial found that quit rates at 12 months were significantly different between placebo and Bupropion treatment alone groups (16% vs. 30%) but this rate was unaltered by a combination of NRT and Bupropion (30%). However, this study showed a lack of response to NRT treatment alone in this group of smokers as the rate of quitting in the placebo group was the same as the NRT group at 12 months (16%).\textsuperscript{44}

The NICE guidance was due for review in March 2005.

4.1.6.1 MHRA Clinical Effectiveness Evidence

Combination therapy of NRT with Bupropion is not covered in the MHRA document.

4.1.6.2 Other Evidence

We identified three RCTs\textsuperscript{7,45,46,47}, that have been published since the NICE guidance in 2002 on NRT and bupropion.\textsuperscript{43} Details of the RCTs are given in Table 25, Table 26 and Table 27. Two of the trials have shown no difference in abstinence with the use of NRT in the form of a patch and Bupropion.\textsuperscript{7,45} These trials were reasonable in size (n=200) and use ITT analysis. Randomisation was well described in one of the trials and both described blinding of patients. The third and most recent trial (currently in press) has shown an improved 12 week abstinence rate with the use of combination NRT (nicotine inhaler) and Bupropion.\textsuperscript{46,47} This trial is of high quality and is a large multicentre trial (n=1700). It used a higher dose of Bupropion (300mg) than the other trials (150mg). Continuation of this combination did not alter relapse rates after the initial 12 week period, but the trial data suggests there may be an advantage to using combination therapy in the initial phase of attempting to quit.

The trial by Simon et al randomised patients to either Bupropion (n=121) or placebo (n=123) with both groups also receiving nicotine patches and a counselling program.\textsuperscript{45} This study was heavily weighted towards a male population with 210 males and 34 females enrolled in the study. The participants were followed up at 1 week, 3 weeks, at the end of treatment at 7 weeks and then at 12 weeks, 6 months and 1 year. The results showed no difference between the two arms at any of the follow-up time points with a slightly greater quit rate with NRT therapy alone at 12 months (24%) compared to NRT with Bupropion (19%), relative risk 0.80 (0.49-1.30). This trial has potentially unusual population as it identified participants from previous smoking cessation studies that were carried out at the investigating centre. These participants have probably tried NRT or other methods in the past and failed. Readiness to quit smoking was also assessed in this group by a counsellor using a previously published ‘stages to change model’. Participants
were only included in the study if they were deemed to be at the ‘contemplation’ or ‘preparation’ stages of attempting to quit smoking.

The trial by Killen et al looked at adolescent smokers and randomised smokers aged 15-18 to either nicotine patch with placebo (n=108) or nicotine patch with Bupropion (n=103) and found that nicotine patches in combination with Bupropion had no effect on abstinence at 10 and 26 weeks (23% and 8%) compared to nicotine patches plus placebo (28% and 8%). Smokers were offered a $100 incentive payment for completing the full program. Despite this, the trial had only 29% in the NRT alone group and 22% in the NRT with Bupropion groups reporting using the treatment for 6 weeks. The treatment program was designed to last 8 weeks in the NRT alone group and 9 weeks in the Bupropion combination group. The analysis in this study has used regression modelling to show increased attendance to classes and increased use of NRT was associated with abstinence. When investigating the impact of treatment on craving, the study only included participants who were abstinent at the end of study. This unsurprisingly showed that craving was reduced over time in this group.

The study by Croghan et al assessed the use of a combination of NRT in the form of a nicotine inhaler with Bupropion and assessed by initial quit rate (abstinence at 12 weeks) and relapse in smokers over the age of 18. The study design had three phases. In phase I the participants were randomised to receive the inhaler (n=566), Bupropion (n=567) or combination (n=567) for the initial 12 weeks. Participants in this trial also received counselling. Following this phase, participants who were successfully abstinent, were re-randomised to either continue treatment or receive placebo in order to determine whether relapse prevention was achieved with the study drugs. This resulted in a fairly high attrition rate into phase II which the author’s suggest is due to participants not wanting to receive placebo. The results showed an improvement in abstinence at 12 weeks in the combination group compared to the NRT or Bupropion groups alone. 14% in the inhaler group, 26% in the Bupropion and 34% in the combination groups achieved abstinence at 12 weeks. The dosage of Bupropion used was 300mg from the onset, which is higher than the 150mg used in the previous trials. Successful quits rates were higher in men than women in the combination therapy arm of this trial 42% vs 30% (p>0.01) suggesting a possible treatment preference. However, continuation on the treatment program in phase II did not alter relapse rates at follow-up. Relapse rates in the groups were similar in phase II. The author’s mention a potential confounding factor in that the amount of additional medication or counselling the participants used outside of the study was not investigated.
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
<th>N (location; number of centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon JA et al 2004</td>
<td>Bupropion 150mg/day for first three days. 150mg twice daily after placebo - identical treatment course</td>
<td>Bupropion: 121 Placebo: 123</td>
<td>&gt;20 cigarettes/day</td>
<td>Self-reported tobacco abstinence (no smoking for 7 days) confirmed by saliva cotinine measurement (should be &lt;15ng/ml) adjusted for nicotine patch use.</td>
<td>Potential participants identified from previous smoking cessation studies at the centre.</td>
</tr>
<tr>
<td></td>
<td>Nicotine patches: doses altered to number of cigarettes smoked. Maximum dose permitted 21mg/day. Counselling program: 30-60 minutes individual counselling program by trained public health educator. Self help literature also made available</td>
<td>1 Centre: San Francisco, California.</td>
<td>Aged over 20. 210 Male only 34 Female Had to be at certain stage of quitting (see comments)</td>
<td>Hospital admissions and 1 year mortality Followed up at 1 week, 3 weeks, at the end of treatment at 7 weeks. Then at 12 weeks, 6 months and 1 year.</td>
<td>Readiness to quit smoking assessed by counsellor using ‘stages to change model’ participants only included if at ‘contemplation’ or ‘preparation’ stages of quitting</td>
</tr>
<tr>
<td>Killen JD et al 2004</td>
<td>Bupropion: 150mg/day 9 weeks</td>
<td>Bupropion: 103 Placebo: 108</td>
<td>aged 15-18 145 male, 66 girls Currently smoke &gt;10 cigarettes/day Smoked for at least 6 months &gt;1 failed smoking attempt Had to score &gt;10 points on nicotine dependence test</td>
<td>Change in amount smoked/day (random regression model) Response to treatment (survival analysis time to relapse) Impact on craving (random regression model) Effect on depression Adverse events</td>
<td>Smokers were offered $100 for completing the full program.</td>
</tr>
<tr>
<td></td>
<td>Nicotine patch: dependent on cigarette use, maximum dose 21mg for 8 weeks Group skills training. Participants met weekly (group size 8) with trained counsellor for 45 mins session.</td>
<td>Recruited from 9 High Schools in San Francisco, California.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

