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[Intervention Review]

Interventions for smokeless tobacco use cessation

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ABSTRACT

Background

Use of smokeless tobacco (ST) can lead to tobacco dependence and long-term use can lead to health problems including periodontal disease, cancer, and cerebrovascular and cardiovascular disease.

Objectives

To assess the effects of behavioural and pharmacologic interventions for the treatment of ST use.

Search methods

We searched the Cochrane Tobacco Addiction Group specialised register in June 2015.

Selection criteria

Randomized trials of behavioural or pharmacological interventions to help users of ST to quit with follow-up of at least six months.

Data collection and analysis

We used standard methodological procedures as expected by the Cochrane Collaboration. We summarised outcomes as risk ratios (RRs). For subgroups of trials with similar types of intervention and without substantial statistical heterogeneity, we estimated pooled effects using a Mantel-Haenszel fixed-effect method.

Main results

We identified 34 trials that met the inclusion criteria, of which nine were new for this update, representing over 16,000 participants. There was moderate quality evidence from two studies suggesting that varenicline increases ST abstinence rates (risk ratio [RR] 1.34, 95% confidence interval (CI) 1.08 to 1.68, 507 participants). Pooled results from two trials of bupropion did not detect a benefit of treatment at six months or longer (RR 0.89, 95% CI 0.54 to 1.44, 293 participants) but the confidence interval was wide. Neither nicotine patch (five trials, RR 1.13, 95% CI 0.93 to 1.37, 1083 participants) nor nicotine gum (two trials, RR 0.99, 95% CI 0.68 to 1.43, 310 participants) increased abstinence. Pooling five studies of nicotine lozenges did increase tobacco abstinence (RR 1.36, 95% CI 1.17 to 1.59, 1529 participants) but confidence in this estimate is low as the result is sensitive to the exclusion of three trials which did not use a placebo control.

Statistical heterogeneity was evident among the 17 trials of behavioural interventions: eight of them reported statistically and clinically significant benefits; six suggested benefit but with wide CIs and no statistical significance; and three had similar intervention and

control quit rates and relatively narrow CIs. Heterogeneity was not explained by study design (individual or cluster randomization), whether participants were selected for interest in quitting, or specific intervention components. In a post hoc subgroup analysis, trials of behavioural interventions incorporating telephone support, with or without oral examination and feedback, were associated with larger effect sizes, but oral examination and feedback alone were not associated with benefit.

In one trial an interactive website increased abstinence more than a static website. One trial comparing immediate cessation using nicotine patch versus a reduction approach using either nicotine lozenge or brand switching showed greater success for the abrupt cessation group.

Authors' conclusions

Varenicline, nicotine lozenges and behavioural interventions may help ST users to quit. Confidence in results for nicotine lozenges is limited. Confidence in the size of effect from behavioural interventions is limited because the components of behavioural interventions that contribute to their impact are not clear.

PLAIN LANGUAGE SUMMARY

Ways to help people stop using smokeless tobacco (including chewing tobacco, snuff and snus)

Background

Smokeless tobacco is any product in which tobacco is held in the mouth so that nicotine is absorbed through the lining of the mouth. Smokeless tobacco is less dangerous than cigarettes and other products where tobacco is burnt and nicotine absorbed through the lungs. However, smokeless tobacco still leads to nicotine addiction and can be harmful, especially to the mouth. Many types of smokeless tobacco are used around the world, including chewing tobacco, snuff and snus. The risks to health vary with the type of product.

Methods

We reviewed the evidence from randomized trials about interventions to help people stop using smokeless tobacco, including nicotine replacement therapy, other pharmacotherapies and behavioural support. This evidence is current to June 2015. Trials had to report the number of participants who had stopped using smokeless tobacco or other products after six months.

Results

We found 34 relevant trials covering over 16,000 participants. All except one were conducted in the USA. Some studies in dental health clinics provided advice about oral health problems to smokeless tobacco users whether or not they were interested in stopping. Some studies recruited users who wanted to stop.

Sixteen trials with 3,722 participants tested pharmacotherapies. Twelve studies tested different types of nicotine replacement therapy (five gum, two patch, five lozenge). The evidence suggests that the nicotine lozenge might help people quit, but the quality of evidence was low and more research is needed. There was not enough evidence to be sure whether nicotine gum or patches could help. Two trials of varenicline (a medication that helps smokers to quit) suggested it can also help people quit using smokeless tobacco.Two small trials of bupropion (an antidepressant that helps smokers to quit) did not find that bupropion helped people quit using smokeless tobacco.

Seventeen trials with 12,394 participants tested behavioural support. The behavioural support could include brief advice, self-help materials, telephone support, access to a website, and combinations of elements. There was a lot of variation in results with some trials showing clear evidence of benefit and some not showing any effect. We could not be certain what the important elements of effective support were, but providing access to telephone support generally seemed to be helpful.

BACKGROUND

Smokeless tobacco (ST) is tobacco that is orally consumed and not burned. A variety of types of ST are consumed throughout the world and ST use is an important worldwide public health issue. In the United States, the principal types of ST are chewing tobacco (cut tobacco leaves) and snuff (moist ground tobacco). In Sweden, 'snus' (finely ground moist tobacco) is most commonly used. In India, ST contains tobacco leaf mixed with other ingredients, such as betel leaf, areca nut and lime (i.e., gutkha) (Critchley 2003). In Sudan, toombak is made from a fermented ground powdered tobacco mixed with sodium bicarbonate (Idris 1998).

Around the world, ST is used by 300 million people in at least 70 countries. The majority of smokeless tobacco users (89%) are in Southeast Asia (NCI & CDC 2014). In the US in 2012, 3.5% of individuals aged 12 or older (9 million people) used ST in the past month (SAMHSA 2014). Rates of past month ST use have remained stable between 2002 and 2012 in the U.S. In India, smokeless tobacco remains by far the most prevalent form of tobacco used (26% of population) (Kostova 2015). In 2013 in Sweden, 20% of men and 4% of women used ST daily and 3% and 1%, respectively, did so occasionally (Norberg 2015).

Available literature suggests that adverse health consequences may vary by the type of ST use, which is strongly associated with geography. According to the 1986 report of the US Surgeon General, the use of ST products can lead to nicotine addiction (NIH 1986). ST consumed in the US has been associated with periodontal disease (Ernster 1990; Fisher 2005), precancerous oral lesions (Mattson 1989), oral cancer (Stockwell 1986), and cancer of the kidney (Goodman 1986; Muscat 1995), pancreas (Muscat 1997), and digestive system (Henley 2005). ST has been shown to act as an autonomic and haemodynamic stimulus by increasing heart rate, blood pressure, and epinephrine levels (Wolk 2005), and has been associated with death from cardiovascular disease, cerebrovascular disease and cancer (Henley 2005). A recent systematic review concluded that betel quid and tobacco use in India are associated with substantial risks of oral cancer, but studies from the US and Scandinavia do not show a consistent association (Critchley 2003). Studies have suggested that ST use during pregnancy is likely to be harmful to the foetus (England 2003; Gupta 2004; Gupta 2006).

Two of the world's largest cigarette manufacturers, Phillip Morris USA and R.J. Reynolds, entered the ST market in the mid 2000s. Phillip Morris USA marketed Marlboro Snus and R.J. Reynolds marketed Camel Snus (Rogers 2010). These products were marketed as low-nitrosamine ST products (Alpert 2008) which potentially confer a lower risk of cancer. At the same time, ST was increasingly being proposed as a harm reduction strategy for cigarette smokers (McNeill 2004; NIH 2006). Although the health risks of ST use are lower than those from smoked tobacco, concern existed that the promotion of ST use may lead to smokers using both products rather than quitting tobacco use altogether, and to former smokers and never smokers initiating ST use. The impact of these factors on the prevalence of ST use remains unclear, but suggests an ongoing need for developing effective treatments for ST use.

Despite the widespread use of ST products and their potentially adverse health consequences, medical and oral health professionals have had a lack of evidence summaries or evidence-based guidelines to assist them in providing effective treatment for ST use. Smokeless tobacco cessation guidelines for health professionals in England were published after the first version of the present review was published in 2004 (West 2004). An evidence summary of ST interventions has also been published (NCI & CDC 2014).

OBJECTIVES

To assess the effects of behavioural and pharmacotherapeutic interventions to treat smokeless tobacco (ST) use.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or pseudo-randomized controlled trials allocating smokeless tobacco (ST) users to an intervention or control, or to different interventions. We also included trials in which dentists or other healthcare providers were randomized to provide intervention or control, and trials in which the unit of randomization was the school, workplace or institution.

Types of participants

Users of any tobacco product that is placed in the mouth and not burned, including moist snuff, chewing tobacco, Swedish snus, and Indian ST products (e.g. gutkha and pan masala). This does not include electronic cigarettes, which are covered in a separate Cochrane review (McRobbie 2014).

Types of interventions

Interventions could be pharmacological (i.e. nicotine replacement therapy (NRT), bupropion, varenicline) or behavioural, and could be directed at individual ST users or at groups of users (e.g. ST users visiting the dentist, attending school, or working). The control condition could be usual care, a placebo, or a less intensive intervention.

Types of outcome measures

The preferred outcome for the meta-analysis was complete abstinence from all tobacco use six months or more after the start of the intervention. If total tobacco abstinence was not reported, abstinence from ST alone was used. Trials with shorter follow-up (less than six months) or that did not report quit rates were excluded. Biochemical validation of self-reported abstinence was not required, but validated rates were used where reported.

Search methods for identification of studies

For the most recent update we searched the Cochrane Tobacco Addiction Group specialised register in June 2015. At the time of the search the Register included the results of searches of: the Cochrane Central Register of Controlled trials (CENTRAL), issue 5, 2015; MEDLINE (via OVID) to update 20150501; EMBASE (via OVID) to week 201519; and PsycINFO (via OVID) to update 20150506. See the Tobacco Addiction Group Module in the Cochrane Library for full search strategies and list of other resources searched for the register. Additional sources were also searched for early versions of the review (Ebbert 2003); these included Web of Science, Dissertation Abstracts Online, Scopus, Healthstar, ERIC, National Technical Information Service database, and Current Contents.

The search strategy for the Tobacco Addiction Group specialised register used the following terms for smokeless tobacco: chewing tobacco; oral tobacco; spit tobacco; snuff; smokeless tobacco; quid; chew; plug; and tobacco, smokeless (MeSH), appearing in titles, abstracts or keywords. No intervention terms were used. No language restrictions were imposed.

We scanned the reference lists of retrieved studies including review articles, conference proceedings, and personal reference files. For early versions of the review we asked content experts through electronic mail and telephone contact to identify unpublished randomized controlled trials (RCTs). We corresponded with experts in tobacco and ST use research.

Data collection and analysis

Selection of studies

One author examined each title generated from the search and identified potentially eligible articles for which we obtained the abstracts. These were considered by two authors. For abstracts consistent with study eligibility, we obtained the full article text. Any difference of opinion about study inclusion would have been resolved by consensus.

Data extraction and management

Two authors independently extracted data about participants, interventions, outcomes and methodological quality. Any discrepancies in extracted data were resolved by consensus.

We extracted data on the number of users quit at the longest follow-up, using the strictest definition of abstinence reported. We selected continuous or prolonged abstinence in preference to point prevalence where both were reported. Participants who were randomized but dropped out or were lost to follow-up were assumed to be continuing users.

Assessment of risk of bias in included studies

We assessed the risk of selection bias. To be judged low risk for selection bias a trial had to report both an adequate method of random sequence generation, and of allocation sequence concealment. Studies reporting a method of sequence generation which did not allow allocation concealment (for example, allocation on the basis of patient record number) were judged to be at high risk of bias. Studies which did not report an acceptable method of allocation concealment, for example central enrolment and allocation, or consecutively numbered sealed opaque envelopes, were rated at high risk of bias. Studies which did not give sufficient detail to assess quality were rated unclear. We conducted a sensitivity analysis of the effect of including trials at high risk of selection bias in the meta-analysis.

We also considered the completeness of follow-up (attrition bias), judging risk of bias as low if more than 80% of participants provided data at follow-up, unclear if the proportion reached was lower but similar in each condition, and at high risk of bias if there was evidence of differential loss by intervention condition. Other possible indicators of quality include: blinding status of participants, investigators and outcome assessors; group similarity at baseline; equal treatment of groups during study conduct; analysis and conduct by the intention-to-treat principle; and use of a placebo or active intervention in the control group (Guyatt 1993). We did not formally assess the impact of differences in these criteria on the results. In the table 'Characteristics of included studies' we noted the use of biochemical validation, and reported differences in baseline characteristics, any co-interventions and the control intervention. If we were not able to extract data allowing an intention-to-treat analysis, this was recorded.

Measures of treatment effect

We use risk ratios (RRs) to represent the point estimate of the magnitude of association between intervention exposure and treatment outcomes, and 95% confidence intervals (CIs) to represent the precision around this point estimate. A RR greater than one indicates that the rates of tobacco abstinence were higher in the intervention group than in the control group. Earlier versions of the review used odds ratios because of the possibility that some cluster randomized trials would report adjusted odds ratios. We

now use risk ratios as the majority of the included studies are individually randomized, risk ratios allow comparisons of effects with other Cochrane reviews, and are easier to interpret (Cochrane Handbook 9.2.2.2, Higgins 2011).

Data synthesis

We pooled results of studies when it was clinically and statistically appropriate to combine them. We did not combine pharmacotherapy and behavioural interventions. We conducted meta-analyses using a fixed-effect model, unless there was evidence of between-study heterogeneity (Fleiss 1993). Heterogeneity was quantified using the I^2 statistic (Higgins 2003). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Values over 50% suggest moderate heterogeneity. Where heterogeneity was higher than this we explored possible explanations, and did not report a pooled estimate of the effect.

For the pharmacological interventions, we hypothesized that nicotine replacement therapy (NRT) would lead to different outcomes compared with non-NRT pharmacotherapies (i.e., bupropion, varenicline). Underlying this hypothesis is the difference in the mechanisms of action between different pharmacotherapies (Fiore 2000). Thus, we kept different pharmacotherapies in separate prespecified subgroups.

We also hypothesized that the behavioural interventions involving recruitment of individual ST users would be associated with higher abstinence rates for intervention compared to control than those recruiting ST users at the organizational level. This was based upon the presumption that ST users receiving interventions at the organizational level (e.g. dental practice or athletic teams) may receive interventions although they are not actively seeking treatment for ST use, which will potentially lead to lower abstinence rates in this group.

RESULTS

Description of studies

The search of the Tobacco Addiction Group specialised register in June 2015 identified 12 new potentially relevant trials since the previous update in 2011.

Included studies

We identified 34 trials that met the inclusion criteria, of which nine were new for this update (Ebbert 2011; Schiller 2012; Danaher 2013; Ebbert 2013a; Ebbert 2013b; Danaher 2015a; Danaher 2015b; Severson 2015; Virtanen 2015). Sixteen of the trials assessed the effect of pharmacological interventions for ST use (Boyle 1992; Hatsukami 1996; Howard-Pitney 1999; Hatsukami 2000; Dale 2002; Stotts 2003; Dale 2007; Ebbert 2007; Ebbert 2009; Ebbert 2010a; Ebbert 2011; Ebbert 2013b; Ebbert 2013a; Fagerstrom 2010; Danaher 2015b; Severson 2015) and 19 studied the effect of behavioural interventions for ST use (Cummings 1995; Stevens 1995; Hatsukami 1996; Severson 1998; Walsh 1999; Severson 2000; Cigrang 2002; Stotts 2003; Walsh 2003; Boyle 2004; Gansky 2005; Severson 2007; Boyle 2008; Severson 2008; Severson 2009; Walsh 2010; Danaher 2013; Danaher 2015a; Virtanen 2015). These totals include two studies that contribute data to both pharmacological and behavioural analyses; one study assessed both nicotine gum and a minimal contact or intensive behavioural intervention in a factorial design (Hatsukami 1996), and one compared a minimal intervention to an intensive behavioural intervention with either active or placebo nicotine patches (Stotts 2003). One study contributing to the pharmacological analysis compared a telephone counselling intervention and nicotine lozenges to the counselling alone; a third arm providing nicotine lozenges without support was not used in this analysis (Severson 2015). One study compared an immediate cessation versus a reduction approach for ST users without plans to quit (Schiller 2012) and was not pooled with other studies.

