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Appendix 1
Smoking Cessation Guideline Update:
Technical report of evidence review and Summary of Findings

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Contents

Introduction

The Royal Australian College of General Practitioners produce clinical guidelines for GPs and other health professionals for a range of topics. In 2018, RACGP commissioned the Joanna Briggs Institute (JBI) and the JBI Adelaide GRADE Centre to assist with the update of the smoking cessation guideline. The RACGP requested this guideline be updated using GRADE methods. When using GRADE to develop guidelines, an evidence review is required where the end result is a GRADE Summary of Findings table, a summarised representation of the major synthesised findings along with a rating of the certainty in the synthesised evidence.

These Summary of Findings tables are then incorporated in Evidence to Decision Frameworks which the guideline panel work through to move from the evidence to making a recommendation, whilst ensuring that all the important aspects related to making structured recommendations are taken into account. This results in transparent recommendations that form the basis of any guideline.

This document provides the technical report of the evidence review and Summary of Findings table for the smoking cessation guideline update. It includes a description of the methods, a detailed assessment of the risk of bias of all included studies, an extraction of characteristics of each study, synthesised results per outcome and a summary of findings table per question including a rating of certainty in the evidence. This technical report addresses five clinical questions for the smoking cessation guideline update.

General Methods

Search strategy

PubMed was searched to locate relevant studies. Searches were conducted by the RACGP and the search details (terms and dates) are also provided for inclusion in this report. Authors of ongoing, relevant Cochrane review projects were also contacted to identify any relevant trials.

Search Terms

The following search strategies were used to locate studies for each question. All searches were filtered to 1 July 2014 onwards, and clinical trials / randomised controlled trials (RCTs) only.

Searches were conducted in February 2018.

PICO Question	Search Query
#1	("Tobacco Use Cessation Products"[Mesh] OR tobacco OR nicotine OR smoking OR "Smoking Cessation"[Mesh]) AND (gum OR patch* OR "Transdermal Patch"[Mesh] OR lozenge* OR "Nicotine Chewing Gum"[Mesh]) OR "nicotine replacement therapy" OR "nicotine replacement therapies" OR NRT
#2	("Tobacco Use Cessation Products"[Mesh] OR tobacco OR nicotine OR smoking OR "Smoking Cessation"[Mesh]) AND (gum OR patch* OR "Transdermal Patch"[Mesh] OR lozenge* OR "Nicotine Chewing Gum"[Mesh]) OR "nicotine replacement therapy" OR "nicotine replacement therapies" OR NRT) AND ("Varenicline"[Mesh] OR Varenicline)
#3	"Tobacco Use Cessation Products"[Mesh] OR tobacco OR nicotine OR smoking OR "Smoking Cessation"[Mesh]) AND (gum OR patch* OR "Transdermal Patch"[Mesh] OR lozenge* OR

	"Nicotine Chewing Gum"[Mesh]) OR "nicotine replacement therapy" OR "nicotine replacement therapies" OR NRT
#4	"Tobacco Use Cessation Products"[Mesh] OR tobacco OR nicotine OR smoking OR "Smoking Cessation"[Mesh]) AND (gum OR patch* OR "Transdermal Patch"[Mesh] OR lozenge* OR "Nicotine Chewing Gum"[Mesh]) OR "nicotine replacement therapy" OR "nicotine replacement therapies" OR NRT
#5	"Varenicline"[Mesh] OR Varenicline
#6	("Tobacco Use Cessation Products"[Mesh] OR tobacco OR nicotine OR smoking OR "Smoking Cessation"[Mesh]) AND (gum OR patch* OR "Transdermal Patch"[Mesh] OR lozenge* OR "Nicotine Chewing Gum"[Mesh]) OR "nicotine replacement therapy" OR "nicotine replacement therapies" OR NRT) AND ("Varenicline"[Mesh] OR Varenicline)
#7, #8, #9	("Tobacco Use Cessation Products"[Mesh] OR tobacco OR nicotine OR smoking OR "Smoking Cessation"[Mesh]) AND (gum OR patch* OR "Transdermal Patch"[Mesh] OR lozenge* OR "Nicotine Chewing Gum"[Mesh]) OR "nicotine replacement therapy" OR "nicotine replacement therapies" OR NRT) AND ("Pregnancy"[Mesh] OR pregnan*)

Study selection

Study selection was performed in 2 Phases. Phase 1 was completed by the RACGP. During Phase 1, titles, and where necessary, abstracts of all citations returned from database searching were screened to determine if they met the inclusion criteria for any question. Inclusion was limited to Systematic reviews and RCTs. Potentially relevant studies were retrieved and the citation details of the majority of identified studies aligned to the nine PICO questions presented in this report.

Phase 2 was performed by the authors of this report. Full text of the citations identified in Phase 1 were reviewed independently by two members of the review team to determine eligibility for each of the nine PICO questions. Where necessary, inclusion was determined by discussion between reviewers. Reasons for exclusion of any studies retrieved in full text were recorded by reviewers (see Appendix 1).

Risk of Bias assessment

Where evidence/studies from eligible Cochrane reviews was included, existing risk of bias assessments of relevant studies were extracted and presented in this report to allow for ready completion of GRADE processes. Where results of other systematic reviews (non-Cochrane) were included, risk of bias assessments using the Cochrane risk of bias tool were performed by the review team.

Reviewers independently assessed the risk of bias of included RCTs (n = 5) using the Cochrane Collaboration's tool (see Appendix 2). Assessment was based on method of randomisation, concealment of allocation, reasons for participant losses to follow-up, blinding, and selective outcome reporting.

Any disagreement between reviewers regarding assessment of risk of bias was resolved by discussion and achieving consensus between the reviewers.

Data extraction

Descriptive details and predetermined outcome data were extracted from each included RCT into individual tables of study characteristics for each question. Where possible, completed meta-analyses and syntheses were also extracted from systematic reviews (see Synthesis and meta-analysis below).

Synthesis and meta-analysis

Where meta-analyses from eligible Cochrane reviews and other systematic reviews were available, these were extracted and presented in this report to allow for ready completion of GRADE processes. Where additional meta-analyses are included, relevant data was extracted from available systematic reviews or included RCTs and the statistical analysis completed in JBI SUMARI systematic review software by the review team (Joanna Briggs Institute, The University of Adelaide; 2017. Available from https://www.jbisumari.org/) or Review Manager (RevMan V5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014).

Establishing Certainty of the Evidence

Summary of findings tables were developed using processes established by the GRADE working group and within the GRADEpro Guideline Development Tool software (GRADEpro GDT; McMaster University, 2015 (developed by Evidence Prime, Inc.), available from gradepro.org. The members of the review team discussed and reached consensus regarding each criterion for each outcome and comparison. Considerations for 'imprecision' were assessed from a non-contextualised point of view. The judgements relating to the GRADE criteria are therefore not final and the feedback of the guideline group on the judgements, particularly indirectness and imprecision, was requested; Summary of findings tables have been updated accordingly, based on the feedback received.

Results

Nine clinical questions and potentially relevant citations and studies located by the search were provided by the RACGP. Review of full text of all identified studies/publications during 'Study Selection, Phase 2', established that the identified evidence responded to four (4) of the questions originally posed, Questions 1, 2, 4 and 7. Question 5 was also addressed following minor modification to the use of Varenicline for relapse prevention rather than duration of Varenicline treatment (see Appendix 3). The remaining questions, 3, 5 (original), 6, 8 and 9 (see Appendix 3) are not addressed in this technical report.

Clinical question 1

Is combination NRT (patch and oral form) more effective than patch alone and if so is this effect for all smokers or only for more dependent smokers?

Criteria for inclusion and exclusion of studies

1. **Population**:
    - Smokers (all)
    - More dependent smokers
2. **Intervention**: Combination NRT (any form).
3. **Comparison**: Monotherapy NRT (any)
4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.
5. **Study designs:** Randomised controlled trials, systematic reviews of RCTs.
6. **Other criteria:** 6 months follow up or longer

Summary of Findings

Question: Is combination NRT (any form) more effective than patch alone?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination NRT**	**Single NRT**	**Relative** (95% CI)	**Absolute** (95% CI)	
Smoking Cessation (Overall) (assessed with: CO expiration)											
12	randomised trials	serious [a]	serious [b,c]	not serious	not serious [d]	none	554/2697 (20.5%)	578/3621 (16.0%)	**RR 1.28** (1.15 to 1.42)	**45 more per 1,000** (from 24 more to 67 more)	⨁⨁◯◯ LOW
50% CPD reduction											
0									not estimable		-

CI: Confidence interval**; RR:** Risk ratio

Explanations

a. Concerns over performance bias

b. High statistical heterogeneity. Widely differing estimates of treatment effect

c. Guideline panel might want to consider forms of NRT used and placebo comparator

d. Confidence intervals are relatively narrow and range from negligible (1.15) to a potentially small beneficial effect (1.42). High number of events, 1132 events meets the Optimal Information Size threshold of 1116.

Study selection

The search of PubMed for question 1 returned 201 records. Based on citation details, one umbrella review (overview), three systematic reviews and three RCTs were identified as being potentially relevant (see General Methods: Study Selection, Phase 1).

Review of full text during Phase 2 of Study Selection resulted in the exclusion of two of the identified systematic reviews (see Appendix 1) and one RCT; full review of all studies for the project identified an added RCT as being relevant to Q1 (Caldwell et al. 2016). Overall, papers for question 1 included one umbrella review with network meta-analysis (Cahill et al. 2013), one systematic review (Stead et al. 2012) and three RCTs (Baker et al. 2016; Caldwell et al. 2016; and Tulloch et al. 2016).

Nine trials included in the Cochrane systematic review by Stead et al. 2012 compared combinations of two forms of nicotine therapy with only one form: patch with gum to patch alone (Cooney et al. 2009; Kornitzer et al. 1995); patch with gum to gum alone (Puska et al. 1995); patch with nasal spray to patch alone (Blondal 1999); patch with inhaler to inhaler alone (Bohadana 2000); patch with lozenge to either one alone (Piper et al. 2009; Smith et al. 2009); patch with inhaler to either one alone (Tonnesen et al. 2000); and patch with nasal spray to either one alone (Croghan et al. 2003). Comparisons investigated by the three added RCTs identified for this project included: patch with inhaler to patch with placebo inhaler (Caldwell et al. 2016), patch with lozenge to patch alone (Baker et al. 2016) and patch with gum or inhaler to patch alone (Tulloch et al. 2016). Cahill et al. 2013 performed a network meta-analyses for combination NRT (any) compared to patch, gum and other forms of NRT.

Methodological quality

Overall the risk of bias of included studies, both from Stead et al. 2012 and the new RCTs was low, with the majority of the potential for bias coming from unclear reporting of domains. An exception to this was the risk of performance and detection bias resulting from a lack of blinding, which was the only domain where any studies were classed as being at a high risk of bias (Table 1.1).

Allocation

Random assignment was generally well carried out and reported with two thirds of studies included in Stead et al. 2012 and all of the new RCTs being assessed as low risk of bias. Of the three trials from the systematic review which were not at low risk of bias – Puska et al. 1995, Piper et al. 2009 and Smith et al. 2009 – all were reported as being at Unclear risk of bias as randomisation was claimed but not sufficiently described.

Blinding

Blind assignment was generally well performed and reported, with only three trials from Stead et al. 2012 being of Unclear risk of bias (two of which, Puska et al. 1995 and Smith et al. 2009 - the same studies that had Unclear risk of allocation bias) as well as a fourth RCT, Baker et al. 2016, from the new trials. However, lack of blinding of researchers and participants created a major risk of bias with the majority of trials (five) included in Stead et al. 2012 assessed as being Unclear, and two, Smith et al. 2009 and Croghan et al. 2003 being at high risk of bias, with only two Kornitzer et al. 1995 and Blondal et al. 1999, assessed as low risk. Amongst the new RCTs two, Baker et al 2016 and Tulloch et al. 2016, were at high risk of bias.

Detection bias (biochemical validation of smoking outcomes)

Biochemical validation of smoking cessation is important due to negative views of smoking and 'failure' to successfully quit. Stead et al. 2012 reported that biochemical validation was carried out in

all relevant studies (although it was not an item in their risk of bias summary). Biochemical validation was also carried out in all new RCTs identified in this review.

Incomplete outcome data

Overall, the trials included in Stead et al. 2012 were at low risk of attrition bias resulting from incomplete outcome reporting, with just three, Kornitzer et al 2015, Bohadana et al. 1999 and Tonnesen et al. 2000 assessed as Unclear. All of the new RCTs were at low risk of attrition bias.

Selective reporting

Although Stead et al. 2012 did not investigate selective reporting, the large amount of time that has passed since the majority of these studies were conducted, and the relatively recent requirements for trial registration, makes it unlikely that the included studies would have contained the necessary details for an assessment other than 'Unclear'. All of the new RCTs, however, followed pre-registered protocols.

Other potential sources of bias

No other risks of bias were identified that required consideration and assessment by Stead et al. 2012 or the additional included studies. Therefore, all studies have been assigned a low risk of 'other' bias (Table 1.1).

Table 1.1: Methodological quality summary: judgements extracted from Cochrane review (Stead et al. 2012) and those of individual RCTs assessed for this report.

	Random sequence generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Detection bias (biochemical validation of smoking outcomes)	Other bias
Cooney 2009*	+	+	?	+		+	+
Kornitzer 1995*	+	+	+	?		+	+
Puska 1995*	?	?	?	+		+	+
Blondal 1999*	+	+	+	+		+	+
Bohadana 2000*	+	+	?	?		+	+
Piper 2009*	?	+	?	+		+	+
Smith 2009*	?	?	-	+		+	+
Tonnesen 2000*	+	?	?	?		+	+
Croghan 2003*	+	+	-	+		+	+
Baker 2016**	+	?	-	+	+	+	+
Caldwell 2016**	+	+	+	+	+	+	+
Tulloch 2016**	+	+	-	+	+	+	+

* Denotes study assessment extracted directly from Cochrane review Stead et al. 2012.

**Denotes study assessment performed by review team. Corresponding details can be referred to in Table 1.2 below. + denotes low risk of bias, ? unclear risk of bias and – denotes high risk of bias. Where no indication is made (blank) data was not available (earlier version of Cochrane tool).

Table 1.2: Critical appraisal results of included RCTs assessed using the Cochrane Risk of Bias tool (see Appendix 3).

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Baker 2016	Computer-based randomisation used, stratified by site, gender and race. L	Method of concealment is not described in sufficient detail to allow a definite judgment. U	Participants and study personnel were unblinded to the treatment assignment. H	Primary outcome was in the form of a self-report questionnaire and biochemical confirmation of exhaled carbon monoxide to indicate abstinence. No detail was provided regarding blinding of outcome assessors, but the outcome is not likely to be influenced by the lack of blinding. L	Withdrawal rates varied by treatment, but missing outcome data was imputed as 'Smoking' with sensitivity analyses supporting this assumption. L	Trial was registered as NCT01553084; variation in a primary outcome was justified as being due to emergent evidence on appropriate cut-off. L	This study appears free from other sources of bias. L
Caldwell 2016	Sequential randomisation list used, in a 1:1 ratio of active:placebo inhalers. L	Allocation was concealed using the trial database. Database provided staff with product code, which identified which inhaler to give each subject. Inhalers were identical in appearance and flavouring. L	Subjects and staff were masked to treatment assignment and the interventions were not distinguishable. L	Staff and participants were blind and there was biochemical validation. L	Withdrawals were relatively balanced and imputation (missing data assumed to be Smoking). Per protocol analysis of absence had similar results. L	Trial was registered as ACTRN12609000481279. Primary outcome was reported as specified. L	This study appears free from other sources of bias. L

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Tulloch 2016	Computer-generated block randomisation schedule by a statistical consultant not involved in the trial. Stratified by psychiatric status. L	No direct reference in the text regarding measures taken to ensure allocation concealment. However, a citation was provided detailing the methods that were followed. Investigation of the citation shows that randomisation numbers were placed in opaque, sealed and consecutively numbered envelopes and opened following completion of the baseline data. L	Participants and study personnel were unblinded to the treatment assignment. H	The primary outcome, abstinence at 6 months, was assessed through biochemical validation by a blind research co-ordinator, although all other staff and participants were not blind. L	There was some difference in withdrawals by treatment. Missing data was imputed as smoking, with sensitivity analyses supporting the validity of this assumption. L	Trial was registered as NCT01623505. Primary endpoint was reported as specified. L	This study appears free from other sources of bias. L

Included study characteristics

ID	Cooney 2009
Bibliographic reference	Cooney NL, Cooney JL, Perry BL, Carbone M, Cohen EH, Steinberg H, et al. Smoking cessation during alcohol treatment: a randomized trial of combination nicotine patch plus nicotine gum. *Addiction* 2009;104(9):1588-96.
Study type	RCT
Country	USA
Study Setting	Community volunteers and referrals from substance abuse clinic
Number of participants	45 assigned to intervention, 51 assigned to control
Number of withdrawals	Withdrawals at 12 months; 8 from intervention, 19 from placebo
Patient characteristics	Alcohol-dependent tobacco smokers **(≥15 cpd**) 25% F, av.age 45, **av.cpd 25**, motivated to quit, av.FTND 6, 31% veterans
Intervention	Nicotine patch (titrated, 21 mg/d for 8 wks, 14 mg/d for 2 wks, 7mg/d for 2 wks) + nicotine gum (2 mg for 24 wks, ad lib but advised 6-20/day) Level of support: high. 16 individual 1hr weekly outpatient sessions of behavioural alcohol and smoking treatment over 6m.
Comparison	Nicotine patch + placebo gum (doses as above)
Length of follow-up	12 months
Outcome measures/Results	Continuous abstinence at 12m (with 30d grace period immediately following quit date) Validation: CO<10ppm
Source of funding	Funding from National Institute on Alcohol Abuse and Alcoholism and Department of Veterans Affairs.
Additional comments	None

ID	Kornitzer 1995
Bibliographic reference	Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Preventive Medicine* 1995;24:41-7.

Study type	RCT
Country	Belgium
Study Setting	Worksite volunteers
Number of participants	374 (149 received intervention, 150 received control 1, 75 received control 2)
Number of withdrawals	1 person withdrawn from intervention due to adverse events, 2 from control 1. After 12 weeks an average of 52% had full treatment compliance, after 24 weeks this was 41%
Patient characteristics	Healthy smokers (**>10 cpd** for >3yrs), motivated to quit. 61% M, av. age 40, **av.cpd 25**
Intervention	Nicotine patch (12 wks 15 mg/16hr, 6 wks 10mg, 6 wks 5 mg) and nicotine gum (2 mg, as required) Level of support: high (nurse counselling)
Comparison	Nicotine patch and placebo gum As well as Placebo patch and placebo gum.
Length of follow-up	12 months
Outcome measures/Results	Sustained abstinence at 12 months Validation: CO<10 ppm
Source of funding	Study was supported by Pharmacia Consumer Pharma.
Additional comments	None

ID	**Puska 1995**
Bibliographic reference	Puska P, Korhonen HJ, Vartiainen E, Urjanheimo EL, Gustavsson G, Westin A. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. *Tobacco Control* 1995;4:231-5.
Study type	RCT
Country	Finland

Study Setting	Community volunteers (health care centres)
Number of participants	300 (150 assigned to intervention, 150 assigned to control
Number of withdrawals	At 52 weeks 105 retained in intervention, 92 in control
Patient characteristics	Aged 20-65, smoking **>10 cpd** for >3 yrs, no serious illness
Intervention	Nicotine patch (15 mg/16hrs, 12 wks+ 6 wks taper) plus nicotine gum (2 mg at least 4 daily) Level of support: low (advice from study nurses)
Comparison	Placebo patch plus nicotine gum (same regimen)
Length of follow-up	12 months
Outcome measures/Results	Sustained abstinence at 12m Validation: expired CO<10ppm
Source of funding	Sources of support not stated.
Additional comments	None

ID	**Blondal 1999**
Bibliographic reference	Blondal T, Gudmundsson LJ, Olafsdottir I, Gustavsson G, Westin A. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ* 1999;318:285-9.
Study type	RCT
Country	Iceland
Study Setting	Community volunteers (health centre)
Number of participants	237
Number of withdrawals	For intervention 117 completed, for control 118 completed
Patient characteristics	smokers **(≥10 cpd**) 67% F, av.age 41-43, av. **tobacco use 25g/day**

Intervention	Nicotine nasal spray (NNS) (0.5 mg/dose) + 15 mg nicotine patches for 3m, weaning over further 2m. NNS could be continued for 1 yr Level of support: high (4 supportive group meetings)
Comparison	Placebo nasal spray + 15 mg nicotine patches on same schedule
Length of follow-up	12 months
Outcome measures/Results	Sustained abstinence at 12m (6 yr data also reported) Validation: CO<10ppm
Source of funding	Study supported by Pharmacia & Upjohn.
Additional comments	6yr abstinence 19/118 vs 10/119, OR 2.1

ID	**Bohadana 2000**
Bibliographic reference	Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation - A randomized, double-blind, placebo-controlled trial. *Archives of Internal Medicine* 2000;160:3128-34.
Study type	RCT
Country	France
Study Setting	Community volunteers (hospital)
Number of participants	400 (200 assigned to intervention, 200 assigned to control)
Number of withdrawals	52 retained in intervention at 12 months, 45 retained in control at 12 months
Patient characteristics	Smokers, 18-70 yrs, **>10 cpd**, >1 previous quit attempt, motivated. 51% F**, Av cpd: Group 1: 26.1, Group 2: 23.5**; FTND>6 Participants required to be motivated to quit.
Intervention	Nicotine inhaler, 26 wks, combined with nicotine patch (15 mg/16hr) for first 6 wks, placebo patch for next 6 wks Level of support: high. All received brief counselling and support from investigator at each visit
Comparison	Nicotine inhaler, 26 wks, placebo patch for first 12 wks
Length of follow-up	12 months

Outcome measures/Results	Sustained abstinence at 12 months (prolonged from wk 2, no slips allowed) Validation: CO<10ppm at each visit (2 wks, 6 wks, 6m, 12m)
Source of funding	Study funded by Pharmacia & Upjohn.
Additional comments	None

ID	**Piper 2009**
Bibliographic reference	Piper ME, Smith SS, Schlam TR, Fiore MC, Jorenby DE, Fraser D, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Archives of General Psychiatry* 2009;66(11):1253-62.
Study type	RCT
Country	USA
Study Setting	Community volunteers (two urban research sites)
Number of participants	1504 (267 in relevant intervention and 41 in relevant placebo)
Number of withdrawals	Intervention had 6 withdrawals during treatment, 3 during follow up.
Patient characteristics	Smokers motivated to quit. 58% F, av.age 45, **av.cpd 21.4.**
Intervention	Nicotine lozenge 2 or 4 mg for 12 wks (based on dose-for-dependence level as per instructions) with nicotine patch (24hr, 21, 14, and 7mg titrated down over 8 wk period post-quit) Level of support: high. All participants received 7 one-to-one 10-20min counselling sessions
Comparison	Placebo patch and lozenge
Length of follow-up	6 months
Outcome measures/Results	7d point prevalence (PP) abstinence at 6 months; initial cessation. Validation: CO<10ppm
Source of funding	Majority of funding from National Institute on Drug Abuse and National Center for Research Resources. Medication provided to participants at no extra cost by GlaxoSmithKline.

Additional comments	Placebo outcomes not reported by subgroup; outcomes generated by applying overall percentage of events in placebo group to individual subgroups.

ID	**Smith 2009**
Bibliographic reference	Smith SS, McCarthy DE, Japuntich SJ, Christiansen B, Piper ME, Jorenby DE, et al. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. *Archives of Internal Medicine* 2009;169(22):2148-55.
Study type	RCT
Country	USA
Study Setting	Primary care (12 clinics)
Number of participants	Intervention= 279, Control 1= 263, Control 2 282
Number of withdrawals	Intervention had 16 withdrawals and 1 death, control 1 had 27 withdrawals and 1 death, control 2 had 28 withdrawals and 4 deaths (deaths not related to study medication)
Patient characteristics	Smokers of **>10 cpd** for past 6 months. 56% F, av.age 44, **av.cpd 20.3**, motivated to quit.
Intervention	Patch and lozenge (dosage as below)
Comparison	Nicotine lozenge only (4 mg lozenge if first cig of day smoked >30 min after waking, 2 mg otherwise. 1 lozenge every 1-2hrs post-quit wk 1-6; 1 lozenge every 2-4hrs wk 7-9; 1 lozenge every 4-8hrs wk 10-12) And also Nicotine patch only (21 mg post-quit wk 1-4; 14 mg wk 5-6; 7mg wk 7-8)
Length of follow-up	6 months
Outcome measures/Results	7d PP at 6 months and number of days to relapse. No validation
Source of funding	Majority of funding from National Institutes of Health, National Institute on Drug Abuse, and National Cancer Institute. Medication provided to participants at no cost by GlaxoSmithKline.
Additional comments	Analyses completed on ITT basis.

ID	**Tonnesen 2000**
Bibliographic reference	Tonnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. *European Respiratory Journal* 2000;16:717-22.
Study type	RCT
Country	Denmark
Study Setting	Referrals to lung clinic
Number of participants	446 (115 in intervention, 109 in control 1, 104 in control 2)
Number of withdrawals	11% follow up at 1 year
Patient characteristics	smokers **≥10 cpd** 52% F, av.age 49, **av.cpd 18**
Intervention	Combination, 15 mg patch and inhaler Level of support: High (Physician advice at baseline, brief (15min) nurse counselling at 2, 6 wks, 3, 6, 9, 12m)
Comparison	5 mg nicotine patch (placebo) As well as 15 mg (16hr) nicotine patch for 12 wks (up to 9m on request)
Length of follow-up	12months
Outcome measures/Results	Sustained abstinence at 12m, (from wk 2, paper also reports PP and with slips rates) Validation: CO<10ppm at all visits
Source of funding	Study funding and support not reported.
Additional comments	None

ID	**Croghan 2003**
Bibliographic reference	Croghan GA, Sloan JA, Croghan IT, Novotny P, Hurt RD, DeKrey WL, et al. Comparison of nicotine patch alone versus nicotine nasal sparay alone versus a combination for treating smokers: A minimal intervention, randomized multicenter trial in a nonspecialized setting. *Nicotine & Tobacco Research* 2003;5(2):181-7.

Study type	RCT
Country	USA
Study Setting	Multi-centre community volunteers (15 regional cancer control oncology centres)
Number of participants	1384
Number of withdrawals	30% completed through to 6 month evaluation
Patient characteristics	Smokers (**≥15cpd**) 58% F, av.age 42, **av.cpd 26**
Intervention	15 mg/16hr nicotine patch plus 0.5 mg/dose nasal spray, max 5/hr, 40/day, for 6 wks Level of support: low (advice at each visit, 30-45 mins total)
Comparison	Nicotine nasal spray only As well as Nicotine patch only
Length of follow-up	6 months
Outcome measures/Results	PP abstinence at 6 months Validation: CO
Source of funding	Study was funded by the National Cancer Institute; Medication provided by McNeil Consumer Products.
Additional comments	None

ID	**Baker 2016**
Bibliographic reference	Baker TB, Piper ME, Stein JH, Smith SS1, Bolt DM, Fraser DL, Fiore MC. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. *JAMA.* 2016 Jan 26;315(4):371-9. doi: 10.1001/jama.2015.19284.
Study type	RCT
Country	USA
Study Setting	Community volunteers and existing longitudinal study participants

Number of participants	Intervention 421, Control 241.
Number of withdrawals	Intervention had 13 withdrawals, control had 15 withdrawals
Patient characteristics	Smoking **≥ 5 cpd,** > 17 years old, motivated to quit. **Mean cpd 17.0**, mean years of smoking 28.6, mean age 48.1, F 52.1%
Intervention	Lozenges with patch: 2 mg or 4 mg nicotine lozenges, 5 times per day, based on morning smoking latency for 12 weeks with patch (as below) 20 minutes counselling per contact in visits 1-3, and 10 minutes per contact for phone calls and visits 4 and 5.
Comparison	Patch: 8 weeks of 21 mg, then 2 weeks of 14 mg, and then 2 weeks of 7 mg patches (those smoking 5–10 cigs/day prequit received 10 weeks of 14 mg patches and then 2 weeks of 7 mg patches).
Length of follow-up	12 months
Outcome measures/Results	7 day pp at 26 weeks with exhaled CO ≤5 (primary) confirmation at 12 months
Source of funding	Supported by the National Heart, Lung and Blood Institute.
Additional comments	None

ID	**Caldwell 2016**
Bibliographic reference	Caldwell BO, Crane J. Combination Nicotine Metered Dose Inhaler and Nicotine Patch for Smoking Cessation: A Randomized Controlled Trial. *Nicotine Tob Res*. 2016 Oct;18(10):1944-1951.
Study type	RCT
Country	New Zealand
Study Setting	Community volunteers (University)
Number of participants	246 randomised to intervention, 256 randomised to control
Number of withdrawals	158 from intervention assessed at 6 months, 154 from control assessed at 6 months.
Patient characteristics	Smokers of **≥9 cpd** with FTND ≥3 motivated to quit, aged 18-70 years.

	Mean age 45 years, mean **19 cpd**, started smoking at mean age 16 years.
Intervention	Pressurized nicotine inhaler at 200µg per puff, with patch as below
Comparison	Patch with placebo inhaler: active nicotine patch for 5 months (21mg/day for 18 weeks, 14mg/day for 2 weeks, 7mg/day for 2 weeks).
Length of follow-up	6 months
Outcome measures/Results	6 month abstinence self-report 7day pp with biochemical confirmation (CO <10 parts per million)
Source of funding	The Health Research Council of New Zealand
Additional comments	12 month follow up was planned but cancelled due to budgetary constraints. Prospectively registered protocol does not mention 12 months. No smoking at all between 1 and 6 months was not significant, but between 3 and 6 months was (in both groups majority of relapse was early).

ID	**Tulloch 2016**
Bibliographic reference	Tulloch HE, Pipe AL, Els C, Clyde MJ, Reid RD. Flexible, dual-form nicotine replacement therapy or Varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. *BMC Med.* 2016 Jun 7;14:80.
Study type	RCT
Country	Canada
Study Setting	Community volunteers
Number of participants	Intervention 245, Control 245
Number of withdrawals	Intervention completion 70.0%, control 62.0%
Patient characteristics	Smokers **≥ 10 cpd**, motivated to quit. Mean age 48.6 years, **23.2 cpd,** 6.1 FTND
Intervention	Patches (35 mg daily maximum) and gum or inhaler for up to 22 weeks Six standardised 15-minute smoking cessation counselling sessions by experienced nurses.
Comparison	Patches (21 mg daily maximum) for 10 weeks

Length of follow-up	52 weeks
Outcome measures/Results	CO (≤9) confirmed continuous abstinence during weeks 5-52, as well as 7 day pp at 52 weeks
Source of funding	Heart and Stroke Foundation of Ontario
Additional comments	None

Synthesis and meta-analysis

Smoking cessation

Nine trials located and analysed by Stead et al. 2012 compared the use of combinations of different types of NRT with the use of a single type only; when pooled overall with the newly identified trials, the analysis suggests a statistically significant benefit (RR 1.28, 95% CI 1.15 to 1.42, Figure 1.1), with moderate statistical heterogeneity (I^2=56%). Three trials, one comparing nasal spray and patch with patch alone (Blondal et al. 1999), one comparing patch plus lozenge versus either one alone (Smith et al. 2009) and one comparing patch with inhaler to patch with placebo inhaler (Caldwell et al. 2016) showed a significantly higher rate of sustained abstinence at 6 months (Caldwell et al. 2016) to one year with the combined therapy (Blondal et al. 1999, Smith et al. 2009).

Overall, the included trials were heterogeneous in their combinations and comparison therapies used. These included patch with gum to patch alone (Cooney et al. 2009; Kornitzer et al. 1995); patch with gum to gum alone (Puska et al. 1995); patch with nasal spray to patch alone (Blondal et al. 1999); patch with inhaler to inhaler alone (Bohadana et al. 2000); patch with lozenge to either one alone (Piper et al. 2009; Smith et al. 2009); patch with inhaler to either one alone (Tonnesen et al. 2000); and patch with nasal spray to either one alone (Croghan et al. 2003). Considering the newly identified trials, Caldwell et al. 2016 compared patch with inhaler to patch with placebo inhaler and found a significant improvement in 6 month 7 day point prevalence (pp) abstinence (31.71% (78/246) compared to 17.97% (46/256); OR 2.12, 95%CI 1.40 to 3.23). However, Tulloch et al. 2016 found no difference in abstinence (from 5 to 52 weeks) for patch with inhaler compared to patch alone (12.4% compared to 10.0%; aOR= 1.28, 95%CI 0.67 to 2.70). No difference was found for 7 day pp at 52 weeks either (aOR= 1.31, 95%CI 0.79 to 2.70). In Figure 1.1, Analysis 10 below, two studies, Piper et al. 2009 and Smith et al. 2009 were combined and showed a significant effect for patch with lozenge compared to either patch or lozenge alone. Baker et al. 2016 compared patch plus lozenge to patch alone but did not find any difference in abstinence (20.2% (85/421) compared to 22.8% (55/241)).