53
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Intervention and control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croghan et al 2006</td>
<td>Nicotine inhaler (up to 16 cartridges/day)</td>
</tr>
<tr>
<td></td>
<td>Bupropion (300mg)</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
</tr>
<tr>
<td></td>
<td>Counselling (12-18 sessions of 10 minutes) and supportive material (booklets etc) also given.</td>
</tr>
<tr>
<td></td>
<td>Phase I. 12 weeks: randomisation to treatment</td>
</tr>
<tr>
<td></td>
<td>Phase II. 40 weeks: re-randomisation. Those abstinent re-randomised to continue treatment or placebo. Those unsuccessful were re-randomised to a new treatment.</td>
</tr>
<tr>
<td></td>
<td>Phase III. 15 months follow up of relapse rates.</td>
</tr>
<tr>
<td></td>
<td>Multi-centre RCT</td>
</tr>
<tr>
<td></td>
<td>1700 smokers</td>
</tr>
<tr>
<td></td>
<td>566 inhaler</td>
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<tr>
<td></td>
<td>567 Bupropion</td>
</tr>
<tr>
<td></td>
<td>567 Combination</td>
</tr>
<tr>
<td></td>
<td>19 centres, USA (North Central Cancer Treatment Group).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N (location; number of centres)</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eligibility. 18 years or older</td>
<td>Minimum 10 cigarettes/day for 12 months.</td>
<td>Primary outcome was biochemically confirmed 7 day smoking abstinence rate at week 12. Air CO of &lt; 8 parts per million or less.</td>
</tr>
<tr>
<td></td>
<td>Excluded. Co-morbidity, pregnancy, depression, sensitivity to study drugs.</td>
<td></td>
<td>Secondary outcomes were relapse rate in phase II, and toxicity severity.</td>
</tr>
</tbody>
</table>

54
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Randomisation and concealment</th>
<th>Blinding</th>
<th>Duration, missing data and loss to follow-up</th>
<th>ITT analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon JA et al 2004⁴⁵</td>
<td>Computer algorithm generated random list of treatment assignments.</td>
<td>Study personnel blinded to treatment assignment Placebo described as identical (further details not given)</td>
<td>7 week treatment program. 5 subjects (2%) died during study period, and 3 (1%) were lost to follow-up.</td>
<td>5 dead subjects excluded and lost to follow-up included in ITT analysis as smokers requiring biochemical or spousal confirmation of quitting.</td>
<td></td>
</tr>
<tr>
<td>Killen JD et al 2004⁷</td>
<td>No details of method in paper</td>
<td>Described as double blind Participants were asked to guess their treatment. 30% in placebo and 31% in Bupropion group were correct.</td>
<td>9 weeks treatment 26 weeks follow-up 20% lost to follow-up. Participants not providing biochemical measures were classified as smokers.</td>
<td>Losses counted as smokers. Groups remained as allocation.</td>
<td>Possible compliance issue. 41% of participants reported using the patch on 2 weeks or less. 29% reported using 5 weeks treatment. 44% of participants reported using pill on 2 weeks or less. Only 22% reported using 6 weeks treatment.</td>
</tr>
<tr>
<td>Croghan et al 2006⁶⁶,⁴¹</td>
<td>Randomisation well described. Stratification used for site, gender, number of cigarettes smoked/day, years smoked.</td>
<td>No mention of blinding. Difficult with inhaler, but assume placebo was matched to study drug in phase II.</td>
<td>Phase I. 1700 smokers Phase II. 941 eligible to continue (837 did). Full details given of all drop-outs. Drop-outs possible high due to chance of receiving placebo in phase II after receiving study drugs in phase I.</td>
<td>ITT analysis using worst case scenario (smoking) for missing subjects.</td>
<td>Study was powered (90%) to detect a clinically significant 10-point difference in abstinence rates. Assuming baseline success of 25%. Fairly large drop-out at the end of phase I.</td>
</tr>
</tbody>
</table>
Table 27 Combination NRT+Bupropion: Trial Results

