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INVITED REVIEW

ADDICTION SSA

Effects of interventions to combat tobacco addiction: Cochrane update of 2019 and 2020 reviews

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Abstract

Aims: To summarize evidence on tobacco addiction interventions published by the Cochrane Tobacco Addiction Group (CTAG) from 2019 to 2020.

Methods: Narrative summary of all new and updated Cochrane Reviews published by CTAG in 2019 and 2020, outlining key results and promising avenues for future research.

Results: CTAG published six new reviews and updated 15 reviews. There is high-certainty evidence that combining fast-acting nicotine replacement therapy (NRT) with transdermal patches helped more people to quit than single-form NRT [risk ratio (RR) = 1.25, 95% confidence interval (CI) = 1.15–1.36, 14 studies, n = 11 356; I^2 = 4%] and moderate-certainty evidence that using NRT before quitting can increase quit rates more than using NRT from quit day onwards (RR = 1.25, 95% CI = 1.08–1.44, nine studies, n = 4395; I^2 = 0%). Reducing smoking in order to quit completely results in similar quit rates to abrupt quitting (RR = 1.01, 95% CI= 0.87–1.17; I^2 = 29%; 22 studies, n = 9219; moderate-certainty). Electronic cigarettes may help more people quit than NRT (RR = 1.53, 95% CI = 1.21–1.93; I^2 = 0%; four studies, n = 1924; moderate certainty), nicotine-free electronic cigarettes (RR = 1.94, 95% CI = 1.21–3.13; I^2 = 0%; five studies, n = 1447; moderate-certainty) and behavioural/no support (RR = 2.61, 95% CI = 1.44–4.74; I^2 = 0%; six studies, n = 2886; very low-certainty). Varenicline may help prevent relapse in abstainers (RR = 1.23, 95% CI = 1.08–1.41; I^2 = 82%; 11 studies, n = 1297; moderate-certainty), but behavioural support did not prevent relapse (RR = 0.98, 95% CI = 0.87–1.11; I^2 = 52%; 11 studies, n = 5523; moderate-certainty). Financial incentives increased quit rates in the general population (RR = 1.49, 95% CI = 1.28–1.73; I^2 = 33%; 30 studies, adjusted n = 20 097; high-certainty) and during pregnancy (RR = 2.38, 95% CI = 1.54–3.69; I^2 = 41%; nine studies, n = 2273; moderate-certainty). This overview also provides detail on a wider range of interventions.

Conclusions: There is high certainty that using nicotine replacement therapy from quit day increases smoking abstinence and no further research is required. Evidence is less certain that nicotine replacement increases abstinence when used in higher doses tailored to particular groups of smokers or use prior to quit day, and further research would be helpful. There is moderate-certainty evidence to support the use of e-cigarettes as

cessation aids, but research on their role in preventing relapse would be particularly helpful.

KEYWORDS
Behavioural interventions, Cochrane, electronic cigarettes, pharmacotherapy, smoking, systematic review, tobacco

INTRODUCTION

Tobacco smoking is a leading source of preventable death, killing more than 8 million people each year [1]. It is also a leading cause of health inequalities [2]. Quitting tobacco smoking has a profound effect on improving health and quality of life, and significantly reduces risk of tobacco-related disease and death [3]. It is therefore of high importance to health-care providers and policymakers to support smoking cessation, both through policy-level interventions and through evidence-based individual cessation therapies. The evidence base for tobacco cessation interventions is continually evolving. Evidence of the effectiveness of interventions is synthesized in Cochrane Reviews.

Cochrane is an international not-for-profit organization dedicated to helping health-care professionals, policymakers and members of the public to make well-informed decisions about health care. It pursues this goal by producing and publishing systematic reviews in the Cochrane Database of Systematic Reviews. Cochrane Review methods are codified in the Cochrane Handbook of Systematic reviews [4], and focus particularly on identifying and mitigating potential sources of bias in reviews.

Cochrane comprises subject-specific review groups, each with an international network of contributors, editors and peer and consumer referees. The Cochrane Tobacco Addiction Group (CTAG), based at the University of Oxford, is an example of one of these groups. Cochrane review groups provide editorial support and also author new reviews and update existing reviews, focusing on questions of effectiveness, prognosis, diagnosis and contextually relevant factors, addressing both individual health-care and public health. Although researchers can and do suggest topics for reviews, CTAG determine whether to support these requests based on a 2016 priority setting exercise involving members of the public who smoked, policymakers, researchers and clinicians interested in tobacco control [5]. All Cochrane Reviews are updated when necessary, following the same procedures as the original review, but sometimes reflecting updated standards for reviews. CTAG aims to integrate its work with guideline developers and policymakers world-wide, such as the World Health Organization, National Institute for Health and Care Excellence (NICE), the US Preventive Services Task Force, Royal Australian College of General Practitioners, the Brazilian Society of Cardiology, Academy of Medicine Malaysia and Public Health England.

This update is the latest in a series that summarizes new and updated CTAG reviews to bring key new findings to the attention of researchers, clinicians and policymakers, and to recommend priority areas for future research [6,7]. This paper focuses on new and updated reviews of interventions to combat tobacco addiction published in 2019 and 2020. Some of these key results were also disseminated to wider audiences through articles published in *The Conversation* (London, UK), on the topics of different regimens of nicotine replacement therapy (NRT), electronic cigarettes and financial incentives for smoking cessation.

METHODS

In 2019 and 2020, CTAG published six new reviews, updated 15 previously published reviews (Table 1) and published two new protocols for reviews that will be conducted during 2021. The new protocols concern the use of mindfulness for smoking cessation [8] and the impact of heated tobacco products on smoking cessation and reducing smoking prevalence [9].

This paper outlines key findings from the new and updated reviews, focusing on new results and updates in which conclusions have changed. In Table 2 we summarize key abstinence results, and in Table 3 we summarize key results measuring harms from interventions. In each table we provide summary statistics for each key comparison (defined as those reporting meta-analysis results in the reviews' Summary of Findings tables), consisting of effect estimates with 95% confidence intervals (CIs), sample size, number of contributing studies, the certainty of the evidence, statistical heterogeneity (measured using the I^2 statistic) and an indication of whether this represents a new or changed conclusion. Certainty of evidence is determined using the five GRADE (Grading of Recommendations, Assessment, Development and Evaluations) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias). Certainty ratings range from high certainty, indicating confidence that the true effect lies close to that of the estimate of the effect, down to very low certainty, indicating minimal confidence in the effect estimate, and that the true effect is likely to be substantially different from the estimate of effect. As a rule, all meta-analyses of behavioural interventions conducted by CTAG use a random-effects model to reflect the degree of heterogeneity inherent in these interventions. Pharmacotherapies and e-cigarettes are analysed with a fixed-effect model. Analyses of cessation outcomes are conducted on an intention-to-treat basis and count participants lost to follow-up as continuing to smoke, as recommended by the Russell Standard [10]. Analyses of adverse events are conducted on a complete case basis where sufficient data are available, and on an intention-to-treat basis otherwise.