Cahill et al. 2013 conducted an umbrella systematic review (a systematic review of systematic reviews) and applied network meta-analysis (treatments are compared through both direct comparisons and indirect comparisons across trials based on common comparators) to further investigate the effectiveness of combination therapies. They estimated significant improvements for combination NRT compared to patch alone (OR 1.43, CredI 1.08 to 1.91), combination NRT compared to gum alone (OR 1.63, CredI 1.21 to 2.2) and combination NRT compared to other forms of NRT (OR 1.34, CredI 1 to 1.8).

50% reduction in cigarettes per day

No included study reported the outcome of cigarettes smoked/day.

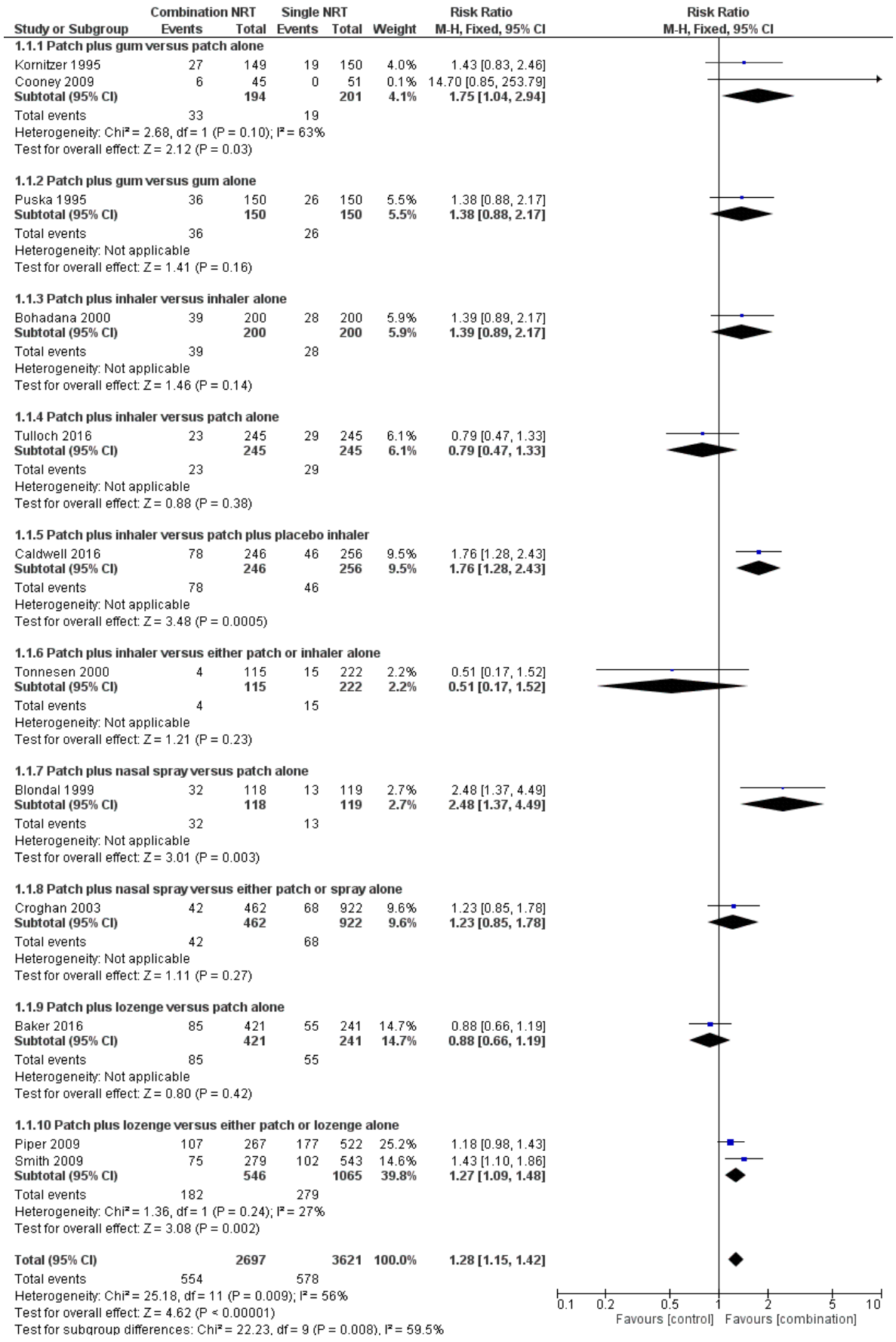


Figure 1.1 Long term smoking cessation (reproduced from Stead et al. 2012 with additional trials included Analyses 4, 5 and 9)

Adverse events

Stead et al. 2012 reported that variation in reporting of the nature, timing and duration of symptoms was too extensive for the quantitative synthesis of incidence of adverse effects. Major side effects of nicotine gum were hiccups, gastrointestinal disturbances, jaw pain and orodental problems. Patches could cause (usually mild) skin sensitivity and irritation, and nicotine inhalers (as well as nasal and oral sprays) could cause local irritation at the site of administration. The effect of combination NRT on adverse events was not considered.

Baker et al. 2016 reported an increased risk of indigestion, mouth problems and hiccups in patients treated with patch and lozenge compared to patch alone. Caldwell et al. 2016 reported slightly higher levels of adverse effects overall for participants receiving the inhaler with patch (99.6%) compared to participants receiving placebo inhaler with patch (96.5%) although the actual difference was small. However, the difference in adverse effects relating to inhaler use was greater (97% compared to 74%). Adverse events relating to patch use (active in both groups) was similar (87% compared to 90%). In Tulloch et al. 2016 the frequency of serious adverse effects did not differ between groups (2.4% in the patch with gum or inhaler compared to 3.7% in patch alone). Overall, the use of combination therapy does not appear to increase the risk of adverse events substantially from that of monotherapy beyond the potential for irritating the two routes of administration.

Conclusion

Overall, the use of combination NRT appears to be marginally more effective than single source NRT. Trials were heterogeneous and no form of combination NRT can be recommended as superior to any other, although direct positive findings were made for lozenge with patch (Smith et al. 2009, Figure 1.1, Analysis 10) nasal spray with patch (Blondal et al. 1999, Figure 1.1, Analysis 7) and inhaler with patch (Caldwell et al. 2016, Figure 1.1, Analysis 5). The available evidence does not allow for assessment of combination NRT for heavy versus light smokers.

Clinical question 2

Is combination of Varenicline and NRT more effective than Varenicline alone and if so is this effect for all smokers or only for more dependent smokers?

Criteria for inclusion and exclusion of studies

1. **Population**:
    - Smokers (all)
    - More dependent smokers
2. **Intervention**: Varenicline and NRT (any NRT monotherapy).
3. **Comparison**: Varenicline
4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.
5. **Study designs:** Randomised controlled trials (RCTs), systematic reviews of RCTs.
6. **Other criteria:** 6 months follow up or longer

Summary of Findings

Question: Is combination Varenicline and NRT more effective than Varenicline alone on smoking cessation/abstinence.? If so, is this effects for all smokers or only for more dependent smokers?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varenicline and NRT**	**Varenicline alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Continuous abstinence 24 weeks post-TQD (assessed with: Exhaled CO concentrations (<10ppm))											
2	randomised trials	not serious	not serious	not serious	serious [a]	none	127/392 (32.4%)	90/395 (22.8%)	**OR 1.62** (1.18 to 2.23)	**96 more per 1,000** (from 30 more to 169 more)	⨁⨁⨁◯ MODERATE
50% CPD reduction											
0									not estimable		-

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Confidence intervals are wide and range from negligible (1.18) to potentially beneficial (2.23). Low number of events, 217 events does not meet the Optimal Information Size threshold of 340. In addition, as slight concerns regarding inconsistency, we have decided this is serious.

After voting by the panel, no consensus was reached. Further discussion required.

Study selection

The search of PubMed for question 2 returned 30 records. Based on citation details, two systematic reviews and three RCTs were identified as being potentially relevant (see General Methods: Study Selection, Phase 1).

Review of full text during Phase 2 of Study Selection led to the exclusion of all of the identified citations. Among the full suite of retrieved studies a further systematic review (Chang et al. 2015; Hajek et al. 2013; Koegelenberg et al. 2014; Ramon et al. 2014) and three RCTs were identified as being relevant. During the process of data extraction (see below) one RCT was excluded as only short term 9-14 weeks follow up was reported (Hajek et al 2015; see Appendix 1).

Methodological quality

Chang et al. (2015) concluded that the overall quality of the included studies was high, using the Jadad score (aka Oxford Quality Scoring System). 'Risk of Bias' assessment with the Cochrane tool, similarly revealed overall quality of the included studies to be moderate to high (Table 2.1). Where domains were assessed to have been "unclear", it was generally due to an absence of methodological details of the procedures used to ensure blinding.

The study by Koegelenberg et al. (2014) it is at potential risk of within-cluster bias as it was a cluster RCT; inadequate details were provided to confidently assess this factor.

Two domains of the Ramon et al. (2014) study were assessed to be at a high risk of bias. No detail was provided as to the level of blinding of study personnel, and deviations from the study protocol were observed. Primary outcomes were reported as described, as were most secondary outcomes. However, the 36 and 52 week follow ups specified in the protocol have not been reported, thus suggesting this domain to be at a high risk of bias.

The Risk of Bias assessments for the included RCTs have been included in Table 2.2.

Table 2.1: Methodological quality summary: judgements for individual RCTs assessed for this report.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias (other sources of bias)
Koegelenberg 2014	+	+	?	?	+	+	?
Ramon 2014	+	+	?	+	+	-	+

+ denotes low risk of bias, ? unclear risk of bias and – denotes high risk of bias. Corresponding details can be referred to in Table 2.2 below.

Table 2.2: Critical appraisal results of included RCTs assessed using the Cochrane Risk of Bias tool (see Appendix 3).

ID	Source of bias						
	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Koegelenberg 2014	Randomisation of treatments was performed in a 1:1 ratio using centrally generated block randomisation within each site (blocks of 4 with 2 active and 2 placebo patches): L	Central allocation to treatment was utilised to conceal allocation: L	It is stated that investigators were blind, although it is not explained how. Participants received a placebo similar to the intervention patch. U	It is stated that investigators were blind, but no methodological details are given. U	Missing outcome data appears to be relatively balanced between groups. Missing data was analysed if smoking related (i.e. non-abstainers) to underestimate effect size (ITT): L	Link has been provided to study protocol and registration. Outcomes reported in the protocol have been reported in the research. L	Risk of within cluster bias; participants from 7 different centres. An intra-cluster correlation coefficient (ICC) was not produced. More detail needed for a judgment on this domain: U
Ramon 2014	Randomisation was performed using a computer generated randomization system. L	Random numbers were placed in sealed envelopes which were opened in front of the therapist and patient by an independent study collaborator. L	Participant received a placebo, however there is no mention of investigators being blinded. U	Primary outcome was continuous abstinence defined as not smoking from week 2 to week 12. Determined measuring expired CO concentrations (<10ppm determined abstinence). No details provided re blinding of outcome assessors; outcome is unlikely to be affected by lack of blinding: L	Missing outcome data appears to be relatively balanced between groups, however no information is provided about lack of follow up at each time point. However, missing data was analysed if smoking related (i.e. non-abstainers) to underestimate effect size (ITT): L	Registered as NCT01538394. Primary outcomes reported as described, as were most secondary outcomes. However, the 36 and 52 week follow ups specified in the protocol have not been reported. H	The study appears free of other sources of bias; L

Included study characteristics

<table>
<tr><th>ID</th><th>Koegelenberg 2014</th></tr>
<tr><td>Bibliographic reference</td><td>Koegelenberg, C.F., Noor, F., Bateman, E.D., van Zyl-Smit, R.N., Bruning, A., O'brien, J.A., Smith, C., Abdool-Gaffar, M.S., Emanuel, S., Esterhuizen, T.M. and Irusen, E.M., 2014. Efficacy of Varenicline combined with nicotine replacement therapy vs Varenicline alone for smoking cessation: a randomized clinical trial. Jama, 312(2), pp.155-161.</td></tr>
<tr><td>Study type</td><td>Multicentre, Randomised Controlled Trial</td></tr>
<tr><td>Country</td><td>South Africa (Cape Town, Johannesburg and Durban)</td></tr>
<tr><td>Study Setting</td><td>Hospital/Centre</td></tr>
<tr><td>Number of participants</td><td>446 enrolled and randomized (222 intervention + Varenicline) (224 placebo + Varenicline)
Of those in intervention group 6 withdrew prior to receiving treatment, in placebo group 5 withdrew prior to receiving treatment)</td></tr>
<tr><td>Number of withdrawals</td><td>Time point 1 (12weeks)
Intervention:
18 withdrew consent; 13 lost to follow-up; 6 withdrawn due to adverse event. 179 Completed treatment period
Placebo:
15 withdrew consent; 19 lost to follow-up; 11 withdrawn due to adverse events; 1 withdrawn due to protocol violation. 173 completed treatment period
Time point 2 (24 weeks)
Intervention:
28 withdrew consent; 7 lost to follow-up. 144 completed study period
Placebo:
28 withdrew consent; 11 lost to follow-up. 134 completed study period</td></tr>
<tr><td>Patient characteristics</td><td>Baseline characteristics were well-balanced. Especially in regards to years smoked, cigarettes per day, pack-years smoked and previous quit attempts.
<table>
<tr><th></th><th>Mean (SD)</th><th></th></tr>
<tr><th>Characteristic</th><th>Varenicline and Active Nicotine Patch (n=222)</th><th>Varenicline and Placebo Patch (n=224)</th></tr>
<tr><td>Age, mean (SD), y</td><td>46.6 (11.9)</td><td>46.1 (11.9)</td></tr>
<tr><td>Male, No. (%)</td><td>87 (39.2)</td><td>84 (37.5)</td></tr>
<tr><td>Body mass index [a]</td><td>27.1 (4.8)</td><td>27.5 (5.5)</td></tr>
<tr><td>Fagerström score [b]</td><td>4.5 (1.3)</td><td>4.5 (1.4)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Smoking History</td><td></td><td></td></tr>
<tr><td>Years Smoked</td><td>26.8 (11.2)</td><td>26.9 (11.8)</td></tr>
<tr><td>Cigarettes, No./d</td><td>15.5 (6.8)</td><td>16.1 (6.9)</td></tr>
<tr><td>Pack-years</td><td>21.3 (14.8)</td><td>21.4 (14.1)</td></tr>
<tr><td>Previous quit attempts, mean (range), No.</td><td>1.55 (0-11)</td><td>1.37 (0-15)</td></tr>
</table>
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] The Fagerström score for nicotine dependence ranges from 0 to 10; a higher score denotes greater dependency.
</td></tr>
<tr><td>Intervention</td><td>The intervention of interest was combined Varenicline and NRT. Every participant was provided with a ten minute smoking cessation counselling session at each visit. Participants in intervention group were first prescribed active, 15mg nicotine patches, administered for 16h/d 2 weeks before target quit date (TQD), and continued till week 12. Varenicline was then administered 1 week before TQD (0.5mg once daily for three days, titrated to 0.5mg twice daily for days 4-7 and then to the maintenance dose of 1mg twice daily through to week 12). Smoking status was determined at the TQD and at 1, 2, 4, 8, 12, 16 and 24 weeks thereafter</td></tr>
<tr><td>Comparison</td><td>The comparison was Varenicline treatment alone. Participants in comparison group were prescribed placebo patches, administered for 16h/d 2 weeks before TQD, and continued till week 12. Varenicline was then administered 1 week before TQD (0.5mg once daily for three days, titrated to 0.5mg twice daily for days 4-7 and then to the maintenance dose of 1mg twice daily through to week 12).</td></tr>
<tr><td>Length of follow-up</td><td>24 weeks</td></tr>
<tr><td>Outcome measures/Results</td><td>Continuous abstinence from smoking. Confirmed with end-expiratory exhaled carbon monoxide measurements of 10ppm or less. Authors defined ‘continuous abstinence’ as not smoking (CO expiration <10ppm) at week 9 and 12 and at week 9, 12, 16 and 24 post-TQD.
<table>
<tr><th colspan="2">Varenicline and Active Nicotine Patch</th><th colspan="2">Vareniciline and Placebo Patch</th><th>Odds Ratio</th><th></th></tr>
<tr><th>Abstinence Events</th><th>Total</th><th>Abstinence Events</th><th>Total</th><th>OR (95% CI)</th><th>p value</th></tr>
<tr><td>71</td><td>222</td><td>42</td><td>224</td><td>2.06 (1.33-3.21)</td><td>.001</td></tr>
</table>
*note: this study also included continuous abstinence measures at 8 weeks; 12 weeks and 16 weeks post-TQD</td></tr>
<tr><td>Source of funding</td><td>This study was supported by unrestricted grants from Pfizer, New York, New York, and McNeil, Helsingborg, Sweden. Varenicline was supplied by Pfizer, and both active and placebo NRT patches were supplied by McNeil.</td></tr>
<tr><td>Additional comments</td><td>Only 62.3% of randomised participants completed the study and the researchers deliberately limited their study population to “relatively healthy smokers” as “the potential for unexpected adverse events was unknown”.</td></tr>
</table>

ID	Ramon 2014			
Bibliographic reference	Ramon, J.M., Morchon, S., Baena, A. and Masuet-Aumatell, C., 2014. Combining Varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. BMC medicine, 12(1), p.172.			
Study type	Randomised Controlled Trial			
Country	Barcelona, Spain			
Study Setting	University Bellvitge Hospital			
Number of participants	341 participants randomised (170 intervention + Varenicline) (171 placebo + Varenicline)			
Number of withdrawals	**Intervention:** 26 did not complete follow-up, 12 could not be contacted, 3 revoked participation, 5 adverse effects. *124 completed follow up* **Placebo:** 30 did not complete follow-up, 13 could not be contacted, 5 revoked participation, 4 adverse effects. *120 completed follow up*			
Patient characteristics		Varenicline and Nicotine Patch (n=170)	Varenicline and Placebo Patch (n=171)	*p*-value
	Gender Number (%)			
	Male	95 (55.95%)	102 (59.6%)	
	Female	75 (44.1%)	69 (40.4%)	0.55[a]
	Age			
	Mean (±SD)	44.1 (±14.8)	46.2 (±13.1)	0.38[b]
	Cigarettes/day Number (%)			
	≤29 cig/day	78 (45.9%)	84 (49.1%)	
	>29 cig/day	92 (54.1%)	87 (50.9%)	0.6[a]
	Previous attempts Number (%)			
	None	33 (19.4%)	27 (15.8%)	
	1	73 (42.9%)	67 39.2%)	
	2 to 3	44 (25.95%)	60 (35.1%)	
	>3	20 (1.8%)	17 (9.9%)	0.31[a]
	FTND			
	Mean (±SD)	6.1 (±1.6)	6.8 (±1.8)	0.9[b]
	[a] χ^2 squared test; [b]T-test; FTND, Fagerström test for nicotine dependence; SD Standard deviation.			

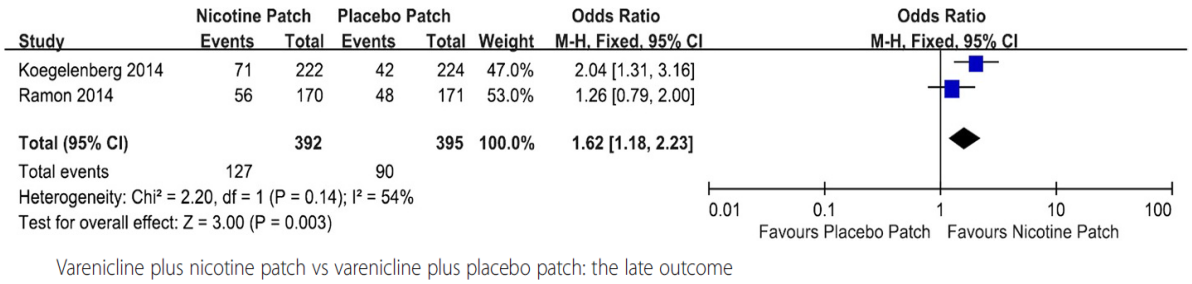
<table>
<tr><td>Intervention</td><td>The intervention of interest was combined Varenicline and nicotine patch. Every participant was provided with a ten minute (minimum) smoking cessation counselling session at each visit. Participants in intervention group were first prescribed Varenicline 1 week before TQD (0.5mg once daily for three days, 0.5mg twice daily for four days, followed by 1 mg twice for 11 weeks. On TQD intervention group received active nicotine patches (21mg/24 hours).</td></tr>
<tr><td>Comparison</td><td>The comparison was Varenicline treatment alone. Participants in intervention group were first prescribed Varenicline 1 week before TQD (0.5mg once daily for three days, 0.5mg twice daily for four days, followed by 1 mg twice for 11 weeks. On TQD intervention group received placebo patches.</td></tr>
<tr><td>Length of follow-up</td><td>24 weeks</td></tr>
<tr><td>Outcome measures/Results</td><td>Continuous abstinence from smoking. Confirmed with exhaled carbon monoxide measurements of 10ppm or less. Authors defined ‘continuous abstinence’ as not smoking (CO expiration <10ppm) at week 8, 12 and 24 post-TQD.

<table>
<tr><th colspan="2">Varenicline and Nicotine Patch</th><th colspan="2">Vareniciline and Placebo Patch</th><th></th></tr>
<tr><th>Abstinence Events</th><th>Total</th><th>Abstinence Events</th><th>Total</th><th>OR (95% CI)</th></tr>
<tr><td>56</td><td>170</td><td>48</td><td>171</td><td>1.25 (0.8-2.0)</td></tr>
</table>
*note: this study also included continuous abstinence data for 8 weeks and 12 weeks post-TQD.</td></tr>
<tr><td>Source of funding</td><td>A grant from Pfizer was used for the recruitment and acquisition of active patches. The Varenicline was provided by Pfizer, Inc., and the placebo patches were provided by Novartis.</td></tr>
<tr><td>Additional comments</td><td>Potential limitation is the possibility for bias in the non-pharmacological interventions. The study involved three different therapists trained in the standardised study protocol who were experts in smoking cessation. However, and although no differences were observed between different therapists, the counsellor may still have been a source of bias in this study.</td></tr>
</table>

Synthesis and meta-analysis

Abstinence

Chang et al. (2015) presented a meta-analysis that included two studies (Koegelenberg et al. 2014; Ramon et al. 2014) and 787 participants at 24 weeks. The analysis has indicated that combination Varenicline and active nicotine patch was more effective for long-term (24 weeks) smoking abstinence, than mono-treatment with Varenicline alone, Odds Ratio (OR) 1.62, 95% Confidence Interval (CI) 1.18, 2.23), $Chi^2 = 2.2$, $I^2 = 54\%$; Figure 2.1).



Varenicline plus nicotine patch vs varenicline plus placebo patch: the late outcome

Figure 2.1 Abstinence at 24 weeks (reproduced from Chang et al., 2015)

Smoking dependency

Both Koegelenberg et al. (2014) and Ramon et al. (2014) included the Fagerström Test for Nicotine Dependence (FTND). FTND scores of ≥8 indicate a high dependence; 5-7 indicate moderate dependence; 3-4 low to moderate dependence and 1-2 indicates low dependence. The FTND scores (Mean ± SD) for Koegelenberg et al. (2014) were 4.5 ± 1.3 (Combination Therapy) and 4.5 ± 1.4 (Placebo Therapy), while the FTND scores for Ramon et al. (2014) were 6.1 ±1.6 (Combination Therapy) and 6.8 ± 1.8 (Placebo Therapy). Number of cigarettes smoked/day is presented in the study characteristics tables above. There are discernible differences in nicotine dependence between the participants of the studies. This heterogeneity in participant characteristics suggests that caution is warranted when interpreting these results. Greater nicotine dependency may reduce efficacy of combination Varenicline and active nicotine patch on long-term abstinence.

50% reduction in cigarettes per day

No included study reported the outcome of cigarettes smoked/day.

Adverse events

Chang *et al.* (2015) aggregated the reported number of adverse events, and generated pooled Odds Ratios with a fixed-effect model. Compared to mono-Varenicline therapy (Varenicline and placebo patch alone), participants receiving combination Varenicline and NRT reported more incidents of nausea (28.4 % vs 25.7 %; OR 1.15 (CI 0.85, 1.56)), insomnia (18.7 % vs 15.4 %; OR 1.27 (0.89, 1.80)) and abnormal dreams (13.6 % vs 10.7 %; OR 1.20 (0.78, 1.84)). Frequency of headaches was similar between groups (7.1 % vs 7.8 %; OR 1.01 (0.60, 1.72)). The study of Koegelenberg *et al.* (2014) reported that skin reactions (of any type), were more prevalent in the combination therapy group (14.4 % vs 7.8 %; p = 0.03). Some serious adverse events were also reported in the included studies. Koegelenberg *et al.* (2014) also reported a female participant, randomised to the Varenicline mono-therapy group who became pregnant during the treatment phase. This participant gave birth to an

infant with Down syndrome and congenital heart defects which was considered relevant to the study medications.

Conclusion

Based on these findings Chang et al. (2015) suggest that combination Varenicline and active nicotine patch therapy is more effective than Varenicline alone in long-term abstinence from smoking, however concede that larger, and more RCT's are needed to make robust conclusions.

Clinical question 4

Does adding any further course of NRT (any form) reduce relapse in smokers who have quit at the completion of a standard course of NRT?

If so, is this effect for all smokers or for more dependent smokers?

Criteria for inclusion and exclusion of studies

1. **Population**:

- Smokers (all)
- More dependent smokers

2. **Intervention**: Any further course of NRT (any form) for people who have quit successfully at end of standard course

3. **Comparison**: Standard duration 12 weeks NRT (any) plus placebo for further 12 weeks

4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.

5. **Study designs:** Randomised controlled trials, systematic reviews of RCTs.

6. **Other criteria:** 6 months follow up or longer.

Summary of Findings

Question: Does adding any further course of NRT (any form) reduce relapse in smokers who have quit at the completion of a standard course of NRT? If so, is this effect for all smokers or for more dependent smokers?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Standard NRT followed by an additional course of NRT**	**Standard NRT alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Confirmed abstinence 9 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))											
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	20/37 (54.1%)	13/37 (35.1%)	**OR 2.17** (0.85 to 5.53)	**189 more per 1,000** (from 36 fewer to 398 more)	⨁⨁◯◯ LOW
Confirmed abstinence 12 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))											
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	9/37 (24.3%)	6/37 (16.2%)	**OR 1.66** (0.52 to 5.26)	**81 more per 1,000** (from 71 fewer to 342 more)	⨁⨁◯◯ LOW
Reduction of CPD (50%)											
0									not estimable		-

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Small sample size. Confidence intervals are wide and range from negligible (0.85) to potentially substantially beneficial (5.53). Low number of events, 33 events does not meet the Optimal Information Size threshold of 107.

b. Small sample size. Confidence intervals are wide and range from negligible (0.52) to potentially beneficial (5.26). Low number of events, 15 events does not meet the Optimal Information Size threshold of 386.

Study selection

The search of PubMed for question 4 returned 201 records. One systematic review and three RCTs were originally suggested for question 4 based on citation details (see General Methods: Study Selection, Phase 1).

Review of full text during Phase 2 of Study Selection led to the exclusion of three RCTs (see Appendix 1). One systematic review (Hajek et al. 2013) was deemed eligible for inclusion, which presented the results an individual trial that was relevant (Croghan et al. 2007).

Methodological quality

Overall the quality of the included study was high (Table 4.1). Where domains were assessed to be 'unclear', it was due to insufficient information provided by the study authors as to the methodological detail used to ensure blinding. In addition, a study protocol was not referenced, this lack of available information precludes either a high or low judgment of this domain.

It should be noted, that only one study included in the Cochrane review by Hajek et al. (2013) had outcome data using a participant sub-group relevant to the PICO of question 4. This sub-group is further detailed and analysed below.

Table 4.1: Methodological quality summary: judgements extracted from Cochrane review (Hajek et al. 2013).

	Random sequence generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)**	Detection bias (biochemical validation of smoking outcomes)	Overall assessment of risk of bias
Croghan et al. (2007)*	+	+	?	+	?	+	+

* Denotes study assessment extracted directly from Cochrane review Hajek et al. 2013; + denotes low risk of bias, ? denotes unclear risk of bias.

Included study characteristics

ID	Croghan 2007
Bibliographic reference	Croghan, I.T., Hurt, R.D., Dakhil, S.R., Croghan, G.A., Sloan, J.A., Novotny, P.J., Rowland, K.M., Bernath, A., Loots, M.L., Le-Lindqwister, N.A. and Tschetter, L.K., 2007, February. Randomized comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention. In Mayo Clinic Proceedings. Vol. 82, No. 2, pp. 186-195.
Study type	Multicentre, randomised controlled trial
Country	United States through the North Central Cancer Treatment Group.
Study Setting	19 Clinics
Number of participants	1700 smokers. 566 randomised to NRT (Nicotine Inhaler). 74 participants were confirmed abstainers after the three month therapy period. Of this group, 37 were randomised to continue receiving NRT (Nicotine Inhaler) and 37 were randomised to receive placebo, for 9 months. This 74 participant sub-group is the only sub-group relevant to the PICO of question 4.
Number of withdrawals	There is no specific detail provided on the withdrawal rates of the 74 participant sub-group that is relevant to the PICO of question 4. While data is provided for withdrawal rate for other aspects of this study it would suggest that no withdrawal was experienced in this sub-group.
Patient characteristics	The following participant characteristics table, extracted from the study, contains only the data of the original 1700 participants that were randomised to the *initial* cessation intervention. No participant's characteristics were included for the subgroup that is directly relevant to question 4. I.e. those participants who successfully abstained using NRT (n=74) and were then subsequently randomised to either continue NRT for 9 months, or continue with a placebo for 9 months.