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Smoking cessation</th>
<th>Safety</th>
<th>Other</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon JA et al 2004&lt;sup&gt;25&lt;/sup&gt;</td>
<td>No difference in self-reported quit rates or actual quit rates at 6 and 12 months between the two arms. NRT therapy alone at 12 months (24%) compared to NRT with Bupropion (19%), relative risk 0.80 (0.49-1.30 p =0.36) No difference in median quit attempts after 12 months: 3.6 Bupropion vs 3.1 placebo (p=0.74)</td>
<td>Rates of hospitalisation similar in two groups: 13% Bupropion vs 19% placebo (p=0.22). No details given on reasons for hospitalisation. 60% in Bupropion group and 49% in placebo reported at least 1 adverse event (p=0.07). Insomnia (18%), dry mouth (15%), abnormal dreams (8%). More dry mouth in Bupropion group 22% vs 8% p&lt;0.01 and GI upset 9% vs 1% p&lt;0.01 More headache in placebo group 7% vs 2% p=0.06</td>
<td>No difference in weight gain between study groups: 2.92kg Bupropion vs 2.43kg Placebo (p=0.78) Overall successful quitters gained more weight than non-quitters: 2.65kg vs 0.41kg (p=0.1) Per protocol analysis also included with patients who took 80% of their medication (62% in each group) 12 months validated quit rates were 33% in Bupropion group and 27% in placebo (p=0.48)</td>
<td></td>
</tr>
<tr>
<td>Killen JD et al 2004&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Abstinence defined as not smoking in the past 7 days and saliva cotinine level below 20ng/ml. Percentage abstinent at 10 weeks was not different between groups: Bupropion 23% vs placebo 28% (p=ns) Regression analysis showed attending more sessions and reported use of patch were associated with abstinence. In contrast amount of cigarettes smoked was not associated with attendance to sessions.</td>
<td>A total of 47 adverse events were reported (25 placebo and 22 in Bupropion group) the most common was nausea. No adverse events were judged to be severe.</td>
<td>The survival analysis showed no difference in time to relapse between the groups. Impact of treatment on craving (only participants who were abstinent at end of study used). Unsurprisingly craving was reduced over time in this group. Depression symptom scores also decreased over time</td>
<td></td>
</tr>
</tbody>
</table>
Combination therapy achieved higher abstinence rates compared to the single interventions at 12 weeks (34% vs. 14% inhaler, 26% Bupropion), but relapse rates were unaffected by the type of intervention after the 12 week abstinence period.

No details on adverse event measurement given.

The study also used logistic regression with variables including treatment arm, gender, cigarettes smoked, years smoked, ethnicity, marriage status, BMI, depression score, prior quit attempts, education level.

The logistic modelling showed abstinence rates at 12 weeks were more likely in white, older subjects with lower nicotine dependence scores. The least likely to quit were subjects on the inhaler who had not previously tried to stop smoking and had high nicotine dependence.

Men achieved higher abstinence than women on combination therapy 41% vs 30% p<0.01 but not in other arms.

Ethnic minorities showed lower overall abstinence rates in all arms.
4.2 Cost-Effectiveness

It is not possible to undertake any *de novo* modelling within the resources available for this report. We have searched for existing cost-effectiveness models for these population subgroups. Where these are not available, we will consider the implications of population-specific issues and how these might affect the results of a cost-effectiveness analysis, using the existing model previously developed by WMHTAC for NRT in the general population of smokers as a reference point.48

4.2.1 Existing Economic Evidence/Models

The tables below give the results of the cost-effectiveness analysis previously published by WMHTAC for NRT and bupropion SR, alone or in combination, compared to brief advice or counselling for smoking cessation. Table 28 gives estimated 12 month quit rates for each intervention and the incremental cost-effectiveness per lifetime quitter. Table 29 and Table 30 consider three different scenarios for cost per life year gained and cost per QALY respectively; a gain of 1, 2 or 3 life years saved per quitter, and a QALY gain of 2.7, 1.35 and 4.05 per quitter (based on an assumed QALY gain of 1.35 per life year saved). Full details of this analysis and the inputs to the model are given in Woolacott et al, 2002.48

Table 28 Baseline estimates of the cost (£) per lifetime quitter of smoking-cessation interventions

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost per attempt</th>
<th>12 month quit rate</th>
<th>Lifetime quit rate</th>
<th>Cost per lifetime quitter</th>
<th>ICER1</th>
<th>ICER2</th>
<th>ICER3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard intervention: brief advice</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief advice only</td>
<td>3.53</td>
<td>0.0300</td>
<td>0.018</td>
<td>196</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Brief advice + NRT</td>
<td>75.5</td>
<td>0.0550</td>
<td>0.033</td>
<td>2288</td>
<td>4798</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Brief advice + bupropion SR</td>
<td>76.08</td>
<td>0.0705</td>
<td>0.0423</td>
<td>1799</td>
<td>2986</td>
<td>62</td>
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<tr>
<td>Brief advice + NRT + bupropion SR</td>
<td>143.91</td>
<td>0.0894</td>
<td>0.0536</td>
<td>2683</td>
<td>3939</td>
<td>3314</td>
<td>5981</td>
</tr>
</tbody>
</table>

| **Standard intervention: counselling** |                  |                    |                    |                          |       |       |       |
| Counselling                       | 35.25            | 0.0900             | 0.0540             | 653                      | –     | –     | –     |
| Counselling + NRT                 | 103.08           | 0.1465             | 0.0879             | 1173                     | 2001  | –     | –     |
| Counselling + bupropion SR        | 103.66           | 0.1792             | 0.1075             | 964                      | 1278  | 30    | –     |
| Counselling + NRT + bupropion SR  | 171.49           | 0.2175             | 0.1305             | 1314                     | 1781  | 1606  | 2952  |