TABLE 1 Included reviews

Review ID	Review title	New/ update?	Total included studies	New studies	Notes
Barnes 2019	Hypnotherapy for smoking cessation	Update	14	3	
Campbell 2020	Factors influencing the uptake and use of nicotine replacement therapy and e-cigarettes in pregnant women who smoke: a qualitative evidence synthesis	New	21	NA	Published in collaboration with Cochrane Qualitative and Implementation Methods Group, and Cochrane's Editorial and Methods Department (EMD) Editorial Service
Carson-Chahhoud 2019	Community pharmacy personnel interventions for smoking cessation	Update	7	5	
Clair 2019	Biomedical risk assessment as an aid for smoking cessation	Update	20	5	
Claire 2020	Pharmacological interventions for promoting smoking cessation during pregnancy	Update	11	2	Published in collaboration with the Cochrane Pregnancy and Childbirth Group
Fanshawe 2019	Competitions for smoking cessation	New	20	NA	Merged and updated two reviews: now contains Quit and Win contests (previously included in: 'Quit and Win contests for smoking cessation') and other competitions (previously included in: 'Competitions and incentives for smoking cessation')
Hartmann-Boyce 2019	Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation	Update	83	36	
Hartmann-Boyce 2021	Electronic cigarettes for smoking cessation	Update	61	46	Converted to Living Review format 2020: results from latest version as of September 2021
Hollands 2019	Interventions to increase adherence to medications for tobacco dependence	Update	10	2	
Howes 2020	Antidepressants for smoking cessation	Update	115	33	
Lindson 2019a	Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation	New	63	NA	
Lindson 2019b	Motivational interviewing for smoking cessation	Update	37	16	
Lindson 2019c	Smoking reduction interventions for smoking cessation	New	51	NA	New review superseding an existing review on a narrower topic ('Reduction versus abrupt cessation in smokers who want to quit'), which included 10 studies
Livingstone-Banks 2019a	Print-based self-help interventions for smoking cessation	Update	75	3	
Livingstone-Banks 2019b	Relapse prevention interventions for smoking cessation	Update	81	5	Updated twice in 2019, first update included 77 studies (15 new)
Matkin 2019	Telephone counselling for smoking cessation	Update	104	30	
Notley 2019	Incentives for smoking cessation	Update	43	16	
Roelsgaard 2019	Smoking cessation intervention for reducing disease activity in chronic autoimmune inflammatory joint diseases	New	2	NA	
Tzelepis 2019	Real-time video counselling for smoking cessation	New	2	NA	

(Continues)

TABLE 1 (Continued)

Review ID	Review title	New/ update?	Total included studies	New studies	Notes
Ussher 2019	Exercise interventions for smoking cessation	Update	24	6	
Whittaker 2019	Mobile phone text messaging and app-based interventions for smoking cessation	Update	26	14	Title changed from: 'Mobile phone-based interventions for smoking cessation'

NA = not applicable.

RESULTS

In 2019 and 2020, CTAG published six new reviews and updated 15 previously published reviews Many of these reviews were updated as part of a National Institute for Health Research (NIHR)-funded Cochrane programme grant in order to feed into an overview of reviews with a component network meta-analysis of behavioural interventions for smoking cessation [11]. Others were updated at the request of NICE to inform guideline updates [12–14].

Pharmacotherapies for smoking cessation

One of CTAG's earliest reviews assessed 'Nicotine replacement therapy for smoking cessation'. In 2018 this was split into two, with a 2018 update confined to studies that compared NRT to no intervention or placebo [15]. There was high certainty evidence giving a precise estimate of effectiveness, with sufficient evidence to reassure clinicians, patients and decision-makers of the safety and tolerability of this medication. The 2019 review compared different doses, durations and modes of delivery of nicotine replacement therapy (NRT) with one another [16]. The authors found high-certainty evidence that combination NRT, in the form of a fast-acting form of NRT (e.g. gum, lozenges, sprays) combined with transdermal patches, helped more people to quit than single-form NRT alone [risk ratio (RR) = 1.25, 95% CI = 1.15–1.36, 14 studies, 11 356 participants; I^2 = 4%]. There was mixed evidence regarding higher doses of NRT. Review authors found no evidence that 42/44-mg patches were more effective than 21/22-mg patches (RR = 1.09, 95% CI = 0.93–1.29, five studies, 1655 participants; I^2 = 38%; moderate-certainty evidence) but that 21-mg 24-hour patches helped more people to quit than 14-mg patches (RR = 1.48, 95% CI = 1.06–2.08, one study, 537 participants). They also found moderate-certainty evidence suggesting there may have been a benefit of 25-mg 16-hour patches over 15-mg patches. However, the possible effect was modest and the lower limit of the CI was compatible with there being no difference in effect (RR = 1.19, 95% CI = 1.00–1.41, three studies, 3446 participants; I^2 = 0%). Another analysis found that 4-mg gum was more effective than 2-mg gum (RR = 1.43, 95% CI = 1.12–1.83, five studies, 856 participants; I^2 = 63%). However, subgroup analysis suggested that this benefit was limited to people who were highly dependent upon cigarettes. There was also evidence that using NRT prior to quit date, 'pre-loading', as opposed to using it from the quit date onwards, helped more people to quit (RR = 1.25, 95% CI = 1.08–1.44, nine studies, 4395 participants; I^2 = 0%; moderate-certainty evidence). There was no evidence that fast-acting NRT differed in effectiveness from nicotine patches (RR = 0.90, 95% CI = 0.77–1.05, eight studies, 3319 participants; I^2 = 0%; high-certainty evidence) and no evidence of difference between different forms of fast-acting NRT, but there were few such trials.