	Inhaler (n=566)	Bupropion (n=567)	Inhaler and bupropion (n=567)	Total (N=1700)	*p*-valu
Mean age (y) (SD)	42.6 (11.65)	42.7 (11.35)	43.1 (11.56)	42.8 (11.52)	0.77
Race					
White	512 (90)	491. (87)	509 (90)	1512 (89)	
Black	42 (7)	54 (10)	42 (7)	138 (8)	
Other	12 (2)	19 (3)	14 (2)	45 (3)	
Unknown	0 (0)	3 (0.5)	2 (0.4)	5 (0.3)	
Sex					.99
Female	338 (60)	338 (60)	340 (60)	1016 (60)	
Male	228 (40)	229 (40)	227 (40)	684 (40)	
Mean BMI (SD)	28.0 (6)	28.6 (7)	28.2 (6)	28.3 (6)	.28
Marital Status					.95
Missing	2	2	2	6	
Married	324 (57)	325 (57)	315 (56)	964 (57)	

	Divorced	123 (22)	124 (22)	127 (22)	374 (22)	
	Never married	80 (14)	86 (15)	82 (14)	248 (15)	
	Widowed	15 (3)	12 (2)	21 (4)	48 (3)	
	Separated	13 (2)	12(2)	11 (2)	36 (2)	
	Other	9 (2)	6 (1)	9 (2)	24 (1)	
	Highest education					.17
	Missing	3	6	4	13	
	Did not graduate high school	19 (3)	20 (4)	35 (6)	74 (4)	
	Graduated high school	142 (25)	157 (28)	130 (23)	429 (25)	
	<4 years of post-high school education	297 (52)	276 (40)	279 (40)	852 (50)	
	Graduated college	97 (17)	100 (18)	107 (19)	304 (18)	
	Other	8 (1)	8 (1)	12 (2)	28 (2)	
	Mean age started smoking (y) (SD)	19.1 (6.16)	19.2 (6.18)	18.9 (5.95)	19 (6.10)	.68
	Mean baseline No. of cigarettes smoked p/day (SD)	23.0 (8.82)	23.5 (10.22)	23.4 (9.47)	23.3 (9.52)	.63
	Mean No, of years smoking cigarettes (SD)	23.5 (11.04)	23.6 (11.29)	24.3 (11.3)	23.8 (11.21)	.46
	Baseline major depression*					
	Missing	21	17	24	62	
	No	430 (76)	428 (75)	440 (78)	1298 (76)	
	Yes	115 (20	122 (22)	103 (18)	340 (20)	
	Mean overall Fagerström score (SD)	5.8 (2.160	5.8 (2.13)	5.8 (2.12)	5.8 (2.14)	.94
	Mean No. of times tried to stop smoking (SD)	3.5 (4.27)	3.5 (3.93)	3.1 (3.31)	3.4 (3.85)	.17
	Data are number (percentage) of participants unless indicated other. BMI = body mass index. *As determined by 3 questions of the Health Status Questionnaire.					
Intervention	37 participants of the 74 who exhibited biochemically validated smoking cessation using Nicotine Replacement Therapy (Nicotine Inhaler) were randomised to continue NRT for a further 9 months, post-smoking cessation. During "phase 1" of this study every participant was provided with a ten minute (minimum) smoking cessation counselling session at each visit. However, no methodological detail is provided as to if this counselling session continued into phase 2.					
Comparison	37 participants of the 74 who exhibited biochemically validated smoking cessation using Nicotine Replacement Therapy (Nicotine Inhaler) were randomised to receive a placebo therapy for a further 9 months, post-smoking cessation.					
Length of follow-up	9 months of continued therapy after initial smoking cessation then 3 month follow-up.					
Outcome measures/Results	Biochemically confirmed smoking abstinence of the 74 participants who had received the nicotine inhaler in the first phase, stopped smoking and were randomised to the relapse prevention phase. Abstinence was determined by the study authors if the participants reported that they had not smoked for the previous 7-days and had a confirmatory expired air carbon monoxide level of ≤8ppm.					
		Nicotine Inhaler		**Placebo Inhaler**		***P*-value***

		Abstinence Events (%)	**Total**	**Abstinence Events (%)**	**Total**	
	9 months (post-phase 1; 9 month relapse prevention)	20 (54)	37	13 (35)	37	0.1
	12 months (post-phase 2; 3 month follow-up)	9 (24)	37	6 (16)	37	*0.39*
	* The χ^2 test, with statistical significance based on $p \leq 0.5$					
Source of funding	This study was supported in part by Public Health Service grants CA25224, CA37404, CA15083, CA63826, CA35195, CA35448, CA35431, CA35101, CA35113, CA35103, CA52352 and CA63848.					

Synthesis and meta-analysis

Abstinence

The meta-analyses presented here have been generated by the review team. Although the Cochrane review by Hajek et al. (2013) contained a meta-analysis using the outcome data from the relevant study, this combined data from two sub-groups, one of which (original cessation therapy was combination of NRT and Bupropion) was not relevant to the PICO of question 4.

The analysis indicated, that continued NRT, following biochemically validated cessation using the same NRT (nicotine inhaler) was no more effective than the placebo control for continued abstinence both at 9 months- (Figure 4.1) and 12 months- (Figure 4.2) post-smoking cessation.

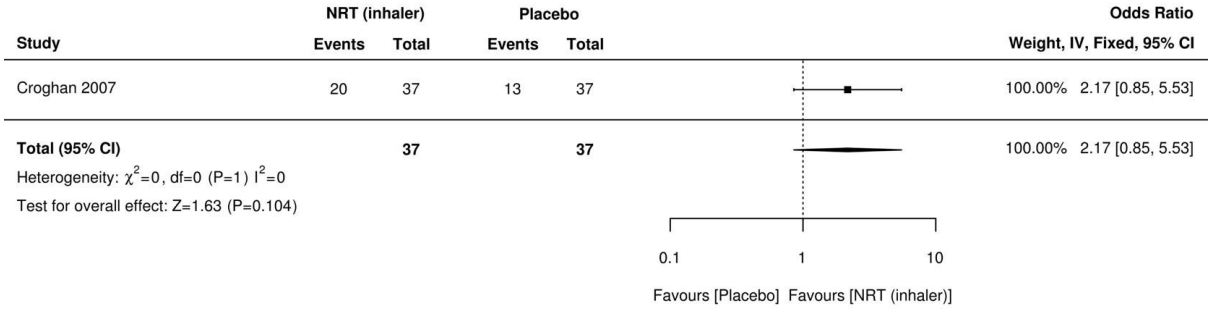


Figure 4.1. No. abstinence events after 9 months of continued NRT or placebo therapy after biochemically validated smoking cessation achieved through NRT.

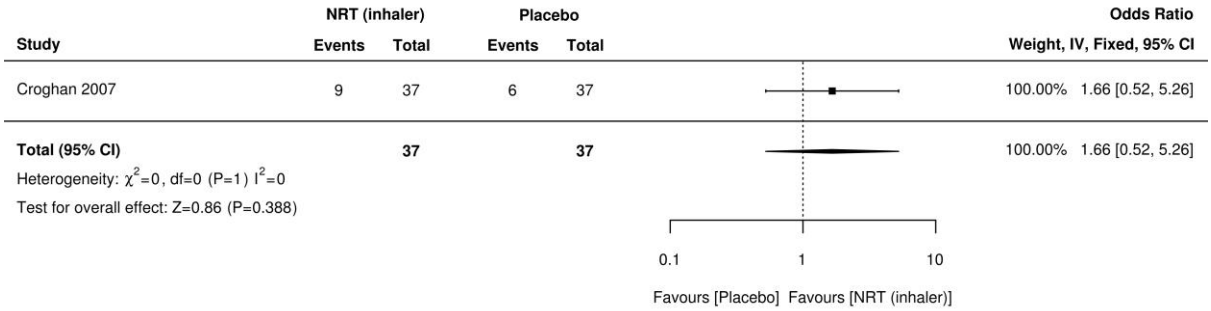


Figure 4.2. No. abstinence events after 12-months of continued NRT or placebo therapy after biochemically validated smoking cessation achieved through NRT.

Croghan et al. (2007) included the Fagerström Test for Nicotine Dependence (FTND). FTND scores of ≥8 indicate a high dependence; 5-7 indicate moderate dependence; 3-4 low to moderate dependence and 1-2 indicates low dependence. The average FTND scores were 5.8 (2.14) (mean (SD)), indicating moderate dependence. Number of cigarettes per day smoked are presented in the table of study characteristics above. However, no data was provided on FTND scores on the sub-group specifically relevant to the PICO of question 4, and analysed above. This suggests that the findings presented by Croghan et al. (2007) can be limited to only smokers with moderate nicotine dependence, however more RCT's are needed to make robust conclusions.

50% reduction in cigarettes per day

No included study reported the outcome reduction in CPD.

Adverse events

No descriptive or statistical information was provided in the systematic review by Hajek et al. (2013) as to the nature and severity of the adverse events experienced by participants in the study by Croghan et al. (2007). The only information provided directly by Croghan et al. (2007) was that 4% of the randomised participants for phase 1 and 1% of the randomised participants for phase 2 did not provide follow-up data, due to being removed from the study due to an adverse event.

Conclusion

Based on these findings, it is unclear whether continuing NRT post- achieving biochemically validated smoking abstinence improves long-term (12 month) continued abstinence rates.

Clinical question 5 (modified)

Does adding any further course of Varenicline (>12 weeks) reduce relapse in smokers who have quit at the completion of a standard course of Varenicline (12 weeks)?

If so, is this effect for all smokers or for more dependent smokers?

Criteria for inclusion and exclusion of studies

1. **Population**:

- Smokers (all)
- More dependent smokers

2. **Intervention**: Any further course of Varenicline (>12 weeks) for people who have quit successfully at end of standard course (12 weeks) i.e. 24 week total

3. **Comparison**: Standard duration 12 weeks Varenicline plus placebo for further 12 weeks

4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.

5. **Study designs:** Randomised controlled trials, systematic reviews of RCTs.

6. **Other criteria:** 6 months follow up or longer.

Summary of Findings

Question: Does adding any further course of Varenicline (>12 weeks) reduce relapse in smokers who have quit at the completion of a standard course of Varenicline (12 weeks)?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varenicline and NRT**	**Varenicline alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Smoking cessation at 52 weeks post-TQD (assessed with: Exhaled CO concentrations (<10ppm))											
2	randomised trials	not serious	not serious	not serious	serious [a]	none	281/643 (43.7%)	231/654 (35.3%)	**RR 1.23 (1.08 to 1.41)**	**81 more per 1,000** (from 28 more to 145 more)	⨁⨁⨁◯ MODERATE
Smoking cessation at 12 weeks post-active Varenicline treatment (assessed with: Exhaled CO concentrations (<10ppm))											
1	randomised trials	not serious	not serious	not serious	serious [b]	none	306/603 (50.7%)	301/607 (49.6%)	**RR 1.02 (0.91 to 1.15)**	**10 more per 1,000** (from 45 fewer to 74 more)	⨁⨁⨁◯ MODERATE

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Confidence intervals are wide and range from potentially negligible (1.08) to potentially beneficial (1.41).

b. Confidence intervals are wide and range from potentially negligible (0.91) to potentially beneficial (1.15).

Study selection

The search of PubMed for the original question 5 (see Appendix 2) returned 91 records. No trials nor systematic reviews were located that responded to this question (see General Methods: Study Selection, Phase 1).

Following personal correspondence with Dr Jonathon Livingstone-Banks (RACGP), Question 5 was modified as presented above, to reflect the use of extended Varenicline for relapse prevention. This review (Livingstone-Banks et al. 2018 unpublished) included two trials.

Methodological quality

Overall the quality of the included study was high (Table 5.1). Two domains were not assessed in the review of Livingstone-Banks et al. (2018). These included selective reporting, and an overall assessment of risk of bias. The only domain assessed to be at a high risk of bias was that for incomplete outcome data (attrition bias) in the study of Evins et al. (2014). This was due to a 55% follow up rate in the control group compared to an 88% follow up rate in the intervention group.

Table 5.1: Methodological quality summary: judgements extracted from Cochrane review (Livingstone-Banks et al. 2018, unpublished).

	Random sequence generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)**	Detection bias (biochemical validation of smoking outcomes)	Overall assessment of risk of bias
Evins et al. (2014)	+	+	+	-		+	
Tonstad et al. (2006)	+	+	+	+		+	

* Denotes study assessment extracted directly from Cochrane review Livingstone-Banks et al. 2018 unpublished); + denotes low risk of bias, ? denotes unclear risk of bias, - denotes high risk of bias. Where blank domain not assessed.

Included study characteristics

<table>
<tr><th>ID</th><th>Evins 2014</th></tr>
<tr><td>Bibliographic reference</td><td>Evins, A.E., Cather, C., Pratt, S.A., Pachas, G.N., Hoeppner, S.S., Goff, D.C., Achtyes, E.D., Ayer, D. and Schoenfeld, D.A., 2014. Maintenance treatment with Varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. JAMA, 311(2), pp.145-154.</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Country</td><td>USA</td></tr>
<tr><td>Study Setting</td><td>Setting: Community mental health centres, USA
Recruitment: Patients of mental health centres</td></tr>
<tr><td>Number of participants</td><td>203 smokers were treated with open-label Varenicline (0.5mg of Varenicline per day for 3 days, 0.5mg twice a day for 4 days, then 1.0mg twice a day for 11 weeks) and cognitive behavioural therapy (CBT). 87 smokers achieved biochemically validated (2 weeks abstinence) smoking cessation. These 87 ex-smokers were then randomised to the intervention (continued 1mg Varenicline twice daily plus CBT) group (n=40), or the placebo group (identical-appearing placebo, plus CBT) (n=47). These treatment continued from weeks 12 to 52.
62% male, average age 47, average cigs/day 23</td></tr>
<tr><td>Number of withdrawals</td><td>Intervention: 40 randomised. 7 lost to follow up. (40 included in analysis)
Comparator: 47 randomised. 28 lost to follow up. (47 included in analysis)</td></tr>
<tr><td>Patient characteristics</td><td>
<table>
<tr><th>Variable</th><th>Total Enrolled (n=203)</th><th>Non randomised (Failed to achieve cessation (n-116))</th><th>Randomised to placebo (n=47)</th><th>Randomised to intervention (n=40)</th></tr>
<tr><td>Age (years)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>47.5 (10.2)</td><td>46.9 (10.0)</td><td>45.7 (10.3)</td><td>51.4 (9.6)</td></tr>
<tr><td>Range</td><td>22-68</td><td>22-68</td><td>23-66</td><td>23-65</td></tr>
<tr><td>Women, Mo. (%)</td><td>80 (39)</td><td>48 (41)</td><td>16 (34)</td><td>16(40)</td></tr>
<tr><td>Race/ethnicity, No. (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>151 (74)</td><td>87 (75)</td><td>34 (72)</td><td>30 (75)</td></tr>
<tr><td>Black</td><td>35 (17)</td><td>20 (17)</td><td>6 (13)</td><td>9 (23)</td></tr>
<tr><td>Other</td><td>17 (8)</td><td>9 (8)</td><td>7 (15)</td><td>1 (3)</td></tr>
<tr><td>Hispanic</td><td>8 (4)</td><td>6 (5)</td><td>0</td><td>2 (5)</td></tr>
</table>
</td></tr>
</table>

	Not a high school graduate, No. (%)	49 (24)	30 (26)	10 (22)	9 (23)
	Never married, No. (%)	132 (65)	80 (69)	31 (66)	21 (53)
	Disabled, No (%)	132 (65)	80 (69)	29 (62)	23 (58)
	Cigarettes smoked per d, average lifetime				
	Mean (SD)	25.9 (14.2)	28.0 (16.5)	22.1 (9.6)	24.2 (9.4)
	Range	4-100	4-100	7-40	10-50
	Expired carbon monoxide, ppm				
	Mean (SD)	23.1 (14.9)	24.4 (15.5)	22.6 (13.2)	20.1 (15.1)
	Range	2-88	2-88	3-60	4-69
	Age at initiation of regular smoking, years				
	Mean (SD)	17.6 (5.7)	18.0 (6.0)	17.1 (5.1)	17.4 (5.7)
	Range	6-45	7-45	6-39	8-32
	FTND score				
	Mean SD	6.1 (1.8)	6.3 (1.8)	5.9 (1.7)	5.9 (2.0)
	≥6, No (%)	127 (64)	76 (67)	28 (61)	23 (58)
	Prior cessation attempts, No. (%)				
	None	25 (12)	20 (17)	3 (6)	2 (5)
	≥5	70 (34)	39 (34)	16 (34)	15 (38)
	Psychiatric symptom ratings				
	SANS composite score				
	Mean (SD)	35.0 (14.7)	35.7 (14.8)	32.7 (15.6)	36.0 (13.3)
	Range	4-73	4-73	6-69	12-72
	BPRS total score				
	Mean (SD)	51.1 (13.1)	50.0 (13.2)	50.3 (11.7)	55.6 (13.8)
	Range	29-98	29-89	33-72	30-98
	CDSS total score				
	Mean (SD)	4.1 (3.3)	3.7 (3.1)	4.7 (3.4)	4.6 (3.9)
	Range	0-15	0-14	0-12	0-15
	Psychiatric diagnosis, No (%)				

	Schizophrenia spectrum	185 (91)	108 (93)	41 (87)	36 (90)
	Bipolar disorder	18 (9)	8 (7)	6 (13)	4 (10)
	Prior substance use disorder	94 (48)	50 (44)	22 (48)	22 (58)
	Antipsychotic medication, No. (%)				
	Conventional antipsychotics only	24 (13)	16 (15)	4 (10)	4 (11)
	Atypical other than clozapine	119 (65)	67 (63)	28 (68)	24 (67)
	Clozapine	41 (22)	24 (22)	9 (22)	8 (22)
	No. of psychotropic medications				
	Mean (SD)	1.1 (0.9)	1.1 (1.0)	1.2 (1.0)	1.1 (0.9)
	Range	0-4	0-3	0-4	0-3
	BMI				
	Mean (SD)	31.7 (6.7)	31.5 (6.9)	31.9 (6.3)	32.0 (6.7)
	Range	19-58	20-58	20-48	19-49
Intervention	Relapse prevention: Varenicline pus CBT over a 40-week period, following biochemically confirmed smoking cessation at 12 weeks post-TQD.				
Comparison	Control: Placebo plus CBT over a 40-week period, following biochemically confirmed smoking cessation at 12 weeks post-TQD.				
Length of follow-up	52 – Week follow up.				
Outcome measures/Results	Continuous abstinence (smoking cessation) at week 52 Validation: CO < 9 ppm at week 52 Validation: CO <9ppm at week 64				
Source of funding	Funding: "This study was funded by grants R01 DA021245 by National Institute on Drug Abuse with supplemental financial and material support from an investigator initiated award from Pfizer for study medications and funding, and by 05B1MACMHS to the Massachusetts Department of Mental Health from the Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Treatment Strategies for Smoking Cessation in Patients with Schizophrenia to the North Suffolk Mental Health Association (Dr Evins). Pfizer provided study medication and supplemental support through an investigator-initiated award after the protocol was approved by the institutional review board and the data and safety monitoring board."				

ID	**Tonstad 2006**

Bibliographic reference	Tonstad, S., Tønnesen, P., Hajek, P., Williams, K.E., Billing, C.B., Reeves, K.R. and Varenicline Phase 3 Study Group, 2006. Effect of maintenance therapy with Varenicline on smoking cessation: a randomized controlled trial. JAMA, 296(1), pp.64-71.
Study type	RCT
Country	USA
Study Setting	Setting: Cessation clinics in 7 countries. 6 sites in United States Recruitment: smokers of ≥ 10/day for cessation phase
Number of participants	1927 smoking adults (≥ 10/day) were treated with open-label Varenicline (0.5mg of Varenicline per day for 3 days, 0.5mg twice a day for 4 days, then 1.0mg twice a day for 11 weeks. 1210 achieved biochemically validated (7 days abstinence) smoking cessation. These 1210 ex-smokers were then randomised to the either the intervention (continued 1mg Varenicline twice daily plus clinic visits) group (n=603), or the placebo group (identical-appearing placebo plus clinic visits) (n=607). These treatments continued from weeks 12 to 52. However, the active component of this therapy (1mg Varenicline) only continued for 12 weeks (e.g. week 13-28), behavioural therapy was still available for the participant for the remaining 28 weeks.
Number of withdrawals	Intervention: 603 randomised, 47 discontinued treatment, 61 discontinued follow up. 494 completed study, but 603 included in analysis. Placebo: 607 randomised, 94 discontinued treatment, 47 discontinued follow-up. 464 completed study, but 607 included in analysis. The quit rate after the open-label phase was 64%

Patient characteristics

Characteristics	Open-Label Varenicline Phase (n=1927)	Randomised to Varenicline (n=603)	Randomised to Placebo (n-607)
Age (years)	44.2 (10.7)	45.4 (10.4)	45.3 (10.4)
Male, No. (%)	941 (48.8)	303 (50.2)	293 (48.3)
Race/ethnicity, No. (%)			
White	1853 (86.2)	583 (96.7)	589 (97)
Black	35 (1.8)	9(1.5)	10(1.6)
Asian	14 (0.7)	3 (0.5)	4 (0.7)
Fagerstrom score, mean (SD)	5.55 (2.04)	5.43 (1.96)	5.35 (1.98)
No. of years of smoking, mean (SD) (range)	27.2 (10.7) (2-59)	28.2 (10.4) (3-58)	29.1 (10.5) (2-58)
No. of cigarettes per day in past month, mean (SD) (range)	21.6 (8.3) (3-99)	20.77 (7.3) (8-60)	20.7 (7.5) (10-65)
Previous serious quit attempts,			
0	341 (17.7)	88 (14.6)	89 (14.7)
≥ 1	586 (82.3)	515 (85.4)	518 (85.3)

	Longest period of abstinence in past year, d			
	Mean (SD)	7.4 (18.4)	8.3 (19.6)	7.6 (18.3)
	Median (range)	0 (0-200)	0 (0-90)	0 (0-90)
	Expired carbon monoxide, ppm			
	Mean (SD)	23.1 (14.9)	24.4 (15.5)	22.6 (13.2)
	Range	2-88	2-88	3-60
	Age at initiation of regular smoking, years			
	Mean (SD)	17.6 (5.7)	18.0 (6.0)	17.1 (5.1)
	Range	6-45	7-45	6-39
	FTND score			
	Mean SD	6.1 (1.8)	6.3 (1.8)	5.9 (1.7)
	≥6, No (%)	127 (64)	76 (67)	28 (61)
	Prior cessation attempts, No. (%)			
	None	25 (12)	20 (17)	3 (6)
	≥5	70 (34)	39 (34)	16 (34)
	Psychiatric symptom ratings			
	SANS composite score			
	Mean (SD)	35.0 (14.7)	35.7 (14.8)	32.7 (15.6)
	Range	4-73	4-73	6-69
	BPRS total score			
	Mean (SD)	51.1 (13.1)	50.0 (13.2)	50.3 (11.7)
	Range	29-98	29-89	33-72
	CDSS total score			
	Mean (SD)	4.1 (3.3)	3.7 (3.1)	4.7 (3.4)
	Range	0-15	0-14	0-12
	Psychiatric diagnosis, No (%)			
	Schizophrenia spectrum	185 (91)	108 (93)	41 (87)
	Bipolar disorder	18 (9)	8 (7)	6 (13)
	Prior substance use disorder	94 (48)	50 (44)	22 (48)

	Antipsychotic medication, No. (%)			
	Conventional antipsychotics only	24 (13)	16 (15)	4 (10)
	Atypical other than clozapine	119 (65)	67 (63)	28 (68)
	Clozapine	41 (22)	24 (22)	9 (22)
	No. of psychotropic medications			
	Mean (SD)	1.1 (0.9)	1.1 (1.0)	1.2 (1.0)
	Range	0-4	0-3	0-4
	BMI			
	Mean (SD)	31.7 (6.7)	31.5 (6.9)	31.9 (6.3)
	Range	19-58	20-58	20-48
Intervention	Relapse prevention: Varenicline (1mg twice daily) (plus clinic visits) following biochemically confirmed smoking cessation at 12 weeks post-TQD for 12 weeks post-cessation date. Behavioural therapy was still offered from cessation date to 52 weeks post-TQD.			
Comparison	Control: Placebo (plus clinic visits) following biochemically confirmed smoking cessation at 12 weeks post-TQD for 12 weeks post-cessation date. Behavioural therapy was still offered from cessation date to 52 weeks post-TQD.			
Length of follow-up	64 weeks			
Outcome measures/Results	Sustained abstinence for 9 months at 1 year Validation: CO < 10 ppm			
Source of funding	This study was sponsored by Pfizer Inc, which provided funding, study drug and placebo, and monitoring			

Synthesis and meta-analysis

Smoking Cessation (52-weeks post- TQD)

The meta-analysis presented here has been extracted from the review by Livingstone-Banks et al. (2018). The analysis indicated that an additional course of Varenicline, post- smoking cessation is more effective than no additional course of Varenicline at maintaining smoking cessation at 52-weeks post-TQD. Risk Ratio (RR) 1.23, 95% Confidence Interval (CI) 1.08, 1.41, $Chi^2 = 5.64$, I^2=82% (Figure 5.1).

Both studies randomised patients who had achieved smoking cessation (biochemically confirmed) using a standard 12 week course of Varenicline. Both studies also included a 40 week treatment period post-randomization. Evins et al. (2014) randomised participants to receive either an additional 40 weeks of active Varenicline treatment versus placebo. Tonstad et al. (2006) however, randomised their participants to receive either, an additional active Varenicline treatment period of 12 weeks (week 13 to 24), followed by 28 weeks of CBT , versus placebo treatment for 12 weeks followed by 28 weeks of CBT. This difference could perhaps explain why the data from Tonstad et al. (2006) is comparatively less favourable to the intervention compared to Evins et al. (2014).

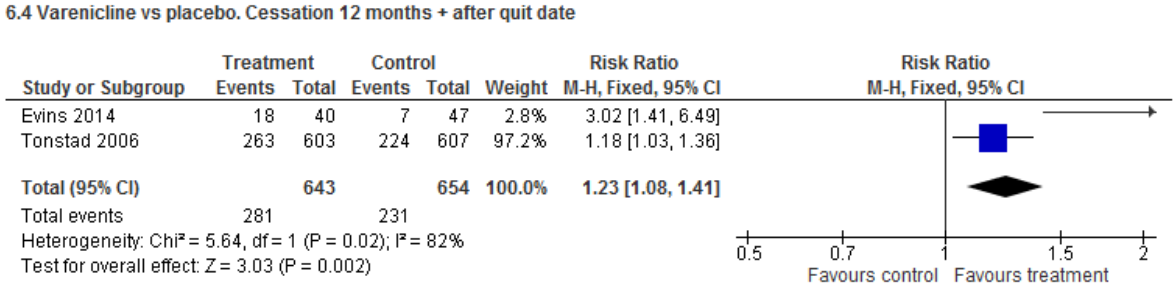


Figure 5.1 Smoking cessation after 52 weeks with extended course of Varenicline following abstinence after standard Varenicline course (reproduced from Livingstone-Banks et al. 2018, unpublished)

Both studies included the Fagerström Test for Nicotine Dependence (FTND). FTND scores of ≥8 indicate a high dependence; 5-7 indicate moderate dependence; 3-4 low to moderate dependence and 1-2 indicates low dependence. In the Evins et al. (2014) study, the mean (±SD) FTND for those randomised to receive Varenicline was 5.9 (1.7), whilst the Varenicline group in Tonstad et al. (2006) was 5.43 (1.96). For the placebo group, Evins et al. (2014) had a mean FTND of 5.9 (2.0) while Tonstad et al. (2006) had a mean 5.35 (1.98). Both groups of each study had comparable FTND scores, indicating moderate nicotine dependence.

Sensitivity analysis – removal of Evins study

It needs to be noted, that the study by Evins et al. (2014) included a small sample that had schizophrenia and/or bipolar disorder, and this needs to be considered when conspiring the results alongside those of Tonstad et al (2006). Removal of the Evins et al. (2014) study from the analyses presented above and considering the results of Tonstad et al. (2006) alone, for the outcome of smoking cessation, 52 weeks post-TQD (compare to Figure 5.1), the results would still favour the intervention, RR 1.18, 95% CI 1.03, 1.36.

Smoking Cessation (12-weeks post-active Varenicline treatment)

The meta-analysis presented here (Figure 5.2) has been performed for this review. The critical outcome for this question was decided by the panel as being smoking cessation, 12-weeks after the discontinuation of active Varenicline therapy. As Evins et al. (2014) did not include study data relevant

to this outcome, it has been omitted from the meta-analysis below. The analysis indicated that an additional 12-week course of Varenicline, post-smoking cessation, is not more effective than no additional course of Varenicline at maintaining smoking cessation and preventing relapse, 12-weeks after the discontinuation of the active Varenicline treatment. RR 1.02, 95% CI 0.91, 1.15 (Figure 5.2).

The outcome data presented here for the treatment group, is from 36-weeks post-TQD, while the outcome data presented for the control group, is from 24-weeks post-TQD. Both time points represent 12-weeks after discontinuation of active Varenicline treatment.

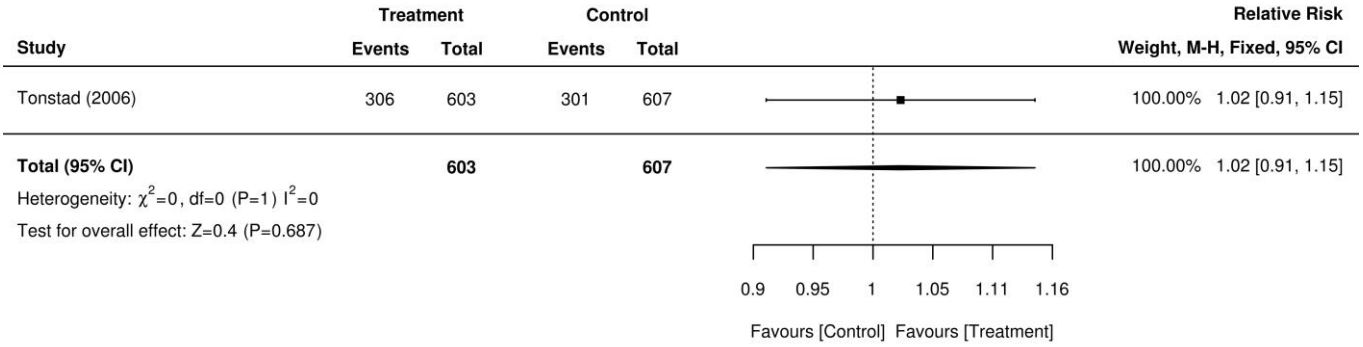


Figure 5.2 Smoking cessation 12-weeks after the discontinuation of active therapy with extended course of Varenicline following abstinence after standard Varenicline course. Outcome data for the treatment group taken at 36-weeks post-TQD. Outcome data for the control group taken at 24-weeks post-TQD.

50% reduction in cigarettes per day

No included study reported the outcome reduction in CPD.

Adverse events

No descriptive or statistical information was provided in the Cochrane review by Livingstone-Banks et al. (2018) as to the nature and severity of the adverse effects experienced by participants. Evins et al. (2014) and Tonstad (2006). Evins et al. (2014) provided details of adverse events associated with each treatment group. A significantly increased rate of headache (No. (%)) 17 (44) was experienced in the placebo group compared to those who received placebo 11 (24) ($P < 0.05$ Fisher exact test; Evins et al. 2014). Tonstad et al. (2016) reported that there were not significant differences between those randomised to receive Varenicline compared to those who received placebo. However, during the open-label Varenicline treatment phase, 11.9% discontinued treatment due to adverse effects, with 3.2% of participant's experiencing nausea, 1% experiencing headaches, 0.9% experiencing depression.

Conclusion

Based on these findings, continuing with Varenicline treatment post- biochemically validated smoking cessation is more effective at maintaining cessation (preventing relapse) only at 52-weeks post-TQD, compared to not continuing with Varenicline. If considering the critical outcome of smoking cessation at 12-weeks post-active Varenicline therapy, then continuing Varenicline treatment post-biochemically validated smoking cessation is not more effective at maintaining cessation (preventing relapse).

Clinical question 7

Is it safe and effective for a pregnant smoker to undergo NRT rather than no NRT?

Criteria for inclusion and exclusion of studies

1. **Population**:

- Female smokers who are pregnant and attempting to quit

2. **Intervention**: NRT (any form, any dose).

3. **Comparison**: No NRT

4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Pregnancy outcomes and adverse events (include miscarriage, stillbirth, preterm birth (< 37 wks), low birthweight (< 2500g), admissions to neonatal care, neonatal deaths, mean infant birthweights. Adverse events have also been included.

5. **Study designs:** Randomised controlled trials, systematic reviews of RCTs.