ICER, cost (£) per lifetime quitter; ICER1, using the brief advice only or counselling only as the reference; ICER2, using the brief advice plus NRT or counselling plus NRT as the reference; ICER3, using the brief advice plus bupropion SR or counselling plus bupropion SR as the reference
Table 29 Costs (£) per life-year saved: baseline estimates and according to different values of life-years saved per quitter

<table>
<thead>
<tr>
<th></th>
<th>2.0 LYS/quitter</th>
<th></th>
<th>1.0 LYS/quitter</th>
<th></th>
<th>3.0 LYS/quitter</th>
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<tbody>
<tr>
<td></td>
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<td>Incremen</td>
<td>Average</td>
<td>Incremental</td>
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<td>Incremental</td>
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<tr>
<td>Standard reference: brief advice</td>
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<tr>
<td>Advice only</td>
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<td>196</td>
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<td>1969</td>
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<td>Standard reference: brief advice</td>
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<tr>
<td>Advice only</td>
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<td>–</td>
<td>145</td>
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<td>48</td>
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<tr>
<td>Advice + NRT</td>
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<td>1695</td>
<td>3554</td>
<td>565</td>
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<td>Advice + bupropion SR</td>
<td>666</td>
<td>1106</td>
<td>1332</td>
<td>2212</td>
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<td>Advice + NRT + bupropion SR</td>
<td>994</td>
<td>1459</td>
<td>1987</td>
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<th>2.7 QALYS/quitter</th>
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<td>Counselling alone</td>
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<td>–</td>
<td>484</td>
<td>–</td>
<td>161</td>
<td>–</td>
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<td>Counselling + NRT</td>
<td>434</td>
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<td>869</td>
<td>1482</td>
<td>290</td>
<td>494</td>
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<tr>
<td>Counselling + bupropion SR</td>
<td>357</td>
<td>473</td>
<td>714</td>
<td>947</td>
<td>238</td>
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<tr>
<td>Counselling + NRT + bupropion SR</td>
<td>487</td>
<td>660</td>
<td>973</td>
<td>1319</td>
<td>324</td>
<td>440</td>
</tr>
</tbody>
</table>

LYS, life-year(s) saved

Table 30 Costs (£) per life-year saved: baseline estimates and according to different values of life-years saved per quitter

<table>
<thead>
<tr>
<th></th>
<th>2.7 QALYS/quitter</th>
<th></th>
<th>1.35 QALYS/quitter</th>
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<th>4.05 QALYS/ quitter</th>
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<tr>
<td></td>
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<td>Standard reference: brief advice</td>
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<tr>
<td>Advice only</td>
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<td>–</td>
<td>145</td>
<td>–</td>
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<td>1459</td>
<td>1987</td>
<td>2918</td>
<td>662</td>
<td>973</td>
</tr>
</tbody>
</table>

| Standard reference: counselling |                 |        |                 |         |                    |         |
| Counselling alone            | 242              | –      | 484              | –      | 161                 | –      |
| Counselling + NRT            | 434              | 741    | 869              | 1482   | 290                 | 494    |
| Counselling + bupropion SR   | 357              | 473    | 714              | 947    | 238                 | 316    |
| Counselling + NRT + bupropion SR | 487 | 660    | 973              | 1319   | 324                 | 440    |
4.2.2 Adolescents

No economic analyses were identified specifically addressing the cost-effectiveness of NRT in this population sub-group. There would appear to be no special considerations required in assessing the cost-effectiveness of NRT in adolescents relative to the models which have been applied in adults i.e. the drivers of cost-effectiveness would be similar. However the analysis of the small number of available RCTs does cast genuine doubt on whether the levels of effectiveness of NRT in adolescents are indeed similar to adults. If so the cost-effectiveness of NRT in adolescents does need to be formally assessed. Even with the paucity of the RCT evidence in adolescents, exploratory modelling may be helpful to identify a minimum effect on smoking cessation which would be compatible with NRT being cost-effective. This in turn could help with power calculations in the design of new RCTs.

4.2.3 Pregnant Women

Assisting pregnant women to quit smoking not only leads to health gains for mother and baby but could lead to savings for the NHS due to the effects of smoking on the foetus and the resulting low birth weight which could lead to potentially costly treatment post-birth. Effective programmes to aid smoking cessation in pregnant women could therefore be very cost-effective.

We identified no economic evaluations on the use of NRT in pregnancy.

Whilst the potential for NRT to be a cost-effective intervention for smoking cessation in pregnancy is clear, there is limited evidence on clinical effectiveness and safety to the foetus, as detailed in Section 4.1.2, with which to accurately undertake such analysis.

The ongoing UK based RCT of NRT use in pregnancy seems to be collecting relevant data on effectiveness, safety and costs which should allow an appropriate analysis to be undertaken.

