SUPPLEMENTAL APPENDIX A: DETAILED RISK OF BIAS ASSESSMENTS

Study code: Abelin 1991-35

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	A random and double-blind allocation, but the method for sequence generation was not provided
Allocation concealment?	Unclear	As above, but method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	As above, but blind approach was not provide. However, judged a low risk of bias given that objective outcomes were all based on robust clinical or laboratory evidences.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Treatment had to be discontinued because of poor skin tolerability in 6 percent of all subjects on nicotine patches (Practitioner study: 5 subjects; University study: 4 subjects). Otherwise, none of 92 drop-outs from the two studies were in connection with side effects of the transdermal nicotine systems. " Two abstinence outcomes, PPA at 6 and 12 month, were extracted. All randomized participants were included in the analysis. Overall, 32% (101/311) dropped out during the 12-month study, among which only 6% were known with adverse events and others with no further information. It was judged a high risk of bias given the low completion rate and lack of information about the early discontinuations.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Ahluwalia 1998-1

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Patients were randomized to one of two study arms based on a computer-generated random numbers table with a block size set at 20."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Both study staff and patients were blinded to patch treatment." "Placebo systems contained a pharmacologically irrelevant amount of nicotine in the drug reservoir to mimic the odor of active systems but delivered less than 1 mg of nicotine in 24 hours. Patients were instructed to apply a new patch system each morning to a dry skin site on the upper torso, upper back, or upper, outer arm on a 7-day cycle. All patches were packaged in unlabeled boxes that held a 2-week supply."
Blinding of subjective outcomes' assessment?	Low	As above, blinding approach was provided and judged to be appropriate.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interested was available.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, SAE, death, CV death, and completed suicide were inferred 0. 74% (152/205) of randomized population in nicotine patch group and 72% (147/205) in placebo patch group completed the safety assessment. Judged a high risk of bias given that the safety data was all inferred 0, the completion rates were lower than 80%, and the statistical methods for safety data were not provided.

Study code: Ahluwalia 2002-468

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Sequential enrollment were randomized. The randomization codes were generated in blocks of 50 and sent to the pharmaceutical company, which packaged the treatment and then shipped the blinded drug to the investigator." Method for sequence generation was not provided.
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	"Blinding was successful. At the end of treatment, 58% (150/259) of participants correctly guessed that they received bupropion SR, and 41% (104/253) correctly guessed that they received placebo. " Blinding approach was not provided. However, a post-study test approves the success of the blinding.
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias for the subjective outcome's assessment.
Incomplete outcome data addressed – for efficacy outcomes?	High	"All statistical analyses were performed on an intention-to-treat basis…For comparisons on 7-day point prevalence cessation at weeks 26, 6, 3 and 1, we considered those subjects who failed to return within their scheduled visit window as smokers. Efficacy outcomes of CAR and PPA at 6 months were extracted. All randomized participants received the assigned treatment and were included in the analysis. 68.3% (205/300) and 68.7% (206/300) of participants in bupropion SR and placebo group completed the 6-month assessment, respectively. Judged a high risk of bias given that the completion rates were below 80%. The conservative approach to handling missing data not only underestimate and variance but also bias the outcome estimates.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes were included, among which those of death, CV death, and completed suicide were inferred 0. As above, the completion rates were below 80%. No statistical analysis strategy for safety data was provided. Judged a high risk of bias.

Study code: Ahluwalia 2006-883

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Randomization codes were generated in blocks of 36. The Investigative Pharmacy at the University of Kansas Medical Center packaged the study medication using codes to maintain blinding. At the randomization visit, a sealed envelope with pre-assigned randomization numbers was drawn to determine which form of counseling the participant would receive. The envelope and box of gum with matching randomization numbers were given to participants in the order in which they were randomized." Method for sequence generation was not provided.
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	In addition to the above, "Study staff and participants were blinded to whether participants received active gum or placebo. However, assignment to MI counseling versus HE was not blinded."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias given that the blinding approach was appropriate for assessors and participants.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"All statistical analyses were performed on an intent-to-treat basis and those lost to follow-up were imputed as smokers for primary analyses." Efficacy outcome of PPA at 6 months was extracted. All randomized participants received the assigned treatment and were included in the analysis. 88.9% (157/189), 86.2% (162/188), 83.1% (157/189) and 84.7% (160/189) of participants in nicotine gum + HE, placebo + HE, nicotine gum + MI, and placebo + MI group completed the 26-week assessment. Judged a low risk of bias given that the completion rates were all greater than 80%. The numbers and reasons for the early discontinuations in four groups and the conservative approach to handling missing data were not likely to bias the outcome estimate.
Incomplete outcome data addressed – for safety outcomes?	Low	Four safety outcomes, including SAE, death, CV death, and completed suicide were inferred 0. Judged a low risk of bias given that the completion rates were all greater than 80%, the lack of statistical strategy for safety outcomes was not likely to bias the result.

Study code: Aubin 2004-1206

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"The computerized randomization schedule, prepared by the sponsor, was inaccessible to the investigator who was provided with a specific set of sequential treatment numbers. Each eligible subject was assigned to a treatment number in chronological order of admission."
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	"Subjects fulfilling the entry criteria were randomized in a double blind manner to study treatment…Blinding was assured by matching the placebo to the bupropion tablets: all the tablets were identical in appearance."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias given that the blinding approach was appropriate for assessors and participants.
Incomplete outcome data addressed – for efficacy outcomes?	High	"The primary efficacy and safety population was the intent-to-treat population (ITT), defined as all randomized subjects having taken study medication at least once." Efficacy outcomes of PPA and CAR at 6 months were extracted. All randomized participants were included in the analysis except for 1 in each group not taking any medication. 51% (83/164) and 64% (216/340) of participants in bupropion 300 mg/d and placebo group completed the 26-week assessment. Judged a high risk of bias given that the completion rates were all below 80%.
Incomplete outcome data addressed – for safety outcomes?	High	The safety outcome of SAE was reported, with death, CV death and completed suicide being inferred 0. As above, judged a high risk of bias given that the completion rates were less than 80%.