6. **Other criteria:** 6 months follow up or longer, including birth

Summary of Findings

Question: Is it safe and effective for a pregnant smoker to undergo NRT rather than no NRT?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT (any form, any dose)	no NRT	Relative (95% CI)	Absolute (95% CI)	
Smoking cessation in later pregnancy (overall)											
8	randomised trials	not serious	serious [a]	not serious [b]	serious [c]	none [d]	143/1133 (12.6%)	91/1066 (8.5%)	**RR 1.41** (1.03 to 1.93)	**35 more per 1,000** (from 3 more to 79 more)	⊕⊕◯◯ LOW
Smoking cessation after childbirth (overall) (follow up: range 3 months to 6 months; assessed with: Self-report questionnaire)											
3	randomised trials	serious [e]	not serious	not serious [b]	serious [f]	none [d]	61/346 (17.6%)	40/279 (14.3%)	**RR 1.22** (0.84 to 1.77)	**32 more per 1,000** (from 23 fewer to 110 more)	⊕⊕◯◯ LOW
Miscarriage and spontaneous abortion											
4	randomised trials	not serious [g]	not serious	not serious	serious [h]	none [d]	7/923 (0.8%)	4/859 (0.5%)	**RR 1.47** (0.45 to 4.77)	**2 more per 1,000** (from 3 fewer to 18 more)	⊕⊕⊕◯ MODERATE
Stillbirths (overall)											
4	randomised trials	not serious [g]	not serious [i]	not serious	serious [j]	none [d]	14/920 (1.5%)	10/857 (1.2%)	**RR 1.24** (0.54 to 2.84)	**3 more per 1,000** (from 5 fewer to 21 more)	⊕⊕⊕◯ MODERATE
Birthweight (overall)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT (any form, any dose)	no NRT	Relative (95% CI)	Absolute (95% CI)	
6	randomised trials	serious [k]	serious [l]	not serious	serious [m]	none [d]	1061	1007	-	MD **100.54 g higher** (20.84 lower to 221.91 higher)	⊕◯◯◯ VERY LOW
Low birthweight (<2500g) (overall)											
6	randomised trials	serious [k]	serious [l]	not serious	serious [n]	none [d]	107/1043 (10.3%)	112/994 (11.3%)	**RR 0.74** (0.41 to 1.34)	**29 fewer per 1,000** (from 38 more to 66 fewer)	⊕◯◯◯ VERY LOW
Preterm birth (<37 weeks) (overall)											
5	randomised trials	serious [k]	not serious	not serious	serious [o]	none [d]	101/1053 (9.6%)	104/995 (10.5%)	**RR 0.87** (0.67 to 1.14)	**14 fewer per 1,000** (from 15 more to 34 fewer)	⊕⊕◯◯ LOW
Neonatal intensive care unit admissions											
4	randomised trials	not serious [g]	not serious	not serious	serious [p]	none [d]	63/908 (6.9%)	63/848 (7.4%)	**RR 0.90** (0.64 to 1.27)	**7 fewer per 1,000** (from 20 more to 27 fewer)	⊕⊕⊕◯ MODERATE
Neonatal death											
4	randomised trials	serious [q]	not serious [r]	not serious	not serious [s]	none [d]	4/898 (0.4%)	5/848 (0.6%)	**RR 0.66** (0.17 to 2.62)	**2 fewer per 1,000** (from 5 fewer to 10 more)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Widely differing estimates of treatment effect.

b. Guideline panel might want to consider co-interventions used and placebo comparator.

c. Confidence intervals are wide and range from negligible (1.03) to potentially beneficial (1.93). Small number of observed events, 234 events does not meet the Optimal Information Size threshold of 889.

d. Only searched one database post-2015

e. Concerns over performance and detection bias due to lack of placebo control

f. Confidence intervals are wide and range from negligible (0.84) to potentially beneficial (1.77). Small number of observed events, 101 events does not meet the Optimal Information Size threshold of 1943.

g. Concerns over performance and detection bias in Pollack study. However, total contribution is <15%. Therefore have not rated down

h. Confidence intervals are wide and range from potentially harmful (0.45) to potentially beneficial (4.77). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 2 more miscarriages per 1000 births with a CI from 3 in 1000 fewer to 18 in 1000 more. Considering absolute effect potential to NOT rate down.

After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group.

i. Widely differing estimates of treatment effect, however this may be attributed to low number of events.

j. Confidence intervals are wide and range from potentially negligible (0.54) to potentially beneficial (2.84). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 3 more stillbirths per 1000 events with a CI from 5 in 1000 fewer to 21 in 1000 more. Considering absolute effect potential to NOT rate down.

After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group.

k. Concerns of performance and detection bias.

l. High statistical heterogeneity

m. Confidence intervals are wide range from negligible (-20.84) to potentially beneficial (221.91) potentially crossing important clinical thresholds.

n. Confidence intervals are wide and range from potentially harmful (0.41) to negligible (1.34). Low number of events, 219 events does not meet the Optimal Information Size threshold of 14817.

o. Confidence intervals are wide and range from negligible (0.67) to negligible (1.14). Low number of events, 205 events does not meet the Optimal Information Size threshold of 19111.

p. Confidence intervals are wide and range from negligible (0.64) to negligible (1.27). Low number of events, 126 events does not meet the Optimal Information Size threshold of 43430.

q. Concerns over performance and detection bias of the Pollak study. This study contributes .25%.

r. Estimate of treatment effect for Berlin study is statistical outlier.

s. Confidence intervals are wide range from potentially harmful (0.17) to potentially beneficial (2.62). Low number of events, however the sample sizes are sufficiently large, using absolute terms there were only 2 fewer neonatal deaths per 1000 events with a CI from 5 in 1000 fewer to 10 in 1000 more. Considering absolute effect potential to NOT rate down.

After discussion with the panel, consensus was to NOT rate down for imprecision. The method group agree with this decision and have subsequently changed the rating for imprecision from 'serious' to 'not serious'.

Study selection

The search of PubMed for questions 7-9 returned 10 records. Three systematic reviews, two literature and three primary studies were originally suggested for question 7 based on citation details (see General Methods: Study Selection, Phase 1).

Review of full text during Phase 2 of Study Selection led to the exclusion of a systematic review as well as all literature reviews and primary studies. Two Cochrane systematic reviews were identified to be eligible for inclusion. One, Coleman et al. 2015, included 9 RCTs, of which 8 addressed NRT in pregnant women. The more recently performed review, Hartman et al. 2018, included pregnant women as a subgroup in an overall investigation of the effectiveness of NRT. It included 6 RCTs relevant to this question, all of which were included in Coleman et al. 2015.

Methodological quality

Coleman et al. 2015, concluded that risk of bias was generally low across included trials with most domains of the Cochrane 'Risk of bias' assessment tool being satisfied in the majority of studies (Table 7.1). Where a trial was judged to be at high overall risk of bias it was generally due to an absence of blinding. 'Risk of bias' presented by Coleman et al. 2015 for each domain is summarised below.

Allocation

Computer-generated random number sequences were used in all studies. One study, Hotham et al. 2006, used sealed envelopes after random numbers had been generated but it was not clear if these were opaque and sequentially numbered. As such, allocation for this study was judged to be unclear whilst others were rated as low.

Blinding

In Coleman et al. 2015 this was judged unsatisfactory in studies that had no placebo control - it was the principal difference between studies judged likely to cause bias. Five relevant trials were placebo-RCTs (Berlin et al. 2014; Coleman et al. 2012; Kapur et al. 2001;Oncken et al. 2008; Wisborg et al. 2000), and three compared behavioural support alone with NRT and behavioural support (El-Mohandes et al. 2013; Hotham et al. 2006; Pollak et al. 2007).

Detection bias (biochemical validation of smoking outcomes)

The use of biochemical validation of smoking cessation is important due to negative social views of smoking. As all included trials validated self-reported smoking outcomes, this is not a major issue here. However, one included study (Wisborg et al. 2000) used an unreliable system for validating cessation, creating a greater risk that participants who were actually smoking would not be detected by the validation process.

Incomplete outcome data

This was judged to be satisfactory across all relevant studies; for smoking data an intention-to-treat analysis was followed in all studies, so that those participants who could not be contacted at follow-up were assumed to have returned to smoking. This approach assumes that where data on smoking status are missing, participants are smoking. Follow-up for birth outcomes was generally high with the exception of (Wisborg et al. 2000) where the treatment group allocation for seven women who experienced miscarriage after being randomised could not be ascertained. As such, this trial was rated as being unclear with respect to this criterion.

Selective reporting

Three studies were judged unsatisfactory with respect to selective reporting bias. Hotham et al. 2006 collected data on a number of outcomes that were not reported in the trial manuscript. Coleman 2015 unsuccessfully requested birthweight data from Hotham et al. 2006 for their meta-analysis while El-

Mohandes et al. (2013) informed them that within their trial some data on secondary smoking cessation outcomes were collected, but had not been reported within the trial manuscript; however, in both studies primary outcomes were reported. No birth outcomes were reported in Kapur et al. 2001.

Other potential sources of bias

One study (El-Mohandes et al. 2013), had an unanticipated potential source of bias wherein two participants were screened and randomised on two separate occasions, each pregnancy was counted as a discrete study participation and both women were included twice in the trial analysis. This was considered by Coleman et al. 2015 as having the potential to introduce bias into what was a relatively small study and this was, therefore allocated a 'high' 'Risk of bias' assessment. Both Hotham et al. 2006 and Pollak et al. 2007 were also judged to be at high risk of other bias, due to concerns regarding lack of blinding using a placebo.

Table 7.1: Methodological quality summary: judgements extracted from Cochrane review (Coleman et al 2015).

	Random sequence generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Detection bias (biochemical validation of	Overall assessment of risk of bias
Berlin 2014*	+	+	+	+	+	+	+
Coleman 2012*	+	+	+	+	+	+	+
El-Mohandes 2013*	+	+	-	+	?	+	-
Hotham 2006*	+	?	-	+	?	+	-
Kapur 2001*	+	+	+	+	?	+	+
Oncken 2008*	+	+	+	+	+	+	+
Pollak 2007*	+	+	-	+	+	+	-
Wisborg 2000*	+	+	+	?	+	?	+

* Denotes study assessment extracted directly from Cochrane review, Coleman et al. 2015. + denotes low risk of bias, ?, unclear risk of bias and – denotes high risk of bias.

Included study characteristics

ID	Berlin 2014
Bibliographic reference	Berlin I, Grange G, Jacob N, Tanguy ML. Nicotine patches in pregnant smokers: randomised, placebo controlled, multicentre trial of efficacy. *BMJ* 2014;348:1622.
Study type	Double-blind, placebo-controlled, parallel-group RCT.
Country	France
Study Setting	23 maternity wards
Number of participants	203 NRT; 199 Control
Number of withdrawals	105 discontinuations of NRT treatment (92 participant's decision, 2 serious adverse events, 11 adverse events); 120 discontinuations of placebo patch (113 participant's decision, 1 serious adverse event, 6 adverse events)
Patient characteristics	Pregnant women aged ≥ 18 years, between 9 and 20 weeks' gestation who smoked at least 5 daily cigarettes and scored at least 5 on a scale measuring motivation for quitting smoking (range 0-10).
Intervention	The intervention patch delivered nicotine as nicotine replacement therapy over a 16-hour period. Both 10 mg and 15 mg patches were used and women's does ranged from 10 mg to 30 mg per day. A saliva sample was collected at women's first trial visit/contact with the research team. Between this and a second visit/contact, which occurred 2 weeks later, women were instructed to either stop smoking or to reduce this to less than 5 daily cigarettes. Women who managed to reduce or stop smoking in this way were, at their second visit, randomised to either placebo or active patch in a 1:1 ratio. The nicotine dose used for women's first prescription of NRT (made at this 2nd trial visit) was based on their saliva cotinine level obtained from the sample given at visit 1 with the aim being to attempt 100% substitution of nicotine obtained from smoking for that obtained via patches. Women were instructed to use NRT from their quit date until delivery. Smoking and using patches was not encouraged (this is described as a 'safety concern'). However, if women did have a temporary lapse to smoking, they were allowed to remain on NRT afterwards. Both groups received counselling on how to use patches.
Comparison	Intervention and control differed only in the provision of active or visually-identical placebo transdermal patches.
Length of follow-up	End of pregnancy (two month post-pregnancy follow up was planned but not reported due to very low attendance)
Outcome measures/Results	There were 2 primary outcomes, 1 maternal and 1 relating to infants; these were complete, continuous abstinence from smoking since the quit date and infant birthweight. A positive abstinence outcome was recorded where women self-reported 7 days abstinence from smoking at each study visit and this was confirmed by an exhaled CO reading of 8 ppm or less. There were up to 7 study visits with the final 1 intended for 1 month prior to delivery; no lapses from smoking were permitted.

Source of funding	Funded by the Ministry of Health, France (grant No MA05 00150) and co-sponsored by Assistance publique-Hôpitaux de Paris (P060604).
Additional comments	The cessation outcome used was more stringent than in many studies; often some allowance for temporary lapses to smoking is permitted and many studies assess smoking status as a smaller number of time points in pregnancy.

ID	**Coleman 2012**
Bibliographic reference	Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, et al. Smoking, Nicotine, and Pregnancy (SNAP) Trial Team. A randomized trial of nicotine-replacement therapy patches in pregnancy. *New England Journal of Medicine* 2012;366:808-18.
Study type	Double-blind placebo-controlled RCT – stratified by trial centre only.
Country	England
Study Setting	7 hospitals
Number of participants	521 NRT; 530 Control
Number of withdrawals	83.1% and 93.1% included in 1 month and delivery follow up for NRT; 81.1% and 93.8% included in 1 month and delivery follow up for placebo
Patient characteristics	Pregnant women (n = 1050) who agreed to set a quit date, were 16 to 50 years of age, were at 12 to 24 weeks of gestation, smoked 10 or more cigarettes daily before pregnancy, currently smoked 5 or more cigarettes daily, and had an exhaled CO concentration of at least 8 ppm.
Intervention	Research midwives were trained to provide behavioural support according to national standards, with the use of a manual that included guidance from a British expert trainer of smoking-cessation professionals and behavioural approaches from the Smoking Cessation or Reduction in Pregnancy Treatment trials that were believed to be relevant to British smokers. At enrolment, research midwives provided behavioural support lasting up to 1 hr, and participants agreed to a quit date within the following 2 weeks; follow-up was timed from the quit date. Subsequently, participants were randomly assigned to receive a 4-week supply of transdermal patches for nicotine-replacement therapy (at a dose of 15 mg per 16 hrs) or visually identical placebos, which were started on the quit date (all study treatment was purchased at market rates from United Pharmaceuticals). 1 month after the quit date, women who were not smoking, as validated by an exhaled CO concentration of less than 8 ppm, were issued another 4-week supply of patches. In addition to behavioural support at enrolment, research midwives provided 3 sessions of behavioural support by telephone to participants: 1 session on the quit date, 1 session 3 days afterward, and 1 at 4 weeks. The women who collected a second month's supply of nicotine-replacement patches also received face-to-face support from the research midwife at the time of collection. Women were offered additional support from local National Health Service smoking cessation services and were encouraged to ask for support from the research midwives or smoking cessation service staff; support was provided according to the manual.

Comparison	Intervention and control conditions differed only in the provision of transdermal patches; the intervention group received active and the control group, visually identical placebo patches.
Length of follow-up	From date of smoking cessation to delivery.
Outcome measures/Results	Prolonged smoking cessation between a quit date soon after enrolment and delivery, validated by both exhaled CO monitoring and saliva cotinine estimation. Cut points: exhaled CO, smoking was defined as > 7 ppm, saliva cotinine, smoking defined as > 9 ng/dL. Birth outcomes including Apgar score at 5 mins after birth, cord arterial blood pH, intraventricular haemorrhage, neonatal convulsions, congenital abnormalities, necrotising enterocolitis, mechanical ventilation of infant, assisted vaginal delivery, maternal death and caesarean section. For infants: survival to 2 years of age without developmental impairment, reported respiratory symptoms. Maternal: self-reported abstinence from smoking for at least 7 days reported at 6, 12 and 24 months after childbirth, prolonged abstinence from smoking since a quit date set in pregnancy and until 24-month follow-up (defined as having validate abstinence at delivery followed by reported abstinence at all outcome points listed above.
Source of funding	Supported by a grant from the NIHR Health Technology Assessment Programme (06/07/01).
Additional comments	None

ID	**El-Mohandes 2013**
Bibliographic reference	Jackson SL, Peterson G, Vial JH, Jupe D. Improving the outcomes of anticoagulation: an evaluation of home follow-up of warfarin initiation. Journal of Internal Medicine. 2004a; 256: 137-44.
Study type	Non-placebo parallel-design RCT.
Country	USA
Study Setting	3 prenatal care sites
Number of participants	26 NRT; 26 Control
Number of withdrawals	9 discontinued NRT (8 refused, 1 Other); 3 discontinued CBT control (2 refused, 1 relocated)
Patient characteristics	English speaking pregnant women who smoked and were residents of Washington DC in the United States, of ethnic minority backgrounds, aged at least 18 years and less than 30 weeks' gestation. Women needed to express a, desire to quit and have an expired air CO reading of 8 ppm or less and a salivary cotinine of 20 ng/mL or less (NB: clincialtrials.gov website says 30 ng/mL: or less) or a urinary cotinine of 100 ng/mL or less.
Intervention	1:1 ratio randomisation, stratified by site and initial salivary cotinine levels to either 1) cognitive behavioural therapy (CBT) and NRT transdermal patches or 2) CBT alone.

	NRT: a 10-week course of 24-hour patches was offered, with initial dosing varying with baseline salivary cotinine measurements. Women with levels of ≥ 100 ng/mL were issued with 21 mg patches for 2 weeks, 14 mg patches for 4 weeks, and finally 7 mg patches for 4 weeks. Women with levels of ≥ 20 ng/mL and ≤ 100 ng/mL were issued with 14 mg patches for 6 weeks and 7 mg patches for 4 weeks. The first batch of patches was issued at the second study visit at which salivary cotinine levels were available. Participants were given clear verbal and written instructions on patch use. They were advised never to smoke while using the patch, to remove the patch before going to sleep and not to use other NRT concurrently. CBT: this was the same for both groups.
Comparison	CBT alone (non-placebo trial)
Length of follow-up	Followed to delivery
Outcome measures/Results	Smoking cessation outcome: during the study participants made 6 visits to the study team in the antenatal period. At visit 2 (V2), trial interventions were initiated and at each of visits V3-V6 (the last before childbirth), women were asked if they had smoked since their previous clinic visit (e.g. at V3, they were asked if they had smoked since V2). Participants who reported smoking cessation had this validated using exhaled CO with abstinence viewed as confirmed by a reading of < 8 ppm. The trial manuscript reports point prevalence of abstinence from smoking at each time point and data from V6 are used in analyses. All data were validated (self-report not available), but the period of abstinence which was validated is unclear and varied with the interval between clinic visits. Secondary outcomes reported in the trial manuscript are: premature birth (i.e. at < 37 weeks' gestation); gestational age at birth; mean birthweight and low birthweight < 2500 g. Authors have clarified that the following outcomes were collected too: ability to not smoke for 24 hrs or more; longest number of days the woman was able to go without even a puff of smoking; frequency of smoking at least puff during the last 7 days; number of cigarettes smoked each day; the number of cigarettes smoked during the past 24 hrs and frequency of use of other forms of tobacco.
Source of funding	This study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (U10 HD036104 and U18 HD031206-07). and also, in part, by the intramural program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.
Additional comments	Title of paper states it was conducted in 'African-American smokers', but in manuscript participants are described as 'ethnic minority women' and inclusion criteria on clinicaltrials.gov includes Hispanic women.

ID	**Hotham 2006**
Bibliographic reference	Hotham ED, Gilbert AL, Atkinson ER. A randomised-controlled pilot study using nicotine patches with pregnant women. *Addictive Behaviors* 2006;31(4):641-8.
Study type	Non-placebo parallel-design RCT.
Country	Australia

Study Setting	A women's and children's hospital
Number of participants	20 NRT; 20 Control
Number of withdrawals	7 withdrew from NRT (4 want to return to normal/ not a good time to quit, 1 concern about using patches, 2 adverse reaction to patches), 7 withdrew from control (5 too much of a hassle/all too hard, 1 not in patch arm, 1 too late to quit now0
Patient characteristics	40 healthy Australian women between 12 and 28 weeks pregnant and smoking >= 15 cigarettes daily with an exhaled breath CO reading of > 8 ppm.
Intervention	Intervention: counselling as above plus an element concerning correct use of NRT *plus* 15 mg/16 hr patches for a maximum of 12 weeks.
Comparison	Control group: 5 min counselling at baseline and further brief counselling (< 2 min duration) at follow-up visits.
Length of follow-up	Primary end point was last antenatal visit, but there was follow up by phone up to 3 months post-delivery.
Outcome measures/Results	Smoking cessation (point prevalence) at final antenatal visit. Women seen 'at least monthly during gestation'; also seen within 48 hrs of delivery when exhaled CO and saliva sample (for cotinine) taken and by telephone at 6 weeks and 3 months.
Source of funding	Supported by the Health Promotion Branch of the (then) South Australian Health Commission, now the Department of Health (SA). The WCH Perinatal Pathology Fund funded cotinine tests.
Additional comments	Exhaled CO readings used to validate point prevalence cessation at final antenatal visit. Cut point = 8 ppm CO. Author clarification used to obtain this information as not clear in research report.

ID	**Kapur 2001**
Bibliographic reference	Kapur B, Hackman R, Selby P, Klein J, Koren G. Randomized, double-blind, placebo-controlled trial of nicotine replacement therapy in pregnancy. *Current Therapeutic Research - Clinical and Experimental* 2001;62(4):274-8.
Study type	Parallel-design RCT with active and placebo patches and clinicians/researchers and participants unaware of allocation.
Country	Canada
Study Setting	A counselling service
Number of participants	17 NRT; 13 Control

Number of withdrawals	4 women assigned to NRT competed the program, 3 continued the program for 3 weeks, and 10 discontinued within 1 week. No women assigned to the placebo completed the program; 3 used the patch for 4-5 weeks, 10 failed to continue beyond 1 week.
Patient characteristics	30 healthy Canadian women between 12 and 24 weeks pregnant and smoking >= 15 cigarettes daily who want to quit smoking and could not do so in 1st trimester.
Intervention	12 week course of NRT: 15 mg/18 hr patch for 8 weeks, then 10 mg/18 hr for 2 weeks and finally 5 mg/18 hr for 2 weeks. Behavioural counselling at baseline and all follow-up points. Counselling at baseline including a video explaining how to use patch; also counselling at all follow-ups. Weekly telephone contact with women.
Comparison	Identical placebo patches
Length of follow-up	8 weeks from commencement of the program.
Outcome measures/Results	Smoking cessation (unclear if point prevalence or continuous cessation measured) 8 weeks into programme (20-32 weeks into pregnancy). Follow-up also at weeks 1 and 4 into programme with saliva and serum cotinine measured at all time points.
Source of funding	Supported by a grant from the Canadian Institute of Health Research
Additional comments	Primary outcome validated at 8 weeks into programme. Cotinine cut point not stated but paper states that 'in no case was smoking cessation associate with thiocyanate levels of > 1 ug/ml'.

ID	**Oncken 2008**
Bibliographic reference	Oncken C, Dornelas E, Greene J, Sankey H, Glasmann A, Feinn R, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. *Obstetrics & Gynecology* 2008;112(4):859-67.
Study type	Parallel-design RCT with active and placebo NRT gum and clinicians / researchers and participants unaware of allocation.
Country	USA
Study Setting	3 prenatal clinics
Number of participants	100 NRT; 94 placebo
Number of withdrawals	97 participants with perinatal outcomes from NRT group (1 withdrew consent, 2 lost to follow up); 89 participants with perinatal outcomes from placebo group (1 who withdrew consent, 4 lost to follow up)
Patient characteristics	194 healthy, US English/Spanish-speaking women <= 26 weeks pregnant, smoking >= 1 cigarette daily and aged >=16 yrs.

Intervention	12 weeks treatment with 2 mg NRT gum. 6 weeks full treatment was followed by 6 weeks tapering of treatment. Instructed not to chew > 20 pieces daily and to use 1 piece of gum for each substituted cigarette. Additionally all participants received individual counselling at baseline and all 8 follow-ups - 2, 35 minute counselling sessions at baseline and within 1 week of quit date and shorter sessions at other follow-ups.
Comparison	Identical placebo gum
Length of follow-up	Up to 6-12 weeks post-partum
Outcome measures/Results	Self-reported 7-day point prevalence abstinence at 32-35 weeks. Exhaled CO of less than 8 ppm used for validation at primary outcome point.
Source of funding	Supported by NIH grants R01 DA15167, GCRC grant M01 RR006192, P50 DA013334, P50 AA015632. Nicotine Gum was provided free of charge from Glaxo-Smith Kline
Additional comments	None

ID	**Pollak 2007**
Bibliographic reference	Pollak KI, Oncken CA, Lipkus IM, Lyna P, Swamy GK, Pletsch PK, et al. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. *American Journal of Preventive Medicine* 2007;33(4):297-305.
Study type	Non-placebo parallel-design RCT.
Country	USA
Study Setting	14 clinical sites across one state
Number of participants	122 NRT; 59 Control
Number of withdrawals	7 withdrew from NRT, 4 withdrew from control
Patient characteristics	181 healthy, US English-speaking women between 13 and 25 weeks pregnant, smoking >= 5 cigarettes daily and aged >=18 years. Must have smoked > 100 cigarettes in lifetime.
Intervention	Intervention group: counselling (5 face-to-face and 1 telephone behavioural counselling sessions with booklet and support materials) additional focus on use of NRT. Women permitted choice of NRT from patch, gum or lozenge. Patch dose depended on CPD: < 10 CPD, 7 mg/16 hr, 10 to 14 CPD 14 mg/16 hr and >= 15 CPD 21 mg/16 hr. Where gum or lozenge used, one 2 mg piece was used for each cigarette smoked daily. Maximum of 6 weeks NRT provided and no NRT provided when women return to smoking.

Comparison	Control group: 5 face-to-face and 1 telephone behavioural counselling sessions with booklet and support materials.
Length of follow-up	3 months post-partum
Outcome measures/Results	Self-reported 7-day point prevalence abstinence at 38 weeks. Also follow-up at 7 weeks after randomisation and 3 months post-partum using self-report data. Saliva samples for cotinine validation were collected at the intervention session that coincided with each telephone survey from all women regardless of smoking status. Cut point for primary outcome <= 10 ng/mL. Validation data were collected at all 3 time points but is only reported for the 2 data collection points within pregnancy.
Source of funding	Supported by National Cancer Institute grant R01CA089053 and operated under IND # 67,259.
Additional comments	Choices of NRT: 72/122 patch = 59%, 32/122 gum = 26.2% and 12/122 lozenge = 9.8%. 19 women chose another formulation as they could not quit with initial selection (changes not recorded).

ID	**Wisborg 2000**
Bibliographic reference	Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstetrics & Gynecology* 2000;96(6):967-71.
Study type	Parallel-design RCT with active and placebo patches and clinicians/researchers and participants unaware of allocation.
Country	Denmark
Study Setting	One hospital
Number of participants	124 NRT; 126 control
Number of withdrawals	Not reported
Patient characteristics	250 healthy Danish women < 22 weeks pregnant and smoking >= 10 cigarettes daily.
Intervention	11 week course of NRT: 15 mg/16 hr for 8 weeks then 10 mg/16 hr for 3 weeks plus behavioural counselling and information pamphlet.
Comparison	Identical placebo patch with counselling and pamphlet
Length of follow-up	Phone follow-up up to 1 year after delivery

Outcome measures/Results	Self-reported abstinence of >= 7 days at 2nd, 3rd and 4th prenatal visits (4 weeks prior to delivery). Follow-ups at times above and also by telephone at 3 months and 1 year after delivery.
Source of funding	Supported by the Danish Cancer Society and the Ministry of Health (The National Health Fund supported this study for Research and Development). Pharmacia & Upjohn provided nicotine patches
Additional comments	Saliva cotinine level < 26 ng/mL at the 4th visit (4 weeks prior to expected delivery date) used to validate reported smoking cessation. The test used could not detect lower than 20 ng/mL (data verified by communication with author). Only self-report data were collected after childbirth.

Synthesis and meta-analysis

Smoking Cessation

Coleman et al. 2015 present a meta-analysis including eight studies and 2199 participants. Analysis indicated that NRT as an adjunct to behavioural support is effective for smoking cessation in pregnancy (risk ratio (RR) (1.41, 95% confidence interval (CI) 1.03 to 1.93, I^2 = 18%, Figure 7.1). In the subgroup analysis that compared active NRT with placebo, heterogeneity between studies was substantially reduced and although the risk ratio for smoking cessation with NRT was lower and in the same direction, it was not significant (RR 1.28, 95% CI 0.99 to 1.66, Tau^2 = 0.00, I^2 = 0%, five studies, 1926 women, Figure 7.1, Analysis 1), whereas, the estimate derived from non-placebo controlled trials indicated efficacy (RR 8.51, 95% CI 2.05 to 35.28, I^2 = 0%, three studies, 273 women) (P value for random-effects subgroup interaction test = 0.01; Figure 7.1, Analysis 2).

Hartmann-Boyce et al. 2018 performed a meta-analysis of abstinence at the time point closest to time of delivery and found a similar result, with NRT showing a statistically significant benefit compared to controls (RR 1.32, 95% CI 1.04 to 1.69, 2129 participants; I^2 = 23%, six studies).

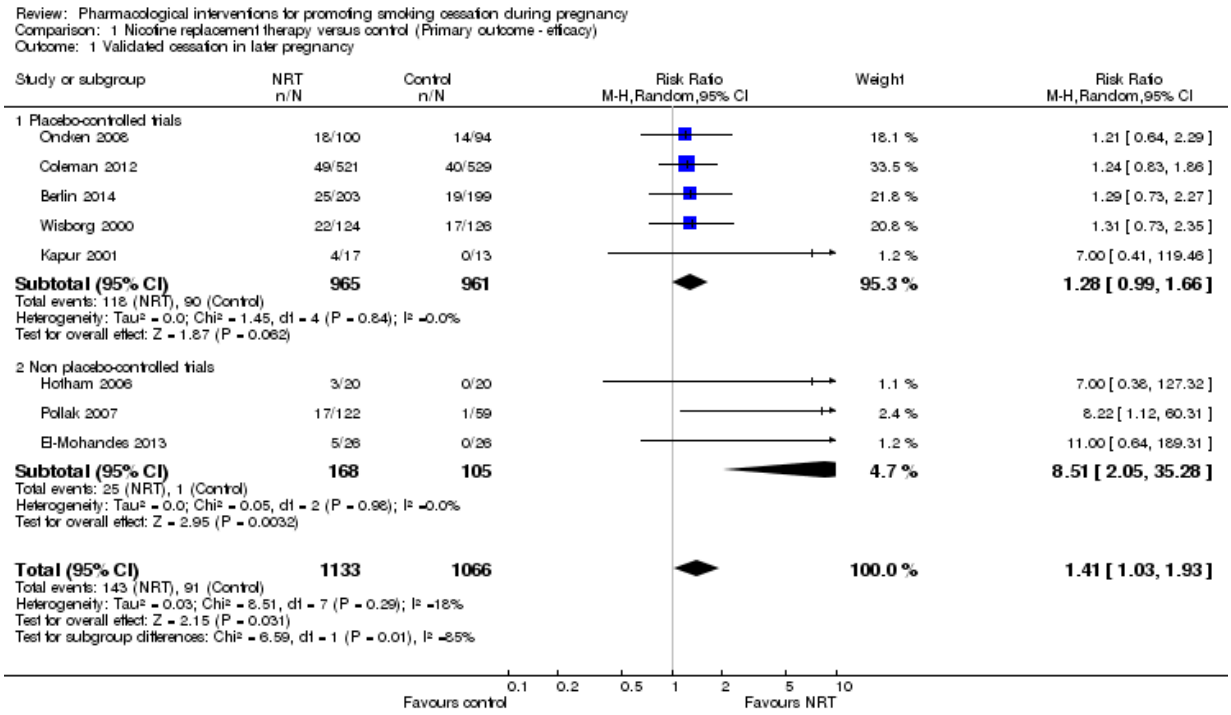


Figure 7.1 Validated cessation in later pregnancy (reproduced from Coleman et al. 2015)

The impact of NRT as an adjunct to behavioural support on cessation at time points after childbirth was investigated by pooling data from studies that provided post-natal follow-up data on smoking behaviour. In a pooled analysis of studies which reported non-validated seven-day point prevalence of abstinence from smoking at or before six months after childbirth (predominantly at or around three months), Coleman et al. 2015 found no evidence that NRT compared to placebo or non-placebo controlled trials was effective for smoking cessation; (RR for cessation with NRT versus placebo 1.15, 95% CI 0.75 to 1.77, I^2 = 0%, two studies, 444 women, Figure 7.2, Analysis 1). Similarly, one study with non-validated seven-day point prevalence of smoking abstinence RR of NRT compared to placebo at one year after childbirth did not indicate that NRT had an effect at this time point; RR 1.04, 95% CI 0.57 to 1.88, I^2 = 0%, one study, 246 women.

Hartmann-Boyce et al. 2018 pooled data from four trials for the longest time-point reported post-partum and also found no significant effect (RR 1.29, 95% CI 0.90 to 1.86, 1675 participants,; I^2 = 0%, four studies).