Pharmacological interventions

Sixteen randomized controlled trials (RCTs) randomized 3722 ST users to pharmacotherapy or control. The efficacy of bupropion SR (sustained-release) given for 12 weeks was assessed in a pilot study (Dale 2002) and a multicenter trial (Dale 2007). Five studies assessed the efficacy of nicotine patch therapy (Howard-Pitney 1999; Hatsukami 2000; Stotts 2003; Ebbert 2007; Ebbert 2013b), two studies assessed the efficacy of nicotine gum (Boyle 1992; Hatsukami 1996), five studies assessed the nicotine lozenge (Ebbert 2009; Ebbert 2010a; Ebbert 2013a; Danaher 2015b; Severson 2015), and two studies assessed the efficacy of varenicline (Fagerstrom 2010; Ebbert 2011).

Both the treatment and control groups received the same behavioural interventions. Brief individual counselling at clinic visits was provided in seven (Hatsukami 2000; Dale 2002; Dale 2007; Ebbert 2007; Ebbert 2009; Fagerstrom 2010; Ebbert 2011), pharmacist advice and telephone support in one (Howard-Pitney 1999), a group programme in one (Boyle 1992), a six-week group programme with additional telephone support in a trial in adolescents (Stotts 2003), brief counselling in a clinical research unit in one (Ebbert 2013b), a web-based intervention in one (Danaher 2015b), and a self-help book in addition to telephone counselling in two (Ebbert 2010a; Severson 2015). Two studies provided instructions on ST reduction (Ebbert 2013a; Virtanen 2015). One compared a group programme to a minimal contact condition in a factorial design (Hatsukami 1996). Hatsukami 2000 also tested mint snuff as an ST substitute in a factorial design; there was no evidence of a benefit, and these arms were collapsed in the analysis.

The bupropion SR studies used a dose of 150 mg by mouth once a day for three days and then increased the dose to 150 mg twice a day (Dale 2002; Dale 2007). One nicotine patch study used 15 mg patches for six weeks (Howard-Pitney 1999); the second used 21 mg patches with a tapering schedule for a total of 10 weeks (Hatsukami 2000), and a third, in adolescents, tailored patch dose to baseline cotinine, using either 21 mg or 14 mg, both tapered over a six-week period (Stotts 2003). The fourth nicotine patch study randomized participants to doses of 21, 42 and 63 mg per day compared to placebo, and the 21 mg and placebo arms were compared for analysis (Ebbert 2007). The fifth nicotine patch study randomized patients to 42 mg of the nicotine patch (two 21 mg patches worn simultaneously) for eight weeks or two matching placebo patches (Ebbert 2013b). One nicotine gum trial instructed enrolled ST users to attempt a target daily dose of 12 pieces of 2 mg nicotine gum per day (Boyle 1992). The other nicotine gum study instructed ST users to use at least six pieces of 2 mg nicotine gum a day for one month and then gradually reduce use (Hatsukami 1996). Four of the nicotine lozenge studies used the 4 mg lozenge given for 12 weeks with a tapering schedule (Ebbert 2009; Ebbert 2010a; Danaher 2015b; Severson 2015). One nicotine lozenge study provided 4 mg lozenges at eight per day for weeks one to six and tapered over 12 weeks (Ebbert 2013a). Varenicline was increased from 0.5 mg once daily for three days to 0.5 mg twice daily for four days followed by 1 mg twice daily through Week 12 in two studies (Fagerstrom 2010; Ebbert 2011).

Twelve studies followed patients for six months (Boyle 1992; Howard-Pitney 1999; Dale 2002; Ebbert 2007; Ebbert 2009; Ebbert 2010a; Fagerstrom 2010; Ebbert 2011; Ebbert 2013a; Ebbert 2013b; Danaher 2015b; Severson 2015) and four for 12 months (Hatsukami 1996; Hatsukami 2000; Stotts 2003; Dale 2007). Five studies assessed continuous abstinence from quit date to longest follow-up (Hatsukami 1996; Hatsukami 2000; Dale 2002; Dale 2007; Ebbert 2007) but one of them (Hatsukami 1996) did not tabulate that outcome, so point prevalence is used in the meta-analysis. Four studies reported prolonged tobacco abstinence (Ebbert 2009; Ebbert 2010a; Ebbert 2011; Ebbert 2013b) defined as continuous tobacco abstinence after a two-week grace period (Hughes 2003). Fagerstrom 2010 reported prolonged abstinence from weeks 9 to 26. Two studies reported repeated point prevalence at three and six months (Danaher 2015b; Severson 2015). The remaining studies only reported point prevalence quit rates at longest follow-up (Boyle 1992; Howard-Pitney 1999; Stotts 2003; Ebbert 2013a). All studies except two (Danaher 2015b; Severson 2015) used biochemical confirmation of self-reported tobacco abstinence using tobacco alkaloid measurements (cotinine, anabasine, or anatabine). For studies determining abstinence from all tobacco products, carbon monoxide measurements and urinary anabasine and anatabine were used to determine abstinence from smoked tobacco. Three studies reported abstinence from smokeless tobacco only (Hatsukami 1996; Howard-Pitney 1999; Hatsukami 2000). Since validation was also required, other forms of regular tobacco use would have been detected, but infrequent smokers might have been included as quitters.

Behavioural interventions

Seven RCTs randomized over 3000 ST users at the organizational level. Severson 1998 randomly allocated 75 dental practices to receive a workshop for their dental health professionals to develop skills in the identification and counselling of ST users or to provide usual care. Cummings 1995 analysed data from the Working Well Trial that randomized energy-related worksites to receive either employee-targeted intense interventions based upon the Social Learning Theory (Bandura 1986) and the Transtheoretical Model of Change (DiClemente 1998), or minimal interventions consisting of mailings and posters displayed in the workplace. Four of the organizational level trials were school-based, of which three targeted athletes. A trial in college athletes (Walsh 1999) randomized college athletes at 16 campuses to receive either a behavioural intervention based upon the Health Belief Model (Rosenstock 1988) and the Social Learning Theory (Bandura 1986), or no intervention. A trial in high school athletes (Walsh 2003) randomized 44 schools to either an intervention that included oral screening, a peer-led discussion, small group cessation counselling and a phone call on quit date, or to a control condition. A trial in college baseball athletes (Gansky 2005) randomized 52 colleges to an intervention based on the diffusion of innovation theory (Rogers 1983) and cognitive social learning theory which included a video conference, an oral-cancer screening examination, a certified athletic trainer (ATC)-facilitated discussion, and a peer-led component. A trial in 41 rural public high schools (Walsh 2010) randomized to an intervention consisting of a peer-led educational session, an oral examination, and three nurse-led group cessation counselling sessions, or a control. Virtanen 2015 randomized Swedish dental clinics to delivering a structured tobacco use intervention based upon the 5 A's referring to the participants oral health and recommending pharmacotherapy but not providing it or to usual care. None of the studies randomized by organization selected ST users according to their motivation to quit.

Eleven RCTs randomized over 9000 ST users at the individual level. Stevens 1995 allocated ST users attending a routine dental visit to a multicomponent intervention consisting of feedback on oral lesions and advice to quit from both hygienist and dentist, as well as self-help materials and a follow-up call from a counsellor. The control group received usual care which may have included advice to quit. Participants were not selected according to motivation to quit. Two studies from the same research group assessed the impact of adding components to a minimal self-help intervention (Severson 2000; Severson 2007). Severson 2000 tested a handheld device for programming gradual reduction, as an adjunct to self-help materials and support. Due to problems with the prototype device, people whose machine failed twice or more were excluded from the reported analysis, and we have not included it in the meta-analysis. Severson 2007 compared telephone sup-

port with self-help written materials alone. Two studies assessed the efficacy of telephone-based counselling for ST users compared to self-help materials alone (Boyle 2004; Boyle 2008). A study in high school adolescents, also included in the pharmacotherapy section, randomized a behavioural intervention of six weekly group sessions with a health educator, plus stage-based follow-up telephone counselling (Stotts 2003). The control group had five to ten minutes of counselling and a single telephone call. A pilot study in personnel on active military service recruited self-identified ST users at a health screening, unselected for motivation to quit. Members of the intervention group were telephoned and asked if they wished to receive self-help materials and to have further support calls, using a motivational interviewing approach (Cigrang 2002). Based upon these promising preliminary results, a similar study was conducted with a larger sample of military recruits (Severson 2009). Two studies assessed the efficacy of a web-based intervention randomising ST users to a basic or enhanced version (Severson 2008; Danaher 2013). One study randomized participants to a web-based intervention, a telephone quitline intervention, web plus quitline, or a control with a printed self-help guide (Danaher 2015a). One study randomized ST users who had no intention of quitting to immediate cessation or a reduction intervention (Schiller 2012). The immediate cessation group was offered two weeks of the nicotine patch and the reduction group was offered 4 mg nicotine lozenges or a different ST brand. This study compared pharmacotherapy-assisted reduction to immediate cessation and was not included in the meta-analysis.

Ten trials had final follow-up at six months (Severson 2000; Cigrang 2002; Boyle 2004; Boyle 2008; Severson 2008; Severson 2009; Danaher 2013; Schiller 2012; Danaher 2015a; Virtanen 2015), seven at 12 months (Severson 1998; Stevens 1995; Walsh 1999; Stotts 2003; Walsh 2003; Gansky 2005; Walsh 2010), and one at two years (Cummings 1995). We used 12 month outcomes for one study that also had 18 month follow-up, because loss to follow-up had increased at the later time point (Severson 2007). All behavioural intervention studies assessed point prevalence abstinence. Seven reported only point prevalence abstinence at final follow-up (Cummings 1995; Walsh 1999; Severson 2000; Stotts 2003; Gansky 2005; Severson 2009; Walsh 2010), and five required self-reported point prevalence abstinence at both an interim and final follow-up (Stevens 1995; Severson 1998; Cigrang 2002; Walsh 2003; Virtanen 2015). Four reported both point prevalence and repeated point prevalence (Severson 2007; Severson 2008; Danaher 2013; Danaher 2015a) and the repeated point prevalence was used for the meta-analysis. Boyle 2008 reported both point prevalence and prolonged abstinence allowing for a 30-day grace period and we used the latter in the meta-analysis. Schiller 2012 reported prolonged and point prevalence abstinence. Stotts 2003 and Schiller 2012 reported using biochemical validation of self-reported quitting. Stevens 1995 attempted to obtain saliva samples, but due to low compliance based the results on self report only. Walsh 1999 obtained samples but did not analyse them, as a method for increasing accuracy of self report. Eight reported smokeless tobacco cessation only (Cummings 1995; Walsh 1999; Severson 2000; Cigrang 2002; Walsh 2003; Gansky 2005; Severson 2009; Walsh 2010), six reported all tobacco use cessation (Severson 1998; Boyle 2004; Severson 2007; Boyle 2008; Schiller 2012; Danaher 2015a) and four reported both smokeless and all tobacco use cessation separately (Stevens 1995; Stotts 2003; Severson 2008; Danaher 2013). The results of the meta-analysis are not affected by choice of outcome in these trials, although quit rates were lower for all tobacco use than for ST alone.

Excluded studies

Sixteen studies are listed as excluded, of which three were new for this update (Gordon 2010; Jain 2014; Raja 2014). Most were not eligible due to short length of follow-up. Details are given in Characteristics of excluded studies.

One ongoing study was identified (Sarkar 2014).

Risk of bias in included studies

Pharmacological interventions

None of the sixteen randomized trials of pharmacological interventions were assessed as being at high risk of selection bias although some had insufficient information on randomization and allocation procedures and the potential for bias was unclear. Thirteen trials used a placebo control, two just provided the same behavioural support to the control (Danaher 2015a; Severson 2015), and one provided nicotine free snuff (Ebbert 2013b). Four studies assessed the efficacy of the blinding procedure by having participants guess their treatment assignment, suggesting that blinding was adequate in two (Dale 2007; Ebbert 2009), and inadequate in another (Ebbert 2007), while the fourth did not report the results (Hatsukami 2000). No studies reported high and differential levels of loss to follow-up.

Behavioural interventions

One study did not use an appropriate method of allocation concealment (Stevens 1995). Eligibility was assessed by a receptionist on the basis of a questionnaire given to all clinic attendees, with allocation on the basis of clinic record number. This method has the potential for selection bias, although allocation was not conducted by the person providing the intervention. We tested the sensitivity of the results to the inclusion of this study. In one cluster randomized trial (cRCT) (Walsh 2010) it was unclear whether individual participants were identified before or after the school status was revealed but there was no evidence of an imbalance in baseline characteristics. This study also reported high loss to follow-up and results are based only on participants reached at follow-up. In a

second cRCT in worksites only participants reached at two-year follow-up were included (Cummings 1995).

Across the behavioural studies, no co-interventions were apparent except for one RCT in which the intervention group was offered nicotine gum, although less than 10% of participants reportedly used it (Walsh 1999).

Randomization at the organizational level and analysis of outcomes at the individual level may lead to errors in estimated confidence intervals (Altman 1997). All the studies using cluster randomization used appropriate methods of analysis and reporting, using cluster level averages (Cummings 1995; Walsh 1999), odds ratios adjusted for clustered responses (Gansky 2005; Walsh 2003), or reported low levels of intraclass correlation and non-significant practice effects (Stevens 1995).

Effects of interventions

Pharmacological interventions

Bupropion

The two bupropion studies with six months or longer follow-up (Dale 2002; Dale 2007) showed no effect on continuous all-tobacco abstinence, though the confidence interval was wide (293 participants, risk ratio (RR) 0.89, 95% CI 0.54 to 1.44, I^2 = 0%, Analysis 1.1).

Nicotine replacement therapy (NRT)

We did not find evidence of heterogeneity within subgroups based on type of NRT. At six months or longer, neither nicotine patch (five trials, 1083 participants, RR 1.13, 95% CI 0.93 to 1.37, I^2 = 14%) nor nicotine gum (two trials, 310 participants, RR 0.99, 95% CI 0.68 to 1.43, I^2 = 0%) increased tobacco abstinence rates. For the study that randomized patients to three different doses of nicotine patches (Ebbert 2007), we used the comparison between the 21 mg patch and placebo. In the trial of nicotine patch for adolescent ST users (Stotts 2003) the quit rates were twice as high in the placebo group, although the difference did not reach statistical significance. Pooled results showed the nicotine lozenge increased tobacco abstinence rates (five trials, 1529 participants, RR 1.36, 95% CI 1.17 to 1.59, I^2 = 0%). However, three of the nicotine lozenge trials did not use a placebo control (Ebbert 2013b; Severson 2015; Danaher 2015b) and in a post hoc sensitivity analysis the result was sensitive to the removal of these three trials. In Severson 2015, we compared the nicotine lozenge plus coaching calls to the coaching calls alone, and the nicotine lozenge-only arm did not contribute to the comparison.

Pooling all twelve trials with a total of 2922 participants, nicotine replacement therapy increased tobacco abstinence rates (RR 1.24, 95% CI 1.11 to 1.39, I^2 = 6%, Analysis 2.1), but again this result was no longer significant when the three lozenge trials without placebo controls were removed.