Study code: Aubin 2008-717

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Using a central computer-generated sequence, they were randomised in a 1:1 ratio to either 12 weeks of treatment with varenicline or 10 weeks of treatment with a nicotine transdermal patch…"
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"This was an open-label randomised trial…" An open label study and the blinding were infeasible due to the different forms of treatments. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	Judged a high risk of bias given that, in an open-label trial, the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Participants who missed a visit but had otherwise met the criteria since the last visit were considered non-smokers. Missing CO data were assumed to be (10 ppm provided other conditions were met. Participants who withdrew from the study were assumed to be smokers for the remainder of the study, regardless of their smoking status at the last visit." "Efficacy and safety analyses were conducted on randomized participants who received at least one dose of study medication (Primary Analysis Population)." Efficacy outcomes of PPA and CAR at 6 and 12 months were extracted. All randomized participants were included in the analysis except for 2 in varenincline group and 9 in nicotine patch group not taking any medication. 65.3% (247/378) and 60.7% (230/379) of the participants in varenincline and nicotine patch group completed the 52-week assessment. Judged a high risk of bias given that the completion rates were below 80%.
Incomplete outcome data addressed – for safety outcomes?	High	Five safety outcomes, including SAE, death, CV death, suicidal ideation and complete suicide, were extracted. As above, judged a high risk of bias given that the completion rates were less than 80%. There was no approach to handling the missing data.

Study code: Blondal 1997-1585

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"The subjects were assigned to either nicotine or placebo treatment according to a computer-generated randomization code."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Subjects and therapists were blind to treatment assignment." In addition to the same regimen as the nasal nicotine spray group, "The placebo spray contained black pepper oleo resin (piperine) to mimic the sensory effect of nicotine." Both group seemed matched and the blinding should be maintained well.
Blinding of subjective outcomes' assessment?	Low	As above, the blinding was secured by the matched placebo in terms of the use and regimen.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"At the follow-up visits, nonsmoking claims were confirmed by a CO measurement of <10 ppm. One subject lost to follow-up was assumed to be a smoker. Subjects who failed to keep their appointments usually had resumed smoking and were contacted by telephone regularly at the follow-up times throughout the study." Efficacy outcomes of CAR at 6, 12 and 24 months were extracted. All randomized participants seemed to complete the 12-month assessment and were included in the analysis. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome (SAE) was extracted; while other three, including death, CV death, and complete suicide, were inferred 0. As above, judged a low risk of bias.

Study code: Blondal 1999-285

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"…they were allocated their treatment by computer generated randomization code at a local pharmacy."
Allocation concealment?	Low	"The randomization code was kept at the pharmacy during the trial and not broken until the data entry and analysis were completed."
Blinding of objective outcomes' assessment?	Low	"The nasal sprays-nicotine or placebo- were taken from boxes labeled A or B, but the bottles themselves were unlabelled. The pharmacy staff were blinded to the content of the bottles. To prevent switching of treatment among participants and to help protect blinding, the same treatment was on four separate occasions dispensed to four couples. The staff of the smoking clinic had no knowledge of the treatment assigned to each participant." "Nasal sprays were dispensed in identical brown bottles containing a colourless solution of either nicotine or black pepper oleo resin (piperine)…Blinding among participants were successful. At the 1 year follow up we found no significant relation between type of treatment and the participants' responses, which proved they had been unable to guess their treatment."
Blinding of subjective outcomes' assessment?	Low	As above, the blinding was secured and approved.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Participants were considered to be smokers if they had, after stopping smoking, taken a single puff of a cigarette, used other forms of tobacco, used a nicotine drug other than that prescribed, had a carbon monoxide concentration of≥10 ppm, or were lost to follow up…no subject was lost at any follow up." Efficacy outcomes of CAR at 6, 12 and 60 months, and PPA at months 6 and 12 were extracted. All randomized participants were included in the analysis, except for two early discontinuing from each of the arms. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome (death) was extracted, and one (SAE) inferred 0. As above, judged a low risk of bias.

Study code: Bohadana 2000-3128

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Subjects were assigned to 1 of 2 treatment groups according to a computer-generated randomization code...."
Allocation concealment?	Low	"Sealed randomization envelopes were provided for each subject and were held by the hospital pharmacy, which was responsible for dispensing medication."
Blinding of objective outcomes' assessment?	Low	"The placebo patch was the same size and appearance but did not contain nicotine. The study was double blind up to week 6, single blind from weeks 6 to 12, and open thereafter….Both groups received identical treatment (placebo) during this period to evaluate whether discontinuation of transdermal nicotine administration during double-blind conditions would result in relapse. "
Blinding of subjective outcomes' assessment?	Low	As above, the blinding was maintained during the double-blinding period.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Subjects unavailable for follow-up were assumed to be smokers." "Data were analyzed on an intent-to-treat basis (ie, all subjects who entered the study and received medication irrespective of medication use or outcome.)" Efficacy outcomes of CAR at 6 and 12 months were extracted. All randomized participants were included in the analysis, However, 26% (52/200) in nicotine inhaler plus nicotine patch group and 22.5% (45/200) in nicotine inhaler plus placebo patch group completed the 12-month study. The completion rates were low and the information about the early discontinuations and the approach to handling missing data were not provided. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	One safety outcome, SAE, was extracted; while three – mortality, cardiovascular mortality and completed suicide inferred 0. As above, judged a high risk of bias.

Study code: Bolliger 2000 - 329

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"....double blind, randomized clinical trial…" Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The placebo inhalers were identical in appearance and contained only menthol. Both treatment groups were allowed to use the inhalers as needed, with the recommendation…"
Blinding of subjective outcomes' assessment?	Low	As above, the blinding was maintained through the study.
Incomplete outcome data addressed – for efficacy outcomes?	High	"The primary analysis was an intention-to-treat analysis including all participants who were randomized and received medication. As in other studies of smoking cessation studies participants who dropped out were regarded as treatment failures. " Efficacy outcomes of CAR and PPA at 12 and 24 months were extracted. All randomized participants received assigned treatment and were included in the analysis. Less than 80% (76% at 4 months and 72% at 24 months) of participants in placebo inhaler group completed the 12-month assessment, compared to those (greater than 83%) in nicotine inhaler group. By definition of smokers, the more dropouts in placebo group would lead to more abstainers in that group, which would probably bias the outcome estimate. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	One safety outcome, SAE, was extracted, and three – mortality, cardiovascular mortality and completed suicide were inferred 0. The statistical strategy for safety outcome data was not provided. Judged a high risk of bias given the dropout rate in placebo group was higher.