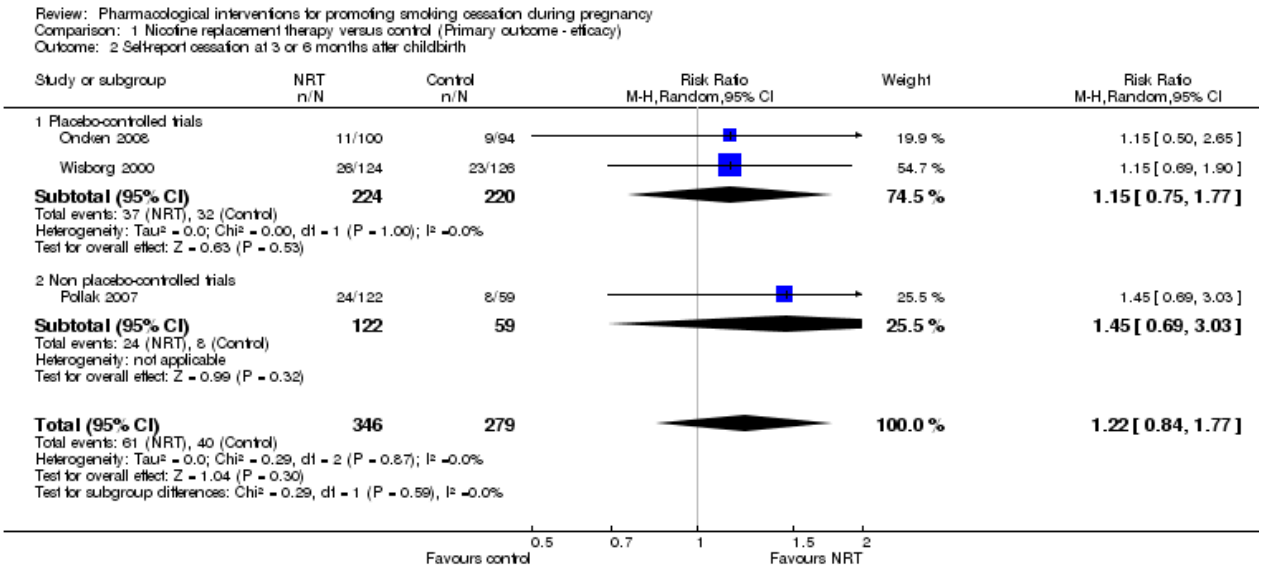


Figure 7.2 Self report cessation at 3 or 6 months after childbirth (reproduced from Coleman et al. 2015)

The one study included by Coleman et al. 2015 which monitored continuous cessation from a quit date set in pregnancy to post-natal time points alongside seven-day point prevalence abstinence data collected at the same time points (Coleman 2012), reported higher point prevalence than continuous cessation rates at each time point and rates of continuous cessation until two years after childbirth were low (2.9% in NRT group versus 1.7% in placebo, adjusted P value = 0.12).

50% Reduction in cigarettes per day

No included study reported the outcome of cigarettes smoked/day.

Foetal outcomes

Analyses presented by Coleman et al. 2015 revealed no statistically significant difference in risk of miscarriage/spontaneous abortion between NRT and control groups (RR 1.47, 95% CI 0.45 to 4.77, I^2 = 0%, four studies, 1782 women, Analysis 7.3).

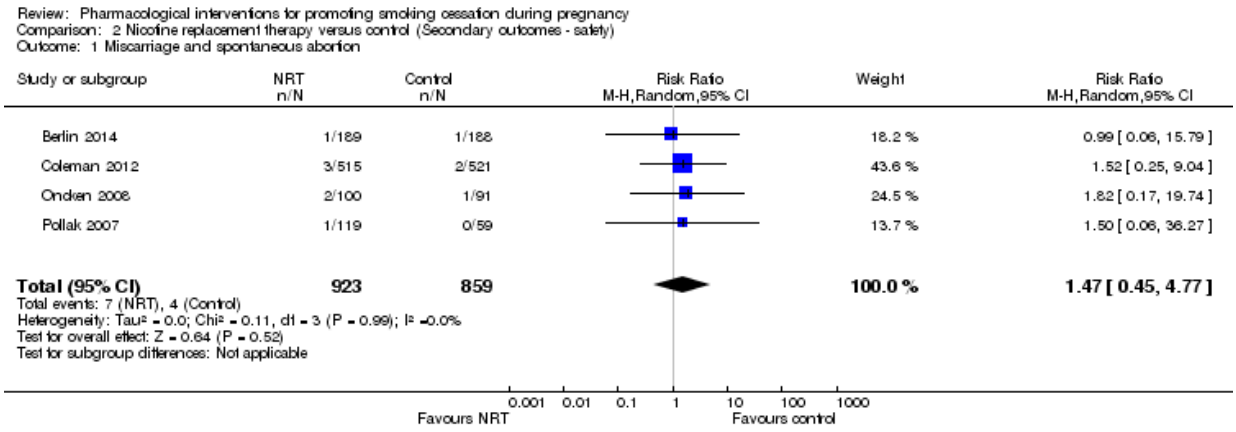


Figure 7.3 Miscarriage and spontaneous abortion (reproduced from Coleman et al. 2015)

Similarly, no statistically significant difference between the numbers of stillbirths in the NRT and control arms of trials (RR 1.24, 95% CI 0.54 to 2.84, I^2 = 0%, four studies, 1777 women, Figure 7.4).

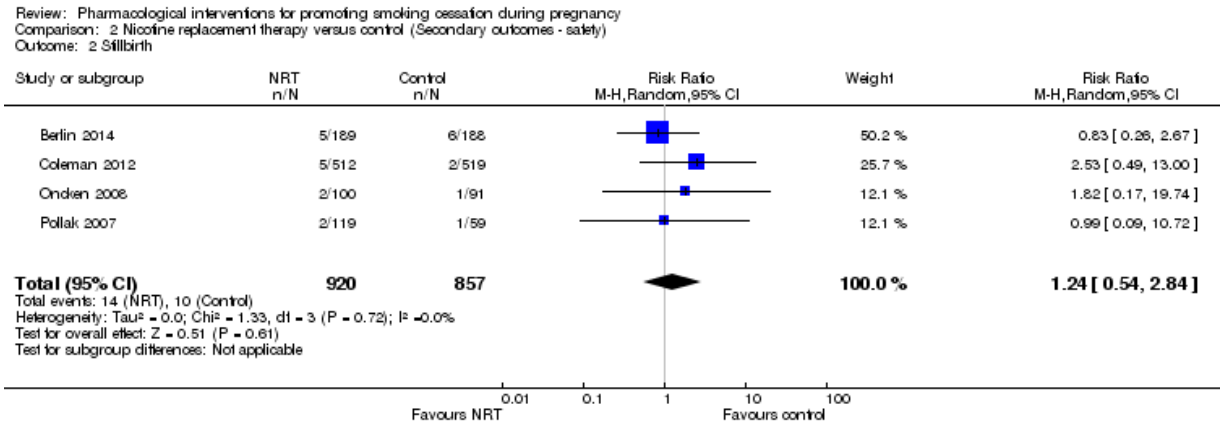


Figure 7.4 Stillbirth (reproduced from Coleman et al. 2015)

The pooled estimate for control group birthweight was higher than for the NRT group, but this difference was not significant (mean difference (MD) 100.54 g, 95% CI -20.84 to 221.91, I^2 = 75%, six studies, 2068 women), and heterogeneity was high and on the borderline for presenting pooled estimates (Figure 7.5); consequently, the result for this comparison must be interpreted with caution.

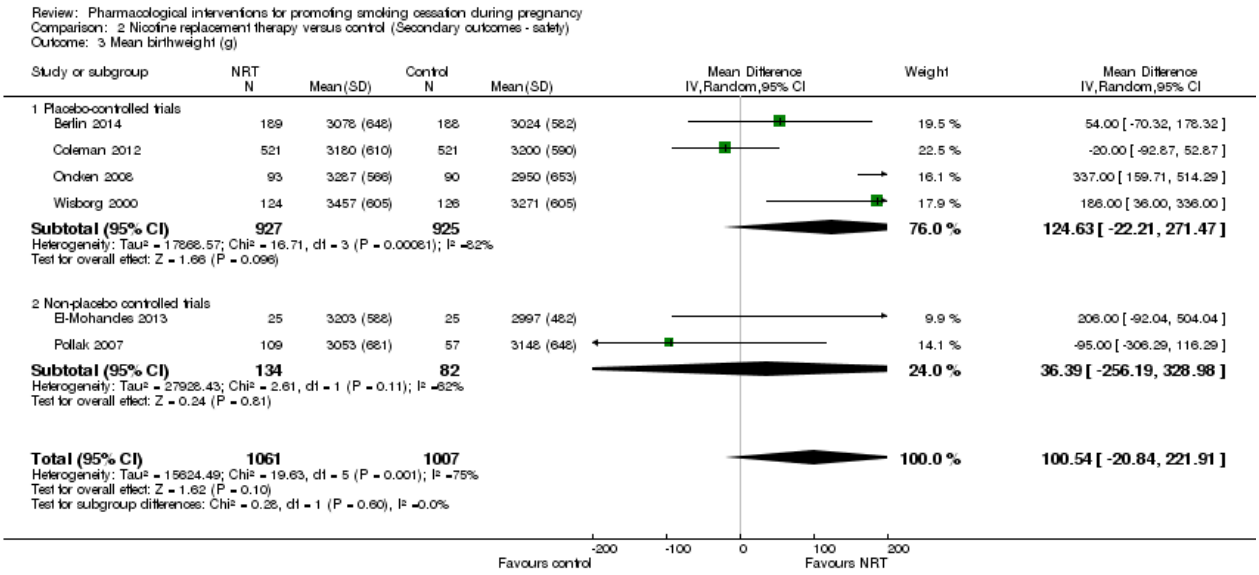


Figure 7.5 Mean birthweight, g (reproduced from Coleman et al. 2015)

There was a lower incidence of low birthweight births in NRT group women but again, this was not significant and was found in the context of much heterogeneity so caution is again warranted (RR 0.74, 95% CI 0.41 to 1.34, I^2 = 71% six trials, 2037 women, Figure 7.6).

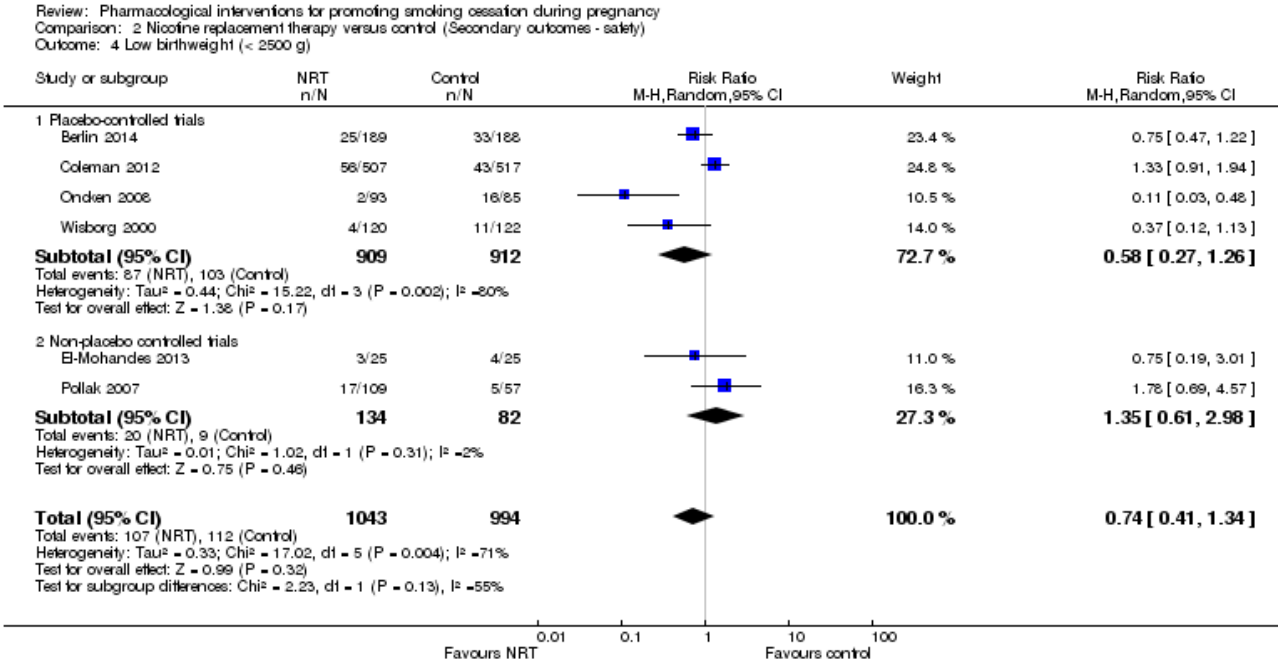


Figure 7.6 Low birthweight <2500 g (reproduced from Coleman et al. 2015)

Preterm births (RR 0.87, 95% CI 0.67 to 1.14, I^2 = 0%, six studies, 2048 women, Figure 7.7), neonatal intensive care unit admissions (RR 0.90, 95% CI, 0.64 to 1.27, Tau^2 = 0.00, I^2 = 0%, four studies, 1756 women, Figure 7.8), and neonatal deaths (RR 0.66, 95% CI 0.17, 2.62, I^2 = 0%, four studies, 1746 women, Figure 7.9), were all less frequent in NRT groups, but differences between NRT and control groups were not significant.

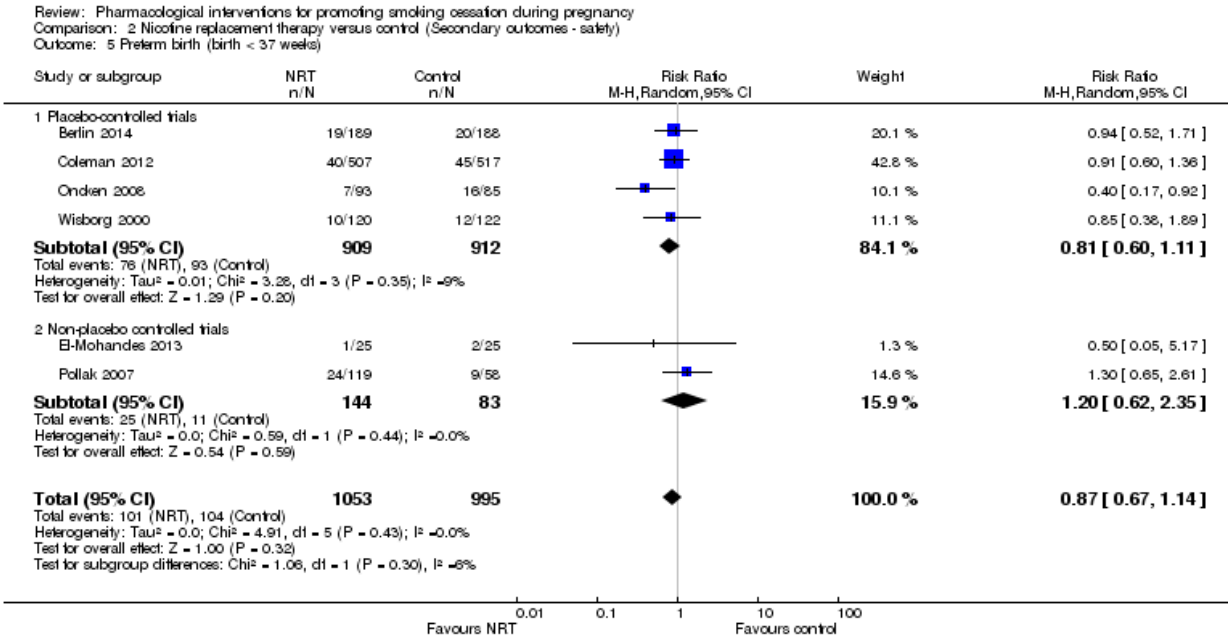


Figure 7.7 Preterm birth < 37 weeks (reproduced from Coleman et al. 2015)

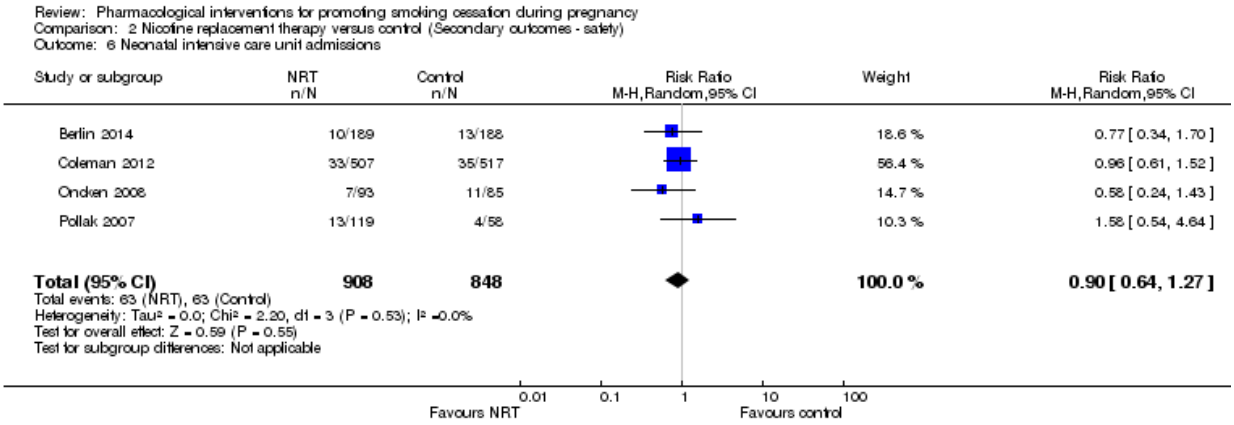


Figure 7.8 Neonatal intensive care unit admissions (reproduced from Coleman et al. 2015)

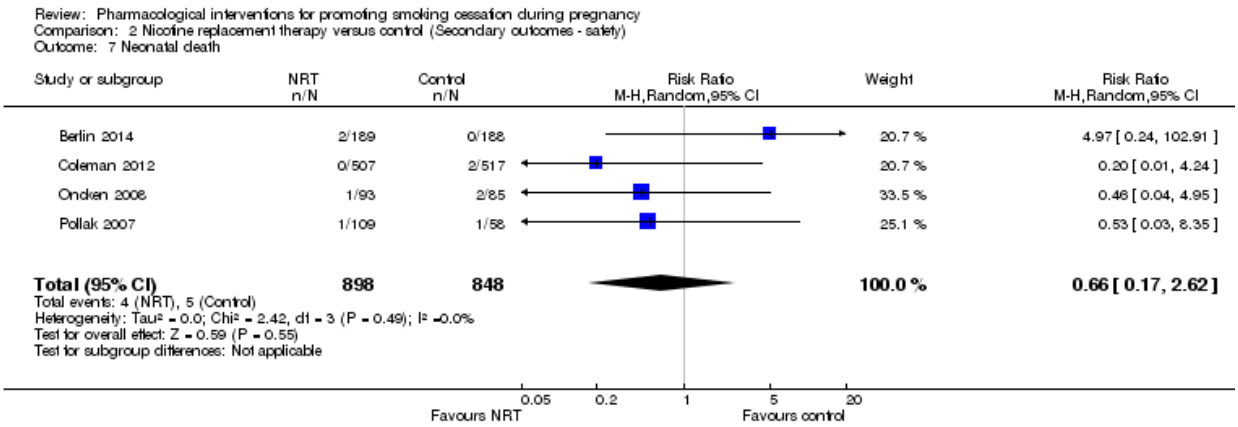


Figure 7.9 Neonatal death (reproduced from Coleman et al. 2015)

Adverse events

Coleman et al. 2015 gave a narrative summary of adverse events, reporting that five trials described non-serious side effects (Berlin et al. 2014, Coleman et al. 2012; Hotham et al. 2006; Oncken et al. 2008; Wisborg et al. 2000): one reported their frequency within women using NRT, noting that five (25%) participants in the NRT group experienced minor symptoms and two women stopped using patches after unpleasant effects (Hotham et al. 2006) although this trial did not monitor non-serious symptoms in the control group. Oncken et al. 2008 reported that at least 10% of participants experienced headache, dizziness, fatigue, heartburn, nausea or vomiting, with 14 (15%) in the NRT and 12 (12%) in the control groups discontinuing treatment due to adverse effects. Wisborg et al. 2000 noted that 11 participants stated that adverse events (e.g. skin irritations and headache) made them discontinue patches, but did not report treatment allocations; also five participants in this trial reported palpitations and two nausea. Coleman et al. 2012 noted 535 non-serious adverse events reported by 521 NRT group participants and 450 reported by the 529 placebo group ones. Berlin 2014 reported a range of non-serious adverse events noting that more non-gynaecological ones occurred in the NRT group; this was principally attributable to skin reactions. In this study, 11% of participants in the NRT suffered a skin reaction at the patch site compared with 4% in the placebo one. Stead et al. 2012 noted that recruitment for Pollak et al. 2007 was suspended early when interim analysis found a higher rate of negative birth outcomes in the NRT arm (primarily preterm birth); however, when adjusted for previous birth outcomes the adverse event rate between the two groups was not significantly different in final analysis.

Conclusion

Based on these findings Coleman et al 2015 concluded that there is weak evidence to suggest that using NRT with behavioural support for smoking cessation in pregnancy is effective, but that there is no evidence that NRT has either a positive or negative impact on pregnancy and infant outcomes.

These efficacy findings should be treated cautiously as their derivation includes data from non-placebo RCTs which appear to have higher risks of bias.

Appendix 1 – Excluded Studies

Studies excluded after full text assessment against eligibility criteria

Citation	Reason for exclusion
Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews. 2016;(5):CD006103. DOI:10.1002/14651858.CD006103.pub7.	Main comparison Varenicline vs placebo, but also includes vs NRT. No studies included/located that investigate VR + NRT vs VR. No NRT vs NRT investigated. No studies identified investigating duration of VR treatment.
Tran K, Argáez C. Smoking Reduction and Cessation Interventions for Pregnant Women and Mothers of Infants: A Review of the Clinical Effectiveness. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Jul. NB. Includes Coleman 2015 review	Review included all interventions. Most are psychosocial. No data provided for NRT beyond Coleman 2015 review.
Baraona LK, Lovelace D, Daniels JL, McDaniel L. Tobacco Harms, Nicotine Pharmacology, and Pharmacologic Tobacco Cessation Interventions for Women. Journal of Midwifery & Women's Health. 2017;62(3):253-269. DOI: 10.1111/jmwh.12616.	Literature review. Includes studies already identified for other questions.
Gould GS, Lim LL, Mattes J. Prevention and Treatment of Smoking and Tobacco Use During Pregnancy in Selected Indigenous Communities in High-Income Countries of the United States, Canada, Australia, and New Zealand: An Evidence-Based Review. Chest. 2017;(4):853-866. DOI: 10.1016/j.chest.2017.06.033.	Literature review. Reference to 2 RCTs that use behavioural counselling rather than NRT.
Hajek P, McRobbie H, Myers Smith K, Phillips A, Cornwall D, Dhanji A. Increasing Varenicline Dose in Smokers Who Do Not Respond to the Standard Dosage A Randomized Clinical Trial. JAMA Intern Med. 2015;175(2):266–271. DOI:10.1001/jamainternmed.2014.6916	Ineligible intervention. No NRT involved in study. Low dose Varenicline 2mg for 3 weeks vs high dose (2mg for 12 days followed by up to 5mg for 1 weeks) then 2mg for remaining 11 weeks. Total 15 wk study duration. Smoking cessation was compared at 15 wks.
Ravva P, Gastonguay MR, Faessel HM, Lee TC, Niaura R. Pharmacokinetic-Pharmacodynamic Modeling of the Effect of Varenicline on Nicotine Craving in Adult Smokers. Nicotine & Tobacco Research. 2015;17(1):106–113. DOI: 10.1093/ntr/ntu154	No eligible comparator or dose or outcome. Compared Varenicline (2mg) vs placebo for relief of cigarette craving.
Piper ME, Fiore MC, Smith SS, Fraser D, Bolt DM, Collins LM, et al. Identifying Effective Intervention Components for Smoking Cessation: A Factorial Screening Experiment. Addiction (Abingdon, England). 2016;111(1):129-141. DOI:10.1111/add.13162	Ineligible comparator (8 week combination NRT). Factorial expt with 6 interventions. Only intervention 6 is active control 16 vs 8 wks of combination patch + gum. Endpoints 7PP at 16wks. Also measured at 2 and 26 wks. Investigating effect of duration of combination therapy, not dose

Citation	Reason for exclusion
Piper ME, Schlam TR, Cook JW, Smith SS, Bolt DM, Loh WY, et al. Toward Precision Smoking Cessation Treatment I: Moderator Results from a Factorial Experiment. Drug and Alcohol Dependence. 2017;171:59-65. DOI:10.1016/j.drugalcdep.2016.11.025	Ineligible comparator (8 week combination NRT). Does not measure standard duration of 12 weeks. Secondary analysis of Piper et al.2016 to investigate moderator effects (gender, race, education, psychiatric history and dependence, smoking rate and living with smoker). No results provided for moderator effects of smoking dependence and rate with NRT.
Piper ME, Cook JW, Schlam TR, Smith SS, Bolt DM, Collins LM, et al. Toward Precision Smoking Cessation Treatment II: Proximal effects of smoking cessation intervention components on putative mechanisms of action. Drug and Alcohol Dependence. 2017;171:50-58. DOI: 10.1016/j.drugalcdep.2016.11.027	Ineligible comparator (8 week combination NRT). Does not measure standard duration of 12 weeks. Secondary analysis of Piper et al.2016 to investigate whether multiple intervention components affect hypothesised change mechanisms and whether related to cessation.
Lindson-Hawley N, Coleman T, Docherty G, Hajek P, Lewis S, Lycett D, et al. Nicotine patch preloading for smoking cessation (the preloading trial): study protocol for a randomized controlled trial. Trials. 2014;15:296. DOI:10.1186/1745-6215-15-296	Protocol only, no results provided – see Aveyard et al HTA 2018 (full study retrieved)
Aveyard P, Lindson N, Tearne S, Adams R, Ahmed K, Alekna R, et al. Nicotine preloading for smoking cessation: the Preloading RCT. Health Technol Assess. 2018;22(41)	Ineligible. Preloading with 21mg patch for 3-8wks vs no treatment. Follow up 4wk, 6mth, 12mths.
Hansson A, Rasmussen T, Kraiczi H. Single-Dose and Multiple-Dose Pharmacokinetics of Nicotine 6 mg Gum. Nicotine & Tobacco Research. 2017;19(4):477-483. DOI: 10.1093/ntr/ntw211.	Two randomised studies. Compared 6mg gum to 2, 4 mg gum and 4 mg lozenge with single dose and multi dose. Blood sample taken up to 12 hrs (single dose) and 1.5hrs (multi dose) after final NRT administration. Plasma nicotine concentration only outcome reported.
Gonzales D, Hajek P, Pliamm L, Nackaerts K, Tseng L-J, McRae TD et al. Retreatment With Varenicline for Smoking Cessation in Smokers Who Have Previously Taken Varenicline: A Randomized, Placebo-Controlled Trial. Clinical Pharmacology and Therapeutics. 2014;96(3):390-396. DOI:10.1038/clpt.2014.124.	Comparator ineligible. Varenicline (incremental dosing) vs placebo treatment in smokers who had used the drug before. 12 wk treatment, 40 wk follow up. Individual counselling provided to all participants (8 sessions, 7 by phone). Continuous abstinence reported at 9-12 wks.
Ferguson SG, Shiffman S. Effect of high-dose nicotine patch on craving and negative affect leading up to lapse episodes. Psychopharmacology (Berl). 2014 Jul;231(13):2595-602. DOI: 10.1007/s00213-013-3429-6	Ineligible comparator and outcomes. Smokers who had previously quit and suffered one lapse received 35mg patch/24 hrs or placebo patch. Both groups also had up to 7 sessions of group CBT. Electronic diary used to assess craving and negative affect.
Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. Nicotine replacement therapy in pregnancy and major congenital anomalies in offspring. Pediatrics. 2015;135(5):859-67. DOI: 10.1542/peds.2014-2560.	Examined risk of NRT and smoking on congenital abnormality in children. Retrospective cohort study. Ineligible design.

Citation	Reason for exclusion
Dennis PA, Kimbrel NA, Dedert EA, Beckham JC, Dennis MF, Calhoun PS. Supplemental nicotine preloading for smoking cessation in post-traumatic stress disorder: Results from a randomized controlled trial. Addictive Behaviors. 2016;59:24-29. DOI:10.1016/j.addbeh.2016.03.004.	Ineligible comparator and intervention. No pharmacological combination therapy has been assessed nor active comparator. Smokers with PTSD. 2wks 'Pre quit' treatment period of active (21mg) patch + CBT vs placebo patch + CBT (CBT, 2 sessions).
Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, et al. Long-term Nicotine Replacement Therapy: A Randomized Clinical Trial. JAMA internal medicine. 2015;175(4):504-511. DOI:10.1001/jamainternmed.2014.8313.	Only comparison of duration of treatment. Compare 8 wk vs 24 wk vs 52 week 21mg patch. All groups received 12 counselling sessions.

Appendix 2 – Cochrane tool

Cochrane tool and criteria to assess the risk of bias of randomised controlled trials*

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

* Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Appendix 3 – Remaining questions with no evidence identified

3. Is a higher dose NRT combination regime more effective than a standard dose and if so, is this effect for all smokers or only for more dependent smokers?			
Population	**Intervention**	**Comparator**	**Outcomes**
Smokers (all)	Higher dose NRT combination regime (Patch and 4mg gum OR patch and inhalator) Higher dose combination would be considered as: • Nicotine patch plus 4mg gum • Nicotine patch plus 4mg lozenge • Nicotine patch plus 10mg inhaler (older studies) max 12 cartridges/day or 15mg inhalator (up to max 6 cartridges/day) • Nicotine patch plus 1mg mouth-spray (up to max 64 sprays/day)	• Standard dose combination regime – patch and 2mg gum • • Standard patch dose: • 21mg/24 hours OR 15mg/16 hours	- Smoking cessation - CPD reduced by 50% Suggest follow Cochrane approach and use the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Length of follow-up: 6 months or longer

5. Is an extended course (24 weeks) of Varenicline more effective than a standard 12 weeks course? If so, is this effect for all smokers or for more dependent smokers?			
Population	**Intervention**	**Comparator**	**Outcomes**
Smokers (all)	• Varenicline extended treatment length (24 weeks)	• Varenicline standard treatment duration (12 weeks)	- Smoking cessation - CPD reduced by 50% - Adverse events Suggest follow Cochrane approach and use the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Length of follow-up: 6 months or longer after treatment completion

6. Is switching to NRT after a standard course of Varenicline more effective than only completing a standard course of Varenicline? If so, is this effect for all smokers or for more dependent smokers?			
Population	**Intervention**	**Comparator**	**Outcomes**
Smokers (all)	• Varenicline standard 12 week treatment, then switch to NRT (for 12 weeks?)	• Varenicline standard treatment duration (12 weeks)	- Smoking cessation - CPD reduced by 50% - Adverse events Suggest follow Cochrane approach and use the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Length of follow-up: 6 months or longer after treatment completion

8. Is it safe and effective for a pregnant smoker to undergo high dose NRT rather than standard dose NRT?			
Population	**Intervention**	**Comparator**	**Outcomes**
Female smokers who are pregnant (all) and attempting to quit	• High dose NRT (any form, combination or monotherapy)	• Monotherapy with oral form or patch	- Smoking cessation - CPD reduced by 50% - Pregnancy outcomes & adverse events (include miscarriage, stillbirth, preterm birth (less than 37 weeks'), low birthweight (less than 2500 g), admissions of babies to neonatal intensive care or neonatal deaths, mean birthweights amongst infants Suggest follow Cochrane approach and use the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Length of follow-up: 6 months or longer, including birth

9. Is it safe and effective for a pregnant smoker to undergo high dose intermittent oral NRT versus continuous dose patches?			
Population	**Intervention**	**Comparator**	**Outcomes**
Female smokers who are pregnant (all)	• High dose NRT (any form, combination or monotherapy)	• Monotherapy with patch only	- Smoking cessation - CPD reduced by 50% - Pregnancy outcomes & adverse events (include miscarriage, stillbirth, preterm birth (less than 37 weeks'), low birthweight (less than 2500 g), admissions of babies to neonatal intensive care or neonatal deaths, mean birthweights amongst infants Suggest follow Cochrane approach and use the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Length of follow-up: 6 months or longer, including birth

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Smoking Cessation Guideline Update:
Evidence to Decision Framework and Recommendations for Practice

December 2018

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Contents

Summary of Recommendations

Following an evidence review and application of the GRADE process for moving from the evidence to a recommendation, the following recommendations were agreed upon by the RACGP smoking cessation guideline update panel.