Varenicline

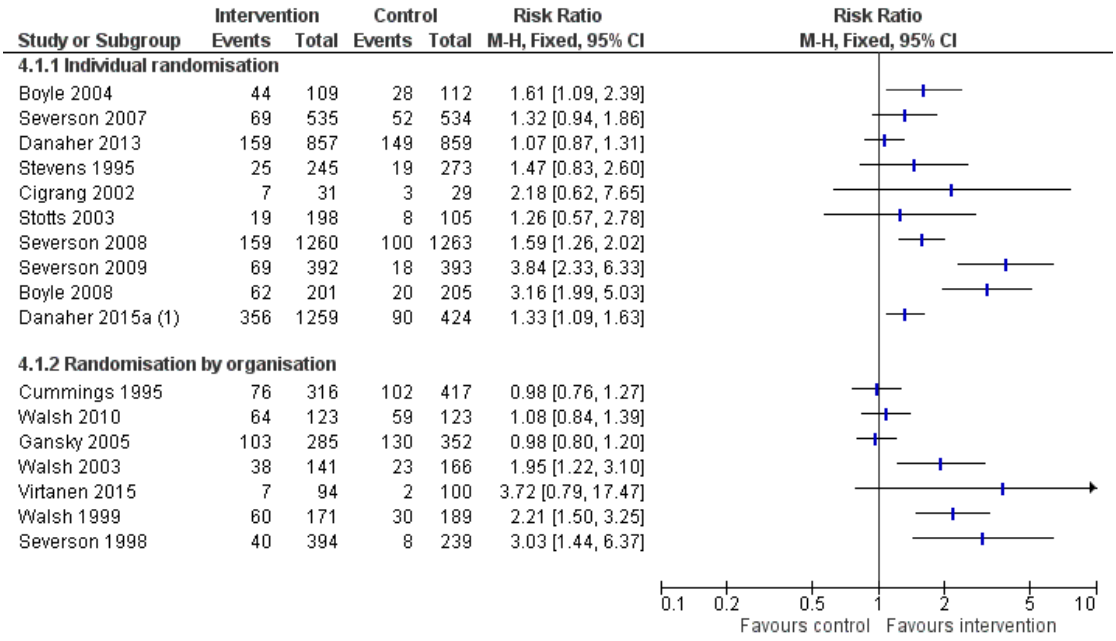
Two trials of varenicline with 507 participants (Fagerstrom 2010; Ebbert 2011) increased tobacco abstinence rates at six months compared to placebo (RR 1.34, 95% CI 1.08 to 1.68, Analysis 3.1). There was no evidence of heterogeneity (I^2 = 0%).

Behavioural interventions

There was evidence of considerable heterogeneity among the 17 trials eligible for the meta-analysis (I^2 = 78%, Analysis 4.1). Excluding the trial that used a potentially biased method for treatment allocation (Stevens 1995) did not affect this. Eight of the trials showed a significant effect of behavioural intervention (Severson 1998; Walsh 1999; Walsh 2003; Boyle 2004; Boyle 2008; Severson 2008; Severson 2009; Danaher 2015a), in six the confidence intervals did not rule out a clinical benefit but did not exclude one (Stevens 1995; Cigrang 2002; Stotts 2003; Severson 2007; Walsh 2010; Virtanen 2015) and three had risk ratios just below or above one, and relatively narrow confidence intervals suggesting no important benefit or harm (Cummings 1995; Gansky 2005; Danaher 2013).

Our prespecified subgroup analysis based on study design did not reduce heterogeneity (Figure 1, Analysis 4.1). Amongst the ten studies randomising individuals the I^2 value was 75%. In this group of studies, five reported significant treatment effects (Boyle 2004; Boyle 2008; Severson 2008; Severson 2009; Danaher 2015a), and the other five had point estimates ranging from RR 1.07 to RR 2.18 (Stevens 1995; Cigrang 2002; Stotts 2003; Severson 2007; Danaher 2013). The largest trial, Severson 2008, reported an RR of 1.59 (95% CI 1.26 to 2.02). Overall these trials suggest a benefit of behavioural interventions, but the larger trials show smaller effects than the smaller trials, and a pooled estimate, whether fixed-effect or random effect, risks overestimating the benefit.

Figure 1. Behavioural interventions: Abstinence from all tobacco use (where reported) at 6 months or more.



Footnotes
(1) Combining 3 intervention arms

Among the seven trials that randomized by organization the I^2 value was 79%. In this subgroup three trials detected large and statistically significant effects, with RRs over two (Severson 1998; Walsh 1999; Walsh 2003).

Since the distinction between individual and cluster designs was based on expectations about the level of motivation of participants, we also considered this factor directly (Analysis 4.2). All the clustered RCTs enrolled unselected participants, but Stevens 1995, Cigrang 2002, and Severson 2009 also recruited any ST user without assessing interest in quitting. Statistical heterogeneity persisted in both subgroups, and there was no evidence that effects were larger in the trials in more motivated populations.

A sensitivity analysis preferring ST abstinence over all tobacco abstinence where trials reported both outcomes did not affect heterogeneity or alter the findings (Analysis 4.7) .

In two further subgroup analyses we considered whether treatment effect might be moderated by including an oral examination and feedback (Analysis 4.3) or telephone support (Analysis 4.4) as intervention components. Intervention characteristics and study design tended to be correlated as Table 1 shows. Most individually randomized studies did not include an oral examination but did include telephone support, whilst cRCTs typically involved oral examination with some also including telephone support. Heterogeneity remained after grouping the 17 trials according to whether or not the intervention included an oral examination component with direct feedback to patients regarding ST-induced mucosal changes (Analysis 4.3). Amongst the six trials including an oral examination the I^2 was 80%, with the largest trial, Gansky 2005, showing the smallest effect. Gansky and colleagues suggested that the lack of effect in their trial could have been due to a 'spill-over' effect due to contact between the athletic trainers in the different groups. Although three of the trials did show significant effects (Severson 1998; Walsh 1999; Walsh 2003), conclusions about the effect of oral examinations have to be cautious. There was also substantial heterogeneity (I^2 = 72%) among the eleven studies without an oral examination component (Cummings 1995; Cigrang 2002; Stotts 2003; Boyle 2004; Boyle 2008; Severson 2007; Severson 2008; Severson 2009; Danaher 2013; Danaher 2015a; Virtanen 2015).

In the telephone support subgroup analysis there were ten studies in which telephone support formed part of the intervention (Stevens 1995; Severson 1998; Walsh 1999; Cigrang 2002; Walsh 2003; Boyle 2004; Boyle 2008; Severson 2007; Severson 2009; Danaher 2015a (quitline intervention arms)) and seven where it did not (Cummings 1995; Gansky 2005; Severson 2008; Walsh 2010; Danaher 2013; Danaher 2015a (web only arm); Virtanen 2015). A trial where brief phone support was included in the con-

trol condition but not the intervention (Stotts 2003) was not included. Heterogeneity within the telephone support subgroup was moderate as opposed to considerable (I^2 = 50%) and the pooled risk ratio indicated benefit (3480 participants, RR 1.77, 95% CI 1.57 to 2.00, Analysis 4.4). Heterogeneity was substantial in the subgroup of seven trials of interventions without telephone support (I^2 = 58%), which included one study showing evidence of benefit (Severson 2008). A second study comparing similar intervention and control conditions did not replicate this effect (Danaher 2013). The pooled estimate for this subgroup suggested only a small benefit with the CI excluding 1 narrowly (6611 participants, RR 1.16, 95% CI 1.05 to 1.28).

In this update we added a further exploratory subgroup analysis combining the oral examination and telephone components (Analysis 4.5). This suggested that the combination of oral examination and telephone support was consistently beneficial (4 studies, 1818 participants, RR 2.07, 95% CI 1.61 to 2.66, I^2 = 0%), whereas oral examination alone did not show evidence of benefit (RR 1.01, 95% CI 0.86 to 1.19). The estimated effect for telephone support without oral exam was slightly smaller, and less consistent than for the combination of components (7 studies, 3965 participants, RR 1.66, 95% CI 1.45 to 1.91, I^2 =57%) but there was not a significant difference between these two subgroups. The estimated effect of interventions without either component was smaller, and uncertain because of heterogeneity (5 studies, 5728 participants, RR 1.22, 95% CI 1.08 to 1.39, I^2 = 64%).

One further behavioural study was not included in the meta-analysis because two active interventions were compared; in this study technical problems with the device for scheduling gradual cessation led to a high drop out rate in that condition and the intention-to-treat analysis was not used. No significant difference was detected between the conditions (Severson 2000). At six months, the self-reported ST abstinence rate was 27.6% (21/76) in the hand-held device group and 30.2% (29/96) in the manual and video group.

One trial (Hatsukami 1996) failed to detect a difference between more intense and less intense behavioural interventions in a 2x2 study of nicotine gum and behavioural interventions (RR 1.34, 95% CI 0.84 to 2.12, Analysis 4.6).

One trial recruiting ST users without plans to quit and which compared immediate cessation using nicotine patch versus a reduction approach using either nicotine lozenge or brand switching (Schiller 2012) showed greater success for the abrupt cessation group (11/97 vs 1/102, RR 11.57, 95% CI 1.52 to 87.91, Analysis 5.1).

Adverse events

No effort was made to perform a quantitative synthesis of the incidence of adverse events reported with the different interventions. One study reported a higher rate of skin reactions and nausea associated with the nicotine patch, but found no difference in the number of people who stopped treatment due to side effects (Howard-Pitney 1999). One study reported the loss of two subjects due to headache and gastro-intestinal distress associated with nicotine gum use (Boyle 1992). Sleep disturbance was more common among patients on active bupropion SR (Dale 2007). Nausea occurred in more than one-third of patients in one varenicline study (Fagerstrom 2010) and in 24% in the other (Ebbert 2011).

DISCUSSION

This systematic review provides evidence from 34 randomized controlled trials enrolling more than 16,000 smokeless tobacco (ST) users, testing pharmacological and behavioural interventions to treat ST use.

Pharmacotherapies

There were 16 trials evaluating pharmacotherapy. Two small trials of bupropion did not detect an effect although confidence intervals do not rule out a small benefit. Twelve trials of NRT including gum, patch and lozenge suggested a statistically significant treatment effect, which appears to be driven by the efficacy of the nicotine lozenge. However, the lozenge subgroup meta-analysis included three studies without a placebo arm and a post hoc analysis found the results were sensitive to the removal of these three trials. Despite the absence of heterogeneity between the different types of NRT, we do not think that there is evidence to support the use of nicotine gum or patch. Two studies in Scandanavian and U.S. populations demonstrated that varenicline increases long term ST abstinence rates by 34% compared to placebo among ST users. In cigarette smokers, however, varenicline increases abstinence rates 131% compared to placebo (RR 2.31, 95% CI 2.01 to 2.66) (Cahill 2012). However, the prolonged abstinence rates in the control group in the ST studies were higher at six months (31.6% (Ebbert 2011) and 34% (Fagerstrom 2010)) than in studies of smokers (e.g. 13.2% (Jorenby 2006) and 10.5% (Gonzales 2006)). This may relate to the low availability of treatment for ST users resulting in high efficacy of behavioral interventions provided in the control arms of these studies.

Behavioural interventions

We found evidence of heterogeneity among the behavioural interventions, with some trials showing a statistically and clinically significant effect, some with non-significant increases in intervention arms and three with very similar intervention and control quit rates and relatively narrow confidence intervals (Cummings 1995; Gansky 2005; Danaher 2013). In seeking to explain the heterogeneity we considered subgroups based on trial design and intervention characteristics. These included whether or not the

studies were individually randomized, or recruited only participants motivated to quit, or whether the intervention included an oral examination or telephone support. Categorization by use of telephone support had lower levels of subgroup heterogeneity, but this was a post hoc analysis. In the earliest version of this review (Ebbert 2004) we suggested that interventions including oral examination and feedback were more effective. In the current review, this observation is not made.

The inference of the effect size of behavioural interventions for increasing ST abstinence rates is weakened by the limited methodological quality of some of these trials, including loss to follow-up and potential baseline differences between the groups. We cannot exclude the possibility that publication bias is also impacting on our results.

AUTHORS' CONCLUSIONS

Implications for practice

Pharmacotherapy

Varenicline appears to increase tobacco abstinence rates among Swedish snus and American ST users and could be offered clinically. The nicotine lozenge also increases ST abstinence rates though confidence in this effect is limited due to the absence of placebo controls. The efficacy of varenicline and the nicotine lozenge are lower than observed with these medications among cigarette smokers attempting to quit smoking (Stead 2012; Cahill 2013). Evidence for the effect of bupropion SR for the treatment of ST use is inconclusive.

Behavioural interventions

Behavioural interventions can increase tobacco abstinence rates among ST users, whether or not they are already motivated to stop and seeking treatment, though limited methodological quality also weakens the strength of this conclusion. Telephone counselling may be a useful component of an intervention.

Implications for research

Possible further research:

1) Studies to deconstruct behavioural interventions to identify effective core components.

2) Placebo-controlled comparisons of different NRT doses, forms, and durations of therapy.

4) Combination therapies using both non-nicotine pharmacotherapy and NRT.

5) The influence of different types of ST (e.g., snuff, chew, betel quid) on abstinence outcomes.

6) Effective treatments for adolescents who use ST.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boyle 1992

Methods	Country: USA Recruitment: community volunteers
Participants	100 adult moist snuff/ chewing tobacco users (1 also smoker); av. age 32, av .11 dips/ day (4-26)
Interventions	Pharmacotherapy: NRT 1. Nicotine gum 2 mg for 6w, target dose 12 pieces/day 2. Placebo gum All participants given S-H manual and attended 4 weekly group meetings covering education/ self-monitoring/ coping skills/ group social support, 20-60 mins, 4-10/group
Outcomes	PP abstinence, all tobacco use, 6m Verification: tobacco alkaloids (salivary cotinine, anabasine and anatabine in urine < 2. 0 ng/ml)
Funding source	None specified. Undertaken as part of a Ph.D.
Notes	For success, required to have attended all meetings Groups not equal at baseline - active gum group had higher cotinine levels

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Subjects were sequentially and randomly assigned to either treatment condition according to a computer-generated randomization code'
Allocation concealment (selection bias)	Low risk	Judged adequate although not explicit that code was concealed at point of enrolment
Incomplete outcome data (attrition bias) All outcomes	Low risk	13/50 I vs 10/50 C lost to follow-up; all treated as non abstinent

Boyle 2004

Methods	Country: USA Recruitment: advertisement in health plan newsletter and community media
Participants	221 male moist snuff users (92% used daily), not regular users of other types of tobacco, interested in quitting; av. age 36, av. uses/day 7.9
Interventions	Behavioural therapy 1. S-H materials 2. S-H material + proactive telephone counselling. Initial call 4 days after S-H material mailing. Subsequent calls were negotiated and placed an emphasis on support, problem-solving, and use of cognitive-behavioural strategies including monitoring tobacco behavior patterns, goal setting, finding alternative coping options, and planning for high-risk situations or cues associated with tobacco use
Outcomes	PP abstinence, all tobacco use, 6m. Repeated PP abstinence at 3 & 6m also reported as significantly different but rates not given. Verification: none
Funding source	NCI Grant CA-74025
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized using computer-generated sequence.
Allocation concealment (selection bias)	Low risk	Judged adequate although not explicit that code was concealed at point of enrolment. No face to face contact
Incomplete outcome data (attrition bias) All outcomes	Low risk	15/221 lost to follow-up at 6 months, treated as non-abstinent

Boyle 2008

Methods	Country: USA Recruitment: advertisements on talk radio, press releases, weekly newspapers, outdoor advertisements, mailings to state and local departments, large employers, and dental hygienists
Participants	406 ST users interested in quitting; av. age 39.9 years with 6.2% also smoking cigarettes
Interventions	Behavioural therapy 1. A self-help manual used (manual only). The manual was called *Enough Snuff: A Guide for Quitting Smokeless Tobacco,* which is set up as a work book with exercises for the user to complete while moving through a four-step process to quit snuff and chewing

Boyle 2008 (*Continued*)

	tobacco. 2. A self-help manual plus proactive telephone-based cessation counselling (Telephone Counseling). The telephone-based treatment included up to four calls in support of quitting, and personalized various cognitive and behavioural strategies that are generally considered effective in tobacco cessation (such as setting a quit date, examining patterns of use, developing stress reduction skills, avoiding known triggers to use)
Outcomes	Prolonged tobacco abstinence following 30 day grace period, 6 m PP tobacco abstinence, 6 months Verification: none
Funding source	Health Partners Research Foundation, ClearWay Minnesota Grant RC-2004-0010
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Individual, computer-generated sequence.
Allocation concealment (selection bias)	Low risk	Statistician was blinded and subjects received assignment letter in mail
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants lost to follow-up were coded as tobacco users.