Study code: Bolliger 2007 - 196

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects were then randomly allocated (block randomization of 4, i.e. after each block of 4 subjects, 2 were allocated to the spray, 1 to the gum and 1 to the inhaler) to the mouth spray (n = 50), the gum (n = 25) and the inhaler (n = 25) group, irrespective of their preference." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned and probably not feasible in this study due to the different forms of nicotine products. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, judged a high risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted or ineffective.
Incomplete outcome data addressed – for efficacy outcomes?	High	"The main analysis was done at 6 months, the time of the last physical visit which included a CO measurement ….Patients not attending a visit were considered dropouts and treatment failures." Efficacy outcomes of CAR and PPA at 6 months were extracted. All randomized participants received assigned treatment and were included in the analysis. 46% (23/50), 52% (13/25) and 48% (12/25) of participants in mouth spray, gum and inhaler group completed the 6-month assessment, respectively. Judged a high risk of bias given the completion rate in each group was low, the information about early discontinuations and the approach to handling missing data were not provided.
Incomplete outcome data addressed – for safety outcomes?	High	All four safety outcomes, SAE, mortality, cardiovascular mortality and completed suicide were inferred 0. The statistical strategy for safety outcome data was not provided. Judged a high risk of bias given the low completion rates in each group.

Study code: Bolliger 2011 -465

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Using a block randomization within each site, eligible participants were randomly assigned in a 2:1 ratio to receive varenicline or placebo." Method for sequence generation was not provided.
Allocation concealment?	Low	"Identification numbers and study treatments were assigned to participants at the screening visit using a Web-based or telephone call-in drug management system directed by the sponsor." A central randomization was adopted and the allocation numbers should be concealed.
Blinding of objective outcomes' assessment?	Low	"Active drug and placebo (provided as matching tablets) were orally administered with water." "All of the study personnel and participants were blinded to treatment assignment until the end of the non treatment follow- up phase."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"All of the primary and secondary end points were analyzed in the full-analysis population, defined as participants who took at least 1 dose, including a partial dose, of study medication." "Participants who discontinued from the study and were lost to follow-up for subsequent visits were assumed to be smokers for the remainder of the study. In binary responder assessments, subjects who discontinued were represented in the denominator but not in the numerator, regardless of smoking status at the time of discontinuation, which might be considered a worst-case-carried-forward analysis and represents a conservative approach to the imputation of missing data." Efficacy outcomes of CAR and PPA at 6 months were extracted. All randomized participants were included in the analysis, except for 4 and 1 in varenicline and placebo group not receiving any treatment, respectively. 85% (336/394) in the varenicline group and 78% (156/199) in the placebo group completed the study. Judged a low risk of bias given that the overall completion rate (83%) and the completion rate in varenicline group were higher than 80%, and the numbers and reasons of early discontinuation seemed parallel in two groups.

Incomplete outcome data addressed – for safety outcomes?	Low	Six safety outcomes, including SAE, mortality, cardiovascular mortality, aggression, suicidal ideation and completed suicide were extracted. As above, judged a low risk of bias.

Study code: British Thoracic Society 1983-595

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"…patients were allocated at random to one of four "treatment" groups…" Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for sequence generation was not provided.
Blinding of objective outcomes' assessment?	Low	"Placebo and nicotine gums were indistinguishable in appearance and taste, and neither the physician not the patient knew which gum had been issued."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Efficacy outcomes of PPA at 6 and 12 months were extracted. Not all randomized participants were included in the analysis, with 60 early discontinuing from the study. 94% (371/395), 94% (377/401), 98% (402/412) and 98% (400/410) of participants in [VA], [VA + Booklet], [VA + Booklet + Placebo gum] and [VA + Booklet + Nicotine gum] completed the 12-month assessment. Judged a low risk of bias given the high completion rates across the arms. .
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome, mortality, was extracted and one, SAE, inferred 0. As above, judged a low risk of bias.

Study code: Bullen 2010-1474

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"People giving verbal consent by telephone were allocated randomly using central computerized randomization, with the randomization sequence concealed until interventions were assigned. We used stratified minimization by ethnicity (Māori versus non-Māori), sex and level of nicotine dependence (as determined by the time to their first cigarette, a key question in the Fagerström Test of Nicotine Dependence to ensure a balance in these characteristics between the study groups. "
Allocation concealment?	Low	"…were allocated randomly using central computerized randomization, with the randomization sequence concealed until interventions were assigned."
Blinding of objective outcomes' assessment?	Low	"Participants were aware of the group to which they were allocated but 3- and 6-month follow-up methods were identical for all participants, and all follow-up telephone calls and outcome verification procedures were made by research assistants blind to treatment allocation." Participants were not blinded but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' knowledge of the allocated interventions after assignment.
Incomplete outcome data addressed – for efficacy outcomes?	High	"… according to a pre-specified plan on an intention-to-treat (ITT) basis, with missing smoking status at 3 and 6 months treated as smoking. Sensitivity analyses were carried out to assess the potential impact of missing data…" Efficacy outcome of PPA at 6 months was extracted. All randomized participants were included in the analysis. 73% (401/549) and 75% (412/551) participants in the pre-cessation NRT and the no-treatment group completed the 6-month study, respectively. Judged a high risk of bias given that the completion rates were below 80% and that the reasons of early discontinuation were partly reported. In addition, the sensitivity analyses to assess the potential impact of missing data were conducted for the self-reported abstinence but not for the bio-chemically verified abstinence.
Incomplete outcome data addressed – for safety outcomes?	High	Three safety outcomes, SAE, CV events and mortality, were extracted. As above, judged a high risk of bias.

Study code: Campbell 1991 - 155

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Before they left hospital, those who had agreed were given packages of identical appearance randomly containing either nicotine (2 mg) or placebo gum. " Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"…had agreed were given packages of identical appearance…"
Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained by indistinguishable product package.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Success was defined as verified non-smoking at 6 and 12 months with claimed non-smoking between these times. Non-attenders were classified as failures. " Efficacy outcome of PAR at 12 months (from months 6 to 12) was extracted. All randomized participants were included in the analysis, except for seven patients who "were not evaluable because of emigration, death or development of terminal cancer." All the remaining 212 seemed to complete the 12-month assessment. Judged a low risk of bias given the high overall completion rate of 97% (212/219).
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome, SAE, was inferred 0. As above, judged a low risk of bias given the high overall completion rate.