Clinical Question 1: Is combination NRT (patch and oral form) more effective than patch alone and if so is this effect for all smokers or only for more dependent smokers?

Recommendation: For people who smoke who are wanting to quit who are currently receiving behavioural support, clinicians should recommend combination NRT over single NRT. (Strong Recommendation; Moderate Certainty)

Clinical Question 2: Is a combination of Varenicline and NRT more effective than Varenicline alone and if so is this effect for all smokers or only for more dependent smokers?

Recommendation: For people who smoke who are wanting to quit, clinicians might recommend the use of Varenicline in combination with NRT as compared to Varenicline alone. (Conditional Recommendation; Moderate Certainty)

Clinical Question 4: Does adding any further course of NRT (any form) reduce relapse in smokers who have quit at the completion of a standard course of NRT?

Recommendation: For people who have abstained from smoking at the end of a standard course of NRT, clinicians may consider recommending an additional course of NRT for sustained abstinence. (Conditional Recommendation for or against the intervention; Low Certainty)

Clinical Question 5: Does adding any further course of Varenicline (>12 weeks) reduce relapse in smokers who have quit at the completion of a standard course of Varenicline (12 weeks)?

If so, is this effect for all smokers or for more dependent smokers?

Recommendation: For people who smoke, who are wanting to quit and who are currently receiving behavioural support, clinicians may consider a further course of Varenicline to prevent relapse. (Conditional Recommendation for or against the intervention; Low Certainty)

Clinical Question 7: Is it safe and effective for a pregnant smoker to undergo NRT rather than no NRT?

Recommendation: For women who are pregnant who aim to quit smoking, clinicians may consider recommending NRT as compared to no NRT. There should be a discussion of benefits vs risks, the small benefit for smoking cessation and the lack of evidence around possible harms. There may also be behavioural interventions that should be used. (Conditional Recommendation for or against the intervention; Low Certainty)

Introduction

The Royal Australian College of General Practitioners (RACGP) produce clinical guidelines for GPs and other health professionals for a range of topics. In 2018, RACGP commissioned the Joanna Briggs Institute (JBI) and the JBI Adelaide GRADE Centre to assist with the update of their smoking cessation guideline. The RACGP requested this guideline be updated using GRADE methods. When using GRADE to develop guidelines, an evidence review is required where the end result is a GRADE Summary of Findings table, a summarised representation of the major synthesised findings along with a rating of the certainty in the synthesised evidence (Appendix 1).

These Summary of Findings tables are then incorporated in Evidence to Decision Frameworks which the guideline panel have worked through during a round table discussion. The results from these discussions have ensured that all the important aspects related to the clinical questions have been considered. This has allowed the panel to make structured and transparent recommendations that form the basis of this guideline update.

This document provides Evidence to Decision Frameworks and final recommendations for the 5 questions assigned to JBI for the smoking cessation guideline update. It includes a description of the methods and a detailed report of the discussion held by the panel members and the final judgments made.

General Methods

Evidence to Decision Framework

The Evidence to Decision Frameworks (EtDF) have been developed using processes established by the GRADE working group and within the GradePro Guideline Development Tool software (Gradepro GDT; McMaster University, 2015 [developed by Evidence Prime, Inc.], available from gradepro.org). The EtDF requires a 'judgment' on a domain related to the question of interest. For example, "Is the problem a priority" can be judged as Yes; Probably Yes; Probably No; and No. These judgments were originally drafted by the methods group, based on the research evidence alone as generated in the Summary of Findings (SoF) tables (Appendix 1). These draft judgments were then considered during a round-table discussion with the 10-member panel, who either agreed or disagreed with the draft judgments made. Where the panel disagreed with the draft judgments made, consensus was reached as to the new judgment. Where consensus could not be reached by the 10-member panel a formal vote took place.

NOTE: The summary of findings tables that are included in the EtDF are the original summary of findings tables as created by the methods group and following initial discussions with panel members. During the panel some changes were made relating to the summary of findings tables (such as the judgement regarding the certainty of the evidence); however, to ensure a transparent record, we have kept the original summary of findings tables and recorded reasons for changing within the additional considerations column.

Search Strategy

The evidence presented in the EtDF has been collated from the generated Summary of Findings Table (Appendix 1) and from a search of PubMed to locate relevant evidence. This search was filtered to July 1st 2014 to remain consistent with the search strategy time-restraints of the original search strategy as presented in the accompanying technical report (Appendix 1). The search strategy was also limited to systematic reviews only. The search strategy used is described below.

Search Terms

PICO Question	Search Query
#1; #2; #4; #5	("smoking cessation"[tiab] OR "smoking abstinence"[tiab] AND "Nicotine Replacement Therapy"[tiab] OR "NRT"[tiab] OR "Varenicline"[tiab] AND (Review[ptyp] AND ("2014/01/07"[PDAT] : "3000/12/31"[PDAT]))
#7	("pregnan*"[tiab] AND "smoking cessation"[tiab] OR "smoking abstinence"[tiab] AND "Nicotine Replacement Therapy"[tiab] OR "NRT"[tiab] OR "Varenicline"[tiab] AND (Review[ptyp] AND ("2014/01/07"[PDAT] : "3000/12/31"[PDAT]))

Evidence to Decision Frameworks

Clinical question 1

Is combination NRT (patch and oral form) more effective than patch alone and if so is this effect for all smokers or only for more dependent smokers?

Criteria for inclusion and exclusion of studies

1. **Population**:
    - Smokers (all)
    - More dependent smokers
2. **Intervention**: Combination NRT (any form).
3. **Comparison**: Monotherapy NRT (any)
4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.
5. **Study designs:** Randomised controlled trials, systematic reviews of RCTs.
6. **Other criteria:** 6 months follow up or longer

Clinical question 1 EtDF

Is combination NRT (patch and oral form) more effective than patch alone and if so is this effect for all smokers or only for more dependent smokers?

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking causes a higher burden of disease than any other behavioural risk factor, representing 13% of the total burden in men and 9.3% in women (9% of the total burden of disease) in 2011 (Australian Institute of Health and Welfare, 2016). Tobacco smoking is responsible for the deaths of almost 18,762 Australians each year (Australian Institute of Health and Welfare, 2016) and smoking-related disease contributes as a comorbidity to many more. The percentage of all tobacco-caused deaths in Australia in 2011: (Australian Institute of Health and Welfare, 2016) – 36% of respiratory diseases – 75% of chronic obstructive pulmonary disease – 80% of lung cancers – 22% of cancers – 3.5% of endocrine disorders Australia has not met the 2018 National Tobacco Strategy target to reduce the national smoking rate to 10% of the population and halve the Indigenous smoking rate over the 2009 rate in the same time (Intergovernmental Committee on Drugs, 2012). Despite the decline in prevalence, smoking remains the behavioural risk factor responsible for the highest levels of preventable disease and premature death (Australian Institute of Health and Welfare, 2016). Smokers tend to report other lifestyle risk factors such as higher levels of alcohol consumption, lower daily fruit and vegetable intake and lower levels of exercise. There is extensive evidence that tobacco use contributes to poverty and inequality; encouraging smokers to quit has the potential to improve health and also to alleviate poverty (Australian Institute of Health and Welfare, 2016).	Panel members unanimously agreed that this problem is a priority.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large	Combination NRT is more effective than single NRT for smoking cessation. In absolute terms, for every 1000 participants treated, 45 more (from 24 more to 67 more) will achieve smoking cessation using combination NRT compared to single NRT.	After discussion by the panel, some members wanted to increase the judgment from small to moderate. Some members were uncomfortable with grading the effect

○ Varies ○ Don't know	**Outcomes**	**№ of participants (studies) Follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
					Risk with Single NRT	**Risk difference with Combination NRT**
	Smoking Cessation (Overall) assessed with: CO monoxide expiration	6318 (12 RCTs)	⨁⨁◯◯ LOW[a,b,c,d,e]	**RR 1.28** (1.15 to 1.42)	Study population	
					160 per 1,000	**45 more per 1,000** (24 more to 67 more)
	50% CPD reduction	0 (0 studies)	-	not estimable	Study population	
					0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Concerns over performance bias
b. High statistical heterogeneity. Widely differing estimates of treatment effect
c. Guideline panel might want to consider forms of NRT used and placebo comparator
d. Confidence intervals are relatively narrow and range from negligible (1.18) to potentially beneficial (1.51). High number of events, 1132 events meets the Optimal Information Size threshold of 1116.
e. Only searched one database post 2012.

No outcome data was included for adverse effects and the effect of combination NRT on adverse effects was not considered. As discussed by Stead et al. (2012), the variation in reporting nature, timing and duration of symptoms was too expensive for the quantitative synthesis of adverse effects. A narrative description of adverse effects was therefore provided by Stead et al. (2012). The major side effects of nicotine gum were hiccups, gastrointestinal disturbances, and jaw pain and orodental problems.

Patches could cause skin sensitivity and irritation. Inhalers, nasal sprays and oral sprays could cause local irritation at the site of administration.

The primary study by Baker et al. (2016) reported an increased risk of indigestion, mouth problems and hiccups in patients treated with patch and lozenge compared to patch alone. Caldwell et al. 2016 reported slightly higher levels of adverse effects overall for participants receiving the inhaler with patch (99.6%) compared to participants receiving placebo inhaler with patch (96.5%) although the actual difference was small. However, the difference in adverse effects relating to inhaler use was greater (97% compared to 74%).

Tulloch et al. 2016 the frequency of serious adverse effects did not differ between groups (2.4% in the patch with gum or inhaler compared to 3.7% in patch alone). Overall, the use of combination therapy does not appear to

small and agreed that the judgment can be kept as small with the caveat that this is a small but important effect.

There was also discussion in regard to the Intention-to-treat (ITT), and that the effect for those that did comply with the entire NRT program would likely be larger. Some of the trials included were discussed to not be relevant to how NRT is used in 2018. The issues addressed were the age of the studies, the use of 2mg NRT products, participants with high cigarettes per day (CPD) usage. This was addressed by the methods group as potentially being a form of indirectness and would be of use when considering the certainty of the evidence.

After a formal vote from all 10 panel members, the final result was a 6-4 voting split in favour of rating the judgment as small. However, the panel felt that the true desirable effects were small-moderate. However, with higher compliance the effect is likely to be larger. However, the evidence is not available to explicitly support such a statement.

	increase the risk of adverse effects substantially beyond the potential for irritating the two routes of administration.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Combination NRT is more effective than single NRT for smoking cessation. In absolute terms, for every 1000 participants treated, 45 more (from 24 more to 67 more) will achieve smoking cessation using combination NRT compared to single NRT.	Panel members unanimously agreed that the undesirable effects are trivial Adverse effects of combination vs single NRT was not studied in depth within trials and there is limited data available. As such, this has not been formally examined with GRADE processes.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Single NRT	Risk difference with Combination NRT
Smoking Cessation (Overall) assessed with: CO monoxide expiration	6318 (12 RCTs)	⨁⨁◯◯ LOW[a,b,c,d,e]	**RR 1.28** (1.15 to 1.42)	Study population	
				160 per 1,000	**45 more per 1,000** (24 more to 67 more)
50% CPD reduction	0 (0 studies)	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Concerns over performance bias
b. High statistical heterogeneity. Widely differing estimates of treatment effect
c. Guideline panel might want to consider forms of NRT used and placebo comparator
d. Confidence intervals are relatively narrow and range from negligible (1.18) to potentially beneficial (1.51). High number of events, 1132 events meets the Optimal Information Size threshold of 1116.
e. Only searched one database post 2012.

No outcome data was included for adverse effects and the effect of combination NRT on adverse effects was not considered. As discussed by Stead et al. (2012), the variation in reporting nature, timing and duration of symptoms was too expensive for the quantitative synthesis of adverse effects. A narrative description of adverse

effects was therefore provided by Stead et al. (2012). The major side effects of nicotine gum were hiccups, gastrointestinal disturbances, and jaw pain and orodental problems.

Patches could cause skin sensitivity and irritation. Inhalers, nasal sprays and oral sprays could cause local irritation at the site of administration.

The primary study by Baker et al. (2016) reported an increased risk of indigestion, mouth problems and hiccups in patients treated with patch and lozenge compared to patch alone. Caldwell et al. 2016 reported slightly higher levels of adverse effects overall for participants receiving the inhaler with patch (99.6%) compared to participants receiving placebo inhaler with patch (96.5%) although the actual difference was small. However, the difference in adverse effects relating to inhaler use was greater (97% compared to 74%).

Tulloch et al. 2016 the frequency of serious adverse effects did not differ between groups (2.4% in the patch with gum or inhaler compared to 3.7% in patch alone). Overall, the use of combination therapy does not appear to increase the risk of adverse effects substantially beyond the potential for irritating the two routes of administration.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- ○ Very low
- ○ Low
- ● Moderate
- ○ High
- ○ No included studies

RESEARCH EVIDENCE

Overall, the certainty of the evidence, for the outcome of smoking cessation was deemed to be low due to high statistical heterogeneity indicating inconsistency. No studies reported any outcome data on CPD reduction.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Single NRT	Risk difference with Combination NRT
Smoking Cessation (Overall) assessed with: CO monoxide expiration	6318 (12 RCTs)	⨁⨁◯◯ LOW[a,b,c,d,e]	**RR 1.28** (1.15 to 1.42)	Study population	
				160 per 1,000	**45 more per 1,000** (24 more to 67 more)
50% CPD reduction	0 (0 studies)	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

ADDITIONAL CONSIDERATIONS

Methods group originally rated down for methodological quality (concerns over performance bias); high statistical heterogeneity and publication bias. The panel members disagreed with the suspicion of publication bias and have decided to not downgrade for that criteria. This therefore raised the certainty to low overall.

Some panel members argued that the evidence for the magnitude of effect were enough to increase the certainty to moderate. One panel member voiced the opinion that rating down for performance bias is not appropriate due to the inherent difficulty of blinding in NRT trials. This was met with consensus by the group and that downgrading the certainty for methodological quality was not appropriate.

After a formal vote from all 10 panel members, the final results was 7-3 voting split in favour of rating the certainty of the evidence as moderate.

	a. Concerns over performance bias b. High statistical heterogeneity. Widely differing estimates of treatment effect c. Guideline panel might want to consider forms of NRT used and placebo comparator d. Confidence intervals are relatively narrow and range from negligible (1.18) to potentially beneficial (1.51). High number of events, 1132 events meets the Optimal Information Size threshold of 1116. e. Only searched one database post 2012.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No peer-reviewed, systematic reviews were identified with the search strategy employed that identified the values and preferences of smokers aiming to achieve smoking cessation using NRT, with focus on combination NRT. In terms of smoking cessation overall: Cahill et al. (2016) showed that incentive programs (material or financial incentives) produce significantly greater cessation rates compared to no-incentive controls. Flemming et al. (2015), presented that motivation to achieve smoking cessation is high among the pregnant population, due to the known health effects that smoking can have on the health outcomes of the baby. However, barriers such as partner smoking status (Flemming et al. 2015) were identified to reduce this motivation over time.	Panel members unanimously agreed that there is no important uncertainty or variability in how much people value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies	The certainty of the evidence for the beneficial outcome of smoking cessation was low, due to inconsistency. No meta-analysis was provided, however Stead et al. (2012) do provide descriptive detail as to the type and magnitude of the adverse effects, however no detail was provided when comparing the occurrences of these events from combination therapy to single therapy. Overall, there was an increased risk of indigestion, mouth problems and hiccups in patients treated with patches and lozenge compared to patches alone. However, the use of combination NRT does not appear to increase the risk of adverse effects substantially beyond the potential for irritating the two routes of administration.	With the upgrade of the certainty of the evidence to moderate, and small-moderate benefits versus trivial harms, the panel group unanimously agreed to increase the judgment to 'Favours the intervention'.

○ Don't know	<table><tr><th>Outcomes</th><th>№ of participants (studies) Follow up</th><th>Certainty of the evidence (GRADE)</th><th>Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><td></td><td></td><td></td><td></td><td>Risk with Single NRT</td><td>Risk difference with Combination NRT</td></tr><tr><td>Smoking Cessation (Overall) assessed with: CO monoxide expiration</td><td>6318 (12 RCTs)</td><td>⨁⨁◯◯ LOW[a,b,c,d,e]</td><td>RR 1.28 (1.15 to 1.42)</td><td colspan="2">Study population</td></tr><tr><td></td><td></td><td></td><td></td><td>160 per 1,000</td><td>45 more per 1,000 (24 more to 67 more)</td></tr><tr><td>50% CPD reduction</td><td>0 (0 studies)</td><td>-</td><td>not estimable</td><td colspan="2">Study population</td></tr><tr><td></td><td></td><td></td><td></td><td>0 per 1,000</td><td>0 fewer per 1,000 (0 fewer to 0 fewer)</td></tr></table> a. Concerns over performance bias b. High statistical heterogeneity. Widely differing estimates of treatment effect c. Guideline panel might want to consider forms of NRT used and placebo comparator d. Confidence intervals are relatively narrow and range from negligible (1.18) to potentially beneficial (1.51). High number of events, 1132 events meets the Optimal Information Size threshold of 1116. e. Only searched one database post 2012.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Balance between desirable and undesirable effects** While no meta-analysis was performed to investigate the nature and severity of the adverse effects encountered, it is likely that combination NRT does not appear to increase the risk of adverse effects substantially beyond the potential for irritating the two routes of administration. Combination NRT is likely to increase the rate of smoking cessation compared to Single NRT (45 more (from 24 more to 67 more)). The forms of NRT used in the studies included in the meta-analysis are already widely available in Australia, for purchase by consumers ready to quit smoking. **Values** *Patient*	Some panel members raised discussion regarding problems associated with government funding. Would the judgment of 'Yes' incentivise government to increased funding for NRT, or suggest that the current funding is sufficient? This would create barriers to low-income earners. Some panel members raised the point that a judgment of yes would be useful in settings outside of personal payments (e.g. hospitals, mental health). After a formal vote from all 10 panel members, the final result was a 7-3 voting split in favour of rating yes. Panel

	No peer-reviewed evidence was identified with the search strategy employed as to the treatment-burden and feasibility associated with NRT use. However, the burden of taking two treatments would be greater than taking one from the perspective of a patient. *Clinician* No peer-reviewed evidence was identified with the search strategy employed as to the values and preferences of GP's in regard to their willingness and acceptance to recommend combination NRT to their patients. **Financial Burden** NRT is available to be purchased under the Pharmaceutical Benefits Scheme (PBS). However, in order to be eligible for this program, consumers must be willing to enter a comprehensive support and counselling program. *Example* A packet of 7, nicotine replacement patches (15mg/16hr) (Nicorette) are available to consumers purchasing under the PBS for $6.40 per pack. 2 packs are available to be purchased at the one time, and this repeats twice. 6 packets, per person, per year are available for purchase under the PBS (42 individual patches) for a total of $38.4. The non-subsidized price of the same NRT (Nicorette - 15mg/16hr patch) can range from $26.99-34.99 per pack. However, it should be noted, that nicotine patches are the ONLY form of NRT available for subsidization under the PBS. Therefore, the recommendation for combination therapy is likely to be associated with significant increases in out-of-pocket expenses for consumers.	members requested a caveat acknowledging that financial burdens might exist.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	NRT is available in most pharmacies and in some super-markets across Australia and as discussed, in subsidised by the PBS. However, combination NRT would involve an increase in required resources and costs. No peer-reviewed evidence was identified with the search strategy employed as to the treatment-burden and feasibility associated with NRT use. However, the burden of taking two treatments would be greater than taking one from the perspective of a patient. No peer-reviewed evidence was identified with the search strategy employed as to the feasibility associated from the perspective of a GP in regards sought regarding the feasibility of implementing combination therapy from a clinician perspective.	Panel members unanimously agreed that the intervention is feasible to implement.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Conclusions

Recommendation

For people who smoke who are wanting to quit who are currently receiving behavioural support, clinicians should recommend combination NRT over single NRT.

Justification

There is a small but not trivial improvement in smoking cessation for combination NRT compared to single NRT.

Most studies included behavioural support. One panel member felt that it should be a requirement that a recommendation should only be made, on the condition that patients are also receiving behavioural support for several weeks. NRT on its own would not be recommended so strongly without this caveat. Panel members unanimously agreed on a strong recommendation for the intervention.

Subgroup considerations

Not for light smokers

Studies include a population of smokers with low-moderate nicotine-dependency. Need to limit to this subgroup

For those that failed mono-NRT therapy and for more nicotine dependant smokers.

Implementation considerations

Issues cost

Need for behavioural support

Correct instructions for use

Research priorities

Combination NRT is more effective for smoking cessation compared to single NRT as displayed in the meta-analysis using 12 randomly controlled trials.

There is a need for future research to prioritise the systematic review of treatment and financial-burden associated with combination NRT. No recent reviews were identified by the search strategy that looked at these effects.

Need to study the effects of combination NRT for more dependent smokers

Need to study the effects in high-priority populations (mental health, ATSI, AOD etc).

Clinical question 2

Is a combination of Varenicline and NRT more effective than Varenicline alone and if so is this effect for all smokers or only for more dependent smokers?

Criteria for inclusion and exclusion of studies

1. **Population**:
    - Smokers (all)
    - More dependent smokers
2. **Intervention**: Varenicline and NRT (any NRT monotherapy).
3. **Comparison**: Varenicline
4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.
5. **Study designs:** Randomised controlled trials (RCTs), systematic reviews of RCTs.
6. **Other criteria:** 6 months follow up or longer

Clinical Question 2 EtDF

Is a combination of Varenicline and NRT more effective than Varenicline alone and if so is this effect for all smokers or only for more dependent smokers?

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking causes a higher burden of disease than any other behavioural risk factor, representing 13% of the total burden in men and 9.3% in women (9% of the total burden of disease) in 2011. (Australian Institute of Health and Welfare, 2016) Tobacco smoking is responsible for the deaths of almost 18,762 Australians each year (Australian Institute of Health and Welfare, 2016) and smoking-related disease contributes as a comorbidity to many more (Collins 2008). The percentage of all tobacco-caused deaths in Australia in 2011: (Australian Institute of Health and Welfare, 2016) – 36% of respiratory diseases – 75% of chronic obstructive pulmonary disease – 80% of lung cancers – 22% of cancers – 3.5% of endocrine disorders. Australia has not met the 2018 National Tobacco Strategy target to reduce the national smoking rate to 10% of the population and halve the Indigenous smoking rate over the 2009 rate in the same time (Intergovernmental Committee on Drugs, 2012). Despite the decline in prevalence, smoking remains the behavioural risk factor responsible for the highest levels of preventable disease and premature death (Australian Institute of Health and Welfare, 2016; Drope 2018). Smokers tend to report other lifestyle risk factors such as higher levels of alcohol consumption, lower daily fruit and vegetable intake and lower levels of exercise. There is extensive evidence that tobacco use contributes to poverty and inequality; encouraging smokers to quit has the potential to improve health and also to alleviate poverty (Australian Institute of Health and Welfare, 2016).	Panel members unanimously agreed that this problem is a priority.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate	Combination NRT and Varenicline therapy is more effective than Varenicline mono-therapy for continuous abstinence at 24 weeks post-TQD (OR, 1.62; CI, 1.18 to 2.23). In absolute terms, for every 1000 participants	Change to moderate to remain internally consistent with the upgrading as seen in the

○ Large ○ Varies ○ Don't know	treated, 96 more (from 30 more to 169 more) will achieve continuous abstinence using combination therapy compared to mono-therapy.	previous question. This upgrade was unanimous between panel members.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Varenicline alone	Risk difference with Varenicline and NRT
Continuous abstinence 24 weeks post-TQD assessed with: Exhaled CO concentrations (<10ppm)	787 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	**OR 1.62** (1.18 to 2.23)	Study population	
				228 per 1,000	**96 more per 1,000** (30 more to 169 more)
50% CPD reduction	0 (0 studies)	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Confidence intervals are wide and range from negligible (1.18) to potentially beneficial (2.23). Low number of events, 217 events does not meet the Optimal Information Size threshold of 340. In addition, as slight concerns regarding inconsistency, we have decided this is serious.

– After discussion with the panel, no consensus was reached. This needs to be discussed further with the panel.

In most cases, there were no significant differences observed between groups for the occurrences of adverse effects. For combination therapy compared to mono-therapy, 28.4 vs 25.7% (OR 1.15 (CI: 0.85, 1.56)) respectively of participants experienced nausea. 18.7 vs 15.4% (OR 1.27 (CI: 0.89, 1.80)) experienced insomnia, 13.6 vs 10.7% (OR 1.20 (CI: 0.78, 1.84)) experienced abnormal dreams and 7.1 vs 7.8% (OR 1.01 (0.60, 1.72)) experienced headaches. None of these adverse effects were significantly different from one another.

One study included in the meta-analysis (Koegelenberg et al. 2014) reported that skin reactions (of any type) were more common in combination therapy vs mono-therapy (14.4 vs 7.8%). Koegelenberg *et al.* (2014) also reported a female participant, randomised to the Varenicline mono-therapy group who became pregnant during the treatment phase. This participant gave birth to an infant with Down syndrome and congenital heart defects which was considered relevant to the study medications.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Combination NRT and Varenicline therapy is more effective than Varenicline mono-therapy for continuous abstinence at 24 weeks post-TQD (OR, 1.62; CI, 1.18 to 2.23). In absolute terms, for every 1000 participants treated, 96 more (from 30 more to 169 more) will achieve continuous abstinence using combination therapy compared to mono-therapy.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Varenicline alone	Risk difference with Varenicline and NRT
Continuous abstinence 24 weeks post-TQD assessed with: Exhaled CO concentrations (<10ppm)	787 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	**OR 1.62** (1.18 to 2.23)	Study population	
				228 per 1,000	**96 more per 1,000** (30 more to 169 more)
50% CPD reduction	0 (0 studies)	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Confidence intervals are wide and range from negligible (1.18) to potentially beneficial (2.23). Low number of events, 217 events does not meet the Optimal Information Size threshold of 340. In addition, as slight concerns regarding inconsistency, we have decided this is serious.

– After discussion with the panel, no consensus was reached. This needs to be discussed further with the panel.

In most cases, there were no significant differences observed between groups for the occurrences of adverse effects. For combination therapy compared to mono-therapy, 28.4 vs 25.7% (OR 1.15 (CI: 0.85, 1.56)) respectively of participants experienced nausea. 18.7 vs 15.4% (OR 1.27 (CI: 0.89, 1.80)) experienced insomnia, 13.6 vs 10.7% (OR 1.20 (CI: 0.78, 1.84)) experienced abnormal dreams and 7.1 vs 7.8% (OR 1.01 (0.60, 1.72)) experienced headaches. None of these adverse effects were significantly different from one another.

ADDITIONAL CONSIDERATIONS

Adverse effects was not studied in depth within trials and there is limited data available that has not been formally examined with GRADE processes.

Some panel members had discomfort over the term trivial but the panel agreed to the judgment of trivial. No formal vote was undertaken.

One study included in the meta-analysis (Koegelenberg et al. 2014) reported that skin reactions (of any type) were more common in combination therapy vs mono-therapy (14.4 vs 7.8%). Koegelenberg *et al.* (2014) also reported a female participant, randomised to the Varenicline mono-therapy group who became pregnant during the treatment phase. This participant gave birth to an infant with Down syndrome and congenital heart defects which was considered relevant to the study medications.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- ○ Very low
- ○ Low
- ● Moderate
- ○ High
- ○ No included studies

RESEARCH EVIDENCE

Overall, the certainty of the evidence, for the outcome of *continuous abstinence* was deemed to be moderate due to imprecision.

No studies reported any outcome data on CPD reduction.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Varenicline alone	Risk difference with Varenicline and NRT
Continuous abstinence 24 weeks post-TQD assessed with: Exhaled CO concentrations (<10ppm)	787 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	**OR 1.62** (1.18 to 2.23)	Study population	
				228 per 1,000	**96 more per 1,000** (30 more to 169 more)
50% CPD reduction	0 (0 studies)	-	not estimable	Study population	
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a. Confidence intervals are wide and range from negligible (1.18) to potentially beneficial (2.23). Low number of events, 217 events does not meet the Optimal Information Size threshold of 340. In addition, as slight concerns regarding inconsistency, we have decided this is serious.

— After discussion with the panel, no consensus was reached. This needs to be discussed further with the panel.

ADDITIONAL CONSIDERATIONS

Methods group originally rated down for imprecision and publication bias. The panel members disagreed with the suspicion of publication bias and have decided to not downgrade for that criteria. This therefore raised the certainty to moderate overall.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No peer-reviewed, systematic reviews were identified with the search strategy employed that identified the values and preferences of smokers aiming to achieve smoking cessation using NRT and/or Varenicline. In terms of smoking cessation overall… Cahill et al. (2016) showed that incentive programs (material or financial incentives) produce significantly greater cessation rates compared to no-incentive controls. Flemming et al. (2015), presented that motivation to achieve smoking cessation is high among the pregnant population, due to the known health effects that smoking can have on the health outcomes of the baby. However, barriers such as partner smoking status (Flemming et al. 2015) were identified to reduce this motivation over time.	Panel members unanimously agreed that there was no important uncertainty or variability in how much people value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The certainty of the evidence for the benefits (continuous abstinence) was moderate due to imprecision. No meta-analysis is provided, however the systematic review of Chang et al (2015) found no significant differences between rates the adverse effects of nausea, insomnia, abnormal dreams and headaches. One study included in the meta-analysis (Koegelenberg et al. 2014) reported that skin reactions (of any type) were more common in combination therapy vs mono-therapy	Panel members unanimously agreed that the balance between desirable and undesirable effects probably favours the intervention however requested to add a caveat that this is only based on two trials that just included patch.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Varenicline alone	Risk difference with Varenicline and NRT
Continuous abstinence 24 weeks post-TQD assessed with: Exhaled CO concentrations (<10ppm)	787 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	**OR 1.62** (1.18 to 2.23)	Study population	
				228 per 1,000	**96 more per 1,000** (30 more to 169 more)

50% CPD reduction	0 (0 studies)	-	not estimable	Study population		
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)	

a. Confidence intervals are wide and range from negligible (1.18) to potentially beneficial (2.23). Low number of events, 217 events does not meet the Optimal Information Size threshold of 340. In addition, as slight concerns regarding inconsistency, we have decided this is serious.

— After discussion with the panel, no consensus was reached. This needs to be discussed further with the panel.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Balance between desirable and undesirable effects.** Of the two studies included in the meta-analysis, adverse effects were only significantly greater in the combination therapy group for skin reactions (of any type). Combination therapy is likely to increase the rate of continuous smoking abstinence compared to mono-therapy (96 more (from 30 more to 169 more). These interventions are already offered to smokers willing to quit. **Values** *Patient* No peer-reviewed evidence was identified with the search strategy employed as to the values and preferences of smokers with particular relation between the use of Varenicline and NRT combination treatment strategies. However, the burden of taking two treatments would be greater than taking one from the perspective of a patient. *Clinician* No peer-reviewed evidence was identified with the search strategy employed as to the values and preferences of GP's in regard to their willingness and acceptance to recommend combination NRT and Varenicline treatments to their patients. **Financial Burden** Varenicline is a prescription-medication available after consultation with a GP. NRT is available in most pharmacies and in some super-markets across Australia. Both NRT and Varenicline is available to be purchased under the Pharmaceutical Benefits Scheme (PBS). However, in order to be eligible for this program, consumers must be willing to enter a comprehensive support and counselling program.	Changed to yes, to remain internally consistent with the upgrading as seen in the previous question. This upgrade was unanimous between panel members. However, this upgrade was with the caveat that cost is an important issue and may be a barrier.

	Example A packet of 7, nicotine replacement patches (15mg/16hr) (Nicorette) are available to consumers purchasing under the PBS for $6.40 per pack. 2 packs are available to be purchased at the one time, and this repeats twice. 6 packets, per person, per year are available for purchase under the PBS (42 individual patches) for a total of $38.4. The non-subsidized price of the same NRT (Nicorette - 15mg/16hr patch) can range from $26.99-34.99. A packet of Varenicline containing, 11 500µg and 42 1mg tablets (Champix) is also available to consumers purchasing under the PBS. This packet is only available to patients who are undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated. Only 1 packet of Varenicline tablets may be purchased under the PBS per person, per year, for $39.50. The non-subsidized price of the same Varenicline medication (Champix) can range from $81.69-96.39. However, Varenicline is ONLY available to consumers if it will be the sole PBS-subsidized therapy for the condition of nicotine dependence.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Varenicline is a prescription-medication available after consultation with a GP. NRT is available in most pharmacies and in some super-markets across Australia. The forms of NRT included in the meta-analysis above only included NRT in the form of nicotine patches that were administered once daily. No peer-reviewed evidence was identified with the search strategy employed as to the treatment-burden and feasibility associated with NRT use. However, the burden of taking two treatments would be greater than taking one from the perspective of a patient. No peer-reviewed evidence was identified with the search strategy employed as to the feasibility associated with recommending combination NRT and Varenicline from the perspective of a GP to their patients.	Panel members unanimously agreed that the intervention is feasible to implement.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

For people who smoke who are wanting to quit, clinicians might recommend the use of Varenicline in combination with NRT as compared to Varenicline alone.