4.2.4 Breastfeeding Women

As with pregnancy, there are benefits to both the mother and baby of giving up smoking and also to the NHS. Thus effective programmes for smoking cessation in breastfeeding women could be very cost effective.

We identified no economic evaluations of the use of NRT in breast feeding.

Whilst the potential for NRT to be a cost-effective intervention for smoking cessation in breastfeeding mothers is clear there is limited evidence on the clinical effectiveness and safety of NRT to the infant, as detailed in Section 4.1.3, with which to accurately undertake such analysis.
4.2.5 Cardiovascular disease

No economic evaluations of NRT specifically in cardiovascular patients were identified. A cost-effectiveness analysis of treatments to reduce cholesterol levels, blood pressure and smoking for the prevention of coronary heart disease in the Spanish population, concluded that NRT to reduce smoking was by far the most cost-effective of the interventions considered. However, the populations for each analysis were not comparable and the cost-effectiveness of NRT was not considered in a cardiovascular population.

There is no evidence to suggest that NRT is less effective in this population compared to other smokers. In smokers with cardiovascular disease, quitting is associated with substantial benefits in terms of both reduced risk of subsequent cardiovascular events and decreased overall mortality. Reductions in 5 year mortality for quitters from 20% to 12%, 30% to 20% and 31% to 16% have been reported. In a study of patients undergoing coronary artery bypass surgery smoking cessation after surgery reduced the risk of death over 20 year follow-up, with the survival benefit increasing from an estimated 3% at 5 years to 14% at 15 years. This suggests that the benefits in terms of life years gained are at least comparable to, if not greater than, those considered by Woolacott et al, for the general population of smokers. Potential cost savings due to reduction in future cardiovascular events are greater in this high risk population.

Although there is some risk of cardiovascular events due to NRT, these risks are substantially smaller than in those who continue to smoke. NRT can be considered a cost-effective and relatively safer treatment option for cardiovascular patients who cannot quit without assistance.

4.2.6 Combination therapy NRT + NRT

No economic evaluations of combination NRT+NRT were found. However, the total costs of combination NRT+NRT is likely to be similar to the cost of NRT+bupropion and the effectiveness of NRT+NRT appears to be at least as high if not higher than combination treatment with NRT+bupropion. The cost-effectiveness of NRT+NRT may be close to that of a single NRT product, if the higher estimates of relative effectiveness are plausible, and is unlikely to be less cost-effective than NRT+bupropion.

4.2.7 Combination therapy NRT + bupropion (Zyban)

The cost-effectiveness of combination NRT + bupropion was considered by Woolacott et al and these results are summarised above.
5. References


6. Appendices

Appendix 1. Search Strategies

Appendix 1.1 Adolescents

Clinical Effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalators or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Adolescent explode all trees
#6 (adolescent* or adolescence* or youth* or child or children)
#7 young next person*
#8 young next people
#9 (#5 OR #6 OR #7 OR #8)
#10 (#4 AND #9)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1  (nrt or nicotine replacement).mp. (1167)
2  (nicotine adj1 (gum$ or inhaled or inhaler or inhalators$ or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1288)
3  or/1-2 (2186)
4  adolescent/ (1159045)
5  exp child/ (1140229)
6  (adolescent$ or adolescence$ or young people or young person$ or youth$).mp. (1176505)
7  (child or children).mp. (1279386)
8  or/4-7 (1873546)
9  3 and 8 (309)
10  limit 9 to "reviews (optimized)" (52)
11  from 10 keep 1-52 (52)
12  randomized controlled trial.pt. (232368)
13  controlled clinical trial.pt. (74663)
14  randomized controlled trials.sh. (47576)
15  random allocation.sh. (58498)
16  double blind method.sh. (90309)
17  single blind method.sh. (10513)
18  or/12-17 (394278)
19  (animals not human).sh. (4070828)
20  18 not 19 (362564)
21  clinical trial.pt. (455477)
22  exp clinical trials/ (193249)
23  (clin$ adj25 trial$).ti,ab. (128418)
24  (((singl$ or doub$l$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
25  placebo$ti,ab. (100005)
26  random$ti,ab. (365132)
27  placebos.sh. (25578)
28  research design.sh. (45680)
29  or/21-28 (844319)
Source - Ovid EMBASE 1980 to 2006 Week 32

1 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1294)
2 (nicotine gum or nicotine replacement therapy).sh. (1783)
3 (nicotine adj1 (gum$ or inhaled or inhaler or inhalators or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2497)
4 or/1-3 (3078)
5 exp adolescent/ (365141)
6 exp adolescence/ (22056)
7 exp child/ (542788)
8 (adolescent$ or adolescence$ or young people or young person$ or youth$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (392599)
9 (child or children).mp. (623047)
10 or/5-9 (866360)
11 4 and 10 (185)
12 limit 11 to "reviews (2 or more terms min difference)" (46)
13 randomized controlled trial/ (108287)
14 exp clinical trial/ (399236)
15 exp controlled study/ (2231444)
16 double blind procedure/ (60747)
17 randomization/ (19895)
18 placebo/ (89020)
19 single blind procedure/ (6029)
20 (control$ adj1 (trial$ or stud$ or evaluation$ or experiment$)).mp. (2272396)
21 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (101937)
22 (placebo$ or matched communities or matched schools or matched populations).mp. (136286)
23 (comparison group$ or control group$).mp. (136874)
24 (clinical trial$ or random$).mp. (640361)
25 (quasalexperimental or quasi experimental or pseudo experimental).mp. (1380)
26 matched pairs.mp. (1877)
27 or/13-26 (2665878)
28 11 and 27 (105)
29 from 28 keep 1-105 (105)