Study code: Campbell 1996 - 47

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"In a double-blind, placebo-controlled, randomized manner, 234 inpatients and outpatients with smoking related respiratory or cardiovascular disease… " Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding approach was not provided but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not ineffective.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Patients who had been classed as smokers at 12 weeks were not followed-up." "A total of 113 patients (57 TNS, 56P) did not complete 12 weeks in the study, 21 (14 TNS, 7P) because of adverse events, and 92 (43 TNS, 49P) who failed to attend for failed to attend for follow-up by this stage. " Efficacy outcome of PAR at 12 months (from months 3 to 12) was extracted. All randomized participants were included in the analysis. 50% (58/115) in nicotine patch group and 42% (50/119) in placebo patch group completed the 12-week follow-up assessment. The completion rates would be expectedly lower in 1-year assessment. Judged a high risk of bias given that the completion rates were far below 80% and that the reasons of early discontinuation were partly reported.
Incomplete outcome data addressed – for safety outcomes?	High	All four safety outcomes, including SAE, mortality, CV mortality and completed suicide were extracted. As above, judged a high risk of bias given the low completion rates.

Study code: Cinciripini 1996 - 314

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Sixty-four participants met all screening criteria and were randomly assigned to two groups: BT alone (n = 32) and BT plus the nicotine patch (BTP; n = 32), balancing for the smoker's screening level of cotinine. " Method for sequence generation was not provided.
Allocation concealment?	Unclear	As above, method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned. This study was very likely to be an open-label study because the intervention provided in two comparison groups were different and easy to recognize. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes were likely to be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Efficacy outcomes of PPA at 6 and 12 were extracted. All randomized participants were included in the analysis and there seemed to be no participant early discontinuing from the study. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Cooney 2009 - 1588

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	" Participants were randomized to study treatments using an urn randomization computer program that balanced the two groups for history of previous substance use treatment, age, sex, baseline drinks/drinking day, and baseline cigarettes/day."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Gum was dispensed under double blind conditions." "Nicotine gum (2 mg uncoated mint Nicorette ®) or placebo gum was given for ad libitum use, with encouragement to use at least six pieces per day, up to a maximum of twenty pieces per day. The placebo gum (manufactured by Fertin Pharma A/S, Vejle, Denmark) contained 2.6% cayenne pepper to simulate the taste of nicotine." "Eighty percent responded "don't know" and the remaining 20 percent correctly guessed the gum contents only 50 percent of the time."
Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained and tested in the end of study. Judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"All participants randomized to treatment and provided nicotine replacement medications were considered part of an intent-to-treat sample, and were followed regardless of their retention in treatment." "…participants with missing data at each time point were coded as smokers." "The average retention across groups for the prolonged CO-verified smoking abstinence outcome measure was 100% at 2 weeks, 91% at 3 months, 82% at 6 months, and 72% at 12 months. There were no between-treatment differences in percent of participants retained over the follow-up periods (all *p*'s > .05). In spite of follow-up attrition, we were able to determine time to smoking relapse for 100% of the sample because all of the attrition occurred after smoking relapse was reported." Efficacy outcome of PAR at 6 and 12 months (from months 2 to 6 and 12) were extracted. All randomized participants were included in the analysis. Although the 12-month overall completion rate was less than 80%, the early discontinuations would probably not bias the outcome estimate given that all of the attrition (in two arms) occurred after smoking relapse was reported.
Incomplete outcome data addressed – for safety outcomes?	High	All four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. Judged a high risk of bias given the overall completion rate was below 80% and the approach to handling missing safety data was not provided.

Study code: Cooper 2005 – 61

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Eligible women were randomized to either the PPA, the nicotine, or the placebo gum group and participated in a 13-week cognitive–behavioral smoking cessation program." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"All group facilitators and participants were blind to treatment conditions." Blinding approach was not provided. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences regardless of the quality of the blinding approach.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not ineffective.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Two of three arms were extracted with the efficacy outcomes of PPA at 6 and 12 months. All randomized participants in nicotine gum and placebo gum group completed the 12-month assessment and were included in the analysis and. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety data of interest was extracted or inferred.

Study code: Cox 2012-290

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"A computer-generated table of random numbers was used to randomly assign 540 eligible participants into the bupropion SR (n = 270 participants) or placebo (n = 270 participants) groups…"
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Study staff and participants were blinded to treatment condition." "Of the 540 participants, 270 participants randomized to the bupropion SR treatment group received 300 mg bupropion per day (150 mg once daily for 3 days and then 150 mg twice daily) and 270 participants in the placebo group received matching placebo pills."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"…at all three time points (weeks 3, 7, and 26), we used the x^2 test to compare self-reported 7-day abstinence, imputing missing participants as smokers." One abstinence outcome, PPA at 6 months was extracted. All randomized participants were included in the analysis. 71% (192/270) and 69% (187/270) participants in Bupropion SR and placebo group completed the study, respectively. Judged a high risk of bias given that the completion rates were below 80% and the reasons of early discontinuation were not provided.
Incomplete outcome data addressed – for safety outcomes?	High	One safety outcome, SAE, was extracted, while three safety outcomes, including, mortality, CV mortality and completed suicide were inferred 0. As above, judged a high risk of bias given the overall completion rate was below 80% and the approach to handling missing safety data was not provided.

Study code: Croghan 2003-181

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Treatment assignment was carried out using a dynamic allocation procedure that balanced the marginal distributions of the stratification factors among the three treatment groups. Stratification factors used were gender, the number of cigarettes smoked per day reported at time of study entry (15–39 vs. 40 or more cigarettes per day), and total years of smoking (fewer than 5 years vs. 5–9 years vs. 10 or more years)."
Allocation concealment?	Low	As above, judged a low risk of bias. .
Blinding of objective outcomes' assessment?	Low	"This multicenter, randomized, open-label clinical trial..." An open-label trial, but judged a low risk of bias judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above. Judged a high risk of bias given that those subjective outcomes' assessment were likely to be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"If a visit was missed, the participant was classified as a smoker for that visit in an intent-to-treat fashion. Similarly, participants lost to follow-up were classified as smokers. This produced conservative estimates of smoking abstinence." "A subtotal of 738 subjects completed the main components of the trial (53% at 6 weeks), and 30% of participants completed the protocol through to the 6-month evaluation;" One abstinence outcome, PPA at 6 months was extracted. All randomized participants were included in the analysis. However, far less than 80% of the randomized participants completed this 6-month study. Judged a high risk of bias.

Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including, SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a high risk of bias given the overall completion rate was far below 80%.