Cigrang 2002

Methods	Country: USA Recruitment: active military at preventive visit
Participants	60 adult male ST users, not selected for motivation to quit; (smoking status not specified)
Interventions	Behavioural therapy 1. Invited to receive mailed manual and video during a telephone call using a motivational interviewing style. Two further 10 min support calls after receipt of materials and on quit date 2. Usual care control, given information on how to sign up for an 8w cessation class
Outcomes	Repeated PP abstinence at 6m (7 day PP at 3m and 6m) Verification: none
Funding source	None specified
Notes	

Cigrang 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated.
Allocation concealment (selection bias)	Unclear risk	No details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/31 I vs 2/29 C lost to follow-up at 6m. Treated as non abstinent here

Cummings 1995

Methods	Country: USA Recruitment: companies as part of Working Well trial
Participants	733 ST users in 39 energy related worksites; av. age 36, results for males only (99% of total) reported. 19% smokers
Interventions	Behavioural therapy 1. Stage-matched ST information, S-H manual and video, ST poster with self-test at worksite, community resources. Intervention over 2 yrs 2. Mailings of printed materials to worksite (10 over 2 yrs), ST poster at worksite
Outcomes	PP abstinence, ST use, 2 yrs. Verification: none
Funding source	NCI funded Working Well
Notes	Study report used worksite as unit of analysis. Average quit rates were 26.97% for intervention worksites and 25.75% for control worksites (P=0.78). MA uses actual number of quitters. Cluster size ranged from 3-38

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Matched pairs of companies randomly allocated using computer procedure
Allocation concealment (selection bias)	Unclear risk	Standard procedures for gathering data from employees in all companies
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Results based on cohort completing 2 yr follow-up. Attrition analyses showed no difference in baseline ST use prevalence,

Cummings 1995 (*Continued*)

		nor difference between conditions

Dale 2002

Methods	Country: USA Recruitment: media
Participants	68 ST users (smokers excluded); 67/68 male, av.age 37
Interventions	Pharmacotherapy: bupropion 1. Bupropion 300 mg 12w 2. Placebo All received 10 min behavioural intervention at each study visit (10 during treatment phase)
Outcomes	Continuous abstinence, all tobacco use, 24w. (PP also reported, also 12w) Verification: urine cotinine
Funding source	None specified. Conducted at Nicotine Research Center of the Mayo Clinic, Rochester, Minnesota)
Notes	1 withdrawal in bupropion group due to generalized rash.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described. Double blind.
Allocation concealment (selection bias)	Low risk	'Subjects and study personnel were blinded to the treatment arms'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Almost half (31/68) withdrew or lost to follow-up during medication phase, no difference between groups, all treated as non-abstinent

Dale 2007

Methods	Country: USA Recruitment: media, community volunteers
Participants	225 male snuff/chewing tobacco users (3 current smokers); av.age 38
Interventions	Pharmacotherapy: bupropion 1. Bupropion 300 mg (150 mg by mouth twice per day) for 12w 2. Placebo. All subjects received oral exam and 16 behavioural counselling sessions during treatment and follow-up period

Dale 2007 (*Continued*)

Outcomes	Continuous, all tobacco abstinence at 24w and 52w. (PP & prolonged also reported, also 24w) Verification: urine tobacco alkaloids	
Funding source	NCI R01 9088	
Notes	More sleep disturbance noted with bupropion (31% vs. 13%; P = 0.002)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomization, block size of 4 within 4 strata
Allocation concealment (selection bias)	Low risk	'Participants, investigators and study staff blinded to assignment'
Incomplete outcome data (attrition bias) All outcomes	Low risk	24/113 I vs 22/112 C withdrew or lost to follow-up, all treated as non abstinent

Danaher 2013

Methods	Country: USA Recruitment: Online marketing tools, newspaper advertisements, and outreach to professionals in schools and tobacco control	
Participants	1716 ST users aged 14-25, wanting to quit, Av. age 21, 96.5% male	
Interventions	Behavioural therapy 1. Basic condition: Static website content including an "Enough Snuff" pocket guide, a resource section with informational materials and links to web sites offering content for ST cessation and relaxation strategies 2. Enhanced condition: Interactive and multimedia features with functionality to create online lists, watch videos, and a Web blog moderated by research staff. Automated email reminders encouraged website use and provided supportive measures	
Outcomes	Point prevalence all tobacco and ST abstinence at both 3 and 6 months Verification: none	
Funding source	NCI R01-CA118575	
Notes	New for 2015 update. Similar conditions compared to those tested in Severson 2008	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Danaher 2013 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated "vector"
Allocation concealment (selection bias)	Unclear risk	"Taken" to the home page of their assigned condition - unclear how this was accomplished
Incomplete outcome data (attrition bias) All outcomes	Low risk	64.6% completed both 3- and 6-months assessments, 'no significant between-condition differences in assessment completion'. Missing cases considered to be using tobacco in meta-analysis

Danaher 2015a

Methods	Country: USA Recruitment: Online recruitment
Participants	1683 ST users, wanting to quit, 97.5% male, av.age 38
Interventions	Behavioural therapy: 1. Web Only: Automated, tailored, and interactive intervention delivered as text, activities, and videos 2. Quitline Only: Proactive telephone counselling through the California Tobacco Chewers' Helpline 3. Web + Quitline: Received the Web and Quitline Interventions 4. Control: Self-help printed guide
Outcomes	Repeated point prevalence all tobacco abstinence at 3 and 6 months Verification: none
Funding source	NCI R01-CA084225
Notes	New for 2015 update. 3 intervention arms had similar effects so combined in comparison with control

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized
Allocation concealment (selection bias)	Unclear risk	Not clear how allocation concealed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	73% completed follow-up and ITT analyses treated losses to follow-up as using tobacco

Danaher 2015b

Methods	Country: USA Recruitment: Online marketing
Participants	407 ST users, wanting to quit, 97.5% male. av.age 35
Interventions	Pharmacotherapy: NRT 1. Web only: interactive intervention with functionality to develop a personalized quit plan, personal lists, watch videos, relaxation videos, and informational resources. Email reminders encouraged engagement 2. Web + Lozenges: Web intervention + 4 mg nicotine lozenge for 12 weeks with taper. Emails encouraged web site use and rationale for using lozenges
Outcomes	Repeated point prevalence all tobacco and ST abstinence at 3 and 6 months Verification: none
Funding source	NCI R01-CA142952. 'GlaxoSmithKline provided the nicotine lozenges for the study but had no role in the conduct of the study (data collection, management,analysis, and interpretation), in the preparation, review, approval of the manuscript, or in the decision to submit the manuscript for publication.'
Notes	New for 2015 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization sequence "vector"
Allocation concealment (selection bias)	Unclear risk	Unclear how allocation was concealed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	71% completed the 3-month follow-up, 73% completed the 6-month follow-up and 65% completed both assessments. ITT analyses conducted

Ebbert 2007

Methods	Country: USA Recruitment: media, community volunteers
Participants	42 male snuff users using at least 3 cans/pouches ST/week (smokers excluded); av.age 34-38
Interventions	Pharmacotherapy: nicotine patch. 1. 63 mg patch 2. 42 mg patch

Ebbert 2007 (*Continued*)

	3. 21 mg patch 4. Placebo All subjects received behavioural counselling during the treatment phase
Outcomes	Continuous all tobacco abstinence at 6m (PP also reported). Verification: urine tobacco alkaloids
Funding source	NCI R01 CA96881
Notes	21 mg dose used in MA 42 mg 3/11 (27%), 63 mg 4/10 (40%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomization schedule'
Allocation concealment (selection bias)	Low risk	'Group assignment with allocation concealment was determined by a randomization schedule, and subjects were assigned the next sequential subject identification number upon arrival'
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 control loss to follow-up treated as non-abstinent

Ebbert 2009

Methods	Country: USA, multicenter (Rochester, MN & Eugene, OR) Recruitment: press releases and advertising.
Participants	270 snuff/chewing tobacco ST users; av. age 37 years
Interventions	Pharmacotherapy: NRT 1. 4 mg nicotine lozenge for 12 weeks 2. Placebo lozenges All participants received a self-help quitting guide developed specifically for ST users. Participants were provided with brief behavioral counselling at each study visit tailored to participant quitting status. Counseling included best practice topics such as the health effects of ST, preparing for quit day, dealing with withdrawal, avoiding relapse, stress and time management, weight management, and wellness and exercise
Outcomes	Prolonged tobacco/ST abstinence, 6 month (unvalidated). PP tobacco/ST abstinence, 6m Verification: Urinary cotinine

Ebbert 2009 (*Continued*)

Funding source	NCI CA121165	
Notes	Prolonged unvalidated abstinence used in MA; using PP validated outcome does not affect MA findings	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer-generated randomization sequence assigned participants in a 1:1 ratio to treatment condition with a block size of four stratified by site
Allocation concealment (selection bias)	Low risk	Study participants, investigators, and all other study staff were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	22/136 I, 38/134 C lost to follow-up treated as using tobacco

Ebbert 2010a

Methods	Country: USA, multicenter (Rochester, MN & Eugene, OR) Recruitment: press releases and advertising.
Participants	60 ST users (with one Indian ST product per arm)
Interventions	Pharmacotherapy: NRT 1. 4 mg nicotine lozenge for 12 weeks 2. Placebo lozenges All subjects received assisted self-help intervention (ASH) included a self-help quitting guide and telephone counselling. The guide presented best-practices topics including: health effects of ST, preparing for quit day, dealing with withdrawal, avoiding relapse, stress and time management,weight management, and wellness and exercise. Counseling support was tailored to the quitting status of the participant with reference to the self-help quitting guide
Outcomes	PP tobacco abstinence, 6m Prolonged tobacco/ST abstinence, 6m Verification: None
Funding source	NCI CA 121165
Notes	
Risk of bias	

Ebbert 2010a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any subjects who missed a visit - considered to be using tobacco

Ebbert 2011

Methods	Country: USA Recruitment: Community recruitment through advertising
Participants	76 ST users
Interventions	Pharmacotherapy: Varenicline 1) Varenicline 0.5 mg once a day for 3 days, then 0.5 mg twice a day for 4 days, then 1. 0 mg by mouth twice a day for a total of 12 weeks of treatment 2) Placebo All subjects received an individualized program containing 4 sessions of brief behavioral counselling 10 min duration. Behavior change strategies incorporated self-management skills. Subjects received an intervention manual
Outcomes	Point prevalence and prolonged all tobacco and ST abstinence at 3 and 6 months Verification: urine cotinine
Funding source	NCI CA132621
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Study personnel with no subject contact prepackaged medication and participants assigned the next number in sequence
Incomplete outcome data (attrition bias) All outcomes	Low risk	16% discontinued study

Ebbert 2013a

Methods	Country: USA Recruitment: Community recruitment through advertising
Participants	ST users who wished to reduce their ST use but not quit. 96.3% male, av.age 38
Interventions	Pharmacotherapy: NRT 1. Nicotine lozenges: 4 mg nicotine lozenges for 12 weeks 2. Tobacco-free snuff All participants received face-to-face and written instruction on ST reduction. Encouraged to achieve a reduction of ST use by 50% by week 4 and 75% by week 8. Encourage to record reduction in a diary
Outcomes	All tobacco abstinence at 6 months Confirmation: Urine anabasine and anatabine < 2 ng/mL
Funding source	NIH R01 CA121165
Notes	New for 2015 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization not described
Allocation concealment (selection bias)	Unclear risk	No mention of concealment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	28% discontinued treatment

Ebbert 2013b

Methods	Country: USA Recruitment: Community recruitment through advertising
Participants	52 male ST users, average age 41
Interventions	Pharmacotherapy: NRT 1. Nicotine patches: 42 mg/d for 6 weeks and 21 mg/d for 2 weeks 2. Placebo patches: Identical placebo for 8 weeks All subjects received a behavioral intervention delivered by study staff consisting of cognitive behavioral self-management strategies including making a personal contract to quit, getting support, identifying and building coping strategies for high risk situations, dealing with nicotine withdrawal, understanding and managing negative cognitions, and dealing with relapse. A self-help manual was provided

Ebbert 2013b (*Continued*)

Outcomes	Prolonged ST abstinence at 6 months. (Point prevalence ST abstinence and all tobacco abstinence also reported) Verification: urinary anabasine <2 ng/ml	
Funding source	NCI CA 140125	
Notes	New for 2015 update	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Allocation concealed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	24% loss to follow-up. Participants lost to follow-up were considered tobacco users for analysis

Fagerstrom 2010

Methods	Country: Norway and Sweden Recruitment: Newspaper advertising	
Participants	431 Swedish snus users; av. age 43.9 years	
Interventions	Pharmacotherapy; varenicline 1. Varenicline for 12 weeks 2. Placebo	
Outcomes	Prolonged tobacco abstinence (week 9-26), 6 m; (PP tobacco abstinence at 6 m also reported) Verification: Salivary cotinine	
Funding source	Pfizer: involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Fagerstrom 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomized to one of two parallel treatment arms in a 1:1 ratio (varenicline: placebo) using a telephonic Interactive Voice Response System (IVRS)
Allocation concealment (selection bias)	Low risk	Double-blinded, randomized allocations
Incomplete outcome data (attrition bias) All outcomes	Low risk	43/213 I, 48/218 C lost to follow-up. Participants who discontinued the study were classified as still using ST for the remainder of the study

Gansky 2005

Methods	Country: USA Recruitment: Contacted athletic trainers (ATCs) at California colleges
Participants	College baseball athletes who used ST (285 intervention, 352 control 30-day users, includes 206 30-day smokers)
Interventions	Behavioural therapy; Based upon the innovation theory and social learning theory. 1. 3hr video conference for ATC's/ dentists/ hygienists, follow-up newsletter for ATCs 2. Dental component: dentists/hygienists provided oral cancer screening, advised ST users to stop, identified oral lesions, provided S-H guide, offered single 10-15 min individual counselling session focusing on ST addiction, set a quit date, developing a plan, training in action and thinking skills to get ready to quit and to prevent relapse. 3. ATC follow-up and referral: follow-up by ATC on quit date and 3 booster sessions 1w apart. 4. Peer-led component: 50-60 min education meeting with included 3 components: 2 videos and slides of facial disfigurement. Control: usual anti-tobacco education
Outcomes	30-day PP ST abstinence at 12m Verification: None
Funding source	Tobacco Surtax Fund of the State of California (Grant 4RT-0068)
Notes	Intraclass correlation: 0.0197. 24% loss to follow-up not broken down by study arm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Cluster randomized by school: schools stratified by tertiles of baseline ST use then within strata

Gansky 2005 (*Continued*)

Allocation concealment (selection bias)	Low risk	Allocation concealed until after baseline data collection
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 randomized site dropped due to potential contamination. 1 year surveys completed by 76% of ST users, no difference across groups

Hatsukami 1996

Methods	Country: USA Recruitment: media
Participants	210 ST users, not regular smokers; all male, av. age 31
Interventions	Pharmacotherapy: NRT crossed in factorial design with behaviour therapy variants 1. 2 mg nicotine gum for 8w. At least 6 pieces/day initially then decrease. Option to use for 3rd month 2. Placebo Group behaviour therapy: 8 x 45-60 min sessions over 10w. Minimal contact: 4 brief sessions with nurse, S-H booklet.
Outcomes	PP abstinence, ST use, 12m. Verification: : salivary cotinine <=20ng/ml and CO < 8ppm at all follow-ups
Funding source	NIH R01 DA0513
Notes	Continuous abstinence rates not tabulated, shown in survival curves

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated
Allocation concealment (selection bias)	Unclear risk	No mention of concealment. Code for gum allocation kept by a third party
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 dropouts before gum provided were excluded. Later losses treated as non abstinent, numbers not stated

