Interventions for smokeless tobacco use cessation: a Cochrane review

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Smokeless tobacco*

- >300 million people worldwide use smokeless tobacco, most in South and Southeast Asia
- Much variety:
 - Form
 - Ingredients
 - Use patterns
 - Health effects
- Potential interventions same as those for combustible tobacco
- Less research attention

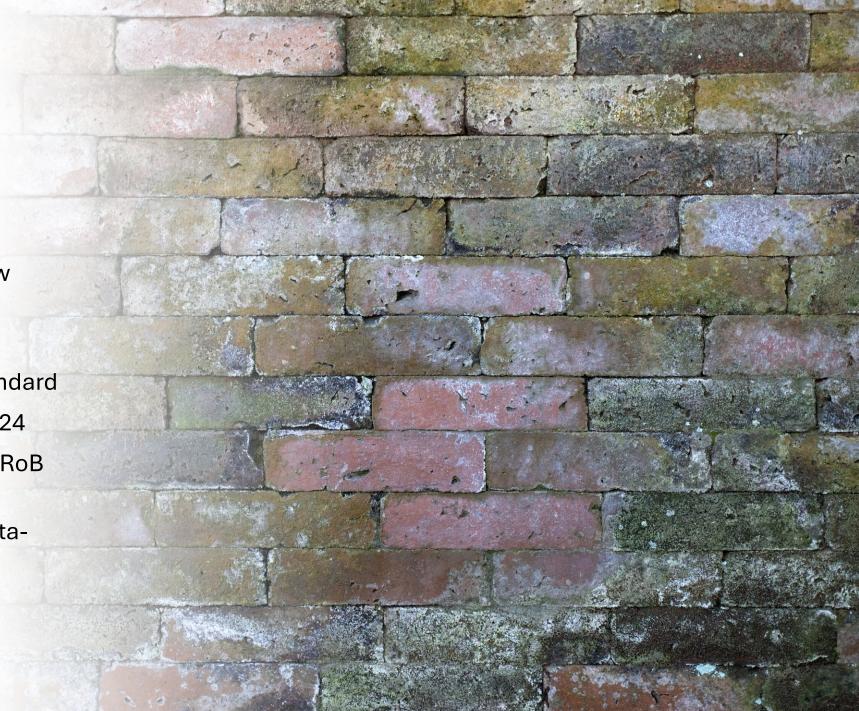
- P: any users of any smokeless tobacco product
- I: any intervention intended to help people quit smokeless tobacco use
- C: placebo, other intervention, no treatment
- **O**: abstinence from all tobacco at > 6 months
- S: RCTs

Objectives

- Replace a previous Cochrane review
- Assess the effects of interventions for smokeless tobacco use cessation
- Explore whether these differ by product type

Methods

- Cochrane systematic review
- Protocol (2022)
- Best practice: Cochrane, PRISMA, CTAG, Russell standard
- Searches to 16 February 2024
- Screening, data extraction, RoB all in duplicate
- Narrative synthesis and metaanalysis
- Certainty of evidence with GRADE



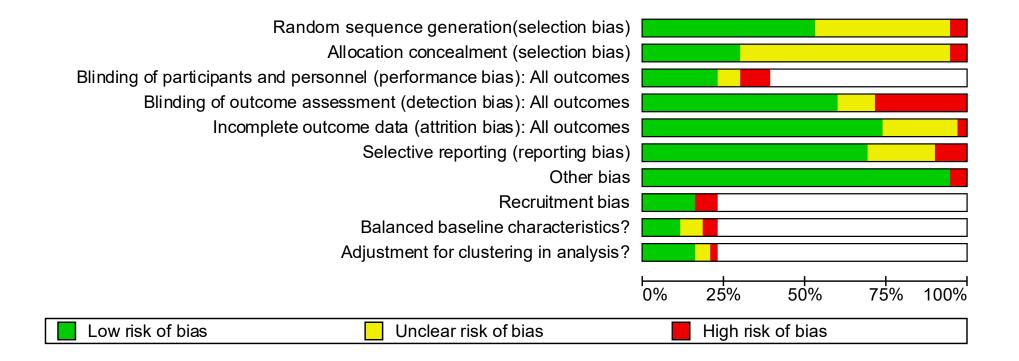
Analysis methods

- Meta-analysis of RRs with 95% CIs
- Intention-to-treat; lost to FU = not abstinent
- Mantel-Haenszel model
- Planned sensitivity analyses:
 - High risk of bias
 - Smokeless-only abstinence
 - High levels of areca or betel use
- Planned subgroup analyses:
 - Geographical/cultural origin of the product
 - Inc. betel, areca, or slaked lime