Many studies provided little evidence to assess the safety or tolerability of variations of NRT versus standard use. Most comparisons found no evidence of difference, but there were higher rates of treatment-related withdrawals among participants using nasal spray compared with patch (RR = 3.47, 95% CI = 1.15–10.46, 922 participants; very low certainty) and participants using 42/44-mg patches compared with 21/22-mg patches (RR = 4.99, 95% CI = 1.60–15.50, two studies, 544 participants; I^2 = 0%; low certainty).

The CTAG review of 'Antidepressants for smoking cessation' was updated in 2020 with funding from the Research England Strategic Priorities Fund. Thirty-three new studies were included, bringing the total to 115 studies [17]. For the most part, conclusions remained unchanged from the 2013 version of the review. The authors found high-certainty evidence that bupropion helped more people to quit compared with placebo or no pharmacotherapy (RR = 1.64, 95% CI = 1.52–1.77; I^2 = 15%; 45 studies, 17 866 participants). They did not find a difference in number of serious adverse events (SAEs) experienced between people receiving bupropion and those receiving placebo, with imprecise CIs encompassing no difference as well as clinically significant harm and benefit (RR = 1.16, 95% CI = 0.90–1.48; I^2 = 0%; 21 studies, 10 625 participants; moderate-certainty evidence). They found evidence that, compared with placebo, bupropion resulted in a higher proportion of people stopping treatment because of adverse events (AEs) (RR = 1.37, 95% CI = 1.21–1.56; I^2 = 19%; 25 studies, 12 340 participants; high-certainty evidence). People receiving bupropion were also more likely to report psychiatric AEs compared with placebo (RR = 1.25, 95% CI = 1.15–1.37; I^2 = 15%; six studies, 4439 participants).

Review authors also examined the use of bupropion in combination with other smoking cessation pharmacotherapies. They did not find evidence of increased smoking cessation among people randomized to bupropion plus NRT compared with those randomized to NRT alone (RR = 1.19, 95% CI = 0.94–1.51; I^2 = 52%; 12 studies, 3487 participants; low-certainty evidence), nor those randomized bupropion

TABLE 2 Summary of primary analyses from new/update reviews

Review	Comparison	Effect size (95% CI)	I^2	Number of participants	Number of studies	Certainty of the evidence	New/updated in 2019/2020?
Barnes 2019	Hypnotherapy versus attention-matched behavioural treatments	RR = 1.21 (0.91–1.61)	36%	957	6	Low	New; analyses restructured
	Hypnotherapy versus brief attention/advice/ smoking cessation education (not matched for contact time)	RR = 0.98 (0.57–1.69)	0%	269	2	Very low	New; analyses restructured
	Hypnotherapy versus intensive behavioural interventions (not matched for contact time)	RR = 0.93 (0.47–1.82)	0%	211	2	Very low	New; analyses restructured
	Hypnotherapy versus no treatment	RR = 19.00 (1.18–305.88)	NA	40	1	Very low	New; analyses restructured
Carson-Chahhoud 2019	Higher-intensity smoking cessation support delivered by community pharmacy personnel versus lower-intensity support	RR = 2.30 (1.33–3.97)	54%	1614	6	Low	New; studies not previously pooled
Clair 2019	Biomedical risk assessment: feedback on smoking exposure versus standard care or minimal intervention	RR = 1.00 (0.83–1.21)	0%	2368	5	Moderate	New; analyses restructured
	Biomedical risk assessment: feedback on smoking-related risk versus standard care or minimal intervention	RR = 0.80 (0.63–1.01)	0%	2064	5	Low	New; analyses restructured
	Biomedical risk assessment: feedback on smoking-related harm versus standard care or minimal intervention	RR = 1.26 (0.99–1.61)	34%	3314	11	Moderate	New; analyses restructured
Claire 2020	NRT versus placebo or no pharmacotherapy plus similar/matched behavioural support during pregnancy	RR = 1.37 (1.08–1.74)	34%	2336	6	Low	Updated; conclusions not changed
	Bupropion versus placebo or no pharmacotherapy plus similar/matched behavioural support during pregnancy	RR = 0.74 (0.21–2.64)	0%	76	2	Low	New analysis
Fanshawe 2019	Performance-based eligibility competitions versus no intervention or non-competition-based smoking cessation intervention	RR = 1.16 (0.77–1.74)	57%	3201	6	Very low	New review
Hartmann-Boyce 2019	Behavioural interventions as adjuncts to pharmacotherapy versus pharmacotherapy alone	RR = 1.15 (1.08–1.22)	8%	23 331	65	High	Updated; conclusions not changed
Hartmann-Boyce 2021	Nicotine e-cigarette versus NRT	RR = 1.53 (1.21–1.93)	0%	1924	4	Moderate	Updated; conclusions changed

(Continues)

TABLE 2 (Continued)

Review	Comparison	Effect size (95% CI)	I^2	Number of participants	Number of studies	Certainty of the evidence	New/updated in 2019/2020?
	Nicotine e-cigarette versus non- nicotine e-cigarette	RR = 1.94 (1.21–3.13)	0%	1447	5	Moderate	Updated; conclusions not changed
	Nicotine e-cigarette versus behavioural support only/no support	RR = 2.61 (1.44–4.74)	0%	2886	6	Very low	New analysis
Hollands 2019	Interventions to increase adherence through information and problem-solving versus behavioural support for smoking cessation (short-term cessation)	RR = 1.08 (0.96–1.21)	0%	1795	5	Low	Updated; conclusions not changed
	Interventions to increase adherence through information and problem-solving versus behavioural support for smoking cessation (long-term cessation)	RR = 1.16 (0.96–1.40)	48%	3593	5	Low	Updated; conclusions changed
Howes 2020	Bupropion versus placebo/no pharmacotherapy	RR = 1.64 (1.52–1.77)	15%	17 866	46	High	Updated; conclusions not changed
	Bupropion plus NRT versus NRT alone	RR = 1.19 (0.94–1.51)	52%	3487	12	Low	No
	Bupropion plus varenicline compared to varenicline alone	RR = 1.21 (0.95–1.55)	15%	1057	3	Moderate	New analysis
Lindson 2019a	Combination versus single-form NRT	RR = 1.25 (1.15–1.36)	4%	11 356	14	High	New review
	16 weeks of combination NRT versus 8 weeks of combination NRT	RR = 0.96 (0.75–1.23)	NA	637	1	Very low	New review
	6 weeks of combination NRT versus 2 weeks of combination NRT	RR = 1.11 (0.94–1.31)	NA	987	1	Low	New review
	NRT 42/44 mg versus NRT 21/22 mg (24-hour patches)	RR = 1.09 (0.93–1.29)	38%	1655	5	Moderate	New review
	NRT 25 mg versus NRT 15 mg (16-hour patches)	RR = 1.19 (1.00–1.41)	0%	3446	3	Moderate	New review
	NRT 21 mg versus NRT 14 mg (24-hour patches)	RR = 1.48 (1.06–2.08)	NA	537	1	Moderate	New review
	Fast-acting NRT versus nicotine patch	RR = 0.90 (0.77–1.05)	0%	3319	8	High	New Review
	Oral spray NRT versus nicotine gum	RR = 0.80 (0.29–2.19)	N/A	75	1	Very low	New Review
	Oral spray NRT versus nicotine inhaler	RR = 2.00 (0.46–8.73)	N/A	75	1	Very low	New Review
	Nicotine gum versus nicotine inhaler	RR = 2.50	N/A	50	1	Very low	New Review