Hatsukami 2000

Methods	Country: USA Recruitment: media
Participants	402 ST users, not regular smokers; 99% male, av. age 31
Interventions	Pharmacotherapy: NRT 1. 21 mg nicotine patch for 10w incl tapering period 2. Placebo A second component, mint snuff was also tested in a factorial design. All received 10 min individual counselling at 8 clinic visits. Some end of treatment quitters assigned to more intensive follow-up, but this was not intended as a treatment component
Outcomes	Continuous abstinence, ST use, 62w. (Also PP). Verification: salivary cotinine <15ng/ml at all follow-ups
Funding source	NIH R01 DA0513
Notes	No evidence of any effect of mint snuff, and no interaction with NRT. Quit rates for any tobacco use were reported to be lower and not significantly different between conditions. Rates not given so ST quit rates used in MA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	75% completed treatment, no significant differences across groups, 90% of completers followed up at 62w. Losses treated as non-abstinent

Howard-Pitney 1999

Methods	Country: USA Recruitment: media
Participants	410 ST users >=18. 5% also smoked; 99% male, av age 36
Interventions	Pharmacotherapy: NRT 1. 15 mg nicotine patch for 6 weeks 2. Placebo All received 2 sessions with pharmacist at baseline and at 4w, S-H materials and telephone support at 48 hours and 10 days post target quit date

Howard-Pitney 1999 (*Continued*)

Outcomes	PP abstinence, ST use, 6m Verification: salivary cotinine <20ng/ml at 6m
Funding source	NCI R01 CA64285. Drug supply agreement with Pharmacia and Upjohn AB
Notes	8 active & 14 placebo patch discontinued due to serious side effects

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomized
Allocation concealment (selection bias)	Low risk	Sequential distribution from computer-randomized blinded list
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	74% response at 6m, distribution by group not stated, losses treated as non-abstinent

Schiller 2012

Methods	Country: USA Recruitment: Community recruitment through advertisements on radio and television and in newspaper
Participants	ST users interested in reducing ST but not quitting within the next 90 days
Interventions	1) Immediate cessation: 21 mg nicotine patch provided for 2 weeks and participants encouraged to purchase more. Participants advised to set a quit date in the next 2 weeks; ST harms discussed along with benefits of quitting. A self-help manual was provided 2) Reduction: Subjects offered either lozenge or brand switching. *Lozenge:* 4 mg nicotine lozenge. Advised to substitute a lozenge for every dip to achieve 50% reduction in the first 2 weeks and then a 3:1 ratio of lozenge:ST to meet a 75% reduction goal. If intolerant to 4 mg, they received the 2 mg lozenge. *Brand switching:* Subjects choosing brand switching were switched to Skoal Long Cut Straight or Long Cut Wintergreen to meet the 25% to 50% reduction for the first 2 weeks. Then switched to Skoal Bandits Wintergreen or Skoal Bandits Straight for the 4 weeks of >= 75% nicotine reduction. A target quit date after the 75% reduction period was established. Strategies for reduction were provided. If quitting, offered same treatment materials as to the immediate cessation group. Phone call at 6 weeks providing behavioral counselling
Outcomes	Point prevalence and prolonged all tobacco abstinence rates at weeks 8, 12, and 26 Verification: Urinary cotinine, carbon monoxide, and urinary anatabine
Funding source	NIH R01 DA14404, T32 HL007741

Notes	Week 32 is longest follow-up but data for immediate cessation not collected at this time point. Comparision is immediate vs. reduction. Not pooled in meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Assigned group assignment at first phone contact.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rate was 47% in immediate group and 53% in reduction group

Severson 1998

Methods	Country: USA Recruitment: ST users at dental hygiene visits Randomization: by dental practice, method not stated
Participants	633 ST users in 75 dental practices, not selected for motivation, no demographic details
Interventions	Behavioural therapy 1. Usual dental care and office intervention (oral examination, advice to quit, quit date setting), S-H materials (pamphlets and oral replacement, video), telephone support (1 call) 2. Usual dental care
Outcomes	Multiple PP (3m & 12m), all tobacco Verification: none
Funding source	NHLBI R01 HL48768
Notes	There were differences between groups at baseline. GEE used for analysis but intraclass correlation was low and practice effects were non significant. Actual numbers of quitters used in MA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cluster randomized by dental practice, method not stated.

Severson 1998 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Patients were recruited after practice allocation, so recruitment bias possible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were more losses to follow-up from intervention practices than usual care. Losses treated as non-abstinent

Severson 2000

Methods	Country: USA Recruitment: media
Participants	198 ST users >=18, motivated to quit. 4% also smoked; 98% male, av. age 39
Interventions	Behavioural therapy 1. Computerized ST gradual reduction and telephone support (1-3 calls, 10-20 min, quit date setting) 2. S-H manual , S-H video and telephone support (1-3 calls, 10-20 min, quit date setting)
Outcomes	PP abstinence, ST and cigarettes, 6m. Verification: none
Funding source	None reported. One author had developed the LifeSign computer for scheduled reduction
Notes	Not used in meta-analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated
Allocation concealment (selection bias)	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	80% assessed at 6m, no difference across groups. Excluded people quitting prior to intervention, with >2 equipment failures with computer for gradual reduction, other losses considered non-abstinent

Severson 2007

Methods	Country: USA Recruitment: media
Participants	1069 ST users >=15 yrs, willing to quit all tobacco use. 5.7% also smoked. 97% male, av age 39 (range 17-82)
Interventions	Behavioural therapy 1. Manual-only: S-H manual (60pp) 2. Assisted S-H: telephone support (2 calls 10-15 min with quit date setting and withdrawal management), S-H manual (60pp), S-H video (20 minutes)
Outcomes	PP abstinence (all tobacco) at 6, 12, 18m. Repeated PP at 12m used in MA Verification: none
Funding source	NCI CA60586 and CA84225.
Notes	First included as Severson 2000b with 12m data from an abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated
Allocation concealment (selection bias)	Unclear risk	No details given, but no direct patient contact
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	71% completed 12m assessment (only 48% completed 6, 12 & 18m assessment so not used in MA), no difference between groups

Severson 2008

Methods	Country: USA Recruitment: Targeted mailings, press releases to print and broadcast media, web-links, paid advertising in newspapers and magazines
Participants	2523 ST users who had used ST for at least 1yr and used at least one tin/week interested in quitting, at least 18 yrs of age, a resident of US or Canada, had an email address checked weekly, and will to provide contact information
Interventions	Behavioural therapy; Web-based 1. Basic website: static textual format including the 'Enough Snuff' pocket guide for quitting, a resource section, and links 2. Enhanced: personal quitting assistant (guided, interactive programme), printable resources, links to other websites, two web forums ('Talk with Others' and 'Ask an Expert') , a planning to quit module, and a staying quit module

Severson 2008 (*Continued*)

Outcomes	PP/Repeated PP (ST & all tobacco) via online surveys or phone for non-respondents at 3m, 6m Verification: none
Funding source	NCI R01 CA84225
Notes	First included as Severson 2007a based on conference abstract. No change to data. Danaher 2013 tested a similar intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described
Allocation concealment (selection bias)	Low risk	Process automated; access to assigned website immediately after consent
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 34% completed both 3 & 6m surveys. No difference between groups reported

Severson 2009

Methods	Country: USA Recruitment: Participants identified at annual dental visits to one of 24 military dental clinics
Participants	785 ST users, not selected by motivation, 99.9% M, av. age 30, 20% current smokers
Interventions	Behavioural therapy 1. Telephone counselling by a trained cessation counsellor and offered assistance in quitting ST use + mailed videotape & S-H guide, tailored for military. First call approximately 1week after dental visit, People accepting materials offered 2 more calls coinciding with receipt of the mailed materials and ST quit date 2. Usual care cessation strategies offered at each military base
Outcomes	Repeated PP, All tobacco, both 3 & 6m, (prolonged ST abstinence at 6m also reported) Verification: none
Funding source	Congressionally Directed Medical Research Program's Peer Review Medical Research Program to HHS (DAMD17-02-2-0)
Notes	First included as Severson 2006 based on conference abstract, using ST abstinence at 6m as outcome

Risk of bias

Severson 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated.
Allocation concealment (selection bias)	Unclear risk	Enrollment forms mailed to study centre for allocation; risk of selection bias due to patient contact low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	64% completed both 3m & 6m assessments, not reported by group. Missing treated as non abstinent in MA; imputation did not alter estimates of effect

Severson 2015

Methods	Country: USA Recruitment: Web recruitment
Participants	1067 ST users, 97.6% male, av.age 36
Interventions	Pharmacotherapy; NRT 1. 4 mg nicotine lozenge for 12 weeks with taper 2. Coach calls: 3 brief proactive counselling calls with a scripted protocol. First call: 1 week after randomization. Second call: 2-3 days after selected quit date. Third call: 14-21 days after the 2nd call 3. Lozenge + Coach calls
Outcomes	Repeated point prevalence all tobacco and ST abstinence at 3 and 6 months Verification: none
Funding source	NCI R01 CA142952. 'GlaxoSmithKline provided the nicotine lozenges for the study, but it had no role in the conduct of the study (data collection, management, analysis, and interpretation) or in preparation, review, approval of the manuscript, or in the decision to submit the manuscript for publication.'
Notes	Comparison of Lozenge + Coach calls vs. Coach calls alone. Arm 1 does not contribute to any comparison

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization mentioned but not described
Allocation concealment (selection bias)	Unclear risk	No assurances of allocation concealment

Severson 2015 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	84% completed the 3 month assessment, and 84% completed the 6 month assessment. 80% completed both assessments

Stevens 1995

Methods	Country: USA, 11 dental clinics Recruitment: at dental hygiene visit, unselected for motivation to quit
Participants	518 male ST users (30% also smoked) Intervention from hygienists and dentists with 2 hr training
Interventions	Behavioural therapy 1. Oral examination with feedback, advice to quit from hygienist and dentist, S-H manual, quit kit, video, quit date, telephone call from counsellor, free helpline, 6 newsletters. 2. Usual care
Outcomes	Abstinence at 12m (2 PP, 3m and 12m), ST only and all tobacco Verification: salivary cotinine, but low compliance so only self-report data given in paper
Funding source	NCI CA44648
Notes	3 clinics assessed usual care for 3m then provided intervention. Pre-intervention results not included here

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Pseudo-random assignment by clinic record number at 8 clinics. At 3 others, all users enrolled
Allocation concealment (selection bias)	High risk	Use of record number prevents allocation concealment, possibility of recruitment bias, although recruitment not done by therapist
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At 12 months 5% refused interview and 12% lost to follow-up. Not reported by group. Losses treated as non abstinent

Stotts 2003

Methods	Country: USA, 41 high schools Recruitment: volunteers motivated to quit
Participants	303 male ST users aged 14-19. 185 returned consent forms and received interventions, intention to treat analysis used. Av. age of consenting participants 17, 80-90% used snuff, 65.6%-81.0% used cigarettes (frequency not stated)
Interventions	Both pharmacotherapy and behavioural therapy All participants offered oral screening 1. Nicotine patch: patch dose tailored to baseline cotinine, >150ng/ml received 21 mg initially, otherwise 14 mg, then tapered, 6w treatment. 6w behavioural intervention, 50 min group sessions with a health educator. Quit date at 3-4w, 1w supply of patches at a time. Stage-based proactive counselling at 2w, 4w, 8w, 3m, 6m, 12m. Free helpline, newsletter. 2. Placebo patch and same behavioural therapy (active & placebo groups attended same sessions; participants and educators blinded). 3. Minimal intervention control; 5-10 min counselling, 1 phone call 2w later
Outcomes	PP at 12m. Snuff/chew/any spit/cigarette and all tobacco reported. All tobacco used in analyses Verification: salivary cotinine
Funding source	NCI 1 R01 CA76969-03
Notes	1+2 vs 3 for behavioural section. No evidence of benefit of NRT so this is more conservative than 2 vs 3. Baseline tobacco use was not reported for those who did not enrol, but was lower in placebo group. Incentives offered for attendance and assessment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code.
Allocation concealment (selection bias)	Unclear risk	Allocation concealed until assigned to patch or usual care, but before consent forms returned. Active/placebo randomisation done later by pharmacist using ID numbers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomization preceded consent, and there was a higher dropout rate in the control group (who knew they would not get chance of NRT). Therefore the intention to treat analysis might underestimate quit

		rates in the control group, and not be conservative

Virtanen 2015

Methods	Country: Sweden Recruitment: Dental clinics
Participants	241 Snus users of which 41 also smoked cigarettes. Not required to be motivated to quit
Interventions	Behavioral therapy: 1. Structured tobacco use intervention based upon the 5 A's specifically referring to oral health with reference to pharmacotherapy, more intensive counselling in the primary care clinic and the telephone quitline. Handouts supplied 2. Usual care Dentistry staff were trained to deliver the intervention during a one-day workshop
Outcomes	7-day point prevalence and 3-month sustained all tobacco abstinence at 6 months Verification: None
Funding source	Swedish National Board of Health and Welfare
Notes	Classified as not involving an oral health examination with feedback, although oral health was mentioned. Sensitivity analysis altering the classification did not change any conclusions from subgroup analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization at the level of the clinics using computer randomization
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% lost to follow-up in intervention and 4% in the control

Walsh 1999

Methods	Country: USA Recruitment: rural colleges with baseball and football teams
Participants	360 ST using college athletes on 16 campuses, <2% were current smokers
Interventions	Behavioural therapy 1. Oral examination with feedback, photos of ST effects, advice to quit, S-H manual, optional brief counselling (15-20 min, quit date, triggers, withdrawal), optional nicotine

Walsh 1999 (*Continued*)

	gum, optional telephone counselling (2 calls, 5-10 min) 2. Oral examination only
Outcomes	PP abstinence, ST use, 12m. Verification: salivary cotinine used as 'bogus pipeline' (i.e. samples not tested), not to correct self reports
Funding source	Tobacco Surtax Fund of the State of California through the Tobacco Related Disease Research Program of the University of California
Notes	3/24 used nicotine gum quit Study report used college as unit of analysis. Average quit rates were 34.5% for intervention and 15.9% for control sites (adjusted difference 20.5, 95% CI 3.6 to 38.0). MA uses numbers from these percentages. Cluster size ranged from 15-35

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cluster randomized by college, matched for baseline ST use and one of pair assigned to intervention
Allocation concealment (selection bias)	Unclear risk	Unclear whether participants enrolled before college assignment known. Participants 'were similar with respect to demographic factors and did not differ remarkably in smokeless tobacco use characteristics or motivation to quit'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers lost 10% intervention 5% control; losses treated as non-abstinent

Walsh 2003

Methods	Country: USA, 44 high schools Recruitment: Randomly selected rural high schools
Participants	Subgroup of 307 ST users among 1084 baseball athletes in 44 high schools (Study also included a prevention component, not assessed in this review)
Interventions	Behavioural therapy 1. Peer-led component: interactive, peer-led team directing education with a videotape and discussion (10-15 min), a slide presentation (20-30 min) and a small-group discussion on tobacco industry advertising (10 min). Dental component: an oral cancer screening exam performed by a dentist or a dental hygienist with advice to quit, a S-H guide, tobacco cessation counselling in small groups (15 min), and a telephone call on the quit date (5-10 min). Theoretical basis: cognitive social learning theory

Walsh 2003 (*Continued*)

	2. No intervention
Outcomes	Abstinence at 1 months and 12 months. Verification: none.
Funding source	Tobacco Surtax Fund of the State of California (Grant No. 4RT-0068) & NCI (CA 67654)
Notes	Subgroup analysis of 1084 high school baseball players. Potential for random error based upon subgroup analysis. Study reports OR from GEE analysis; 2.29 (95% CI 1.36 to 3.87). Main MA uses numbers from percentage quit rates; 27% vs 14%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Cluster randomized by school, stratified on number and size of baseball teams and prevalence of ST use
Allocation concealment (selection bias)	Unclear risk	Unclear whether participants were enrolled before school condition revealed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	23% of intervention and 15% of controls missing. Losses treated as non abstinent