Study code: Dalsgarð 2004 - 55

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"The randomization procedure was computer generated and blinded."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Participants then received identical prefabricated and prenumbered tablets containing either bupropion 150mg or placebo, and all participants were instructed to start taking one tablet daily for the first 3 days and then twice daily for a total of 7 weeks."
Blinding of subjective outcomes' assessment?	Low	As above. Judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"We used an intent-to-treat analysis, in which all randomized patients who took at least one dose of study medication were counted. " Two abstinence outcomes, PPA and CAR at 6 month were extracted. All randomized participants were included in the analysis, except one in bupropion not taking any medication. 67% (148/222) and 56% (64/114) of participants in bupropion and placebo group completed the 6-month assessment. Judged a high risk of bias given that the completion rates were far below than 80%.
Incomplete outcome data addressed – for safety outcomes?	High	One safety outcome, death, was extracted, while SAE was inferred 0. As above, judged a high risk of bias given the overall completion rates were far below 80%.

Study code: Daughton 1991 - 749

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"All 158 study-eligible volunteers were randomly assigned to one of the following three double-blinded treatment regimens..." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The patches to be removed at bedtime were stamped "Remove at Bedtime. All of the patches were physically identical in appearance. The placebo patches included the TTS delivery system without nicotine, and the patches that contained nicotine were identical for the wakeful and 24-hour treatment applications..."
Blinding of subjective outcomes' assessment?	Low	As above. Judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"Only four patients (two receiving an active drug and two receiving placebo) withdrew from the study due to adverse events." One abstinence outcomes, PPA and at 6 month was extracted. All randomized participants were included in the analysis. Judged an unclear risk of bias given the following reasons: 1. Detailed information about the early discontinuations was not reported 2. The brief smoking cessation counseling approaches provided in Site A and B were different, which would potentially have different interactions with the nicotine/placebo patch. 3. Participants' self-reported abstinence was verified in Site A but not in Site B. Further description of the different assessment approaches in two sites was not found.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Four safety outcomes, including, SAE, mortality, CV mortality and completed suicide were inferred 0. As above reasons 1 and 2, judged an unclear risk of bias

Study code: Daughton 1998 - 425

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"To help ensure that an approximately equal number of participants could be assigned to the 2 treatment regimens at each site, a random code was generated so that an equal number of active and placebo patches would be contained in each block of 10 participants." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"This was a double-blind, placebo-controlled, parallel group study." Blinding approach was not provided. However, judged as a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even when the blinding approach was not appropriate.
Blinding of subjective outcomes' assessment?	Unclear	As above, judged as an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not effectively conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"The efficacy data were analyzed based on intent-to-treat, with participants who were unavailable for or lost to follow-up categorized as smokers. " Two abstinence outcomes, CAR at 6 and 12 months were extracted. All randomized participants were included in the analysis and seemed to be followed up at 12 months. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Davidson 1998 - 569

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Eligible individuals were assigned to receive either nicotine patches or placebo patches according to a computer generated randomization schedule provided by Pharmaco LSR, Austin, Tex, before initiation of the study."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The study was conducted as a multicenter trial using a double-blind, randomized, placebo-controlled, parallel group design." Blinding approach was not provided. However, judged as a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even when the blinding approach was not appropriate.
Blinding of subjective outcomes' assessment?	Unclear	As above, judged as an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not effectively conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interest was extracted.
Incomplete outcome data addressed – for safety outcomes?	High	"The primary safety variable was the comparison of participant-reported adverse events between the 2 treatment groups." "Of the 802 participants randomized into the study, 541 (67.5%) withdrew before the study was completed." Four safety outcomes of interest, including SAE, mortality, CV mortality and completed suicide were inferred 0. Judged a high risk of bias given the total completion rate, 32.5%, was far less below 80%.

Study code: de Dios 2012-322

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"A 3-group (NRT, varenicline, and varenicline-placebo) randomized design was used." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The varenicline-placebo control condition conswasted of 12 weeks of identical placebo tablets (prepared by contracted research pharmacy). The participants followed the identical dosing and visit schedule to the active varenicline group. Study personnel and participants in the two-pill groups (varenicline and varenicline-placebo) were blinded to treatment condition. The research pharmacy maintained the study blind."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	One efficacy outcome, PPA at 6 months was extracted. All randomized participants were included in the analysis. 82% (9/11), 70% (7/10) and 64% (7/11) in nicotine patch, varenicline, and varenicline placebo group completed the 6 months assessment. Judged a high risk of bias given the completion rates were marginal to 80% and the total sample size was small.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Ewasenberg 2013-524

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Eligible, consenting patients who met the inclusion and exclusion criteria (Online Table 2) were randomized at least 24 h before discharge in a 1:1 ratio to receive bupropion sustained-release or placebo. Randomization was done via an internet website using random blocks of 2 and 4 and was stratified by center to ensure that similar numbers of patients were randomized to the 2 arms of the study at each study center."
Allocation concealment?	Low	Central randomization.
Blinding of objective outcomes' assessment?	Low	"Patients in the placebo group received a matching placebo administered with the same schedule." "All clinical end points were adjudicated by members of the Endpoints Evaluation Committee who were blinded to treatment assignment (Online Table 5)."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"The primary end point was analyzed on an intention-to-treat (ITT) basis. Because loss to follow-up rates >30% were not unusual in smoking cessation trials, our ITT analysis assumed that those who withdrew consent or were lost to follow-up had returned to smoking at their baseline rates." "For safety analyses, patients who withdrew from the study, were lost to follow-up, or died were accounted for by censoring at the time of death or at the last follow-up contact." Four abstinence outcomes, CAR and PPA at each of 6 and 12 months were extracted. All randomized participants were included in the analysis, except that 9 in bupropion SR group and 6 in placebo group died in the study period. Four abstinence outcomes and three safety outcomes were reported. 71% (136/192) and 80% (159/200) participants in bupropion SR and placebo group completed the study, respectively. Judged a high risk of bias given that the overall completion rate and completion rate in active treatment group were less than 80% and the approach to handling missing data would probably bias the outcome estimates.
Incomplete outcome data addressed – for safety outcomes?	High	Three safety outcomes, SAE, mortality and CV event were extracted. As above, judged a high risk of bias given that the less-than-80% completion rate and the lack of an approach to handling missing data for safety outcomes.