(Continues)

TABLE 2 (Continued)

Review	Comparison	Effect size (95% CI)	I^2	Number of participants	Number of studies	Certainty of the evidence	New/updated in 2019/2020?
		(0.53–11.70)					
	Pre-loading NRT versus standard-use NRT	RR = 1.25 (1.08–1.44)	0%	4395	9	Moderate	New Review
Lindson 2019b	Motivational interviewing versus no treatment	RR = 0.84 (0.63–1.12)	0%	684	4	Low	New; analyses restructured
	Motivational interviewing in addition to other smoking cessation treatment versus other smoking cessation treatment alone	RR = 1.07 (0.85–1.36)	47%	4167	12	Low	New; analyses restructured
	Motivational interviewing versus another smoking cessation intervention	RR = 1.24 (0.91–1.69)	54%	5192	19	Low	New; analyses restructured
	Higher-intensity motivational interviewing versus lower-intensity motivational interviewing	RR = 1.23 (1.11–1.37)	0%	5620 (adjusted)	5	Low	New; analyses restructured
Lindson 2019c	Reduction to quit versus abrupt quitting	RR = 1.01 (0.87–1.17)	29%	9219	22	Moderate	New review
	Reduction to quit versus no treatment	RR = 1.74 (0.90–3.38)	45%	1599	6	Very low	New review
Livingstone-Banks 2019a	Non-tailored print-based self-help materials versus no materials	RR = 1.19(1.03–1.37)	0%	13 241	11	Moderate	No
	Individually tailored print-based self-help materials versus no materials	RR = 1.34(1.19–1.51)	0%	14 359	10	Moderate	Updated; conclusions not changed
Livingstone-Banks 2019b	Behavioural interventions for relapse prevention versus no intervention or a shorter intervention or an intervention not orientated towards relapse prevention for relapse prevention in people who have quit smoking using a cessation intervention	RR = 0.98 (0.87–1.11)	52%	5523	11	Moderate	Updated; conclusions not changed
	NRT versus placebo for relapse prevention in people who have quit smoking using a cessation intervention	RR = 1.04 (0.77–1.4)	0%	553	2	Low	No
	Bupropion versus placebo for relapse prevention in people who have quit smoking using a cessation intervention	RR = 1.15 (0.98–1.35)	0%	1697	6	Moderate	No
	Combination NRT and bupropion versus placebo for relapse prevention in people who have quit smoking using a cessation intervention	RR = 1.18 (0.75–1.87)	66%	243	2	Low	No
	Varenicline versus placebo for relapse prevention in people who have quit smoking using a cessation intervention	RR = 1.23 (1.08–1.41)	82%	1297	2	Moderate	New analysis
Matkin 2019		RR = 1.38 (1.19–1.61)	72%	32 484	14	Moderate	Updated; conclusions not changed

(Continues)

TABLE 2 (Continued)

Review	Comparison	Effect size (95% CI)	I^2	Number of participants	Number of studies	Certainty of the evidence	New/updated in 2019/2020?
	Additional proactive calls versus self-help materials or brief counselling at a single call in people who had called a quitline						
	Proactive telephone counselling versus self-help materials or brief counselling at a single call in people who had not called a quitline	RR = 1.25 (1.15–1.35)	52%	41 233	65	Moderate	Updated; conclusions not changed
Notley 2019	Incentives for smoking cessation versus no incentives	RR = 1.49 (1.28–1.73)	33%	21 627	30 (33 comparisons)	High	Updated; conclusions not changed
	Incentives for smoking cessation versus no incentives in pregnant people	RR = 2.38 (1.54–3.69)	41%	2273	9	Moderate	Updated; conclusions not changed
Tzelepis 2019	Video counselling versus telephone counselling	RR = 2.15 (0.38–12.04)	66%	608	2	Very low	New review
Ussher 2019	Exercise and smoking cessation support or exercise alone versus smoking cessation support only	RR = 1.08 (0.96–1.22)	0%	6607	21	Low	New; studies not previously pooled
	Exercise and smoking cessation support or exercise alone versus smoking cessation support only for relapse prevention in people who had recently quit	RR = 0.98 (0.65–1.47)	0%	453	2	Very low	New; studies not previously pooled
Whittaker 2019	Text messaging versus minimal support	RR = 1.54 (1.19–2.00)	71%	14 133	13	Moderate	Updated; conclusions not changed
	Text messaging + other smoking cessation support versus other smoking cessation support alone	RR = 1.59 (1.09–2.33)	0%	997	4	Moderate	New; analyses restructured
	Smartphone app versus lower-intensity smoking cessation support	RR = 1.00 (0.66–1.52)	59%	3079	5	Very low	New; analyses restructured

CI = confidence interval; *n* = number of participants; NA = not applicable; NRT = nicotine replacement therapy; RR = risk ratio; SMD = standardized mean difference.