Walsh 2010

Methods	Country: USA Recruitment: Rural high schools in California Randomization: Schools randomly selected from a list
Participants	Male enrolled in a study high school who reported tobacco use within the past 30 days
Interventions	Behavioural intervention: 1. A peer-led educational session, an oral exam with feedback, and three nurse-led group cessation counselling sessions. The *peer-led educational session* was scheduled during class time by school staff to reach freshmen through senior students, lasted 45 min, and consisted of student peers showing and then leading a discussion about 2 videos and 10 slides related to ST use and the role of the tobacco industry in targeting young males. The *oral exam* was conducted by the school nurse who also pointed out any tobacco-associated lesions to students in their own mouths and applied a brief tobacco intervention consisting of verbally asking about tobacco use, advising users to quit, assessing readiness to quit in the next month, assisting with the quitting process by offering a self-help guide and the opportunity to participate in three group cessation counselling sessions, and arranging follow-up with interested tobacco users. Students with oral lesions were scheduled 1 week later for a follow-up exam by the nurse. The

	nurse-led counselling consisted of three noncompulsory, 1-hr nurse-led cessation sessions scheduled after school approximately 1 week apart comprised of assessment, education, and preparation to get ready to quit, and the importance of social support. The second session focused on setting a quit date and skills to cope with cravings and temptation to use. The third session reviewed progress and focused on relapse prevention 2. No intervention
Outcomes	ST use dip/chew use in the prior 30 days, 1 year
Funding source	National Institute of Dental and Craniofacial Research at the National Institutes of Health (Grant Number US DHHS NIH/NIDCR P60 DE13058)
Notes	Participating high schools were stratified on size of school and enrolment year. Sensitivity analysis Analysis 4.8.2 using adjusted odds ratio did not affect results.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized high schools, procedure not defined
Allocation concealment (selection bias)	Unclear risk	Unclear whether school condition known when students recruited
Incomplete outcome data (attrition bias) All outcomes	High risk	Denominator includes only those completing the survey (123/229 = 51%). Assumed that missing data were missing completely at random. Baseline ST use was more common in dropouts but there was no evidence of interaction with group

MA: meta-analysis
m: month(s)
min: minute(s)
NCI: National Cancer Institute
PP: point prevalence
S-H: self-help
ST: smokeless tobacco/spit tobacco.
w: week.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chakravorty 1992	Follow-up only 1 month. School-based intervention comparing oral replacement (non-tobacco herbal snuff ('Mintsnuff') or chewing gum for 1m) and lecture on ST health risks and benefits of quitting to a lecture-only condition
Croucher 2003	Small feasibility study of interventions to reduce ST use. Moist snuff users (N=40 males) were randomly assigned to 4 mg nicotine gum, non-tobacco mint snuff, brand switching, or elimination of ST use in specific situations. Abstinence at 26 weeks was a secondary outcome, not reported by treatment group
Ebbert 2010b	Target of intervention was reduction in smokeless tobacco use, not cessation (and only 12 weeks follow-up)
Glover 1994	Follow-up only 4-8 weeks. Interventions differed only on amount of contact with supervisor. Primarily a process evaluation of use of materials
Glover 2002	Follow-up only 3 months. Trial of bupropion SR in 70 male ST users
Gordon 2010	Population is predominately cigarette smokers and individual ST data not provided
Greene 1994	Not randomized.
Gupta 1986	Not randomized.
Hatsukami 2003	Pilot study. Abstinence rates not reported by treatment group. Only 10 participants in each of 4 arms
Hatsukami 2008	Target of intervention was reduction in smokeless tobacco use, not cessation (and only 12 weeks follow-up)
Jain 2014	Follow-up only 12 weeks.
Klesges 2006	Subgroup receiving the smokeless tobacco cessation intervention not separated from overall group. Unable to determine the number in the control group and data unavailable
McChargue 2002	Short-term study of withdrawal symptoms.
Raja 2014	Follow-up only 4 weeks.
Vigg 2003	Follow-up only 8 weeks.
Williams 1995	Follow-up only 3 months. College-based trial of self-help quit manual with peer interaction. Compared 4 assessment sessions to 2 sessions

Characteristics of ongoing studies *[ordered by study ID]*

Sarkar 2014

Trial name or title	Brief Advice and Breathing EXercises (BABEX) for quitting tobacco use in low income communities in India
Methods	Community based cluster randomised trial with two arms
Participants	850 adult tobacco users
Interventions	Intervention Arm: Brief advice based on a script with personalized modifications, training on breathing exercises using a standard video, help the tobacco user practice the breathing exercises briefly to ensure understanding Control Arm: Very Brief Advice based on a script
Outcomes	Self-reported abstinence at six months follow-up
Starting date	July 2012
Contact information	Robert West, University College London, robertwest100@gmail.com
Notes	Will include both smoked and smokeless tobacco

DATA AND ANALYSES

Comparison 1. Pharmacotherapy: Buproprion versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All tobacco abstinence at longest follow-up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 6 months or greater continuous abstinence	2	293	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.54, 1.44]

Comparison 2. Pharmocotherapy: NRT versus placebo/no placebo/control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 6 months or greater abstinence, strictest criteria	12	2922	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.11, 1.39]
1.1 Nicotine Patch	5	1083	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.93, 1.37]
1.2 Nicotine Gum	2	310	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.68, 1.43]
1.3 Nicotine lozenge	5	1529	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.17, 1.59]

Comparison 3. Pharmacotherapy: Varenicline versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All tobacco abstinence at 6 months	2	507	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.08, 1.68]

Comparison 4. Behavioural interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abstinence from all tobacco use (where reported) at 6 months or more	17		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Individual randomisation	10		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Randomisation by organisation	7		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2 Subgroup analysis: Motivation	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Motivated	7	7921	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.25, 1.55]
2.2 Not selected by motivation	10	4473	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.23, 1.53]
3 Subgroup analysis: Use of oral examination and feedback	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Intervention included oral examination and feedback	6	2701	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.17, 1.53]
3.2 Oral examination not part of the intervention	11	9693	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.28, 1.54]
4 Subgroup analysis: Use of telephone support	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Telephone support for intervention, not for control	10	5480	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.57, 2.00]
4.2 No telephone support for either condition	7	6611	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.05, 1.28]
4.3 Telephone support for control group only	1	303	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.57, 2.78]
5 Subgroup analysis: Combined oral examination and telephone	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Oral exam plus telephone	4	1818	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [1.61, 2.66]
5.2 Oral exam, no telephone	2	883	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
5.3 Telephone, no oral exam	7	3965	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.45, 1.91]
5.4 No oral exam, no telephone	5	5728	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.08, 1.39]
6 Behavioural intervention +/- pharmacotherapy versus minimal contact. Long term cessation	1	210	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.84, 2.12]
6.1 Nicotine gum	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [0.98, 3.92]
6.2 Placebo gum	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.50, 1.77]
7 Sensitivity analysis: Abstinence from smokeless tobacco use (where reported) at 6 months or more	17		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 All tobacco use	7		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Smokeless tobacco use	10		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Inverse variance sensitivity Abstinence from all tobacco use (where reported) at 6 months or more	17	15504	Odds Ratio (Fixed, 95% CI)	1.46 [1.33, 1.59]
8.1 Individual randomisation	10	9284	Odds Ratio (Fixed, 95% CI)	1.58 [1.40, 1.79]
8.2 Randomisation by organisation	7	3110	Odds Ratio (Fixed, 95% CI)	1.36 [1.14, 1.61]
8.3 Walsh lower OR Randomisation by organisation	7	3110	Odds Ratio (Fixed, 95% CI)	1.33 [1.12, 1.58]

Comparison 5. Abrupt cessation versus gradual reduction (using NRT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 6 months or greater abstinence, strictest criteria	1	199	Risk Ratio (M-H, Fixed, 95% CI)	11.57 [1.52, 87.91]

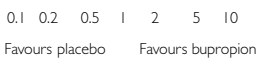
Analysis 1.1. Comparison 1 Pharmacotherapy: Buproprion versus placebo, Outcome 1 All tobacco abstinence at longest follow-up.

Review: Interventions for smokeless tobacco use cessation

Comparison: 1 Pharmacotherapy: Buproprion versus placebo

Outcome: 1 All tobacco abstinence at longest follow-up

Study or subgroup	Buproprion n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 6 months or greater continuous abstinence					
Dale 2007	21/113	24/112		85.8 %	0.87 [0.51, 1.46]
Dale 2002	4/34	4/34		14.2 %	1.00 [0.27, 3.68]
Subtotal (95% CI)	**147**	**146**		**100.0 %**	**0.89 [0.54, 1.44]**
Total events: 25 (Buproprion), 28 (Placebo)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.49 (P = 0.63)					

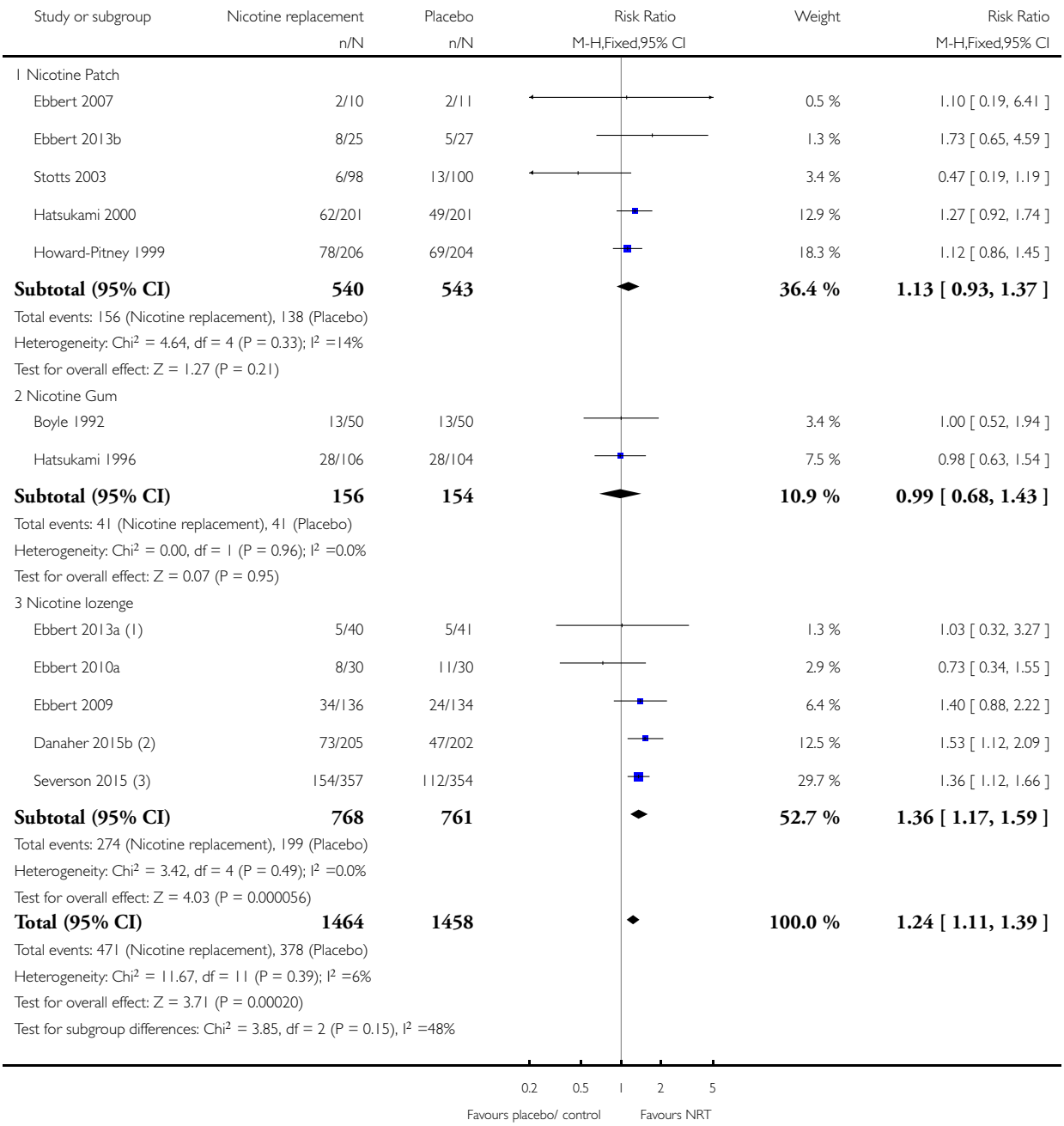


Analysis 2.1. Comparison 2 Pharmocotherapy: NRT versus placebo/no placebo/control, Outcome 1 6 months or greater abstinence, strictest criteria.

Review: Interventions for smokeless tobacco use cessation

Comparison: 2 Pharmocotherapy: NRT versus placebo/no placebo/control

Outcome: 1 6 months or greater abstinence, strictest criteria



(1) Motivated to reduce. No placebo, control was tobacco free snuff

(2) No placebo. Lozenze as adjunct to web

(3) No placebo. Lozenze % telephone calls vs calls only

Analysis 3.1. Comparison 3 Pharmacotherapy: Varenicline versus placebo, Outcome 1 All tobacco abstinence at 6 months.

Review: Interventions for smokeless tobacco use cessation

Comparison: 3 Pharmacotherapy: Varenicline versus placebo

Outcome: 1 All tobacco abstinence at 6 months

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ebbert 2011	17/38	12/38		14.3 %	1.42 [0.79, 2.55]
Fagerstrom 2010	95/213	73/218		85.7 %	1.33 [1.05, 1.69]
Total (95% CI)	**251**	**256**		**100.0 %**	**1.34 [1.08, 1.68]**

Total events: 112 (Experimental), 85 (Control)

Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 2.61 (P = 0.0090)

Test for subgroup differences: Not applicable

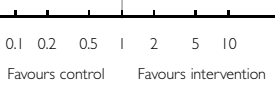
Analysis 4.1. Comparison 4 Behavioural interventions, Outcome 1 Abstinence from all tobacco use (where reported) at 6 months or more.