Study code: Etter 2002-487

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Randomization was based on a computer-generated list of random numbers."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Participants in the placebo group could choose among matching placebo patches, gums, and inhalers (Pharmacia). Participants in the nicotine and placebo groups could switch between products or use several products at the same time."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interest was extracted.
Incomplete outcome data addressed – for safety outcomes?	Low	Three safety outcomes, mortality, CV mortality and completed suicide were extracted. No statistical strategy for safety outcome was provided. All randomized participants were included in the analysis. 97% (258/265), 97% (261/269) and 92% (360/389) of the participants in nicotine, placebo and no-treatment group completed the 6-month assessment. Judged a low risk of bias given that the completion rates were high across the arms, the missing data won't probably bias the safety outcome estimate.

Study code: Etter 2009-1028

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Randomization was based on a list of random numbers generated by a computer."
Allocation concealment?	Unclear	Method for allocation concealment is not provided.
Blinding of objective outcomes' assessment?	Low	"An open, randomized trial…" Judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Participants who did not return the saliva sample or did not come for the carbon monoxide test were considered smokers." One abstinence outcome, PPA at 6 months was extracted. 89% (137/154) in the varenicline group and 88% (140/164) in the placebo group completed the study. Judged a low risk of bias given that the completion rates are high and the numbers and reasons of early discontinuations in 2 groups seem comparable and would not bias the outcome estimates.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome, death, was extracted from the flowchart of study participants (Figure). As above, judged a low risk of bias

Study code: Evins 2001-397 and Evins 2004-307

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects were randomly assigned to 12 weeks of double-blind bupropion SR, 150 mg/day, or an identical appearing placebo tablet added to their usual medication regimen." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Glaxo Wellcome Inc. provided Bupropion HCl sustained release and identical placebo tablets."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Three abstinence outcomes, PPA at 6 months and 2 years and PAR from 4 weeks through 6 months were extracted. All randomized participants were included in the analysis, except for one not receiving any medication. 95% (18/19) among 19 participants who have been routinely treated in a community mental health center for schizophrenia should be closely follow up throughout the study. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Evins 2005-218

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects were randomly assigned to receive bupropion SR 150 mg or identical placebo tablets." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Subjects were randomly assigned to receive bupropion SR 150 mg or identical placebo tablets."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Subjects who received at least 1 week of study medication and were lost to follow-up were included in the analysis as smokers." One abstinence outcome, PPA at 6 months was extracted. All randomized participants were included in the analysis, except for three not receiving any medication. 93% (53/57) of participants who have been routinely treated in five community mental health centers for schizophrenia should be closely follow up throughout the study. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	Two safety outcomes (SAE and suicidal ideation) were extracted and three (mortality, CV mortality and completed suicide) inferred 0. As above, judged a low risk of bias given the high overall completion rate and close follow-up method.

Study code: Evins 2007-380

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Participants were randomly assigned to receive bupropion SR 150 mg or placebo, once daily for 7 days, then twice daily for 11 weeks." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Assessment of the blind by participants and group leaders was collected at Week 12…. Participants and investigators remained blind to the treatment condition (bupropion or placebo) throughout the follow-up period." "GlaxoSmithKline provided sustained release bupropion and identical placebo."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Dropouts were considered smokers for analyses of binary outcomes. As no subjects met criteria for significant reduction at the time of dropout, the potential for bias with this method of handling missing data in this study was low." "Five of 25 subjects in the bupropion group and 8 of 26 on placebo dropped out before Week 12; all were smoking at their baseline level at the time of dropout." Four abstinence outcomes, PPA and CAR at 6 and 12 months, were extracted respectively. All randomized participants were included in the analysis. 80% (20/25) and 69% (18/26) of the participants in "Bupropion SR + Nicotine patch + Nicotine gum + CBT" and "Placebo + Nicotine patch + Nicotine gum + CBT" completed the 12-month follow-up assessment. Although the completion rate in the latter group was lower than 80%, the justification for the approach to handling missing data seemed to lessen the risk of bias for efficacy outcomes. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Two safety outcomes (SAE and CV event) were extracted and three (mortality, CV mortality and completed suicide) inferred 0. Judged a high risk of bias given lower-than-80% completion rate in one arm and the approach to handling missing data for safety outcomes was not provided.

Study code: Fagerstrom 1982 - 343

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The patients were randomly assigned to the experimental (nicotine chewing gum and psychological treatment) or control (placebo gum and psychological treatment) groups in blocks of 10." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"All patients were told that the chewing gum they received contained nicotine, a necessary instruction to ensure motivation to chew the gum, especially for the placebo patients, …" "The patients were given chewing gum from the first session. The nicotine and placebo gums were similarly packaged and the placebo was flavored to resemble the nicotine gum…. The double-blind code was broken by the author when the patients had ceased using the chewing gum, but never before 3 months of abstinence."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"Four patients who attended the clinic only for the information session were not included in the data analysis. Three should have belonged to the experimental group and one to the control group." "A few smokers discontinued chewing gum treatment because of gastric problems." One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in the analysis except for three in experimental group and one in placebo group not receiving any medication. No further information about the early discontinuations and statistical strategy for missing data. Judged an unclear risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Unclear	One safety outcome (SAE) was extracted and three (mortality, CV mortality and completed suicide) inferred 0. As above, judged an unclear risk of bias.

Study code: Fiore 1994 – 524-S1

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Once deemed eligible, subjects provided informed consent. Subjects were randomly assigned to active and placebo groups, stratified by their Fagerstrom Tolerance Questionnaire (high ≥ 7, low ≤ 6), according to a pregenerated computer sequence to prevent confounding based on Fagerstrom score. No effort was made to recruit equal numbers of high- or low-dependence subjects.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Two independent randomized placebo controlled double-blind trials." Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences.
Blinding of subjective outcomes' assessment?	Unclear	As above, judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions if the blinding approach was not appropriate.
Incomplete outcome data addressed – for efficacy outcomes?	High	"End of treatment and 6-month nicotine patch efficacy analyses were based on intent to treat." "Of the 87 study subjects (one was disqualified prior to unblinding because of nicotine gum use), 62 were interviewed at the 6-month follow-up mark. Forty-two of these subjects attended an in-person follow-up visit where CO and a serum nicotine/cotinine sample were obtained; 20 declined to attend the in-person visit and were interviewed over the phone. The 25 subjects who were not interviewed were all classified as smokers for analytic purposes. " One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in the analysis except for one in placebo group misusing nicotine gum and being excluded. Overall, 48% (42/88) completed the 6-month assessment. Judged a high risk of bias given that the overall completion rate was less than 80% and the information of the early discontinuations by groups was not provided.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were inferred 0. As above, judged a high risk of bias.