TABLE 3 Summary of primary outcome measures of harms from new/update reviews

Review	Comparison	Effect estimate (95% CI)	Heterogeneity I^2	Number of participants	Number of studies	Certainty of the evidence	New/updated in 2019/2020?
Claire 2020	NRT versus placebo or no pharmacotherapy plus similar/matched behavioural support during pregnancy: mean birthweight (g)	MD = 99.73 g (−6.65 to 206.10 g)	70%	2202	7	Low	Updated; conclusions not changed
	NRT versus placebo or no pharmacotherapy plus similar/matched behavioural support during pregnancy: miscarriage and spontaneous abortion	RR = 1.60 (0.53–4.83)	0%	1916	5	Low	Updated; conclusions not changed
	Bupropion versus placebo or no pharmacotherapy plus similar/matched behavioural support during pregnancy: mean birthweight (g)	MD = 122.64 g (−98.82 to 344.10 g)	0%	68	2	Low	New analysis
Hartmann-Boyce 2021	Nicotine e-cigarette versus NRT: adverse events	RR = 0.98 (0.80–1.19)	0%	485	2	Low	Updated; conclusions not changed
	Nicotine e-cigarette versus NRT: serious adverse events	RR = 1.44 (0.94–2.19)	0%	1183	3 (only 2 reported events)	Low	New analysis
	Nicotine e-cigarette versus non- nicotine e-cigarette: adverse events	RR = 1.01 (0.91–1.11)	0%	601	3	Moderate	New analysis
	Nicotine e-cigarette versus non- nicotine e-cigarette: serious adverse events	RR = 0.95 (0.52–1.72)	0%	1033	6 (only 3 reported events)	Low	New analysis
	Nicotine e-cigarette versus behavioural support only/no support: adverse events	RR = 1.22 (1.12–1.32)	41%	765	4	Low	New analysis
	Nicotine e-cigarette versus behavioural support only/no support: serious adverse events	RR = 1.51 (0.70–3.24)	0%	1303	7	Very low	New analysis
Howes 2020	Bupropion versus placebo/no pharmacotherapy: serious adverse events	RR = 1.16 (0.90–1.48)	0%	10 625	21	Moderate	New analysis
	Bupropion versus placebo/no pharmacotherapy: dropouts due to adverse events	RR = 1.37 (1.21–1.56)	19%	12 340	25	High	New analysis
	Bupropion plus NRT versus NRT alone: serious adverse events	RR = 1.52 (0.26–8.89)	0%	607	3	Very low	New analysis
	Bupropion plus NRT versus NRT alone: dropouts due to adverse events	RR = 1.67 (0.95–2.92)	0%	538	2	Low	New analysis

(Continues)

TABLE 3 (Continued)

Review	Comparison	Effect estimate (95% CI)	Heterogeneity I^2	Number of participants	Number of studies	Certainty of the evidence	New/updated in 2019/2020?
	Bupropion plus varenicline versus varenicline alone: serious adverse events	RR = 1.23 (0.63–2.42)	0%	1094	5	Low	New analysis
	Bupropion plus varenicline versus varenicline alone: dropouts due to adverse events	RR = 0.80 (0.45–1.45)	0%	1230	4	Low	New analysis
Lindson 2019	Combination versus single-form NRT: serious adverse events	RR = 4.44 (0.76–25.85)	35%	2888	5	Low	New review
	Combination versus single-form NRT: treatment withdrawals	RR = 1.12 (0.57–2.20)	73%	3070	5	Very low	New review
	26 weeks of combination NRT versus 8 weeks of combination NRT: serious adverse events	RR = 1.63 (0.60–4.42)	NA	544	1	Very low	New review
	NRT 42/44 versus NRT 21/22 mg (24-hour patches): serious adverse events	RR = 5.01 (0.87–28.82)	0%	1023	2	Low	New review
	NRT 42/44 versus NRT 21/22 mg (24-hour patches): treatment withdrawals	RR = 4.99 (1.60–15.50)	0%	554	2	Low	New review
	NRT 21 versus NRT 14 mg (24-hour patches): treatment withdrawals	RR = 0.77 (0.36–1.64)	NA	537	1	Low	New review
	Fast-acting NRT versus nicotine patch: treatment withdrawals	RR = 4.23 (1.54–11.63)	0%	1482	3	Very low	New review
	Pre-loading NRT versus standard-use NRT: serious adverse events	RR = 1.11 (0.59–2.09)	0%	3908	4	Low	New review
	Pre-loading NRT versus standard-use NRT: treatment withdrawals	RR = 0.33 (0.01–7.95)	NA	80	1	Very low	New review

CI = confidence interval; MD = mean difference; NA = not applicable; NRT = nicotine replacement therapy; RR = risk ratio.

plus varenicline compared with varenicline alone (RR = 1.21, 95% CI = 0.95–1.55; I^2 = 15%; three studies, 1057 participants; moderate-certainty evidence).

There was evidence that bupropion was less effective than varenicline (RR = 0.71, 95% CI = 0.64–0.79; I^2 = 0%; six studies, 6286 participants), but there was no evidence of a difference in effect between bupropion and NRT when pooling any form of NRT together (RR = 0.99, 95% CI = 0.91–1.09; I^2 = 18%; 10 studies, 8230 participants).

There was also evidence that nortriptyline increased cessation compared with placebo (RR = 2.03, 95% CI = 1.48–2.78; I^2 = 16%; six studies, 975 participants), but not when compared with bupropion [RR = 1.30 (favouring bupropion), 95% CI = 0.93–1.82; I^2 = 0%; three studies, 417 participants). There was no evidence that any of the other antidepressants tested (such as St John's wort, selective serotonin re-uptake inhibitors or monoamine oxidase inhibitors) improved smoking cessation rates.

Electronic cigarettes for smoking cessation

CTAG's review of e-cigarettes for smoking cessation is now a 'living review'. This means that searches of the evidence are carried out monthly; readers are encouraged to visit the Cochrane Library for the most up-to-date version. Where the inclusion of new evidence may change conclusions, then an update of the review is triggered.

An update to the review was published in 2020 [18], but as part of the living review project the review was subsequently updated in April and September 2021 [19,20]. Here we present results from the most recent version (September 2021). Combined, the 2020 and 2021 updates added 46 new studies, bringing the total number of included studies to 61. Review authors reported moderate-certainty evidence that more people quit smoking using nicotine-containing e-cigarettes compared with NRT (RR = 1.53, 95% CI = 1.21–1.93; I^2 = 0%; four studies, *n* = 1924). They also reported low certainty evidence that the rate of adverse events was similar between groups (RR = 0.98, 95% CI = 0.80–1.19; I^2 = 0%; two studies, *n* = 485). SAEs occurred rarely, with many studies reporting no SAEs in either study arm, but there was no evidence to suggest that their frequency differed between nicotine-containing e-cigarettes and NRT (RR = 1.44, 95% CI = 0.94–2.19: I^2 = 0%; three studies, *n* = 1183; low-certainty evidence).