What we found

- 43 trials of 20,346 people
- 33 in North America, 5 in India, 2 in Scandinavia, 1 in Pakistan and 1 in Turkey, 1 across multiple sites in Bangladesh, India and Pakistan
- Main comparisons:
 - Behavioural interventions (vs usual/min care):
 - Counselling (21)
 - Brief advice (7)
 - Pharmacotherapies (vs placebo/no med):
 - NRT (11)
 - Varenicline (2)
 - Bupropion (2)





Risk of bias

Overall:

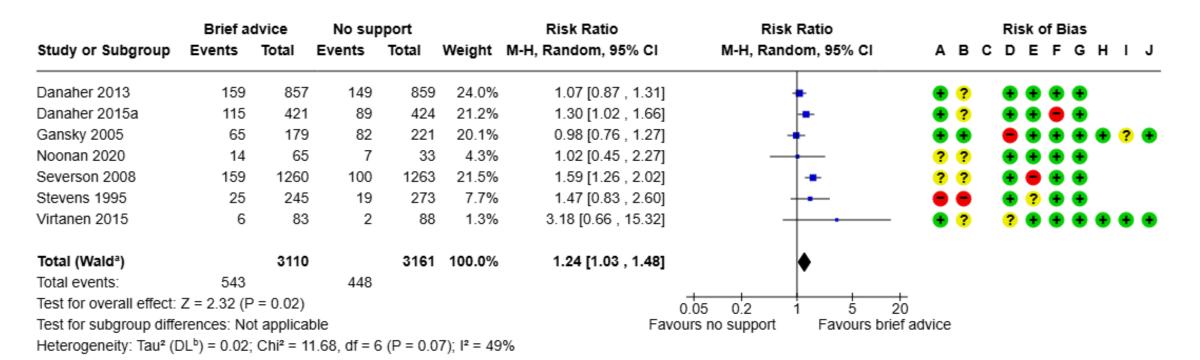
- 5 at low risk of bias,
- 22 at high risk,
- 16 at unclear

Study or Subgroup	Counse Events	lling Total	Minimal su Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	АВС	Risk of Bias	н
1.1.1 Duration ≤ 1 ho	ur									
Cigrang 2002	10	31	5	29	3.1%	1.87 [0.73 , 4.82]	+	??	😑 🕤 🕤 🖶	
Kumbhalwar 2022	22	100	9	100	4.3%	2.44 [1.18 , 5.04]		••	•••?•	
Rasool 2024	5	50	2	50	1.4%	2.50 [0.51 , 12.29]	+	• •	$\bullet \bullet \bullet \bullet$	
Severson 2007	84	535	71	534	7.8%	1.18 [0.88 , 1.58]	+	? 📀	😑 😌 😌 😁	
Severson 2009*	69	392	18	393	5.9%	3.84 [2.33 , 6.33]		??	•••	
Severson 2015*	154	357	116	356	8.5%	1.32 [1.09 , 1.60]	-	??	• • • • •	
Walsh 1999	41	119	21	131	6.2%	2.15 [1.35 , 3.42]	-	??	??	• ?
Subtotal (Wald ^b)		1584		1593	37.2%	1.89 [1.33 , 2.69]	♦			
Total events:	385		242							
Test for overall effect:	Z = 3.57 (P	= 0.0004)							
Heterogeneity: Tau ² (D) = 0.13;	Chi ² = 23	3.04, df = 6 (P = 0.000	08); l² = 7	4%				
1.1.2 Duration 1 to 3	hours									
Boyle 2004	44	109	28	112	6.9%	1.61 [1.09 , 2.39]		📀 😨		
Boyle 2008	62	210	20	205	6.2%	3.03 [1.90 , 4.82]	-		? 😧 🖨 🖷	
Gansky 2002	16	74	11	60	4.5%	1.18 [0.59 , 2.35]	+	2 2		
Mall 2021	30	103	8	103	4.2%	3.75 [1.81 , 7.79]	_ _	• ?		2
Tas 2020	18	45	0	45	0.5%	37.00 [2.30 , 595.88]		$\rightarrow \overline{\bullet} \overline{2}$		
Subtotal (Wald ^b)		541		525	22.3%	2.38 [1.35 , 4.18]		· • •	••••	
Total events:	170		67				•			
Test for overall effect:		= 0.003)								
Heterogeneity: Tau ² (D				P = 0.000	6); l² = 72	%				
1.1.3 Duration > 3 ho										
Hatsukami 1996 ^d	13	50	15	54	4.9%	0.94 [0.50 , 1.77]	-	??		
Hatsukami 1996 ^e	19	55	9	51	4.4%	1.96 [0.98 , 3.92]		??	• • ? • •	
Patten 2014	0	36	0	23		Not estimable		? 😑		••
Savant 2013 ^r	7	103	0	47	0.5%	6.92 [0.40 , 118.76]		→ ••	• ? • •	
Siddiqui 2024	7	66	3	66	1.9%	2.33 [0.63 , 8.64]	+	•••		
Stotts 2003 ⁹	13	101	8	105	3.6%	1.69 [0.73 , 3.90]	+		9 🔁 📍 🔁 🛑	
Walsh 2010	16	90	15	93	4.8%	1.10 [0.58 , 2.09]	+	??	😑 ? ? 🖶 🤅	••
Subtotal (Wald ^b)		501		439	20.1%	1.38 [0.99 , 1.93]	•			
Total events:	75		50							
Test for overall effect:	Z = 1.90 (P	= 0.06)								
Heterogeneity: Tau ² (D)L°) = 0.00;	Chi ² = 5.	06, df = 5 (P	= 0.41);	l² = 1%					
1.1.4 Duration unclea	ar									
Andrews 1999	35	343	7	208	3.8%	3.03 [1.37 , 6.70]		??		
Danaher 2015a ^h	117	417	115	421	8.4%	1.03 [0.83 , 1.28]	+	• ?		-
Danaher 2015a ⁱ	124	421	89	424	8.2%	1.40 [1.11 , 1.78]	•	• ?		
Subtotal (Wald ^b)		1181		1053	20.4%	1.40 [0.94 , 2.07]	•			
Total events:	276		211				•			
Test for overall effect:		= 0.10)	-							
Heterogeneity: Tau ² (D			90, df = 2 (P	= 0.01);	l² = 78%					
Total (Wald ^b)		3807		3610	100.0%	1.76 [1.44 , 2.16]	▲			
Total events:	906		570				•			
Test for overall effect:		< 0.0000				0.0		100		
Test for subgroup diffe			*	27) 12 -	23.6%)1 0.1 1 10 nimal support Favours o	100 ounselling		
in a sublicer and			1.83, df = 20				and appoint avours of	an ann a		