Study code: Fiore 1994 – 524-S2

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Once deemed eligible, subjects provided informed consent. Subjects were randomly assigned to active and placebo groups, stratified by their Fagerstrom Tolerance Questionnaire (high ≥ 7, low ≤ 6), according to a pregenerated computer sequence to prevent confounding based on Fagerstrom score. No effort was made to recruit equal numbers of high- or low-dependence subjects. "
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Two independent randomized placebo controlled double-blind trials." Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences.
Blinding of subjective outcomes' assessment?	Unclear	As above, judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions if the blinding approach was not appropriate.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Of the 1 12 subjects who participated in this study, 72 were interviewed at the 6-month follow-up mark. Fifty-two of these subjects attended an in-person follow-up visit where CO, and a blood nicotine/cotinine assay were performed; 20 declined to attend the in-person visit and were interviewed over the phone. Of these 20, 18 reported that they were smoking. Two of the 20 (one active, one placebo) reported that they were abstinent but refused biochemical confirmation and were classified as smokers for analytic purposes. The 40 who were not interviewed were classified as smokers for analytic purposes; " One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in the analysis. Overall, 46% (52/112) completed the 6-month assessment. Judged a high risk of bias given that the overall completion rate was less than 80% and the information of the early dwascontinuations by groups was not provided.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were inferred 0. As above, judged a high risk of bias.

Study code: Fortman 1995 - 460

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No method of sequence generation was provided.
Allocation concealment?	Unclear	Method of allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"…Those below 9 ppm were randomized to one of 4 treatment conditions in a 2x2 factorial design." Low risk of bias due to robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Unclear	No further methods of randomization were explained. Unclear as to the level of risk for bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Of the 1044 randomized participants, 1003 (96.1%) and 979 (93.8%) completed the 6 and 12 month telephone interviews, respectively." High completion rate of over 80% and a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcomes were extracted or inferred.

Study code: Fossati 2007-1791

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"… GP assigned them a randomization code. They then received, in a 2:1 ratio, either a sustained-release form of bupropion hydrochloride at a dosage of 150 mg/d for 6 days followed by 150 mg twice a day for 7 weeks, or placebo (hereinafter, bupropion group and placebo group, respectively). The 2:1 ratio was chosen to encourage participants' acceptance of the random assignment to treatments." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The drug and the placebo were made and packaged by GlaxoSmithKline (Research Triangle Park, North Carolina), and all the tablets were identical in appearance." "Sixty-four percent (255 of 400) of subjects correctly guessed that they had received bupropion, and 44% (85 of 193) of subjects correctly guessed they had received placebo."

Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"Participants who withdrew from the study were assumed to be smokers as of the date of the skipped scheduled visit." "The percentages of subjects presenting at visits 2, 3, 4, and 5 were 89%, 87%, 84%, and 85%, respectively, in the placebo group and 92%, 91%, 84%, and 83%, respectively, in the bupropion group (P=.14). Twenty-eight percent of the patients discontinued treatment in the placebo group vs 30% in the bupropion group (P=.63). These similar percentages were the result of adverse events in 26% of the placebo group and in 46% of the bupropion group (P=.02). " Three abstinence outcomes, CAR at 12 months and PPA at 6 and 12 months, were extracted. All randomized participants were included in the analysis. Although more than 80% of randomized participants in two arms presented at the 12-month visit and probably all took the assessment, 28% in the placebo group and 30% early discontinued from the study. With the limited information, judged an unclear risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Two safety outcomes, SAE and CV events, were extracted; with three, mortality, CV mortality and completed suicide, being inferred 0. As above, judged an unclear risk of bias.

Study code: Gallagher2007-487

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Participants were randomly assigned to one of the three groups (CR, CR+NRf, self-quit)…" Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Due to the nature of the intervention groups, research staff were not blind to treatment condition. Ideally, those assessing outcomes should be blind to study condition but because staff delivered immediate reinforcement based on CO outcomes, this was not possible." An open-label trial but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Intention-to-Treat (ITT) analyses were conducted wherein data from the last observation of participants lost to follow-up were used. In the two active treatment conditions, that meant available data from the last observation. In the case of the self-quit control group (who had only three visits), this meant baseline data was substituted in week 20 analyses and week 20 data (where available) was substituted for missing week 36 data; otherwwase baseline data was used." "At week 20 and 36 respectively, the CR group lost 37% and 43% of participants, the CR+NRT group lost 35% and 36%, while the self-quit comparison group lost 52% by both follow-up points." One abstinence outcome, PPA at 36 weeks, was extracted and regarded as PPA at 6 months. All randomized participants were included in the analysis. However, the completion rates were less than 80% of randomized participants across three arms and the approach to handling missing data was not appropriate. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Garvey 2000-53+ Kinnunen 2008-373

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects within each level of dependence were then randomly assigned to placebo, 2-mg, or 4-mg nicotine gum treatment." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Subjects within each dependence subgroup were assigned to placebo, 2-mg, or 4-mg gum treatment using a randomized, double-blind procedure." Blinding approach was not provided but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Subjects for whom follow-up information was lacking were classified as relapsers; i.e., an intent-to-treat analysis was used. Self-reports of abstinence were considered valid if they were confirmed by CO values of 8 ppm or less." "Participants who withdrew from the study were assumed to be smokers as of the date of the skipped scheduled visit." "The percentages of subjects presenting at visits 2, 3, 4, and 5 were 89%, 87%, 84%, and 85%, respectively, in the placebo group and 92%, 91%, 84%, and 83%, respectively, in the bupropion group (P=.14). Twenty-eight percent of the patients discontinued treatment in the placebo group vs 30% in the bupropion group (P=.63). These similar percentages were the result of adverse events in 26% of the placebo group and in 46% of the bupropion group (P=.02). " Two abstinence outcomes, PPA and CAR at 12 months, were extracted. All randomized participants were included in the analysis. There seemed to be only three participants withdrawing from the study because of adverse events and all the rest completed the study. It was judged a low risk of bias given the high overall completion rate at 95.5% (605/608).
Incomplete outcome data addressed – for safety outcomes?	Low	Two safety outcomes, SAE and CV events, were extracted; with three, mortality, CV mortality and completed suicide, being inferred 0. As above, judged a low risk of bias.