Review authors found moderate certainty evidence that nicotine-containing e-cigarettes improved abstinence rates compared with nicotine-free e-cigarettes (RR = 1.94, 95% CI = 1.21–3.13; I^2 = 0%; five studies, *n* = 1447). There was no evidence of difference in the rate of AEs (RR = 1.01, 95% CI = 0.91–1.11; I^2 = 0%; three studies, *n* = 601; moderate-certainty evidence) or SAEs (RR = 0.95, 95% CI = 0.52–1.72; I^2 = 0%; six studies, *n* = 1033; low-certainty evidence), although evidence was limited.

A new analysis reported evidence of improved cessation rates from nicotine-containing e-cigarettes compared with behavioural support only or no support (RR = 2.61, 95% CI = 1.44–4.74; I^2 = 0%; six studies, *n* = 2886; very low-certainty evidence). There was no evidence of increased rates of SAEs (RR = 1.51, 95% CI = 0.70–3.24; I^2 = 0%; 7 studies, *n* = 1303; very low-certainty evidence), but some evidence that non-serious AEs were more common in people using nicotine-containing e-cigarettes (RR = 1.22, 95% CI = 1.12–1.32; I^2 = 41%; four studies, *n* = 765; low-certainty evidence).

Behavioural smoking cessation support

A previous review of 'Competitions and incentives for smoking cessation' was split into two reviews, assessing financial incentives for smoking cessation, where successful quitters are rewarded with money or vouchers [21], and competition-based interventions, where successful quitters are entered into a prize draw [22]. The incentives branch, initially published in 2015, was updated in 2019, adding 16 new studies, bringing the total to 43. Previously there was low-certainty evidence of the effectiveness of incentives for smoking cessation, but this update reported that, compared with no incentives, there was high-certainty evidence that guaranteed financial incentives improved smoking cessation rates in people who smoked from the general population (RR = 1.49, 95% CI = 1.28–1.73; I^2 = 33%; 33 comparisons from 30 studies, adjusted *n* = 20 097) and moderate-certainty evidence of increased cessation rates during pregnancy (RR = 2.38, 95% CI = 1.54–3.69; I^2 = 41%; nine studies, *n* = 2273).

The competitions branch also included studies from another previous review of 'Quit and Win contests for smoking cessation'. Whereas the review of incentives found guaranteed financial incentives to be an effective way to increase quit rates, this review found no evidence that performance-based eligibility competitions increased abstinence (RR = 1.16, 95% CI = 0.77–1.74; I^2 = 57%; six studies, *n* = 3201; very low-certainty evidence). Similarly, there was no evidence that performance-based reward competitions increased abstinence, but pooling was not possible because of heterogeneity.

The updated review of print-based self-help included 75 studies, three of which were new for the update [23]. This review found moderate-certainty evidence that when no other support was provided, printed self-help materials helped more people to stop smoking than no intervention (RR = 1.19, 95% CI = 1.03–1.37; I^2 = 0%; 11 studies, *n* = 13 241). However, there was no evidence that printed materials increased cessation rates compared with no materials when participants also received advice from a health professional or NRT (RR = 0.99, 95% CI = 0.76–1.28; I^2 = 32%; 11 studies, *n* = 5365). The authors found moderate-certainty evidence that tailored self-help materials helped more people quit than no intervention (RR = 1.34, 95% CI = 1.19–1.51; I^2 = 0%; 10 studies, *n* = 14 359). However, when compared with non-tailored materials (delivered with the same amount of contact as was required for the tailoring of materials), there was no evidence of increased quit rates (RR = 1.07, 95% CI = 0.89–1.30; I^2 = 50%; 10 studies, *n* = 11 024).

The review of 'Telephone counselling for smoking cessation' was updated in 2019 [24]. Thirty new studies were added, with 104 studies now included. Review authors found moderate-certainty

evidence that, compared with self-help materials or brief counselling, calling participants to provide support over the telephone (proactive counselling) increased quit rates among those who sought help from quitlines (RR = 1.38, 95% CI = 1.19–1.16; I^2 = 72%; 14 studies, *n* = 32 484) and those who did not (RR = 1.25, 95% CI = 1.15–1.35; I^2 = 52%; 65 studies, *n* = 41 233). There was insufficient evidence to assess whether making quitline support available for people who phone up for *ad hoc* support (reactive counselling) increases abstinence.

The 2019 review update investigating mobile-phone interventions for smoking cessation, such as text-message and app-based support, added 14 new studies, bringing the total to 26 [25]. Restructured analyses reported moderate-certainty evidence that automated text message-based smoking cessation interventions increase abstinence compared with minimal support (RR = 1.54, 95% CI = 1.19–2.00; I^2 = 71%; 13 studies, *n* = 14 133). There was also moderate-certainty evidence that text messaging interventions improve the effectiveness of in-person behavioural support compared with behavioural support alone (RR = 1.59, 95% CI = 1.09–2.33; I^2 = 0%; four studies, *n* = 997). However, the review did not find evidence that smartphone apps increased abstinence compared with low intensity or no support (RR = 1.00, 95% CI = 0.66–1.52; I^2 = 59%; five studies, *n* = 3079; very low-certainty evidence).

A new review investigated the effect of smoking cessation counselling delivered by live video-call [26]. The review included only two studies, with no evidence of a difference in quit rates between video counselling and telephone counselling interventions. However, there was substantial imprecision in the estimate, which is reflected in the very low certainty of the evidence (RR = 2.15, 95% CI = 0.38–12.04; I^2 = 66%; two studies, *n* = 608; very low-certainty evidence).

The 2019 update of 'Biomedical risk assessment as an aid for smoking cessation' added five new studies, bringing the total to 20 [27]. The analyses were restructured, grouping studies by the type of feedback participants received. The review update found moderate-certainty evidence that adding spirometry or carotid ultrasound test results to advice to quit smoking increased abstinence, but the estimate of effect lay between no benefit and substantial benefit (RR = 1.26, 95% CI = 0.99–1.61; I^2 = 34%; 11 studies, *n* = 3314). Review authors found evidence suggesting that neither feedback on smoking exposure by carbon monoxide monitoring (RR = 1.00, 95% CI = 0.83–1.21; I^2 = 0%; five studies, *n* = 2368; moderate certainty evidence) nor feedback on smoking-related risk by genetic marker testing (RR = 0.80, 95% CI = 0.63–1.01; I^2 = 0%; five studies, *n* = 2064; low-certainty evidence) increased abstinence.