Counselling vs minimal support

• I² of 69%

• Subgrouping by intensity and modality did not explain, but direction of effect consistent



• $|^2 = 49\%$

Brief advice vs no support

• Cls include no clinically significant benefit

	Anticipated absolute effect	s [*] (95% CI)	Relative	Nº of	Certainty of the
Outcomes	Risk with usual care/minimal support	Corresponding risk with counselling	effect (95% CI)	participants (studies)	evidence (GRADE)
Counselling versus usual care/minimal support Tobacco cessation at 6+ months follow-up	158 per 1000	278 per 1000 (228 to 341)	RR 1.76 (1.44 to 2.16)	7414 (21 studies)	⊕⊕⊕⊖ ^{a,b} Moderate
Brief advice versus no support Tobacco cessation at 6+ months follow-up	150 per 1000	186 per 1000 (155 to 222)	RR 1.24 (1.03 to 1.48)	6271 (7 studies)	⊕⊕⊕⊖ ^{b,c} Moderate

Behavioural support

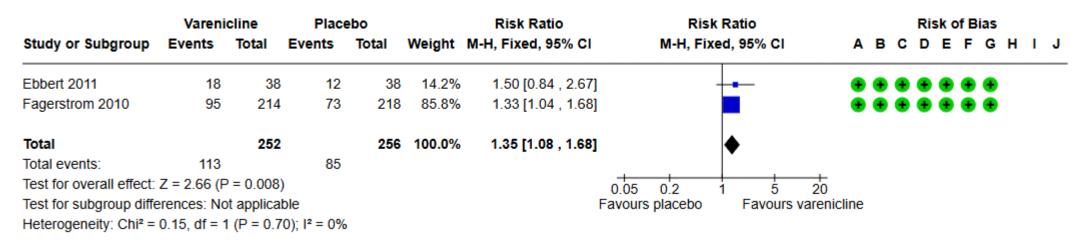
- a Downgraded one level for heterogeneity
- b Majority of studies at high risk of bias but not downgraded
- c Downgraded one level for imprecision