Review: Interventions for smokeless tobacco use cessation

Comparison: 4 Behavioural interventions

Outcome: 1 Abstinence from all tobacco use (where reported) at 6 months or more

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Individual randomisation				
Boyle 2004	44/109	28/112		1.61 [1.09, 2.39]
Severson 2007	69/535	52/534		1.32 [0.94, 1.86]
Danaher 2013	159/857	149/859		1.07 [0.87, 1.31]
Stevens 1995	25/245	19/273		1.47 [0.83, 2.60]
Cigrang 2002	7/31	3/29		2.18 [0.62, 7.65]
Stotts 2003	19/198	8/105		1.26 [0.57, 2.78]
Severson 2008	159/1260	100/1263		1.59 [1.26, 2.02]
Severson 2009	69/392	18/393		3.84 [2.33, 6.33]
Boyle 2008	62/201	20/205		3.16 [1.99, 5.03]
Danaher 2015a (1)	356/1259	90/424		1.33 [1.09, 1.63]
2 Randomisation by organisation				
Cummings 1995	76/316	102/417		0.98 [0.76, 1.27]
Walsh 2010	64/123	59/123		1.08 [0.84, 1.39]
Gansky 2005	103/285	130/352		0.98 [0.80, 1.20]
Walsh 2003	38/141	23/166		1.95 [1.22, 3.10]
Virtanen 2015	7/94	2/100		3.72 [0.79, 17.47]
Walsh 1999	60/171	30/189		2.21 [1.50, 3.25]
Severson 1998	40/394	8/239		3.03 [1.44, 6.37]



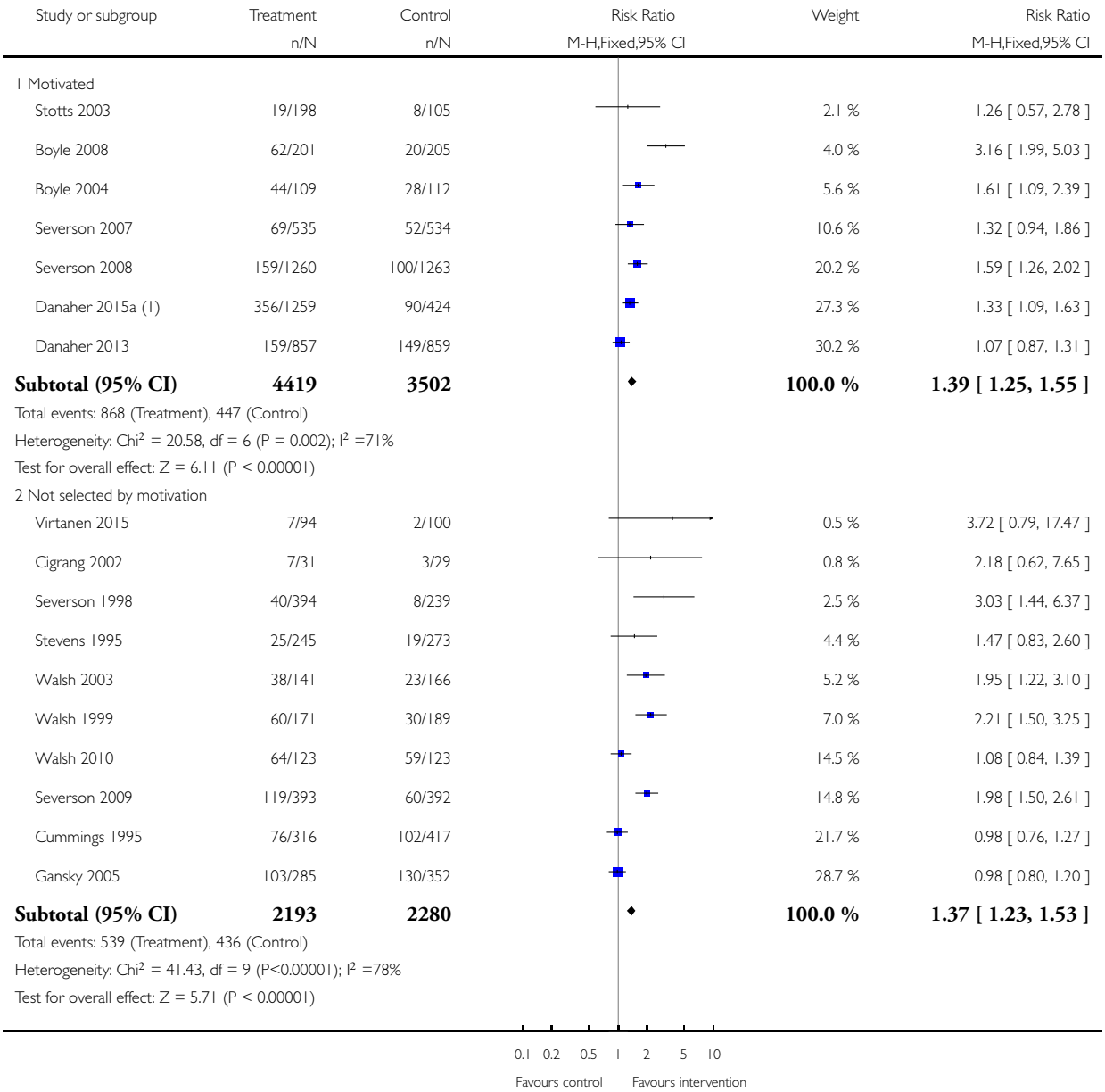
(1) Combining 3 intervention arms

Analysis 4.2. Comparison 4 Behavioural interventions, Outcome 2 Subgroup analysis: Motivation.

Review: Interventions for smokeless tobacco use cessation

Comparison: 4 Behavioural interventions

Outcome: 2 Subgroup analysis: Motivation



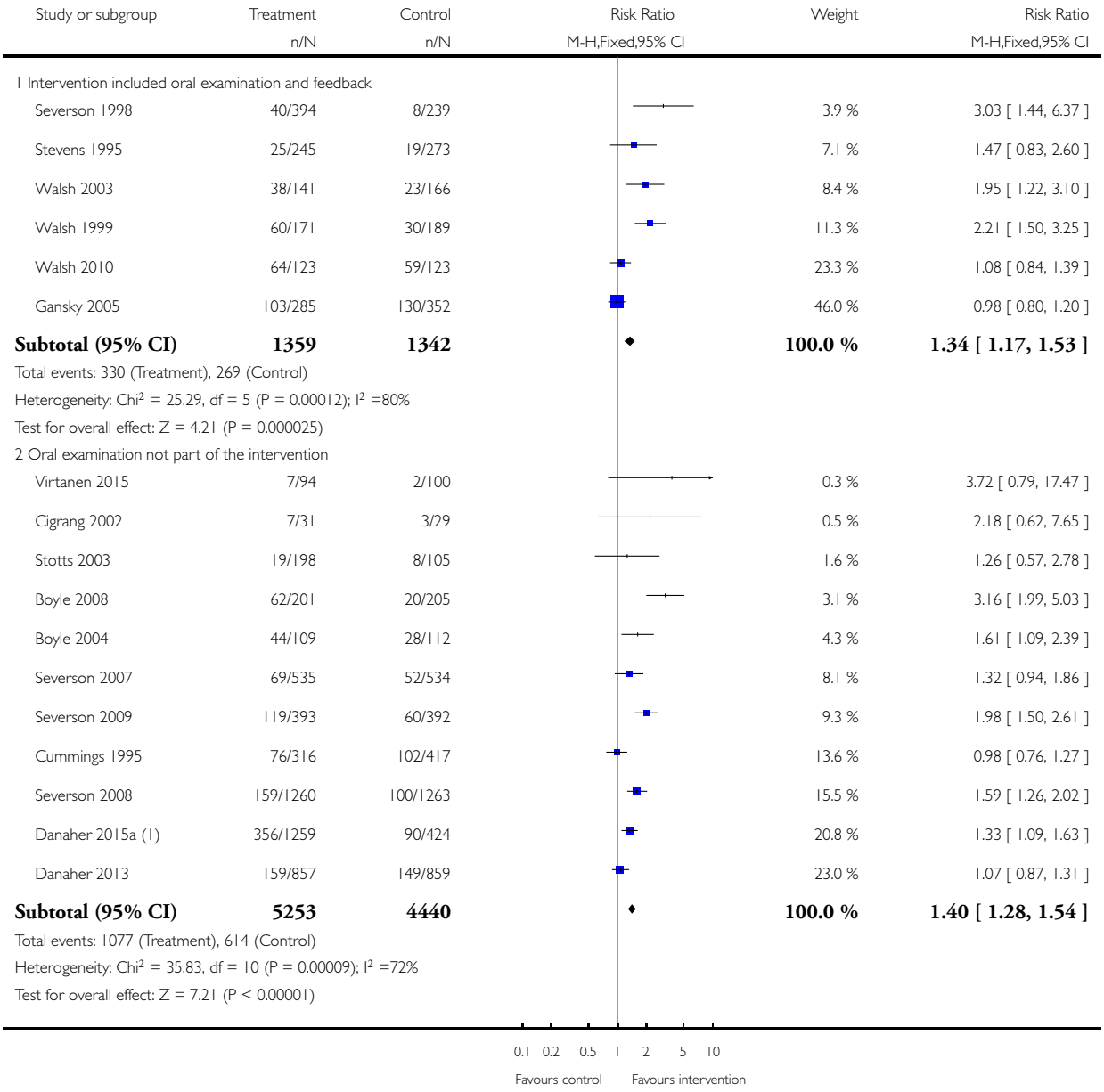
(1) Combining 3 intervention arms

Analysis 4.3. Comparison 4 Behavioural interventions, Outcome 3 Subgroup analysis: Use of oral examination and feedback.

Review: Interventions for smokeless tobacco use cessation

Comparison: 4 Behavioural interventions

Outcome: 3 Subgroup analysis: Use of oral examination and feedback



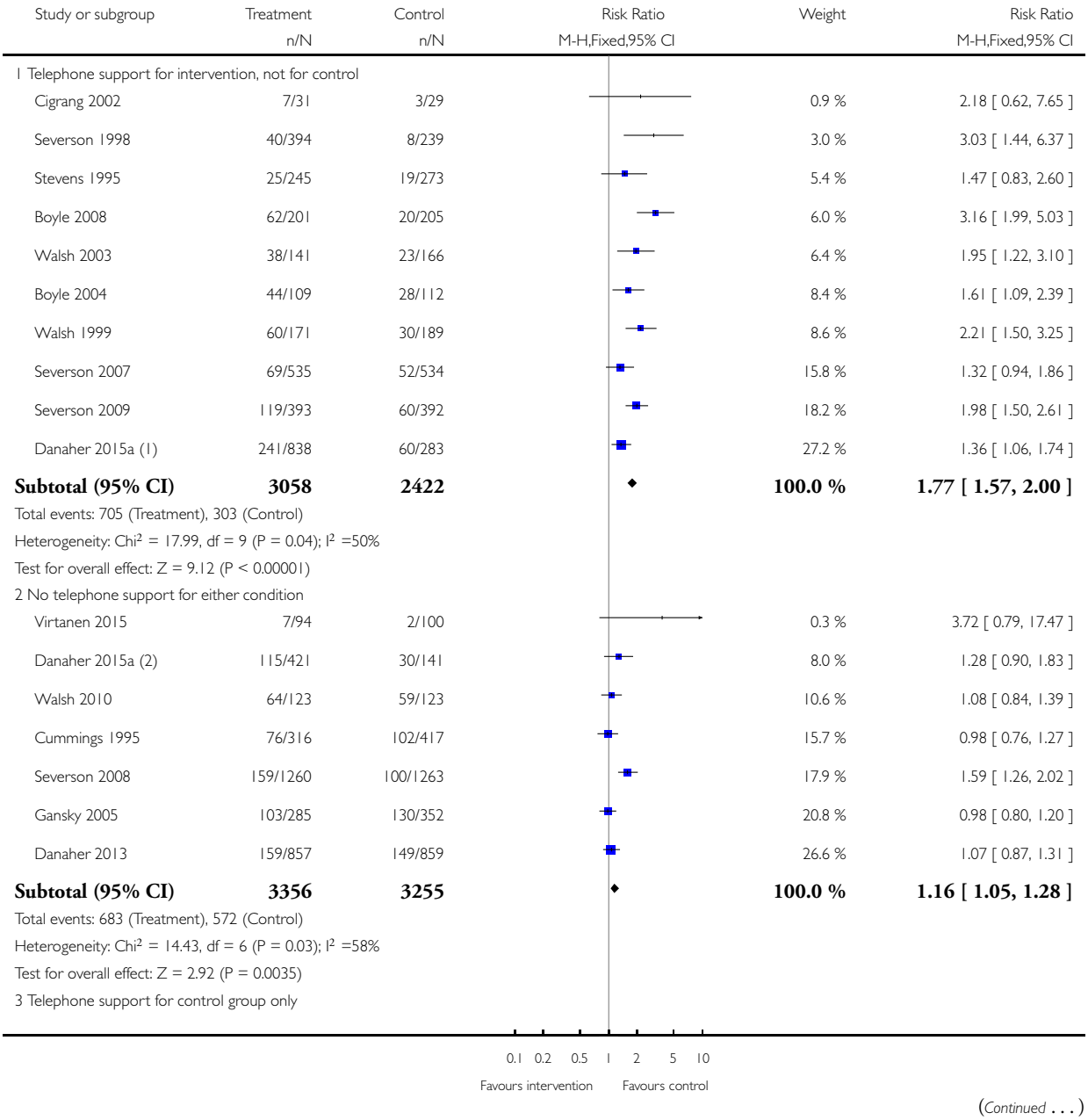
(1) Combining 3 intervention arms

Analysis 4.4. Comparison 4 Behavioural interventions, Outcome 4 Subgroup analysis: Use of telephone support.

Review: Interventions for smokeless tobacco use cessation

Comparison: 4 Behavioural interventions

Outcome: 4 Subgroup analysis: Use of telephone support



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Stotts 2003	19/198	8/105		100.0 %	1.26 [0.57, 2.78]
Subtotal (95% CI)	**198**	**105**		**100.0 %**	**1.26 [0.57, 2.78]**
Total events: 19 (Treatment), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Chi² = 27.83, df = 2 (P = 0.00), I² =93%					

(1) QL % Web +QL arms vs 2/3 control

(2) Web only arm vs 1/3 control

Analysis 4.5. Comparison 4 Behavioural interventions, Outcome 5 Subgroup analysis: Combined oral examination and telephone.

Review: Interventions for smokeless tobacco use cessation

Comparison: 4 Behavioural interventions

Outcome: 5 Subgroup analysis: Combined oral examination and telephone

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oral exam plus telephone					
Stevens 1995	25/245	19/273		23.2 %	1.47 [0.83, 2.60]
Walsh 2003	38/141	23/166		27.2 %	1.95 [1.22, 3.10]
Walsh 1999	60/171	30/189		36.7 %	2.21 [1.50, 3.25]
Severson 1998	40/394	8/239		12.8 %	3.03 [1.44, 6.37]
Subtotal (95% CI)	**951**	**867**		**100.0 %**	**2.07 [1.61, 2.66]**
Total events: 163 (Treatment), 80 (Control)					
Heterogeneity: Chi² = 2.60, df = 3 (P = 0.46); I² =0.0%					
Test for overall effect: Z = 5.72 (P < 0.00001)					
2 Oral exam, no telephone					
Gansky 2005	103/285	130/352		66.3 %	0.98 [0.80, 1.20]

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Walsh 2010	64/123	59/123		33.7 %	1.08 [0.84, 1.39]
Subtotal (95% CI)	**408**	**475**		**100.0 %**	**1.01 [0.86, 1.19]**
Total events: 167 (Treatment), 189 (Control)					
Heterogeneity: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 0.17 (P = 0.86)					
3 Telephone, no oral exam					
Stotts 2003	19/198	8/105		4.0 %	1.26 [0.57, 2.78]
Severson 2007	69/535	52/534		19.8 %	1.32 [0.94, 1.86]
Danaher 2015a (1)	241/838	60/283		34.1 %	1.36 [1.06, 1.74]
Boyle 2004	44/109	28/112		10.5 %	1.61 [1.09, 2.39]
Severson 2009	119/393	60/392		22.9 %	1.98 [1.50, 2.61]
Cigrang 2002	7/31	3/29		1.2 %	2.18 [0.62, 7.65]
Boyle 2008	62/201	20/205		7.5 %	3.16 [1.99, 5.03]
Subtotal (95% CI)	**2305**	**1660**		**100.0 %**	**1.66 [1.45, 1.91]**
Total events: 561 (Treatment), 231 (Control)					
Heterogeneity: Chi^2 = 13.82, df = 6 (P = 0.03); I^2 =57%					
Test for overall effect: Z = 7.16 (P < 0.00001)					
4 No oral exam, no telephone					
Cummings 1995	76/316	102/417		22.9 %	0.98 [0.76, 1.27]
Danaher 2013	159/857	149/859		38.8 %	1.07 [0.87, 1.31]
Danaher 2015a (2)	115/421	30/141		11.7 %	1.28 [0.90, 1.83]
Severson 2008	159/1260	100/1263		26.0 %	1.59 [1.26, 2.02]
Virtanen 2015	7/94	2/100		0.5 %	3.72 [0.79, 17.47]
Subtotal (95% CI)	**2948**	**2780**		**100.0 %**	**1.22 [1.08, 1.39]**
Total events: 516 (Treatment), 383 (Control)					
Heterogeneity: Chi^2 = 11.27, df = 4 (P = 0.02); I^2 =64%					
Test for overall effect: Z = 3.23 (P = 0.0013)					
Test for subgroup differences: Chi^2 = 34.51, df = 3 (P = 0.00), I^2 =91%					