Justification

There is a small but not trivial improvement in smoking cessation for people taking Varenicline in addition to NRT compared to NRT alone

Subgroup considerations

People who had failed (but tolerated) Varenicline treatment

Highly dependent smokers

Research priorities

The cost effectiveness of combination therapy versus mono-therapy can be further prioritised, as the financial burden associated with Varenicline treatment may be significant enough to deter smokers from attempting to achieve smoking cessation.

Future research priorities can also focus on additional primary research that specifically includes combination Varenicline therapy, as only two studies were included in the above meta-analysis.

Important research priority is whether the combination is more effective for highly dependent smokers

Is there an effect of intermittent NRT plus Varenicline vs. Varenicline alone?

Clinical question 4

Does adding any further course of NRT (any form) reduce relapse in smokers who have quit at the completion of a standard course of NRT?

If so, is this effect for all smokers or for more dependent smokers?

Criteria for inclusion and exclusion of studies

1. **Population:**
    - Smokers (all)
    - More dependent smokers
2. **Intervention**: Any further course of NRT (any form) for people who have quit successfully at end of standard course
3. **Comparison**: Standard duration 12 weeks NRT (any) plus placebo for further 12 weeks
4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.
5. **Study designs:** Randomised controlled trials, systematic reviews of RCTs.
6. **Other criteria:** 6 months follow up or longer.

Clinical Question 4 EtDF

Does adding any further course of NRT (any form) reduce relapse in smokers who have quit at the completion of a standard course of NRT?

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking causes a higher burden of disease than any other behavioural risk factor, representing 13% of the total burden in men and 9.3% in women (9% of the total burden of disease) in 2011. (Australian Institute of Health and Welfare, 2016) Tobacco smoking is responsible for the deaths of almost 18,762 Australians each year (Australian Institute of Health and Welfare, 2016) and smoking-related disease contributes as a comorbidity to many more (Collins 2008). The percentage of all tobacco-caused deaths in Australia in 2011: (Australian Institute of Health and Welfare, 2016) – 36% of respiratory diseases – 75% of chronic obstructive pulmonary disease – 80% of lung cancers – 22% of cancers – 3.5% of endocrine disorders Australia has not met the 2018 National Tobacco Strategy target to reduce the national smoking rate to 10% of the population and halve the Indigenous smoking rate over the 2009 rate in the same time (Intergovernmental Committee on Drugs, 2012). Despite the decline in prevalence, smoking remains the behavioural risk factor responsible for the highest levels of preventable disease and premature death (Australian Institute of Health and Welfare, 2016; Drope 2018). Smokers tend to report other lifestyle risk factors such as higher levels of alcohol consumption, lower daily fruit and vegetable intake and lower levels of exercise. There is extensive evidence that tobacco use contributes to poverty and inequality; encouraging smokers to quit has the potential to improve health and also to alleviate poverty (Australian Institute of Health and Welfare, 2016).	Panel members unanimously agreed that this problem is a priority.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small	An additional course of NRT, post-biochemically confirmed smoking cessation using NRT was not more effective than no additional course of NRT at maintaining smoking abstinence at both 9	Due to the significant lack of trials, panel were unanimous in their judgment of 'don't know'.

○ Moderate ○ Large ○ Varies ● Don't know	months (OR, 2.17; CI 0.86 to 5.53) and 12 months (OR, 1.66; CI 0.52 to 5.26). Both of these differences were not statistically significant according to the meta-analyses performed. In absolute terms, for every 1000 participants treated, 189 more would maintain their smoking abstinence for at least 9 months post-TQD if they continued NRT after smoking cessation, compared to those that stopped NRT after smoking cessation. For 12 months post-TQD, for every 1000 participants treated, 81 more would maintain their smoking abstinence if they continued NRT after smoking cessation compared to those that stopped NRT.	There was an extra trial identified by a panel member that may have been relevant, however the methods group argued that it did not fit the question framework as provided. Some discussion was posed about reframing the question, however this was suggested for an additional project. The question asked was therefore not changed and the judgment stayed at don't know.

Outcomes	**Importance**	**Certainty of the evidence (GRADE)**
Confirmed abstinence 9 months post-TQD assessed with: Exhaled CO concentrations (<8ppm)	IMPORTANT	⨁⨁◯◯ LOW[a]
Confirmed abstinence 12 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))	CRITICAL	⨁⨁◯◯ LOW[b]

a. Small sample size. Confidence intervals are wide and range from negligible (0.85) to potentially beneficial (5.53). Low number of events, 33 events does not meet the Optimal Information Size threshold of 107.

b. Small sample size. Confidence intervals are wide and range from negligible (0.52) to potentially beneficial (5.26). Low number of events, 15 events does not meet the Optimal Information Size threshold of 386.

Outcomes	**№ of participants (studies) Follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
				Risk with a standard course of NRT followed by no additional course of NRT	**Risk difference with a standard course of NRT followed by an additional course of NRT**
Confirmed abstinence 9 months post-TQD assessed with: Exhaled CO	74 (1 RCT)	⨁⨁◯◯ LOW[a]	**OR 2.17** (0.85 to 5.53)	Study population	
				351 per 1,000	**189 more per 1,000**

concentrations (<8ppm)					(36 fewer to 398 more)
Confirmed abstinence 12 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))	74 (1 RCT)	⊕⊕◯◯ LOW[b]	**OR 1.66** (0.52 to 5.26)	Study population	
				162 per 1,000	**81 more per 1,000** (71 fewer to 342 more)
Reduction of CPD (50%)	0 (0 studies)	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Small sample size. Confidence intervals are wide and range from negligible (0.85) to potentially beneficial (5.53). Low number of events, 33 events does not meet the Optimal Information Size threshold of 107.

b. Small sample size. Confidence intervals are wide and range from negligible (0.52) to potentially beneficial (5.26). Low number of events, 15 events does not meet the Optimal Information Size threshold of 386.

No descriptive or statistical information provided in the Systematic Review by Hajek *et al.* (2013) as to the nature and severity of the adverse effects experienced in the study by Croghan *et al.* (2007). The only information provided directly from Croghan *et al.* (2007) was that 4% of the randomised participants for phase 1 and 1% of the randomised participants for phase 2 did not provide follow-up data, due to being removed from the study due to an adverse effect. Significantly more information is required before a balance between the desirable and undesirable effects can be assessed.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	An additional course of NRT, post-biochemically confirmed smoking cessation using NRT was not more effective than no additional course of NRT at maintaining smoking abstinence at both 9 months (OR, 2.17; CI 0.86 to 5.53) and 12 months (OR, 1.66; CI 0.52 to 5.26). Both of these differences were not statistically significant according to the meta-analyses performed. In absolute terms, for every 1000 participants treated, 189 more would maintain their smoking abstinence for at least 9 months post-TQD if they continued NRT after smoking cessation, compared to those that stopped NRT after smoking cessation. For 12 months post-TQD, for every 1000 participants treated, 81 more would maintain their smoking abstinence if they continued NRT after smoking cessation compared to those that stopped NRT.	Adverse effects was not studied in depth within trials and there is limited data available that has not been formally examined with GRADE processes. The undesirable effects can be inferred from the evidence presented with the previous questions. The Panel members unanimously decided to judge as trivial.

Outcomes	**Importance**	**Certainty of the evidence (GRADE)**
Confirmed abstinence 9 months post-TQD assessed with: Exhaled CO concentrations (<8ppm)	IMPORTANT	⨁⨁◯◯ LOW[a]
Confirmed abstinence 12 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))	CRITICAL	⨁⨁◯◯ LOW[b]

a. Small sample size. Confidence intervals are wide and range from negligible (0.85) to potentially beneficial (5.53). Low number of events, 33 events does not meet the Optimal Information Size threshold of 107.

b. Small sample size. Confidence intervals are wide and range from negligible (0.52) to potentially beneficial (5.26). Low number of events, 15 events does not meet the Optimal Information Size threshold of 386.

Outcomes	**№ of participants (studies) Follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
				Risk with a standard course of NRT followed by no additional course of NRT	**Risk difference with a standard course of NRT followed by an additional course of NRT**
				Study population	

Confirmed abstinence 9 months post-TQD assessed with: Exhaled CO concentrations (<8ppm)	74 (1 RCT)	⨁⨁◯◯ LOW[a]	**OR 2.17** (0.85 to 5.53)	351 per 1,000	**189 more per 1,000** (36 fewer to 398 more)
Confirmed abstinence 12 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))	74 (1 RCT)	⨁⨁◯◯ LOW[b]	**OR 1.66** (0.52 to 5.26)	Study population	
				162 per 1,000	**81 more per 1,000** (71 fewer to 342 more)
Reduction of CPD (50%)	0 (0 studies)	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Small sample size. Confidence intervals are wide and range from negligible (0.85) to potentially beneficial (5.53). Low number of events, 33 events does not meet the Optimal Information Size threshold of 107.

b. Small sample size. Confidence intervals are wide and range from negligible (0.52) to potentially beneficial (5.26). Low number of events, 15 events does not meet the Optimal Information Size threshold of 386.

No descriptive or statistical information provided in the Systematic Review by Hajek *et al.* (2013) as to the nature and severity of the adverse effects experienced in the study by Croghan *et al.* (2007). The only information provided directly from Croghan *et al.* (2007) was that 4% of the randomised participants for phase 1 and 1% of the randomised participants for phase 2 did not provide follow-up data, due to being removed from the study due to an adverse effect. Significantly more information is required before a balance between the desirable and undesirable effects can be assessed.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Overall, the certainty of the evidence, for both outcomes was deemed to be low, due to imprecision. No studies reported any outcome data on CPD reduction.	Methods group originally rated down for imprecision and publication bias to very low. The panel members disagreed with the suspicion of publication bias and have decided to not downgrade for that criteria. This therefore raised the certainty to low overall.

Outcomes	Importance	Certainty of the evidence (GRADE)
Confirmed abstinence 9 months post-TQD assessed with: Exhaled CO concentrations (<8ppm)	IMPORTANT	⨁⨁◯◯ LOW[a]
Confirmed abstinence 12 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))	CRITICAL	⨁⨁◯◯ LOW[b]
Reduction of CPD (50%)		-

a. Small sample size. Confidence intervals are wide and range from negligible (0.85) to potentially beneficial (5.53). Low number of events, 33 events does not meet the Optimal Information Size threshold of 107.

b. Small sample size. Confidence intervals are wide and range from negligible (0.52) to potentially beneficial (5.26). Low number of events, 15 events does not meet the Optimal Information Size threshold of 386.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with a standard course of NRT followed by no additional course of NRT	Risk difference with a standard course of NRT followed by an additional course of NRT
				Study population	

Confirmed abstinence 9 months post-TQD assessed with: Exhaled CO concentrations (<8ppm)	74 (1 RCT)	⊕⊕◯◯ LOW[a]	**OR 2.17** (0.85 to 5.53)	351 per 1,000	**189 more per 1,000** (36 fewer to 398 more)	
Confirmed abstinence 12 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))	74 (1 RCT)	⊕⊕◯◯ LOW[b]	**OR 1.66** (0.52 to 5.26)	Study population		
				162 per 1,000	**81 more per 1,000** (71 fewer to 342 more)	
Reduction of CPD (50%)	0 (0 studies)	-	not estimable	Study population		
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)	

a. Small sample size. Confidence intervals are wide and range from negligible (0.85) to potentially beneficial (5.53). Low number of events, 33 events does not meet the Optimal Information Size threshold of 107.

b. Small sample size. Confidence intervals are wide and range from negligible (0.52) to potentially beneficial (5.26). Low number of events, 15 events does not meet the Optimal Information Size threshold of 386.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability	Few peer-reviewed, systematic reviews were identified with the search strategy employed that identified the values and preferences of smokers aiming to achieve smoking cessation using NRT. Systematic reviews identified are discussed below.	The Panel members unanimously decided that there was no important uncertainty or variability in how much people valued the main outcome.

○ Probably no important uncertainty or variability ● No important uncertainty or variability	Cahill et al. (2016) showed that incentive programs (material or financial incentives) produce significantly greater cessation rates compared to no-incentive controls. Flemming et al. (2015), presented that motivation to achieve smoking cessation is high among the pregnant population, due to the known health effects that smoking can have on the health outcomes of the baby. However, barriers such as partner smoking status (Flemming et al. 2015) were identified to reduce this motivation over time.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	The certainty of the evidence for the benefits (confirmed abstinence at 9 and 12 months) was low due to imprecision. No meta-analysis is provided as to the severity or rate of adverse effects experienced. The only information provided directly from Croghan et al. (2007) was that 4% of the randomised participants for phase 1 and 1% of the randomised participants for phase 2 did not provide follow-up data, due to being removed from the study due to an adverse effect. Significantly more information is required before a balance between the desirable and undesirable effects can be assessed.	Changed, to remain internally consistent with the grading of 'don't know' for the domain "How substantial are the desirable anticipated effects?" This judgment was unanimous between panel members.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with a standard course of NRT followed by no additional course of NRT	Risk difference with a standard course of NRT followed by an additional course of NRT
Confirmed abstinence 9 months post-TQD assessed with: Exhaled CO concentrations (<8ppm)	74 (1 RCT)	⨁⨁◯◯ LOW[a]	**OR 2.17** (0.85 to 5.53)	Study population	
				351 per 1,000	**189 more per 1,000** (36 fewer to 398 more)

Confirmed abstinence 12 months post-TQD (assessed with: Exhaled CO concentrations (<8ppm))	74 (1 RCT)	⊕⊕◯◯ LOW[b]	**OR 1.66** (0.52 to 5.26)	Study population		
				162 per 1,000	**81 more per 1,000** (71 fewer to 342 more)	
Reduction of CPD (50%)	0 (0 studies)	-	not estimable	Study population		
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)	

a. Small sample size. Confidence intervals are wide and range from negligible (0.85) to potentially beneficial (5.53). Low number of events, 33 events does not meet the Optimal Information Size threshold of 107.

b. Small sample size. Confidence intervals are wide and range from negligible (0.52) to potentially beneficial (5.26). Low number of events, 15 events does not meet the Optimal Information Size threshold of 386.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Balance between desirable and undesirable effects.** While no meta-analysis was performed to investigate the nature and severity of the adverse effects encountered, it is likely that an additional course of NRT does not appear to increase the risk of adverse effects An additional course of NRT, post-biochemically confirmed smoking cessation using NRT was not more effective than no additional course of NRT at maintaining smoking abstinence at both 9 months (OR, 2.17; CI 0.86 to 5.53) and 12 months (OR, 1.66; CI 0.52 to 5.26). **Values and Preferences** *Patient* The recommendation for an additional course of NRT, following confirmed smoking cessation in order to maintain continuous abstinence will require significantly more NRT for consumers. This	Panel members unanimously agreed that the intervention would be acceptable to key stakeholders.

	will invariably be linked with additional costs, as the PBS currently only subsidize a limited number of NRT per person per year. No peer-reviewed evidence was identified with the search strategy employed as to the treatment-burden and acceptability associated with additional NRT use. However, the burden of additional NRT for an extensive period of time would be greater than not following this additional course from the perspective of a patient. *Clinician* No peer-reviewed evidence was identified with the search strategy employed as to the values and preferences of GP's and/or clinicians in regard to their willingness and acceptance to recommend additional NRT to their patients. **Financial Burden** NRT is available to be purchased under the Pharmaceutical Benefits Scheme (PBS). However, in order to be eligible for this program, consumers must be willing to enter a comprehensive support and counselling program. *Example* A packet of 7, nicotine replacement patches (15mg/16hr) (Nicorette) are available to consumers purchasing under the PBS for $6.40 per pack. 2 packs are available to be purchased at the one time, and this repeats twice. 6 packets, per person, per year are available for purchase under the PBS (42 individual patches) for a total of $38.4. The non-subsidized price of the same NRT (Nicorette - 15mg/16hr patch) can range from $26.99-34.99.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	NRT is available in a variety of forms in most pharmacies and in some super-markets across Australia. No peer-reviewed evidence was identified with the search strategy employed as to the treatment-burden and feasibility associated with additional NRT use. However, the burden of additional NRT for an extensive period of time would be greater than not following this additional course from the perspective of a patient. No peer-reviewed evidence was identified with the search strategy employed as to the feasibility associated with recommending an additional course NRT from the perspective of a GP to their patients.	Panel members unanimously agreed that the intervention would be feasible to implement.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

Conclusions

Recommendation

For people who have abstained from smoking at the end of a standard course of NRT, clinicians may consider recommending an additional course of NRT for sustained abstinence.

Justification

Certainly wouldn't recommend AGAINST the intervention, but as the panel have judged 'Don't know' for the domain "How substantial are the desirable anticipated effects?" it does not permit a stronger recommendation.

Subgroup considerations

People that clinicians may be worried about e.g. those that are anxious

People who quit later in the course of the initial treatment

Those with a higher risk of smoking relapse

Research priorities

More primary research is needed as to the efficacy of additional NRT usage to maintain smoking abstinence. The data included in the above meta-analyses only came from the one study, and included only 74 participants. Significantly more primary research is required before we can be certain of the true estimates of effect.

Clinical question 5 (modified)

Does adding any further course of Varenicline (>12 weeks) reduce relapse in smokers who have quit at the completion of a standard course of Varenicline (12 weeks)?

If so, is this effect for all smokers or for more dependent smokers?

Criteria for inclusion and exclusion of studies

1. **Population:**
    - Smokers (all)
    - More dependent smokers
2. **Intervention**: Any further course of Varenicline (>12 weeks) for people who have quit successfully at end of standard course (12 weeks) i.e. 24 week total
3. **Comparison**: Standard duration 12 weeks Varenicline plus placebo for further 12 weeks
4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.
5. **Study designs:** Randomised controlled trials, systematic reviews of RCTs.
6. **Other criteria:** 6 months follow up or longer.

Clinical Question 5 EtDF

Does adding any further course of Varenicline (>12 weeks) reduce relapse in smokers who have quit at the completion of a standard course of Varenicline (12 weeks)?

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking causes a higher burden of disease than any other behavioural risk factor, representing 13% of the total burden in men and 9.3% in women (9% of the total burden of disease) in 2011. (Australian Institute of Health and Welfare, 2016) Tobacco smoking is responsible for the deaths of almost 18,762 Australians each year (Australian Institute of Health and Welfare, 2016) and smoking-related disease contributes as a comorbidity to many more (Collins 2008). The percentage of all tobacco-caused deaths in Australia in 2011: (Australian Institute of Health and Welfare, 2016) – 36% of respiratory diseases – 75% of chronic obstructive pulmonary disease – 80% of lung cancers – 22% of cancers – 3.5% of endocrine disorders Australia has not met the 2018 National Tobacco Strategy target to reduce the national smoking rate to 10% of the population and halve the Indigenous smoking rate over the 2009 rate in the same time (Intergovernmental Committee on Drugs, 2012). Despite the decline in prevalence, smoking remains the behavioural risk factor responsible for the highest levels of preventable disease and premature death (Australian Institute of Health and Welfare, 2016; Drope 2018). Smokers tend to report other lifestyle risk factors such as higher levels of alcohol consumption, lower daily fruit and vegetable intake and lower levels of exercise. There is extensive evidence that tobacco use contributes to poverty and inequality; encouraging smokers to quit has the potential to improve health and also to alleviate poverty (Australian Institute of Health and Welfare, 2016).	Panel members unanimously agreed that the problem is a priority.

Desirable Effects

How substantial are the desirable anticipated effects?

<table>
<tr><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know</td>
<td>
An additional course of Varenicline, post-biochemically confirmed smoking cessation using Varenicline was more effective than no additional course of Varenicline at maintaining smoking abstinence (hence, preventing relapse) (RR, 1.23; CI 1.08 to 1.41).
In absolute terms, for every 1000 participants treated, 81 more would maintain their smoking abstinence if they continued Varenicline after smoking cessation, compared to those that stopped Varenicline after smoking cessation.
<table>
<tr><th>Outcomes</th><th>№ of participants (studies) Follow up</th><th>Certainty of the evidence (GRADE)</th><th>Impact</th><th colspan="2"></th></tr>
<tr><td rowspan="2">Smoking Cessation (52 weeks post-TQD) assessed with: CO monoxide expiration</td><td rowspan="2">1297
(2 RCTs)</td><td rowspan="2">⨁⨁⨁◯
MODERATE[a]</td><td rowspan="2">RR 1.23
(1.08 to 1.41)</td><td colspan="2">Study population</td></tr>
<tr><td>353 per 1,000</td><td>81 more per 1,000
(28 more to 145 more)</td></tr>
<tr><td rowspan="2">Smoking Cessation (12 weeks post-Active Therapy)
assessed with: CO monoxide expiration</td><td rowspan="2">1210
(1 RCT)</td><td rowspan="2">⨁⨁⨁◯
MODERATE[b]</td><td rowspan="2">RR 1.02
(0.91 to 1.15)</td><td colspan="2">Study population</td></tr>
<tr><td>496 per 1,000</td><td>10 more per 1,000
(45 fewer to 74 more)</td></tr>
</table>
a. Confidence intervals are wide and range from potentially negligible (1.08) to potentially beneficial (1.41).
b. Confidence intervals are wide and range from potentially negligible (0.91) to potentially beneficial (1.15).
No descriptive or statistical information provided in the Systematic Review by Livingstone-Banks et al. (2018) as to the nature and severity of the adverse effects experienced in the study the studies Evins et al. (2014) and Tonstad (2006).
Evins et al. (2014) provided a table of the adverse events associated with each treatment group. The only significant difference in the rates of the adverse effects, were those that
</td>
<td>
Panel members decided to change the judgment to moderate to remain internally consistent with the upgrading as seen in the previous questions. This upgrade was unanimous between panel members.
The panel re-visited this domain after the discussion for the domain below and decided to reverse this judgment, and keep the domain judgment as small. The outcome needs to be considered from end of active therapy, and not from 52 weeks post target quit date (TQD).
Following the panel discussion, an additional outcome (SMOKING CESSATION 12 WEEKS POST-ACTIVE THERAPY) was included based on feedback from the panel that utilised data from only one study, Tonstad et al. (2006). This was the only data available for this particular outcome which was judged critical.
5 Panel members voted using PanelVoice. 3 members disagreed with the judgment of Trivial and 2 members agreed with the judgment. Due to this, the judgment has been changed to Small
</td>
</tr>
</table>

	were randomised to receive Varenicline responded with increased rates of headaches (No. (%)) 17 (44) compared to those who received placebo 11 (24) (P <0.05 Fisher exact test). Tonstad et al. (2016) reported that there were not significant differences between those randomised to receive Varenicline compared to those who received placebo. However, during the open-label Varnenicline treatment phase, 11.9% discontinued treatment due to adverse effects, with 3.2% of participant's experiencing nausea, 1% experiencing headaches, .9% experiencing depression.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	An additional course of Varenicline, post-biochemically confirmed smoking cessation using Varenicline was more effective than no additional course of Varenicline at maintaining smoking abstinence (hence, preventing relapse) (RR, 1.23; CI 1.08 to 1.41). In absolute terms, for every 1000 participants treated, 81 more would maintain their smoking abstinence if they continued Varenicline after smoking cessation, compared to those that stopped Varenicline after smoking cessation.	Need to consider the length of time that participants are experiencing these adverse effects, as the extended Varenicline treatment will cause adverse effects to persist for longer. Panel members however, unanimously agreed that the undesirable anticipated effects were small. This is where the inclusion of an additional outcome was suggested by the methods group. The meta-analysis presented by Livingstone-Banks et al. (2018) is for the outcome of smoking cessation 52 weeks post TQD. However, the groups in Evins were randomized to receive either an additional 40 weeks of active Varenicline therapy or placebo. Tonstad however, randomised the groups to receive either an additional 12 weeks of active Varenicline therapy followed by 28 weeks of CBT versus placebo for 12 weeks followed by 28 weeks of CBT. The panel discussed changing the critical outcome to focus on smoking cessation at a time-point (unspecified) after the end of active therapy and changing the 52 week outcome to important, but not critical. This was agreed upon by the panel members as being a less-biased outcome measure. The critical outcome (*smoking cessation 12 weeks post-active therapy*) utilised data from only one

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Impact		
Smoking Cessation (52 weeks post-TQD) assessed with: CO monoxide expiration	1297 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 1.23** (1.08 to 1.41)	Study population	
				353 per 1,000	**81 more per 1,000** (28 more to 145 more)
Smoking Cessation (12 weeks post-Active Therapy) assessed with: CO monoxide expiration	1210 (1 RCT)	⨁⨁⨁◯ MODERATE[b]	**RR 1.02** (0.91 to 1.15)	Study population	
				496 per 1,000	**10 more per 1,000** (45 fewer

					to 74 more)	

a. Confidence intervals are wide and range from potentially negligible (1.08) to potentially beneficial (1.41).

b. Confidence intervals are wide and range from potentially negligible (0.91) to potentially beneficial (1.15).

No descriptive or statistical information provided in the Systematic Review by Livingstone-Banks et al. (2018) as to the nature and severity of the adverse effects experienced in the study the studies Evins et al. (2014) and Tonstad (2006).

Evins et al. (2014) provided a table of the adverse events associated with each treatment group. The only significant difference in the rates of the adverse effects, were those that were randomised to receive Varenicline responded with increased rates of headaches (No. (%)) 17 (44) compared to those who received placebo 11 (24) (P <0.05 Fisher exact test).

Tonstad et al. (2016) reported that there were not significant differences between those randomised to receive Varenicline compared to those who received placebo. However, during the open-label Varnenicline treatment phase, 11.9% discontinued treatment due to adverse effects, with 3.2% of participant's experiencing nausea, 1% experiencing headaches, .9% experiencing depression.

study, Tonstad et al. (2006). This was the only data available for this particular outcome

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Overall, the certainty of the evidence was Moderate.	5 Panel members voted using PanelVoice. 2 members disagreed with the judgment of *Moderate* and 3 members agreed with the judgment. However, after reflection, the chair of the panel determined the judgment as *Low.*

Outcomes	Importance	Certainty of the evidence (GRADE)
Smoking Cessation (52 weeks post-TQD) assessed with: CO monoxide expiration	IMPORTANT	⊕⊕⊕◯ MODERATE[a]
Smoking Cessation (12 weeks post-Active Therapy) assessed with: CO monoxide expiration	CRITICAL	⊕⊕⊕◯ MODERATE[b]

a. Confidence intervals are wide and range from potentially negligible (1.08) to potentially beneficial (1.41).

<table>
<tr><td></td><td>b. Confidence intervals are wide and range from potentially negligible (0.91) to potentially beneficial (1.15).</td><td></td></tr>
<tr><td colspan="3">Values
Is there important uncertainty about or variability in how much people value the main outcomes?</td></tr>
<tr><td>JUDGEMENT</td><td>RESEARCH EVIDENCE</td><td>ADDITIONAL CONSIDERATIONS</td></tr>
<tr><td>○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
● No important uncertainty or variability</td><td>Few peer-reviewed, systematic reviews were identified with the search strategy employed that identified the values and preferences of smokers aiming to achieve smoking cessation using NRT. Systematic reviews identified are discussed below.
Cahill et al. (2016) showed that incentive programs (material or financial incentives) produce significantly greater cessation rates compared to no-incentive controls.
Flemming et al. (2015), presented that motivation to achieve smoking cessation is high among the pregnant population, due to the known health effects that smoking can have on the health outcomes of the baby. However, barriers such as partner smoking status (Flemming et al. 2015) were identified to reduce this motivation over time.</td><td>Panel members unanimously agreed that there is no important uncertainty or variability in how much people value the main outcome.</td></tr>
<tr><td colspan="3">Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?</td></tr>
<tr><td>JUDGEMENT</td><td>RESEARCH EVIDENCE</td><td>ADDITIONAL CONSIDERATIONS</td></tr>
<tr><td>○ Favors the comparison
○ Probably favors the comparison
● Does not favor either the intervention or the comparison
○ Probably favors the intervention
○ Favors the intervention
○ Varies
○ Don't know</td><td>The certainty of the evidence for the benefits was moderate due to imprecision.
No meta-analysis is provided as to the severity or rate of adverse effects experienced.
The only information provided directly from Evins et al. (2014) was that headaches are more likely to occur in those patients who recieve Varenicline. Significantly more information is required before a balance between the desirable and undesirable effects can be assessed.
The only critical outcome included int he meta-analysis was found to be not significant
<table>
<tr><th>Outcomes</th><th>№ of participants (studies) Follow up</th><th>Certainty of the evidence (GRADE)</th><th>Impact</th><th></th></tr>
<tr><td></td><td></td><td></td><td></td><td>Study population</td></tr>
</table></td><td>Panel members unanimously agreed that the balance of effects does not favour either the intervention or the comparison</td></tr>
</table>

Smoking Cessation (52 weeks post-TQD) assessed with: CO monoxide expiration	1297 (2 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 1.23** (1.08 to 1.41)	353 per 1,000	**81 more per 1,000** (28 more to 145 more)
Smoking Cessation (12 weeks post-Active Therapy) assessed with: CO monoxide expiration	1210 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	**RR 1.02** (0.91 to 1.15)	Study population	
				496 per 1,000	**10 more per 1,000** (45 fewer to 74 more)

a. Confidence intervals are wide and range from potentially negligible (1.08) to potentially beneficial (1.41).

b. Confidence intervals are wide and range from potentially negligible (0.91) to potentially beneficial (1.15).

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Balance between desirable and undesirable effects.** While no meta-analysis was performed to investigate the nature and severity of the adverse effects encountered, it is likely that an additional course of NRT does not appear to increase the risk of adverse effects An additional course of Varenicline post-biochemically confirmed smoking cessation was not more effective than no additional course of Varenicline at maintaining smoking abstinence 12 weeks post-active Varenicline therapy **Values and Preferences** *Patient* The recommendation for an additional course of Varenicline, following confirmed smoking cessation in order to maintain continuous abstinence will require significantly more Varenicline for consumers. This will invariably be linked with additional costs. No peer-reviewed evidence was identified with the search strategy employed as to the treatment-burden and acceptability associated with additional Varenicline use. However, the	Panel members unanimously agreed that the intervention was probably acceptable to key stakeholders

	burden of additional Varenicline for an extensive period of time would be greater than not following this additional course from the perspective of a patient. *Clinician* No peer-reviewed evidence was identified with the search strategy employed as to the values and preferences of GP's and/or clinicians in regard to their willingness and acceptance to recommend additional Varenicline to their patients. **Financial Burden** Varenicline is available to be purchased under the Pharmaceutical Benefits Scheme (PBS). However, in order to be eligible for this program, consumers must be willing to enter a comprehensive support and counselling program. *Example* A packet of Varenicline containing, 11 500µg and 42 1mg tablets (Champix) is also available to consumers purchasing under the PBS. This packet is only available to patients who are undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated. Only 1 packet of Varenicline tablets may be purchased under the PBS per person, per year, for $39.50.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Varenicline is a prescription-medication available after consultation with a GP. NRT is available in most pharmacies and in some super-markets across Australia. No peer-reviewed evidence was identified with the search strategy employed as to the treatment-burden and feasibility associated with Varenicline use. No peer-reviewed evidence was identified with the search strategy employed as to the feasibility associated with recommending Varenicline from the perspective of a GP to their patients.	5 Panel members voted using PanelVoice. 1 member disagreed with the judgment of *Yes* and 4 members agreed with the judgment. Therefore, the judgment has remained as *Yes*.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

Conclusions

Recommendation

For people who smoke, who are wanting to quit and who are currently receiving behavioural support, clinicians may consider a further course of Varenicline to prevent relapse.

Justification

5 Panel members voted using PanelVoice. 1 member disagreed with the recommendation made, 1 member did not know if the recommendation was appropriate and 3 members agreed with the recommendation. Therefore, the recommendation has remained the same

Subgroup considerations

Need to consider smokers with higher risk of relapse, e.g. smokers with mental illness or substance use disorders; high nicotine dependence; low self-efficacy

Monitoring and evaluation

Would be useful to conduct follow-up of those given second scripts to see if plausible benefit.