NRT vs placebo/no med

- $I^2 = 39\%$
- RoB sensitivity analysis changed direction of effect

	NR	т	Placebo/n	o meds		Risk Ratio	Risk Ratio				Ri	sk o	fΒ	ias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	Α	в	С	D	Е	F	G	н	I	J
Danaher 2015b	73	205	47	202	13.2%	1.53 [1.12 , 2.09]		•	?	•	•	•	•	•			
Ebbert 2007ª	9	31	2	11	0.8%	1.60 [0.41 , 6.28]		•	÷	?	÷	÷	Ŧ	•			
Ebbert 2009	34	136	24	134	6.7%	1.40 [0.88 , 2.22]		•	÷	•	÷	÷	ē	÷			
Ebbert 2010	11	30	14	30	3.9%	0.79 [0.43 , 1.44]		?	?	÷	?	?	ě	Ť			
Ebbert 2013b	8	25	5	27	1.3%	1.73 [0.65 , 4.59]	_ _	•	÷	÷	÷	•	ě	Ť			
Hatsukami 1996 ^b	9	51	15	54	4.1%	0.64 [0.31 , 1.32]	_ - +	?	?	÷	Ť	?	ě	Ť			
Hatsukami 1996°	13	50	19	55	5.0%	0.75 [0.42 , 1.36]		?	?	÷	Ť	?	ě	Ť			
Hatsukami 2000	21	100	28	101	7.8%			?	?	?	ě	?	ě	Ť			
Howard-Pitney 1999	78	206	69	204	19.3%	1.12 [0.86 , 1.45]	_	•	?	•	Ť	?	ě	Ť			
Severson 2015	154	357	112	354	31.4%	1.36 [1.12 , 1.66]	-	?	?	ē	ē	÷	ē	Ť			
Siddiqui 2024 ^d	4	66	3	66	0.8%			•	÷	ŏ	ě	ě	ē	Ť			
Siddiqui 2024 ^e	9	66	7	66	2.0%	1.29 [0.51 , 3.25]		•	ě	ŏ	ě	ě	ě	ě			
Stotts 2003	6	98	13	101	3.6%	0.48 [0.19 , 1.20]		•	Ŧ	Ŧ	Ŧ	?	Ŧ	•			
Total		1421		1405	100.0%	1.18 [1.05 , 1.33]	•										
Total events:	429		358				ľ										
Test for overall effect:	Z = 2.82 (P	= 0.005)					0.05 0.2 1 5 20										
Test for subgroup diffe						Favours p	lacebo/no meds Favours NRT										
Heterogeneity: Chi ² =				%													

Varenicline/Bupropion vs placebo



	Bupro	pion	Place	ebo		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFGHIJ
Dale 2002	4	34	4	34	14.2%	1.00 [0.27 , 3.68]		? ? 🖶 🖶 ? 🖶
Dale 2007	21	113	24	112	85.8%	0.87 [0.51 , 1.46]		$\bullet ? \bullet \bullet \bullet \bullet \bullet$
Total		147		146	100.0%	0.89 [0.54 , 1.44]	•	
Total events:	25		28					
Test for overall effect:	Z = 0.49 (F	^o = 0.63)					0.05 0.2 1 5	20
Test for subgroup diffe	erences: No	ot applica	ble					s bupropion
Heterogeneity: Chi ² =	0.04, df = 1	1 (P = 0.8	34); I² = 0%	,				

	Anticipated absolute ef	fects [*] (95% CI)	Relative	Nº of	Certainty of the
Outcomes	Risk with placebo or no medication	Corresponding risk with pharmacotherapy	effect (95% CI)	participants (studies)	evidence (GRADE)
Nicotine replacement therapy vs placebo or no medication Tobacco cessation at 6+ months follow-up	273 per 1 000	323 per 1000 (287 to 364)	RR 1.18 (1.05 to 1.33)	2826 (11 studies)	⊕⊕⊝⊝ ^{a,b} Low
Bupropion vs placebo Tobacco cessation at 6+ months follow-up	192 per 1000	171 per 1000 (104 to 276)	RR 0.89 (0.54 to 1.44)	293 (2 studies)	⊕⊕⊝⊝ ^c Low
Varenicline vs placebo Tobacco cessation at 6+ months follow-up	332 per 1000	448 per 1000 (359 to 558)	RR 1.35 (1.08 to 1.68)	508 (2 studies)	⊕⊕⊕⊖ ^d Moderate

Pharmacotherapies vs placebo

- a Downgraded one level for risk of bias
- b Downgraded one level for imprecision
- c Downgraded two levels because of imprecision
- d Downgraded one level for imprecision

Conclusions



Moderate-certainty evidence favouring cessation counselling or brief advice to quit Moderate-certainty evidence favouring varenicline

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Low-certainty evidence favouring NRT

4

Low-certainty evidence does not currently support bupropion as a smokeless tobacco cessation intervention

Next steps

Only 8/43 trials conducted in South and Southeast Asia. However, 20/22 ongoing studies underway in these regions. More work (and transparent reporting) exploring the variety of smokeless tobacco products and dual use with combustible tobacco, betel and areca.

Two trials tested the use of tobacco-free snuff for smokeless tobacco cessation, but no trials tested tobacco-free oral nicotine pouches.

Any questions?