The review of the effectiveness of motivational interviewing (MI) for smoking cessation was updated and restructured, adding 16 new studies, bringing the total to 37 [28]. There was insufficient evidence to determine whether MI helps people to stop smoking compared with no intervention (RR = 0.84, 95% CI = 0.63–1.12; I^2 = 0%; four studies, adjusted *n* = 684; low-certainty evidence) as an addition to other types of behavioural support for smoking cessation (RR = 1.07, 95% CI = 0.85–1.36; I^2 = 47%; 12 studies, adjusted *n* = 4167; low-certainty evidence) or compared with other types of behavioural support for smoking cessation (RR = 1.24, 95% CI = 0.91–1.69; I^2 = 54%; 19 studies, *n* = 5192; low-certainty evidence). There was also inconclusive evidence for a possible benefit of higher- compared with lower-intensity MI (RR = 1.23, 95% CI = 1.11–1.37; I^2 = 0%; five studies, adjusted *n* = 5620; low-certainty evidence).

The review update on behavioural support as an adjunct to pharmacotherapy included 83 studies, 36 of which were new [29]. There was high-certainty evidence that providing more intensive behavioural support for people using pharmacotherapy to stop smoking increases quit rates modestly compared with providing less intensive support (RR = 1.15, 95% CI = 1.08–1.22; I^2 = 8%; 65 studies, *n* = 23 331).

The updated review investigating interventions for improving adherence to smoking cessation medications added two new studies to the previous eight. It found that, in people who were stopping smoking using pharmacotherapy, enhanced behavioural support focusing upon improving adherence can provide modest benefit, improving cessation medication adherence [standardized mean difference (SMD) = 0.10, 95% CI = 0.03–0.18; I^2 = 6%; 10 studies, *n* = 3655; moderate-certainty evidence] compared with behavioural support without this focus [30]. Evidence was insufficient to assess whether there was a benefit for cessation in the short term (RR = 1.08, 95% CI = 0.96–1.21; I^2 = 0%; five studies, *n* = 1795; low-certainty evidence) and at 6 months follow-up or more (RR = 1.16, 95% CI = 0.96–1.40; I^2 = 48%; five studies, *n* = 3593; low-certainty evidence). This evidence was of low certainty because of serious imprecision.

A new review of smoking reduction found moderate-certainty evidence that reduction-to-quit interventions produced similar quit rates to abrupt quitting interventions (RR = 1.01, 95% CI = 0.87–1.17; I^2 = 29%; 22 studies, *n* = 9219) [31].

The 2019 update of the review of 'Exercise interventions for smoking cessation' added six new studies to the previous 18, and conducted a meta-analysis for the first time [32]. The authors found no evidence that adding exercise to smoking cessation support increased quit rates compared with support alone (RR = 1.08, 95% CI = 0.96–1.22; I^2 = 0%; 21 studies, *n* = 6607; low-certainty evidence).

The update of the review of 'Hypnotherapy interventions for smoking cessation' in 2019 added three new studies, bringing the total to 18 [33]. Meta-analyses were restructured for this update. There was no evidence that hypnotherapy increased abstinence rates compared with attention-matched behavioural support (RR = 1.21, 95% CI = 0.91–1.61; I^2 = 36%; six studies, *n* = 957; low-certainty evidence), brief advice (RR = 0.98, 95% CI = 0.57–1.69; I^2 = 0%; two studies, *n* = 269; very low-certainty evidence) or intensive behavioural support (RR = 0.93, 95% CI = 0.47–1.18; I^2 = 0%; two studies, *n* = 211; very low-certainty evidence). Although one study showed benefit of hypnotherapy compared with no treatment, this study was considered at high risk of bias and certainty was judged to be very low (RR = 19, 95% CI = 1.18–305.88; one study, *n* = 40; very low-certainty evidence).

Interventions in specific population groups

Two reviews, carried out in 2020, investigated the use of smoking cessation pharmacotherapy in pregnancy, supported by funding from the National Institute for Health and Care Excellence (NICE). The first was an update, testing the effect of smoking cessation pharmacotherapies and nicotine-containing electronic cigarettes [13]. There was evidence that NRT helped more people to quit in later pregnancy (RR = 1.37, 95% CI = 1.08–1.74; I^2 = 34%, nine studies, n = 2336) when used during pregnancy, but with strong evidence of subgroup differences between placebo-controlled studies and studies with no treatment as comparator. The former suggested a much smaller effect. There was no strong evidence nor suggestive evidence that NRT use in pregnancy increased the risk of problems in pregnancy or harm to the foetus. There was insufficient evidence to assess the impact of bupropion during pregnancy. The second review was a new review of qualitative studies examining factors influencing use of NRT and e-cigarettes in pregnancy [14]. The review included 21 studies in which the authors identified six descriptive themes and a further 18 findings within those themes. Based on this, review authors developed three overarching analytical themes representing key determinants of uptake and adherence to NRT and/or e-cigarettes in pregnancy, namely desire to protect the foetus, advice from health professionals on the effectiveness and safety of NRT and e-cigarettes and past experiences with using these products. This review did not assess the certainty of evidence.

Smoking seems to cause inflammatory rheumatological conditions, so support for quitting may improve the outcome of disease. A new review of intervention studies in people with chronic autoimmune inflammatory joint diseases found only two small studies, which could not be pooled, and proved inconclusive regarding whether cessation improved disease activity. There was no evidence in either study that the intervention tested increased smoking cessation rates [34].

Interventions delivered by specific providers

One review update investigated the effect of smoking cessation support delivered by community pharmacy personnel, adding five new studies, bringing the total to seven [35]. Review authors found that community pharmacists can provide effective behavioural smoking cessation support, with more people quitting when receiving higher-intensity support compared with lower-intensity support from pharmacists (RR = 2.30, 95% CI = 1.33–3.97; I^2 = 54%; six studies, n = 1614; low-certainty evidence).