Economic Evaluations

(see also general economic evaluations below)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers$ or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1288)
3 or/1-2 (2186)
4 adolescent/ (1159045)
5 exp child/ (1140229)
6 (adolescent$ or adolescence$ or young people or young person$ or youth$).mp. (1176505)
7 (child or children).mp. (1279386)
8 or/4-7 (1873546)
9 3 and 8 (309)
10 economics/ (24393)
11 exp "costs and cost analysis"/ (126542)
12 cost of illness/ (8502)
13 exp health care costs/ (27327)
14 economic value of life/ (4800)
Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library
Appendix 1.2  Pregnancy

Clinical effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Pregnancy explode all trees
#6 pregnant* or pregnancy
#7 (#5 OR #6)
#8 (#4 AND #7)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1  (nrt or nicotine replacement).mp. (1167)
2  (nicotine adj1 (gum$ or inhaled or inhaler or inhalers$ or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1288)
3  or/1-2 (2186)
4  exp pregnancy/ (551560)
5  pregnant$.mp. (81011)
6  or/4-5 (559928)
7  3 and 6 (88)
8  limit 7 to "reviews (optimized)" (37)
9  randomized controlled trial.pt. (232368)
10  controlled clinical trial.pt. (74663)
11  randomized controlled trials.sh. (47576)
12  random allocation.sh. (58498)
13  double blind method.sh. (90309)
14  single blind method.sh. (10513)
15  or/9-14 (394278)
16  (animals not human).sh. (4070828)
17  15 not 16 (362564)
18  clinical trial.pt. (455477)
19  exp clinical trials/ (193249)
20  (clin$ adj25 trial$).ti,ab. (128418)
21  ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
22  placebo$.ti,ab. (100005)
23  random$.ti,ab. (365132)
24  placebos.sh. (25578)
25  research design.sh. (45680)
26  or/18-25 (844319)
27  26 not 16 (743540)
28  27 not 17 (394686)
29  comparative study.sh. (1339476)
30  exp evaluation studies/ (592681)
31  follow up studies.sh. (337060)
32  prospective studies.sh. (217352)
33  (control$ or prospectiv$ or volunteer$).ti,ab. (1741598)
34  or/29-33 (3449098)
35  34 not 16 (2428789)
36  34 not (17 or 28) (2925137)
37  17 or 28 or 36 (3682387)
38  7 and 37 (37)

Source – Ovid EMBASE 1980 to 2006 Week 32
Economic evaluations

(see also general economic evaluations below)

Source - Ovid MEDLINE(R) <1966 to August Week 2 2006>
Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library
Appendix 1.3   Breastfeeding

All studies (clinical effectiveness and economic evaluations)

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 breast next feeding
#6 breast next feed
#7 breast next fed
#8 breastfeed* or breastfed
#9 lactat*
#10 lactate or lactating or lactation or lactates
#11 MeSH descriptor Breast Feeding, this term only
#12 MeSH descriptor Lactation, this term only
#13 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 (#4 AND #13)

Source - Ovid MEDLINE(R) 1966 to September Week 1 2006

1     (nrt or nicotine replacement).mp. (1177)
2     (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1294)
3     or/1-2 (2200)
4     breast feeding.mp. (20357)
5     (breastfed or breast fed or breast feed$ or breastfeed$ or lactate or lactating or lactation or lactates).mp. (142736)
6     or/4-5 (142736)
7     3 and 6 (12)

Source – Ovid EMBASE 1980 to 2006 Week 33

1     (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$)).mp. (1296)
2     (nicotine gum or nicotine replacement therapy).sh. (1789)
3     (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalators or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2502)
4     or/1-3 (3086)
5     breast feeding.mp. (12895)
6     (breast fed or breastfed or breast feed$ or breastfeed$ or lactate or lactating or lactation or lactates).mp. (82009)
7     or/5-6 (82009)
8     4 and 7 (17)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library
Appendix 1.4  Cardiovascular disease

Clinical Effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge8 or transdermal*))
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Cardiovascular Diseases explode all trees
#6 cardiovascular next disease*
#7 coronary next heart next disease*
#8 fibrillation
#9 infarction
#10 ischaemia or ischemia or ischaemic or ischemic
#11 stroke*
#12 cardiac disease*
#13 coronary artery disease*
#14 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 (#4 AND #14)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3 or/1-2 (2186)
4 exp cardiovascular diseases/ (1296186)
5 cardiovascular disease$.mp. (73695)
6 coronary heart disease$.mp. (26580)
7 fibrillation.mp. (41432)
8 infarction.mp. (166067)
9 (ischaemia or ischemia or ischaemic or ischemic).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (199266)
10 stroke$.mp. (91189)
11 cardiac disease$.mp. (7897)
12 coronary artery disease$.mp. (36748)
13 or/4-12 (1372531)
14 3 and 13 (159)
15 limit 14 to "reviews (optimized)" (59)
16 from 15 keep 1-59 (59)
17 randomized controlled trial.pt. (232368)
18 controlled clinical trial.pt. (74663)
19 randomized controlled trials.sh. (47576)
20 random allocation.sh. (58498)
21 double blind method.sh. (90309)
22 single blind method.sh. (10513)
23 or/17-22 (394278)
24 (animals not human).sh. (4070828)
25 23 not 24 (362564)
26 clinical trial.pt. (455477)
27 exp clinical trials/ (193249)
28 (clin$ adj25 trial$).ti,ab. (128418)
29 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
30 placebo$.ti,ab. (100005)
31 random$.ti,ab. (365132)
32 placebos.sh. (25578)
33 research design.sh. (45680)