(1) Phone and Phone % web arms vs 2/3 control

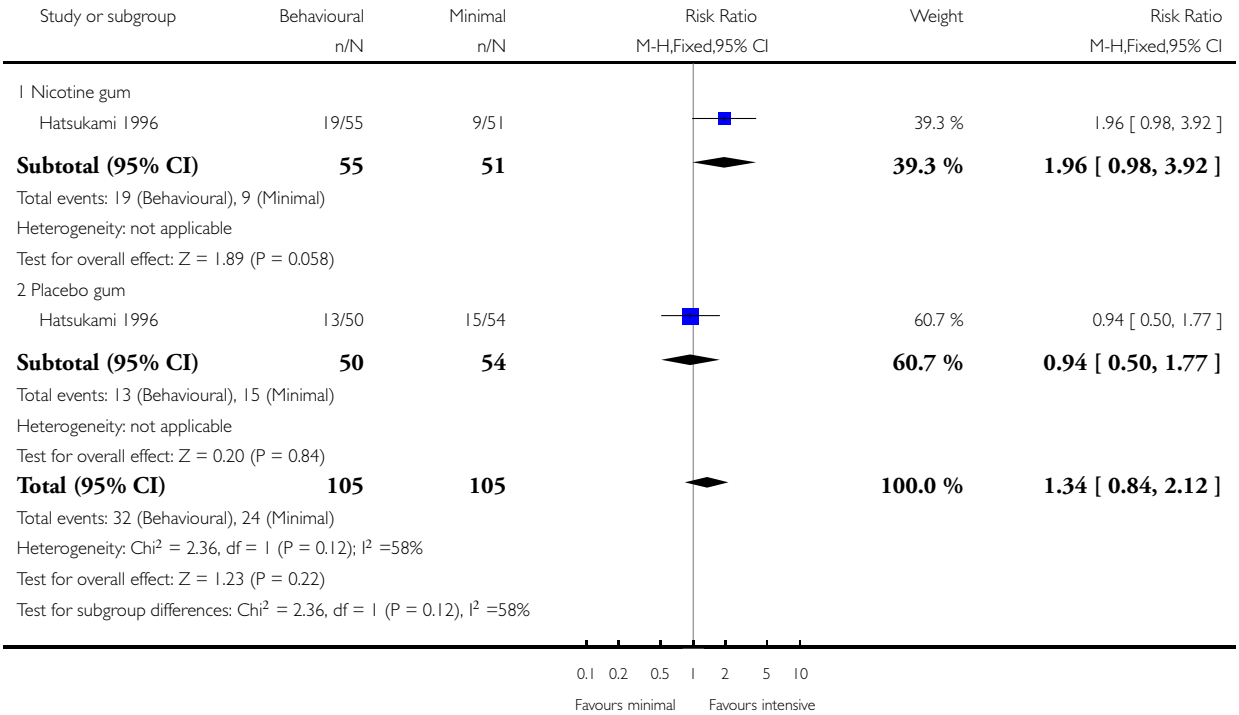
(2) Web only arms vs 1/3 control

Analysis 4.6. Comparison 4 Behavioural interventions, Outcome 6 Behavioural intervention +/- pharmacotherapy versus minimal contact. Long term cessation.

Review: Interventions for smokeless tobacco use cessation

Comparison: 4 Behavioural interventions

Outcome: 6 Behavioural intervention +/- pharmacotherapy versus minimal contact. Long term cessation



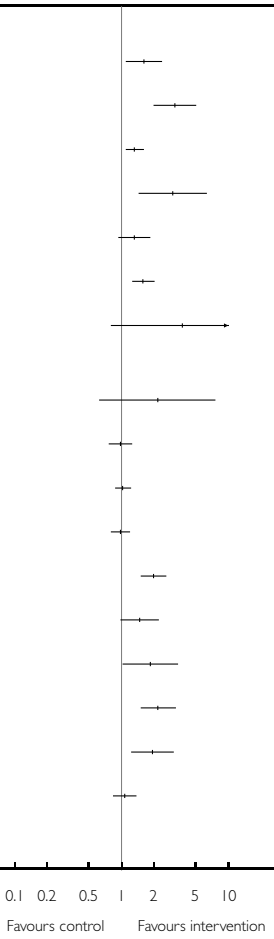
Analysis 4.7. Comparison 4 Behavioural interventions, Outcome 7 Sensitivity analysis: Abstinence from smokeless tobacco use (where reported) at 6 months or more.

Review: Interventions for smokeless tobacco use cessation

Comparison: 4 Behavioural interventions

Outcome: 7 Sensitivity analysis: Abstinence from smokeless tobacco use (where reported) at 6 months or more

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 All tobacco use				
Boyle 2004	44/109	28/112		1.61 [1.09, 2.39]
Boyle 2008	62/201	20/205		3.16 [1.99, 5.03]
Danaher 2015a (1)	356/1259	90/424		1.33 [1.09, 1.63]
Severson 1998	40/394	8/239		3.03 [1.44, 6.37]
Severson 2007	69/535	52/534		1.32 [0.94, 1.86]
Severson 2008	159/1260	100/1263		1.59 [1.26, 2.02]
Virtanen 2015	7/94	2/100		3.72 [0.79, 17.47]
2 Smokeless tobacco use				
Cigrang 2002	7/31	3/29		2.18 [0.62, 7.65]
Cummings 1995	76/316	102/417		0.98 [0.76, 1.27]
Danaher 2013	194/857	188/859		1.03 [0.87, 1.23]
Gansky 2005	103/285	130/352		0.98 [0.80, 1.20]
Severson 2009	119/393	60/392		1.98 [1.50, 2.61]
Stevens 1995	45/245	34/273		1.47 [0.98, 2.22]
Stotts 2003	42/198	12/105		1.86 [1.02, 3.37]
Walsh 1999	60/171	30/189		2.21 [1.50, 3.25]
Walsh 2003	38/141	23/166		1.95 [1.22, 3.10]
Walsh 2010	64/123	59/123		1.08 [0.84, 1.39]



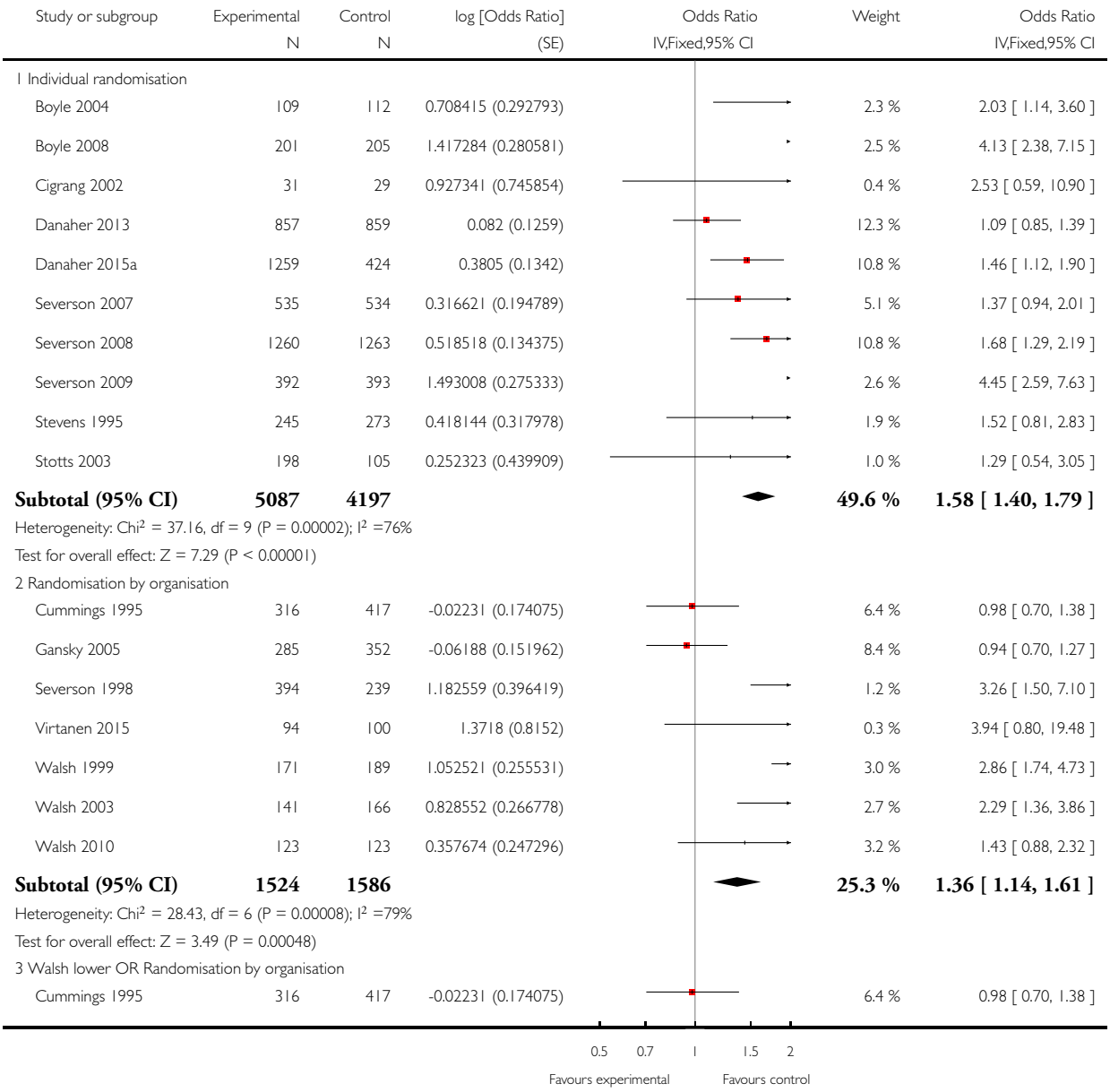
(1) Combining 3 intervention arms

Analysis 4.8. Comparison 4 Behavioural interventions, Outcome 8 Inverse variance sensitivity Abstinence from all tobacco use (where reported) at 6 months or more.

Review: Interventions for smokeless tobacco use cessation

Comparison: 4 Behavioural interventions

Outcome: 8 Inverse variance sensitivity Abstinence from all tobacco use (where reported) at 6 months or more



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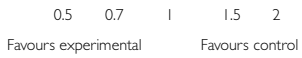
Study or subgroup	Experimental N	Control N	log [Odds Ratio] (SE)	Odds Ratio IV,Fixed,95% CI	Weight	Odds Ratio IV,Fixed,95% CI
Gansky 2005	285	352	-0.06188 (0.151962)		8.4 %	0.94 [0.70, 1.27]
Severson 1998	394	239	1.182559 (0.396419)		1.2 %	3.26 [1.50, 7.10]
Virtanen 2015	94	100	1.3718 (0.8152)		0.3 %	3.94 [0.80, 19.48]
Walsh 1999	171	189	1.052521 (0.255531)		3.0 %	2.86 [1.74, 4.73]
Walsh 2003	141	166	0.828552 (0.266778)		2.7 %	2.29 [1.36, 3.86]
Walsh 2010	123	123	0.162691 (0.255237)		3.0 %	1.18 [0.71, 1.94]
Subtotal (95% CI)	**1524**	**1586**			**25.1 %**	**1.33 [1.12, 1.58]**
Heterogeneity: Chi^2 = 28.63, df = 6 (P = 0.00007); I^2 =79%						
Test for overall effect: Z = 3.21 (P = 0.0013)						
Total (95% CI)	**8135**	**7369**			**100.0 %**	**1.46 [1.33, 1.59]**
Heterogeneity: Chi^2 = 97.65, df = 23 (P<0.00001); I^2 =76%						
Test for overall effect: Z = 8.50 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 3.43, df = 2 (P = 0.18), I^2 =42%						



Analysis 5.1. Comparison 5 Abrupt cessation versus gradual reduction (using NRT), Outcome 1 6 months or greater abstinence, strictest criteria.

Review: Interventions for smokeless tobacco use cessation

Comparison: 5 Abrupt cessation versus gradual reduction (using NRT)

Outcome: 1 6 months or greater abstinence, strictest criteria

Study or subgroup	Abrupt cessation n/N	Gradual reduction n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Schiller 2012	11/97	1/102		100.0 %	11.57 [1.52, 87.91]
Total (95% CI)	**97**	**102**		**100.0 %**	**11.57 [1.52, 87.91]**
Total events: 11 (Abrupt cessation), 1 (Gradual reduction)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.37 (P = 0.018)					
Test for subgroup differences: Not applicable					

ADDITIONAL TABLES

Table 1. Summary of behavioural intervention study characteristics

Study	Design	Selection?	Oral exam?	Telephone support?	Setting	Control
Boyle 2004	RCT	Motivated	No oral exam	Phone support	Community	S-H only
Boyle 2008	RCT	Motivated	No oral exam	Phone support	Community	S-H only
Danaher 2015a	RCT	Motivated	No oral exam	Both phone & no phone arms	Community	S-H only
Severson 2007	RCT	Motivated	No oral exam	Phone support	Community	S-H only
Stotts 2003	RCT	Motivated	No oral exam	Phone in both	High School	Brief Intervention
Severson 2008	RCT	Motivated	No oral exam	No phone	Community	Basic website
Danaher 2013	RCT	Motivated	No oral exam	No phone	Community	Basic website
Cigrang 2002	RCT	Unselected	No oral exam	Phone support	Military	UC
Severson 2009	RCT	Unselected	No oral exam	Phone support	Military	UC
Stevens 1995	RCT	Unselected	Oral exam & feedback	Phone support	Dental	UC
Gansky 2005	cRCT	Unselected	Oral exam & feedback	No phone	College	UC
Severson 1998	cRCT	Unselected	Oral exam & feedback	Phone support	Dental	UC
Virtanen 2015	cRCT	Unselected	No oral exam	No phone	Dental	UC
Walsh 1999	cRCT	Unselected	Oral exam & feedback	Phone support	College	Oral exam no feedback
Walsh 2003	cRCT	Unselected	Oral exam & feedback	Phone support	High School	No intervention
Walsh 2010	cRCT	Unselected	Oral exam & feedback	No phone	High School	No intervention

Table 1. Summary of behavioural intervention study characteristics (*Continued*)

Cummings 1995	cRCT	Unselected	No oral exam	No phone	Workplaces	No intervention

WHAT'S NEW

Last assessed as up-to-date: 25 June 2015.

Date	Event	Description
25 August 2015	New search has been performed	Searches updated, 9 new studies included
25 August 2015	New citation required and conclusions have changed	New citation for update, change of authors. Weak evidence that NRT (specifically lozenge) increases abstinence rates. Oral examinations no longer clearly associated with effect

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 3, 2004

Date	Event	Description
16 February 2011	Amended	Date assessed up to date corrected.
16 December 2010	New citation required and conclusions have changed	Change in authorship. Minor change to conclusions; one trial of varenicline shows efficacy
3 November 2010	New search has been performed	5 new studies added.
28 October 2008	Amended	Converted to new review format.
20 July 2007	New citation required and conclusions have changed	Updated with six new studies

CONTRIBUTIONS OF AUTHORS

JE conceived, designed, and coordinated the review. He was in charge of data collection and worked with PJE to develop search strategies. He assisted LS in entering data into RevMan and was involved in the interpretation and data analysis. He principally authored the review.

LS conducted searches for the most recent version of the review, screened search results, checked data extraction, and contributed to the text.

ME verified data and contributed to the text.

DECLARATIONS OF INTEREST

JE has served as a principal investigator and co-investigator on some of the studies included in this review. Data extraction and interpretation of these studies was checked by LS. JE has received support for research involving varenicline from Pfizer; none of that research was eligible for this review.

LS and ME have no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Nuffield Department of Primary Care Health Sciences, University of Oxford, UK.

External sources

- NHS National Institute for Health Research, UK.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Tobacco, Smokeless; Benzazepines [therapeutic use]; Bupropion [therapeutic use]; Chewing Gum; Counseling; Nicotine [therapeutic use]; Nicotinic Agonists [therapeutic use]; Quinoxalines [therapeutic use]; Randomized Controlled Trials as Topic; Tobacco Use Cessation [*methods]; Varenicline [therapeutic use]

MeSH check words

Humans