Research priorities

Further studies of this strategy are needed.

Research investigating whether prolonged pharmacotherapy in general improves outcomes beyond delaying relapse for the period of additional use is an important issue with significant cost implications.

Clinical question 7

Is it safe and effective for a pregnant smoker to undergo NRT rather than no NRT?

Criteria for inclusion and exclusion of studies

1. **Population:**
    - Female smokers who are pregnant and attempting to quit
2. **Intervention**: NRT (any form, any dose).
3. **Comparison**: No NRT
4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Pregnancy outcomes and adverse events (include miscarriage, stillbirth, preterm birth (< 37 wks), low birthweight (< 2500g), admissions to neonatal care, neonatal deaths, mean infant birthweights. Adverse events have also been included.
5. **Study designs:** Randomised controlled trials, systematic reviews of RCTs.
6. **Other criteria:** 6 months follow up or longer, including birth

Clinical Question 7 EtDF

Is it safe and effective for a pregnant smoker to undergo NRT rather than no NRT?

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking causes a higher burden of disease than any other behavioural risk factor, representing 13% of the total burden in men and 9.3% in women (9% of the total burden of disease) in 2011. (Australian Institute of Health and Welfare, 2016) Tobacco smoking is responsible for the deaths of almost 18,762 Australians each year (Australian Institute of Health and Welfare, 2016) and smoking-related disease contributes as a comorbidity to many more. The percentage of all tobacco-caused deaths in Australia in 2011: (Australian Institute of Health and Welfare, 2016) – 36% of respiratory diseases – 75% of chronic obstructive pulmonary disease – 80% of lung cancers – 22% of cancers – 3.5% of endocrine disorders All woman of childbearing age should be encouraged to stop smoking. Smoking during pregnancy has adverse effects in three areas: the foetus, the pregnancy and the mother, any level of nicotine or tobacco smoke exposure increases the risk of these adverse effects (Fiore 2008; England 2017; Hackshaw 2018). The rate of smoking during pregnancy in Australia continues to fall; however, approximately 10% of women continue to smoke during pregnancy (AIHW Mothers and Babies, 2018). About 1 in 6 Australian women (15.7%) smoked tobacco before they knew they were pregnant, and this rate dropped to 1 in 10 (11.3%) after they found out they were pregnant. Many of these women relapse either during pregnancy or after the baby is born (AIHW NDS 2017). Younger mothers under 20 years and disadvantaged women remain significantly less likely to quit smoking during pregnancy (Passmore 2015). A systematic review of smoking cessation interventions during pregnancy concluded that only 13% are abstinent at term and of these, 43% re-start by 6 months postpartum (Jones 2016).	Panel members unanimously agreed that the problem is a priority.

Desirable Effects

How substantial are the desirable anticipated effects?

<table>
<tr><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know</td>
<td>Analysis indicated that NRT (as an adjunct to behavioural support) is effective for smoking cessation in pregnancy (risk ratio (RR) (1.41, 95% confidence interval (CI) 1.03 to 1.93). In the subgroup analysis that compared active NRT with placebo the risk ratio for smoking cessation with NRT was lower, but it was not significant (RR 1.28, 95% CI 0.99 to 1.66). However, non-placebo-controlled trials indicated significance (RR 8.51, 95% CI 2.05 to 35.28.
No evidence that NRT compared to placebo or non-placebo-controlled trials was effective for smoking cessation after childbirth; (RR for cessation with NRT versus placebo 1.15, 95% CI 0.75 to 1.77) (RR for cessation with NRT versus non- placebo 1.45, 95% CI 0.69 to 3.03). The overall effects were also found to be not significant (RR 1.22, 95% CI 0.84 to 1.77).
Analyses revealed no statistically significant difference in risk of miscarriage/spontaneous abortion between NRT and control groups (RR 1.47, 95% CI 0.45 to 4.77)
No statistically significant difference between the numbers of stillbirths between NRT and control groups (RR 1.24, 95% CI 0.54 to 2.84)
Pooled estimate for control group birthweight was higher than for the NRT group, but this difference was not significant (mean difference (MD) 100.54 g, 95% CI -20.84 to 221.91)
There was a lower incidence of low birthweight in NRT group women but again, this was not significant (RR 0.74, 95% CI 0.41 to 1.34)
Preterm births (RR 0.87, 95% CI 0.67 to 1.14), neonatal intensive care unit admissions (RR 0.90, 95% CI, 0.64 to 1.27), and neonatal deaths (RR 0.66, 95% CI 0.17, 2.62), were all less frequent in NRT groups, but differences between NRT and control groups were not significant.
<table>
<tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr>
<tr><td>Smoking cessation in later pregnancy (overall)</td><td>CRITICAL</td><td>⨁⨁◯◯
LOW[a,b,c,d]</td></tr>
<tr><td>Smoking cessation after childbirth (overall)
assessed with: Self-report questionnaire
follow up: range 3 months to 6 months</td><td>IMPORTANT[e]</td><td>⨁⨁◯◯
LOW[b,d,f,g]</td></tr>
<tr><td>Miscarriage and spontaneous abortion</td><td>IMPORTANT[e]</td><td>⨁⨁⨁◯
MODERATE[d,h,i]</td></tr>
<tr><td>Stillbirths (overall)</td><td>IMPORTANT[e]</td><td>⨁⨁⨁◯
MODERATE[d,i,j,k]</td></tr>
</table>
</td>
<td>Panel members unanimously agreed that the desirable effects were small.</td>
</tr>
</table>

Birthweight (overall)	IMPORTANT[e]	⨁◯◯◯ VERY LOW[d,l,m,n]	
Low birthweight (<2500g) (overall)	IMPORTANT[e]	⨁◯◯◯ VERY LOW[d,l,n,o]	
Preterm birth (<37 weeks) (overall)	IMPORTANT[e]	⨁⨁◯◯ LOW[d,n,p]	
Neonatal intensive care unit admissions	IMPORTANT[e]	⨁⨁⨁◯ MODERATE[d,i,q]	
Neonatal death	IMPORTANT[e]	⨁⨁⨁◯ MODERATE[d,r,s,t]	

a. Widely differing estimates of treatment effect.
b. Guideline panel might want to consider co-interventions used and placebo comparator.
c. Confidence intervals are wide and range from negligible (1.03) to potentially beneficial (1.93). Small number of observed events, 234 events does not meet the Optimal Information Size threshold of 889.
d. Only searched one database post-2015
e. Originally assigned as critical, however after discussion, panel members unanimously agreed to grade this as important, but not critical
f. Confidence intervals are wide and range from negligible (0.84) to potentially beneficial (1.77). Small number of observed events, 101 events does not meet the Optimal Information Size threshold of 1943.
g. Concerns over performance and detection bias due to lack of placebo control
h. Confidence intervals are wide and range from potentially harmful (0.45) to potentially beneficial (4.77). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 2 more miscarriages per 1000 births with a CI from 3 in 1000 fewer to 18 in 1000 more. Considering absolute effect potential to NOT rate down.
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i. Concerns over performance and detection bias in Pollack study. However, total contribution is <15%. Therefore have not rated down

	j. Widely differing estimates of treatment effect, however this may be attributed to low number of events. k. Confidence intervals are wide and range from potentially negligible (0.54) to potentially beneficial (2.84). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 3 more stillbirths per 1000 events with a CI from 5 in 1000 fewer to 21 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group. l. High statistical heterogeneity m. Confidence intervals are wide range from negligible (-20.84) to potentially beneficial (221.91) potentially crossing important clinical thresholds. n. Concerns of performance and detection bias. o. Confidence intervals are wide and range from potentially harmful (0.41) to negligible (1.34). Low number of events, 219 events does not meet the Optimal Information Size threshold of 14817. p. Confidence intervals are wide and range from negligible (0.67) to negligible (1.14). Low number of events, 205 events does not meet the Optimal Information Size threshold of 19111. q. Confidence intervals are wide and range from negligible (0.64) to negligible (1.27). Low number of events, 126 events does not meet the Optimal Information Size threshold of 43430. r. Estimate of treatment effect for Berlin study is statistical outlier. s. Confidence intervals are wide range from potentially harmful (0.17) to potentially beneficial (2.62). Low number of events, however the sample sizes are sufficiently large, using absolute terms there were only 2 fewer neonatal deaths per 1000 events with a CI from 5 in 1000 fewer to 10 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group agree with this decision and have subsequently changed the rating for imprecision from 'serious' to 'not serious'. t. Concerns over performance and detection bias of the Pollak study. This study contributes .25%.	

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no NRT	Risk difference with NRT (any form, any dose)
Smoking cessation in later pregnancy (overall)	2199 (8 RCTs)	⨁⨁◯◯ LOW[a,b,c,d]	**RR 1.41** (1.03 to 1.93)	Study population	
				85 per 1,000	**35 more per 1,000** (3 more to 79 more)
Smoking cessation after childbirth (overall) assessed with: Self-report questionnaire follow up: range 3 months to 6 months	625 (3 RCTs)	⨁⨁◯◯ LOW[b,d,e,f]	**RR 1.22** (0.84 to 1.77)	Study population	
				143 per 1,000	**32 more per 1,000** (23 fewer to 110 more)
Miscarriage and spontaneous abortion	1782 (4 RCTs)	⨁⨁⨁◯ MODERATE[d,g,h]	**RR 1.47** (0.45 to 4.77)	Study population	
				5 per 1,000	**2 more per 1,000** (3 fewer to 18 more)
Stillbirths (overall)	1777 (4 RCTs)	⨁⨁⨁◯ MODERATE[d,h,i,j]	**RR 1.24** (0.54 to 2.84)	Study population	
				12 per 1,000	**3 more per 1,000** (5 fewer to 21 more)

Birthweight (overall)	2068 (6 RCTs)	⊕◯◯◯ VERY LOW[d,k,l,m]	-	The mean birthweight (overall) was **3098** g	MD **100.54 g higher** (20.84 lower to 221.91 higher)
Low birthweight (<2500g) (overall)	2037 (6 RCTs)	⊕◯◯◯ VERY LOW[d,k,m,n]	**RR 0.74** (0.41 to 1.34)	Study population	
				113 per 1,000	**29 fewer per 1,000** (66 fewer to 38 more)
Preterm birth (<37 weeks) (overall)	2048 (5 RCTs)	⊕⊕◯◯ LOW[d,m,o]	**RR 0.87** (0.67 to 1.14)	Study population	
				105 per 1,000	**14 fewer per 1,000** (34 fewer to 15 more)
Neonatal intensive care unit admissions	1756 (4 RCTs)	⊕⊕⊕◯ MODERATE[d,h,p]	**RR 0.90** (0.64 to 1.27)	Study population	
				74 per 1,000	**7 fewer per 1,000** (27 fewer to 20 more)
Neonatal death	1746 (4 RCTs)	⊕⊕⊕◯ MODERATE[d,q,r,s]	**RR 0.66** (0.17 to 2.62)	Study population	
				6 per 1,000	**2 fewer per 1,000** (5 fewer to 10 more)

a. Widely differing estimates of treatment effect.

b. Guideline panel might want to consider co-interventions used and placebo comparator.

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	terms there were only 2 fewer neonatal deaths per 1000 events with a CI from 5 in 1000 fewer to 10 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group agree with this decision and have subsequently changed the rating for imprecision from 'serious' to 'not serious'. s. Concerns over performance and detection bias of the Pollak study. This study contributes .25%. NRT resulted in no significant increases in adverse effects compared to no NRT therapy.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Analysis indicated that NRT (as an adjunct to behavioural support) is effective for smoking cessation in pregnancy (risk ratio (RR) (1.41, 95% confidence interval (CI) 1.03 to 1.93). In the subgroup analysis that compared active NRT with placebo the risk ratio for smoking cessation with NRT was lower, but it was not significant (RR 1.28, 95% CI 0.99 to 1.66). However, non-placebo-controlled trials indicated significance (RR 8.51, 95% CI 2.05 to 35.28. No evidence that NRT compared to placebo or non-placebo-controlled trials was effective for smoking cessation after childbirth; (RR for cessation with NRT versus placebo 1.15, 95% CI 0.75 to 1.77) (RR for cessation with NRT versus non- placebo 1.45, 95% CI 0.69 to 3.03). The overall effects were also found to be not significant (RR 1.22, 95% CI 0.84 to 1.77). Analyses revealed no statistically significant difference in risk of miscarriage/spontaneous abortion between NRT and control groups (RR 1.47, 95% CI 0.45 to 4.77) No statistically significant difference between the numbers of stillbirths between NRT and control groups (RR 1.24, 95% CI 0.54 to 2.84) Pooled estimate for control group birthweight was higher than for the NRT group, but this difference was not significant (mean difference (MD) 100.54 g, 95% CI -20.84 to 221.91) There was a lower incidence of low birthweight in NRT group women but again, this was not significant (RR 0.74, 95% CI 0.41 to 1.34) Preterm births (RR 0.87, 95% CI 0.67 to 1.14), neonatal intensive care unit admissions (RR 0.90, 95% CI, 0.64 to 1.27), and neonatal deaths (RR 0.66, 95% CI 0.17, 2.62), were all less frequent in NRT groups, but differences between NRT and control groups were not significant.	Panel raised the issue that long-term neurocognitive disorders have not been measured, and coupled with the low power of the included studies the Panel members unanimously agreed that the judgment should be “don’t know”.

Outcomes	Importance	Certainty of the evidence (GRADE)
Smoking cessation in later pregnancy (overall)	CRITICAL	⨁⨁◯◯ LOW[a,b,c,d]
Smoking cessation after childbirth (overall) assessed with: Self-report questionnaire follow up: range 3 months to 6 months	IMPORTANT[e]	⨁⨁◯◯ LOW[b,d,f,g]
Miscarriage and spontaneous abortion	IMPORTANT[e]	⨁⨁⨁◯ MODERATE[d,h,i]
Stillbirths (overall)	IMPORTANT[e]	⨁⨁⨁◯ MODERATE[d,i,j,k]
Birthweight (overall)	IMPORTANT[e]	⨁◯◯◯ VERY LOW[d,l,m,n]
Low birthweight (<2500g) (overall)	IMPORTANT[e]	⨁◯◯◯ VERY LOW[d,l,n,o]
Preterm birth (<37 weeks) (overall)	IMPORTANT[e]	⨁⨁◯◯ LOW[d,n,p]
Neonatal intensive care unit admissions	IMPORTANT[e]	⨁⨁⨁◯ MODERATE[d,i,q]
Neonatal death	IMPORTANT[e]	⨁⨁⨁◯ MODERATE[d,r,s,t]

a. Widely differing estimates of treatment effect.
b. Guideline panel might want to consider co-interventions used and placebo comparator.
c. Confidence intervals are wide and range from negligible (1.03) to potentially beneficial (1.93). Small number of observed events, 234 events does not meet the Optimal Information Size threshold of 889.
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Birthweight (overall)	2068 (6 RCTs)	⊕◯◯◯ VERY LOW[d,k,l,m]	-	The mean birthweight (overall) was **3098** g	MD **100.54 g higher** (20.84 lower to 221.91 higher)
Low birthweight (<2500g) (overall)	2037 (6 RCTs)	⊕◯◯◯ VERY LOW[d,k,m,n]	**RR 0.74** (0.41 to 1.34)	Study population	
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Neonatal death				Study population	

1746 (4 RCTs)	⊕⊕⊕◯ MODERATE[d,q,r,s]	**RR 0.66** (0.17 to 2.62)	6 per 1,000	**2 fewer per 1,000** (5 fewer to 10 more)	

a. Widely differing estimates of treatment effect.
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l. Confidence intervals are wide range from negligible (-20.84) to potentially beneficial (221.91) potentially crossing important clinical thresholds.
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s. Concerns over performance and detection bias of the Pollak study. This study contributes .25%.

NRT resulted in no significant increases in adverse effects compared to no NRT therapy.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Overall, the certainty of the evidence was low. In the majority of cases, certainty was marked down due to imprecision.	Panel wanted to separate the outcomes into those related to the infant and those related to the mother and to then grade the certainty of the evidence based on these subgroups. One panel member wanted to abstain from this procedure as they did not feel it was appropriate to grade the overall certainty of the evidence with the outcomes being so different. This member raised the point that they are completely different questions and should be addressed as such. This member also argued that the only critical outcome should be smoking cessation in later pregnancy, and all

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the other outcomes should be treated as important.

The panel overall agreed with this sentiment, and every outcome, except for smoking cessation in later pregnancy would be listed as important, but not critical. Therefore, the Panel members unanimously agreed that the overall certainty of the evidence would be graded as low.

	– After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group. i. Concerns over performance and detection bias in Pollack study. However, total contribution is <15%. Therefore have not rated down j. Widely differing estimates of treatment effect, however this may be attributed to low number of events. k. Confidence intervals are wide and range from potentially negligible (0.54) to potentially beneficial (2.84). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 3 more stillbirths per 1000 events with a CI from 5 in 1000 fewer to 21 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group. l. High statistical heterogeneity m. Confidence intervals are wide range from negligible (-20.84) to potentially beneficial (221.91) potentially crossing important clinical thresholds. n. Concerns of performance and detection bias. o. Confidence intervals are wide and range from potentially harmful (0.41) to negligible (1.34). Low number of events, 219 events does not meet the Optimal Information Size threshold of 14817. p. Confidence intervals are wide and range from negligible (0.67) to negligible (1.14). Low number of events, 205 events does not meet the Optimal Information Size threshold of 19111. q. Confidence intervals are wide and range from negligible (0.64) to negligible (1.27). Low number of events, 126 events does not meet the Optimal Information Size threshold of 43430. r. Estimate of treatment effect for Berlin study is statistical outlier. s. Confidence intervals are wide range from potentially harmful (0.17) to potentially beneficial (2.62). Low number of events, however the sample sizes are sufficiently large, using absolute terms there were only 2 fewer neonatal deaths per 1000 events with a CI from 5 in 1000 fewer to 10 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group agree with this decision and have subsequently changed the rating for imprecision from 'serious' to 'not serious'. t. Concerns over performance and detection bias of the Pollak study. This study contributes .25%.	

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				12 per 1,000	**3 more per 1,000** (5 fewer to 21 more)

Birthweight (overall)	2068 (6 RCTs)	⊕◯◯◯ VERY LOW[d,k,l,m]	-	The mean birthweight (overall) was **3098** g	MD **100.54 g higher** (20.84 lower to 221.91 higher)
Low birthweight (<2500g) (overall)	2037 (6 RCTs)	⊕◯◯◯ VERY LOW[d,k,m,n]	**RR 0.74** (0.41 to 1.34)	Study population	
				113 per 1,000	**29 fewer per 1,000** (66 fewer to 38 more)
Preterm birth (<37 weeks) (overall)	2048 (5 RCTs)	⊕⊕◯◯ LOW[d,m,o]	**RR 0.87** (0.67 to 1.14)	Study population	
				105 per 1,000	**14 fewer per 1,000** (34 fewer to 15 more)
Neonatal intensive care unit admissions	1756 (4 RCTs)	⊕⊕⊕◯ MODERATE[d,h,p]	**RR 0.90** (0.64 to 1.27)	Study population	
				74 per 1,000	**7 fewer per 1,000** (27 fewer to 20 more)
Neonatal death	1746 (4 RCTs)	⊕⊕⊕◯ MODERATE[d,q,r,s]	**RR 0.66** (0.17 to 2.62)	Study population	
				6 per 1,000	**2 fewer per 1,000** (5 fewer to 10 more)

a. Widely differing estimates of treatment effect.

b. Guideline panel might want to consider co-interventions used and placebo comparator.

c. Confidence intervals are wide and range from negligible (1.03) to potentially beneficial (1.93). Small number of observed events, 234 events does not meet the Optimal Information Size threshold of 889.

	d. Only searched one database post-2015 e. Confidence intervals are wide and range from negligible (0.84) to potentially beneficial (1.77). Small number of observed events, 101 events does not meet the Optimal Information Size threshold of 1943. f. Concerns over performance and detection bias due to lack of placebo control g. Confidence intervals are wide and range from potentially harmful (0.45) to potentially beneficial (4.77). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 2 more miscarriages per 1000 births with a CI from 3 in 1000 fewer to 18 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group. h. Concerns over performance and detection bias in Pollack study. However, total contribution is <15%. Therefore have not rated down i. Widely differing estimates of treatment effect, however this may be attributed to low number of events. j. Confidence intervals are wide and range from potentially negligible (0.54) to potentially beneficial (2.84). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 3 more stillbirths per 1000 events with a CI from 5 in 1000 fewer to 21 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group. k. High statistical heterogeneity l. Confidence intervals are wide range from negligible (-20.84) to potentially beneficial (221.91) potentially crossing important clinical thresholds. m. Concerns of performance and detection bias. n. Confidence intervals are wide and range from potentially harmful (0.41) to negligible (1.34). Low number of events, 219 events does not meet the Optimal Information Size threshold of 14817. o. Confidence intervals are wide and range from negligible (0.67) to negligible (1.14). Low number of events, 205 events does not meet the Optimal Information Size threshold of 19111. p. Confidence intervals are wide and range from negligible (0.64) to negligible (1.27). Low number of events, 126 events does not meet the Optimal Information Size threshold of 43430. q. Estimate of treatment effect for Berlin study is statistical outlier. r. Confidence intervals are wide range from potentially harmful (0.17) to potentially beneficial (2.62). Low number of events, however the sample sizes are sufficiently large, using absolute	

	terms there were only 2 fewer neonatal deaths per 1000 events with a CI from 5 in 1000 fewer to 10 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group agree with this decision and have subsequently changed the rating for imprecision from 'serious' to 'not serious'. s. Concerns over performance and detection bias of the Pollak study. This study contributes .25%.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Multiple systematic reviews were identified using the search strategy employed that identified the health effects of smoking on pregnant women and the subsequent effects on their children. However, very few identified the individual values that the pregnant, smoking women have when using NRT or wanting to achieve smoking cessation overall. Flemming et al. (2015), presented that motivation to achieve smoking cessation is high among the pregnant population, due to the known health effects that smoking can have on the health outcomes of the baby. However, smoking is embedded in these women's whole lives, from behavioural routine to interactions with their partners and purely addressing the biological mechanism of addiction is not sufficient. Health professionals should understand the barriers to smoking cessation for pregnant women such as the influence of close relationships on smoking status, the use of smoking as a way of coping with stress and the difficulty of managing nicotine withdrawal (Bauld 2017). Significantly more research is required as to the values and preferences of pregnant women when using NRT for smoking cessation.	Panel members unanimously agreed that there is possibly some important uncertainty or variability in how much people value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The certainty of evidence for every outcome was either low or moderate due to imprecision. Statistical significance for the effects of NRT versus no NRT was only observed for the outcome of smoking cessation in later pregnancy (RR, 1.41 CI, 1.03 to 1.93). As no significance was observed for any of the adverse effects (undesirable outcomes) measured, the balance between desirable and undesirable effects probably favours the intervention. However as low certainty in the evidence this suggestion remains provisional.	Panel members discussed that the evidence was limited and not significant when discussing the adverse effects, and this could possibly lead to a judgment of "don't know". After a formal vote from 9 panel members (1 panel member left prior to this vote taking place) the final result was a 6-3 voting split in favour of keeping the judgment at "Probably favours the intervention".

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no NRT	Risk difference with NRT (any form, any dose)
Smoking cessation in later pregnancy (overall)	2199 (8 RCTs)	⨁⨁◯◯ LOW[a,b,c,d]	**RR 1.41** (1.03 to 1.93)	Study population	
				85 per 1,000	**35 more per 1,000** (3 more to 79 more)
Smoking cessation after childbirth (overall) assessed with: Self-report questionnaire follow up: range 3 months to 6 months	625 (3 RCTs)	⨁⨁◯◯ LOW[b,d,e,f]	**RR 1.22** (0.84 to 1.77)	Study population	
				143 per 1,000	**32 more per 1,000** (23 fewer to 110 more)
Miscarriage and spontaneous abortion	1782 (4 RCTs)	⨁⨁⨁◯ MODERATE[d,g,h]	**RR 1.47** (0.45 to 4.77)	Study population	
				5 per 1,000	**2 more per 1,000** (3 fewer to 18 more)

Stillbirths (overall)	1777 (4 RCTs)	⊕⊕⊕◯ MODERATE[d,g,i,j]	**RR 1.24** (0.54 to 2.84)	Study population		
				12 per 1,000	**3 more per 1,000** (5 fewer to 21 more)	
Birthweight (overall)	2068 (6 RCTs)	⊕◯◯◯ VERY LOW[d,k,l,m]	-	The mean birthweight (overall) was **3098** g	MD **100.54 g higher** (20.84 lower to 221.91 higher)	
Low birthweight (<2500g) (overall)	2037 (6 RCTs)	⊕◯◯◯ VERY LOW[d,k,l,n]	**RR 0.74** (0.41 to 1.34)	Study population		
				113 per 1,000	**29 fewer per 1,000** (66 fewer to 38 more)	
Preterm birth (<37 weeks) (overall)	2048 (5 RCTs)	⊕⊕◯◯ LOW[d,k,o]	**RR 0.87** (0.67 to 1.14)	Study population		
				105 per 1,000	**14 fewer per 1,000** (34 fewer to 15 more)	
Neonatal intensive care unit admissions	1756 (4 RCTs)	⊕⊕⊕◯ MODERATE[d,g,p]	**RR 0.90** (0.64 to 1.27)	Study population		
				74 per 1,000	**7 fewer per 1,000** (27 fewer to 20 more)	
Neonatal death	1746 (4 RCTs)	⊕⊕⊕◯ MODERATE[d,q,r,s]	**RR 0.66** (0.17 to 2.62)	Study population		
				6 per 1,000	**2 fewer per 1,000**	

					(5 fewer to 10 more)

a. Widely differing estimates of treatment effect.
b. Guideline panel might want to consider co-interventions used and placebo comparator.
c. Confidence intervals are wide and range from negligible (1.03) to potentially beneficial (1.93). Small number of observed events, 234 events does not meet the Optimal Information Size threshold of 889.
d. Only searched one database post-2015
e. Concerns over performance and detection bias due to lack of placebo control
f. Confidence intervals are wide and range from negligible (0.84) to potentially beneficial (1.77). Small number of observed events, 101 events does not meet the Optimal Information Size threshold of 1943.
g. Concerns over performance and detection bias in Pollack study. However, total contribution is <15%. Therefore have not rated down
h. Confidence intervals are wide and range from potentially harmful (0.45) to potentially beneficial (4.77). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 2 more miscarriages per 1000 births with a CI from 3 in 1000 fewer to 18 in 1000 more. Considering absolute effect potential to NOT rate down.
   – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group.
i. Widely differing estimates of treatment effect, however this may be attributed to low number of events.
j. Confidence intervals are wide and range from potentially negligible (0.54) to potentially beneficial (2.84). Low number of events, however, the sample sizes are sufficiently large, using absolute terms there were only 3 more stillbirths per 1000 events with a CI from 5 in 1000 fewer to 21 in 1000 more. Considering absolute effect potential to NOT rate down.
   – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group disagree with this decision and this requires further discussion with the methods group.
k. Concerns of performance and detection bias.
l. High statistical heterogeneity
m. Confidence intervals are wide range from negligible (-20.84) to potentially beneficial (221.91) potentially crossing important clinical thresholds.

	n. Confidence intervals are wide and range from potentially harmful (0.41) to negligible (1.34). Low number of events, 219 events does not meet the Optimal Information Size threshold of 14817. o. Confidence intervals are wide and range from negligible (0.67) to negligible (1.14). Low number of events, 205 events does not meet the Optimal Information Size threshold of 19111. p. Confidence intervals are wide and range from negligible (0.64) to negligible (1.27). Low number of events, 126 events does not meet the Optimal Information Size threshold of 43430. q. Concerns over performance and detection bias of the Pollak study. This study contributes .25%. r. Estimate of treatment effect for Berlin study is statistical outlier. s. Confidence intervals are wide range from potentially harmful (0.17) to potentially beneficial (2.62). Low number of events, however the sample sizes are sufficiently large, using absolute terms there were only 2 fewer neonatal deaths per 1000 events with a CI from 5 in 1000 fewer to 10 in 1000 more. Considering absolute effect potential to NOT rate down. – After discussion with the panel, consensus was to NOT rate down for imprecision. The method group agree with this decision and have subsequently changed the rating for imprecision from 'serious' to 'not serious'.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Balance between desirable and undesirable effects.** According to the meta-analyses performed, statistical significance for the effects of NRT versus no NRT was only observed for the outcome of smoking cessation in later pregnancy (RR, 1.41 CI, 1.03 to 1.93). As no significance was observed for any of the adverse effects (undesirable outcomes) measured, the recommendation of NRT appears acceptable to consumers. **Values and Preferences** *Patient* Little, peer-reviewed evidence was identified with the search strategy employed as to the values and preferences of pregnant women, choosing to use NRT for smoking cessation. Flemming et al. (2015), presented that motivation to achieve smoking cessation is high among the pregnant population, due to the known health effects that smoking can have on the health outcomes of the baby. However, Flemming et al. (2015); Jones et al. (2016) and Loakeimidis et al. (2018) noted that this motivation to quit smoking was not seen in the number of women who achieved smoking cessation, or, who relapsed and resumed smoking post-partum. Significantly more information is required.	Panel members unanimously agreed that the acceptability of the intervention will vary for key stakeholders.

	Clinician No peer-reviewed evidence was identified with the search strategy employed as to the values and preferences of GP's in regard to their willingness and acceptance to recommend NRT for use in their pregnant patients. It is reasonable to assume that some clinicians or GP's may have reservations about recommending NRT to pregnant smokers. Significantly more information is required. **Financial Burden** NRT is available to be purchased under the Pharmaceutical Benefits Scheme (PBS). However, in order to be eligible for this program, consumers must be willing to enter a comprehensive support and counselling program. *Example* A packet of 7, nicotine replacement patches (15mg/16hr) (Nicorette) are available to consumers purchasing under the PBS for $6.40 per pack. 2 packs are available to be purchased at the one time, and this repeats twice. 6 packets, per person, per year are available for purchase under the PBS (42 individual patches) for a total of $38.4. The non-subsidized price of the same NRT (Nicorette - 15mg/16hr patch) can range from $26.99-34.99 per pack.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	NRT is available in a variety of forms in most pharmacies and in some super-markets across Australia. No peer-reviewed evidence was identified with the search strategy employed as to the treatment-burden and feasibility associated with NRT use specifically for a pregnant smoking population. No peer-reviewed evidence was identified with the search strategy employed as to the feasibility associated with recommending NRT use from the perspective of a GP to their pregnant patients.	Panel members unanimously agreed that the intervention would be feasible to implement.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

Conclusions

Recommendation

For women who are pregnant who aim to quit smoking, clinicians may consider recommending NRT as compared to no NRT. There should be a discussion of benefits vs risks, the small benefit for smoking cessation and the lack of evidence around possible harms. There may also be behavioural interventions that should be used.

Justification

Panel members discussed that a conditional recommendation for either the intervention or the comparison was appropriate due to the small benefit on cessation but lack of evidence/clarity on harms, however acknowledged that you wouldn't recommend against the intervention. One panel member raised that there is sufficient uncertainty surrounding long term adverse effects on the infants, which precludes a stronger recommendation. There was unanimous agreeance that any recommendation should be made after discussion with the woman about the potential benefits and the uncertainty of risks and that behavioural interventions should be used. This all needs to be done as part of a stepped care approach.

There are important reductions in smoking cessation outcomes whilst there does not appear to be an increase in harms.

Implementation considerations

Issues with stigma

Need shared decision making

Social support and social context considerations

Preference other interventions.

Research priorities

Significantly more research is required to target the individual values of pregnant smokers. Particularly with focus to the balance of values between their own health outcomes versus the health outcomes of the baby. As identified by Flemming et al. (2015), pregnant women do, seemingly, have a high motivation to quit smoking, and this can likely be attributed to the known negative health outcomes that smoking has on the baby. However, significantly more research is required as to why this high motivation to quit is not followed by high smoking cessation rates among pregnant women. In fact, the opposite is frequently reported in the literature (Jones et al. 2016; Ioakeimidis et al. 2018).

In addition, the values and perspectives of GP's and clinicians is also required. It is reasonable to expect that some GP's may have reservations about recommending NRT to a pregnant smoking population. There is also a need long term follow-up studies looking for benefits and harms