Relapse prevention interventions

The relapse prevention review examines the effectiveness of interventions to support people who are already abstinent from returning to smoking and was updated twice in 2019 [12,36]. The second update was at the request of NICE, and was supported by NICE and the Research England Strategic Priorities Fund. Between the two updates, 20 new studies were added, bringing the total to 81. Review authors found no evidence of benefit for relapse prevention from behavioural interventions that taught assisted abstainers to recognize situations that were high risk for relapse, together with strategies to cope compared with no intervention (RR = 0.98, 95% CI = 0.87–1.11; I^2 = 52%; 11 studies, n = 5523; moderate-certainty evidence). Similarly, review authors found no evidence that tobacco abstainers were less likely to relapse when receiving NRT (RR = 1.04, 95% CI = 0.77–1.40; I^2 = 0%; two studies, n = 553; low-certainty evidence), bupropion (RR = 1.15, 95% CI = 0.98–1.35; I^2 = 0%; six studies, n = 1697; moderate-certainty evidence) or combination NRT and bupropion (RR = 1.18, 95% CI = 0.75–1.87; I^2 = 66%; two studies, n = 243; low-certainty evidence) compared with placebo. However, new studies allowed a new analysis comparing varenicline with placebo, which found moderate-certainty evidence that varenicline prevented relapse in people who had already achieved abstinence from smoking (RR = 1.23, 95% CI = 1.08–1.41; I^2 = 82%; 11 studies, n = 1297).

DISCUSSION

No further trials of single-form NRT versus placebo are required, arguably even for licensing new forms, as the effect estimate appears stable and the adverse event and safety profile favours use for smoking cessation. However, many trials excluded lighter smokers, and placebo-controlled trials including only people smoking relatively few cigarettes per day would be useful. Further research to define optimum combinations of NRT to examine the effectiveness of pre-loading and defining who benefits from higher doses of NRT would clarify the existing evidence.

There is some remaining uncertainty about the adverse event profile of bupropion but not its effectiveness. However, further trials of bupropion may not be worthwhile. We have sufficient evidence to show that it is less effective than varenicline and has a higher rate of withdrawal and more psychiatric adverse events. With varenicline coming off patent and cytisine potentially being licensed around the world, it is unlikely that bupropion will have a big place to play in supporting cessation in the future.

The evidence for the effectiveness and tolerability of e-cigarettes has been strengthened with each update, but further trials would be welcome, particularly testing pod devices and defining their effectiveness against other aids to cessation. Further studies evaluating long-term outcomes regarding safety, relapse to smoking and continued e-cigarette use are also needed. There is some evidence that use of e-cigarettes after cessation may increase smoking relapse risk [37]. Further research could establish whether this happens when e-cigarettes are used as a cessation aid. Other key questions about e-cigarettes mainly lie outside the realm in which randomized controlled trials (RCTs) are useful, and relate to the population impact of policies that promote their use for people who smoke compared with alternative policy positions that try to restrict their use. In countries

with promoting policies, such as the United Kingdom, the use of e-cigarettes is far more common than other aids to cessation and showing the potential for benefit, but the increasing rates of continued use and use by people who have never smoked show that there is also potential for population harm [38,39]. Policy studies are needed to address these questions, and CTAG is in the process of planning a new review evaluating the relationship between e-cigarette use and availability and youth smoking.

Unlike for pharmacotherapy, evidence for the effectiveness of behavioural support is unlikely to converge on a single point estimate of effect because of the variation in the content delivery and context of support. The evidence for the effectiveness of text messages is strong, and while not at the leading edge of technology, it provides a means to reach the large majority of people who smoke, who live in low- and middle-income countries and who may not have access to or can afford data-rich telephone connections. Trials in such contexts would be welcome. Similarly, trials of printed behavioural support programmes have taken place predominantly in high-income countries, where there is already an established context of awareness and cessation support. Even against this context, this inexpensive technology appears somewhat effective and is low cost. Trials in low- and middle-income countries, where less support may be available as standard, would be useful and may demonstrate a more pronounced effect.

Biomedical feedback is typically delivered in a medical context and is an adjunct to advice to quit smoking. The accumulated evidence suggests that the effects are modest. A key challenge is that the majority of people who smoke are likely to test 'normal' on any single test and the motivating effect on cessation will depend upon the way a person processes the test results. This may be influenced by the way results are conveyed and meaning ascribed to them by medical professionals, which has received less attention in studies than the testing itself. Given the evidence that advice focused upon increasing motivation to quit is less effective than offering support on how to do so [11], biomedical testing for smoking-related damage may not be a priority for further research.

There is weak evidence that NRT helps pregnant people stop smoking for the duration of the pregnancy. Despite nine trials of this intervention, evidence is clouded by differences in outcomes between placebo controlled and no placebo trials. It would be helpful for future trials to continue to follow-up women beyond pregnancy to examine impact upon long-term cessation rates, given the high return to smoking after pregnancy [40]. One reason why the effectiveness of NRT may differ from the general population is that nicotine is more rapidly metabolized, meaning that 'replacement' blood concentrations may be too low to be effective. However, the prime reason is likely to be reticence about using and adhering to NRT while pregnant. Drawing on both our review of qualitative studies for this and our review of interventions to improve adherence to pharmacotherapy may address this particularly complex problem.

Assisting smokers who have maintained a period of abstinence after a quit attempt to remain abstinent for life has proved challenging, with few clues in the accumulated research. Teaching about high-risk situations and ways to manage those situations has proved ineffective, and a new approach is needed; nor has pharmacotherapy proved effective, with only varenicline showing some modest benefit, confined principally to those who have attained complete abstinence recently. Given what we know about relapse, which is that emotional factors seem to play a large role, finding ways to provide support that people may engage with in these difficult moments may be helpful but obviously is challenging.

CTAG look forward to continuing to incorporate new high-quality studies into our reviews. So far in 2021, we have published an overview of reviews with component network meta-analysis of behavioural interventions for smoking cessation, review updates on e-cigarettes for smoking cessation and interventions delivered by dental professionals and a new review on the impact of smoking cessation on mental health. We look forward to summarizing these in a subsequent update, as well as reviews on mindfulness-based cessation interventions, interventions to prevent weight gain after quitting and the impact of heated tobacco products on smoking prevalence, which are currently under way.

DECLARATION OF INTERESTS

All authors are members of the Cochrane Tobacco Addiction Group and have each authored several of the reviews included in this summary. None have any conflicts of interest.

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AUTHOR CONTRIBUTION

JLB drafted the manuscript. All authors reviewed, edited, and commented on the text and tables.

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