72
Ovid EMBASE 1980 to 2006 Week 33

1  (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1296)
2  (nicotine gum or nicotine replacement therapy).sh. (1789)
3  (nicotine adj1 (gum$ or inhaled or inhaler or inhalators or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2502)
4  or/1-3 (3086)
5  exp Cardiovascular Disease/ (1096297)
6  cardiovascular disease$.mp. (68317)
7  coronary heart disease$.mp. (22029)
8  fibrillation.mp. (35697)
9  infarction.mp. (136770)
10 (ischaemia or ischemia or ischemic or ischaemic).mp. (206990)
11 stroke$.mp. (85681)
12 cardiac disease$.mp. (6661)
13 coronary artery disease$.mp. (55877)
14 or/5-13 (1146907)
15 4 and 14 (497)
16 limit 15 to "reviews (1 term min difference)" (160)
17 randomized controlled trial/ (108481)
18 exp clinical trial/ (400143)
19 exp controlled study/ (2236619)
20 double blind procedure/ (60815)
21 randomization/ (19963)
22 placebo/ (89222)
23 single blind procedure/ (6038)
24 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (2277643)
25 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (102042)
26 (placebo$ or matched communities or matched schools or matched populations).mp. (136522)
27 (comparison group$ or control group$).mp. (137119)
28 (clinical trial$ or random$).mp. (641620)
29 (quasiexperimental or quasi experimental or pseudo experimental).mp. (1381)
30 matched pairs.mp. (1879)
31 or/17-30 (2671832)
32 15 and 31 (287)

Economic Evaluations

Ovid MEDLINE(R) 1966 to August Week 2 2006

1  (nrt or nicotine replacement).mp. (1167)
2  (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3  or/1-2 (2186)
4  exp cardiovascular diseases/ (1296186)
5  cardiovascular disease$.mp. (73695)
6  coronary heart disease$.mp. (26580)
7  fibrillation.mp. (41432)
8  infarction.mp. (166067)
9  (ischaemia or ischemia or ischemic or ischaemic).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (199266)
10 stroke$.mp. (91189)
Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library
Appendix 1.5  Combination Therapy NRT + NRT

Clinical effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 concurrently or concurrent or combined or combination:ti,ab
#6 MeSH descriptor Combined Modality Therapy, this term only
#7 (#5 OR #6)
#8 (#4 AND #7)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1     (nrt or nicotine replacement).mp. (1167)
2     (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3     or/1-2 (2186)
4     (combined or concurrent or concurrently or combination).mp. (819935)
5     combined modality therapy/ (117119)
6     or/4-5 (819935)
7     3 and 6 (346)
8     limit 7 to "reviews (optimized)" (112)
9     randomized controlled trial.pt. (232368)
10    controlled clinical trial.pt. (74663)
11    randomized controlled trials.sh. (47576)
12    random allocation.sh. (58498)
13    double blind method.sh. (90309)
14    single blind method.sh. (10513)
15    or/9-14 (394278)
16    (animals not human).sh. (4070828)
17    15 not 16 (362564)
18    clinical trial.pt. (455477)
19    exp clinical trials/ (193249)
20    (clini$ adj25 trial$).ti,ab. (128418)
21    ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
22    placebo$.ti,ab. (100005)
23    random$ti,ab. (365132)
24    placebos.sh. (25578)
25    research design.sh. (45680)
26    or/18-25 (844319)
27    26 not 16 (743540)
28    27 not 17 (394686)
29    17 or 28 (757250)
30    7 and 29 (208)

Source – Ovid EMBASE 1980 to 2006 Week 33

1     (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1296)
2     (nicotine gum or nicotine replacement therapy).sh. (1789)
3     (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2502)
4     or/1-3 (3086)
5     (combined or concurrent or concurrently or combination).mp. (523468)
6 4 and 5 (282)
7 limit 6 to "reviews (2 or more terms min difference)" (98)
8 from 7 keep 1-98 (98)
9 limit 6 to "treatment (1 term min difference)" (138)

Economic evaluations

(see also general economic evaluations below)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3 or/1-2 (2186)
4 (combined or concurrent or concurrently or combination).mp. (819935)
5 combined modality therapy/ (117119)
6 or/4-5 (819935)
7 3 and 6 (346)
8 economics/ (24393)
9 exp "costs and cost analysis"/ (126542)
10 cost of illness/ (8502)
11 exp health care costs/ (27327)
12 economic value of life/ (4800)
13 exp economics medical/ (10041)
14 exp economics hospital/ (14211)
15 economics pharmaceutical/ (1670)
16 exp "fees and charges"/ (22567)
17 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (234138)
18 (expenditure$ not energy).tw. (9949)
19 (value adj1 money).tw. (11)
20 budget$.tw. (10197)
21 or/8-20 (343820)
22 7 and 21 (23)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library
Appendix 1.6  Combination Therapy NRT + Bupropion

Clinical Effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers* or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Bupropion, this term only
#6 zyban or bupropion or buproprion or amfebutamone or wellbutrin
#7 (#5 OR #6)
#8 (#4 AND #7)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1  (nrt or nicotine replacement).mp. (1167)
2  (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3  or/1-2 (2186)
4  bupropion/ (1285)
5  (zyban or amfebutamone or bupropion or buproprion or wellbutrin).mp. (1760)
6  or/4-5 (1760)
7  3 and 6 (260)
8  limit 7 to "reviews (specificity)" (28)
9  from 8 keep 1-28 (28)
10 randomized controlled trial.pt. (232368)
11 controlled clinical trial.pt. (74663)
12 randomized controlled trials.sh. (47576)
13 random allocation.sh. (58498)
14 double blind method.sh. (90309)
15 single blind method.sh. (10513)
16 or/10-15 (394278)
17 (animals not human).sh. (4070828)
18 16 not 17 (362564)
19 clinical trial.pt. (455477)
20 exp clinical trials/ (193249)
21 (clim$ adj25 trial$).ti,ab. (128418)
22 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
23 placebo$.ti,ab. (100005)
24 random$.ti,ab. (365132)
25 placebos.sh. (22578)
26 research design.sh. (45680)
27 or/19-26 (844319)
28 27 not 17 (743540)
29 28 not 18 (394686)
30 18 or 29 (757250)
31 7 and 30 (109)

Source – Ovid EMBASE 1980 to 2006 Week 32

1  (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1294)
2  (nicotine gum or nicotine replacement therapy).sh. (1783)
3  (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2497)
4  or/1-3 (3078)
5  (zyban or amfebutamone or bupropion or buproprion or wellbutrin).mp. (5877)

77
6  4 and 5 (623)
7  limit 6 to "reviews (2 or more terms high specificity)" (21)
8  from 7 keep 1-21 (21)
9  randomized controlled trial/ (108287)
10  exp clinical trial/ (399236)
11  exp controlled study/ (2231444)
12  double blind procedure/ (60747)
13  randomization/ (19895)
14  placebo/ (89020)
15  single blind procedure/ (6029)
16  (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (2272396)
17  ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (101937)
18  (placebo$ or matched communities or matched schools or matched populations).mp. (136286)
19  (comparison group$ or control group$).mp. (136874)
20  (clinical trial$ or random$).mp. (640361)
21  (quasixperimental or quasi experimental or pseudo experimental).mp. (1380)
22  matched pairs.mp. (1877)
23  or/9-22 (2665878)
24  limit 6 to "treatment (2 or more terms min difference)" (180)

Economic evaluations

(see also general economic evaluations below)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1  (nrt or nicotine replacement).mp. (1167)
2  (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3  or/1-2 (2186)
4  bupropion/ (1285)
5  (zyban or amfetamone or bupropion or buproprion or wellbutrin).mp. (1760)
6  or/4-5 (1760)
7  3 and 6 (260)
8  economics/ (24393)
9  exp "costs and cost analysis"/ (126542)
10  cost of illness/ (8502)
11  exp health care costs/ (27327)
12  economic value of life/ (4800)
13  exp economics medical/ (10041)
14  exp economics hospital/ (14211)
15  economics pharmaceutical/ (1670)
16  exp "fees and charges"/ (22567)
17  (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (234138)
18  (expenditure$ not energy).tw. (9949)
19  (value adj1 money).tw. (11)
20  budget$.tw. (10197)
21  or/8-20 (343820)
22  7 and 21 (45)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library
Appendix 1.7 General Economic and Decision Analytic Model Searches

Source – HEED August 2006

A series of searches were done which incorporated the following terms: NRT OR nicotine replacement OR nicotine gum OR nicotine inhaler(s) OR inhaled nicotine OR nicotine inhalator(s) OR nicotine patch(es) OR nicotine spray(s) OR nicotine lozenge(s) OR nicotine tablet(s) OR transdermal nicotine

Source - Ovid MEDLINE(R) 1966 to September Week 1 2006

1  (nrt or nicotine replacement).mp. (1177)
2  (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1294)
3  or/1-2 (2200)
4  decision support techniques/ (5939)
5  markov.mp. (5169)
6  exp models economic/ (4939)
7  decision analysis.mp. (2268)
8  cost benefit analysis/ (39581)
9  economic model$.mp. (696)
10  monte carlo method$.mp. (9449)
11  monte carlo.mp. (11965)
12  exp decision theory/ (6453)
13  (decision$ adj2 (tree$ or analy$ or model$)).mp. (10756)
14  or/4-13 (70344)
15  economics/ (24405)
16  exp "costs and cost analysis"/ (127296)
17  cost of illness/ (8586)
18  exp health care costs/ (27572)
19  economic value of life/ (4903)
20  exp economics medical/ (10048)
21  exp economics hospital/ (14283)
22  economics pharmaceutical/ (1679)
23  exp "fees and charges"/ (22637)
24  (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (236102)
25  (expenditure$ not energy).tw. (10005)
26  (value adj1 money).tw. (11)
27  budget$.tw. (10257)
28  or/15-27 (346257)
29  14 or 28 (371750)
30  3 and 29 (163)