Study code: George 2002 - 53

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Eligible subjects (n=32) were randomly assigned to either bupropion (BUP, 300 mg/day; 150 mg p.o. b.i.d.) or matching placebo (PLA)." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Both subjects and research staff were blinded to study medication assignment. Study medications were prepared by research pharmacists at CMHC, using encapsulation of SR bupropion tablets with blue 00 opaque capsules; placebo capsules contained only a dextrose matrix"
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"For determination of smoking abstinence rates, an "intention-to-treat" analysis was used. Subjects who were lost during the trial or at 6-month follow-up were counted as smokers." One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in the analysis. There seemed to be no participant early discontinuing from the study given that the participants were closely followed up in an outpatient center. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a low risk of bias.

Study code: George 2008 - 1092

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Fifty-nine subjects were randomized." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Bupropion SR 150-mg tablets (Zyban; GlaxoSmithKline, Research Triangle Park, North Carolina) and Nicoderm CQ TNP (21 mg/24 hours; GlaxoSmithKline) were obtained from commercial suppliers. BUP study medications were prepared using blue 00 opaque capsules, and matching placebo capsules contained only a dextrose matrix."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Fifty-nine subjects were randomized. Fifty-eight subjects received at least one dose of the study medication; therefore, data from 58 randomized smokers with schizophrenia who received study medication were reported as the intention-to-treat sample. Twenty-three of 29 subjects in the BUP+TNP group and 19 of 29 subjects in the PLO+TNP group completed the trial." One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in the analysis, except for one not taking any medications. 79% (23/29) in [bupropion + nicotine patch] and 66% (19/29) in [placebo + nicotine patch] group completed the study. Judged a high risk of bias given that the completions rate were less than 80% and that the information about the early discontinuations and the approach to handling missing data were not provided.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a high risk of bias.

Study code: Gifford 2004 - 689

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	Randomization is mentioned but the approach used is not described.
Allocation concealment?	Unclear	No mention of allocation concealment or the approach used.
Blinding of objective outcomes' assessment?	Low	No mention of blinding but the abstinence outcomes assessed in this study are biochemically verified.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	NRT Group: 35/43 (81.4%) ACT Group: 20/33 (60.6%) Overall: 55/76 (72.4%) "Although there wasmore attrition from the ACT condition, attrition at 1 year was not significantly related to condition, X2(76) = 4.04, p = .07. In addition, there was no relationship between assessment attrition and primary or secondary outcome variables, indicating that smoking status and treatment process were not related to study attrition." As for dealing with missing data, the authors write, " Of the original 76 participants, 6 participants had missing data at all three time points (postmeasurement; 6 months; and 12 months). Because the GEE develops its estimates from previous data (implicit imputation), the missing data analyses were conducted on 70 participants." This overall judgment however is that it remains unclear why the overall completion is below 80% and that the difference in attrition between both groups is quite large.

Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcomes of interest were assessed as part of this study.

Study code: **Gilbert 1989-49**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Each physician's patients were randomized to either the support group or the support-plus-gum group, with the restriction that allocation was balanced within each block of four patients for each physician." No mention of the method used for sequence generation.
Allocation concealment?	Low	"After obtaining informed consent from patients, physicians were presented with a sealed envelope indicating treatment allocation by the receptionist."
Blinding of objective outcomes' assessment?	Low	No mention of blinding but the abstinence outcomes assessed in this study are biochemically verified.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"At the one-year validation, 11 patients in the support group and eight patients in the support-plus-gum group were not located, giving a follow-up rate of 91.5 percent. Patients not located were considered to be smokers for the purpose of analysis."
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcomes of interest were assessed as part of this study.

Study code: **Glavas 2003 - 219**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No mention of the method used for sequence generation.
Allocation concealment?	Low	"Each examinee received a pre-sealed envelope, labeled after random numbering, which contained either 8 transdermal nicotine system patches or matching placebo stickers."
Blinding of objective outcomes' assessment?	Low	Matching placebos were used. The outcomes assessed are biochemically verified.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 107/112 (95.5%) Nicotine patch group: 54/56 (96.4%) Placebo group: 53/56 (94.6%)
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcomes of interest were assessed as part of this study.

Study code: **Glover 2002 - 441**

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"At baseline (day before quit date, visit 4), subjects were sequentially randomized to receive either active or placebo treatment according to a computer-generated randomization code."
Allocation concealment?	Unclear	No mention of allocation concealment.
Blinding of objective outcomes' assessment?	Low	"All tablets were identical in appearance (round, flat, bevel-edged, 6mm in diameter). […] Each placebo tablet contained 3 mg of capsaicin to mimic the oral effects of nicotine and to maintain blinding. All tablets were packed in press through packages (blister strips) that contained

		15 tablets." The abstinent outcomes were both biochemically verified and the safety outcomes included cardiovascular events that were objectively defined.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 241/241 Active sublingual tablet: 120/120 Placebo: 121/121
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 241/241 Active sublingual tablet: 120/120 Placebo: 121/121

Study code: **Goldstein 1989-56**

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Unclear	No mention of the method used for sequence generation.
Allocation concealment?	Unclear	No mention of the method used for allocation concealment.
Blinding of objective outcomes' assessment?	Low	The abstinent outcome was biochemically verified
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.

Incomplete outcome data addressed – for efficacy outcomes?	Low	Across all groups, all patients (100%) were included in the final follow-up assessment for efficacy.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcomes of interest were assessed as part of this study.

Study code: **Gonzales 2001 - 438**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	Method used for sequence generation was not described.
Allocation concealment?	Unclear	"Eligible participants were assigned a protocol-specific treatment number on the basis of a randomization code provided by GlaxoWellcome."
Blinding of objective outcomes' assessment?	Low	The abstinent outcomes were both biochemically verified. Additionally, the safety outcomes are objectively defined.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 1025/1025 Varenicline: 352/352 Bupropion: 329/329 Placebo: 344/344
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 1022/1025 Varenicline: 349/352 Bupropion: 329/329 Placebo: 344/344

Study code: Gonzales 2006 - 47

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"A predefined, central computer-generated randomization sequence assigned participants in a 1:1:1 ratio…in blocks of 6…" Sufficient methods of sequence generation and a low risk of bias.
Allocation concealment?	Unclear	Method of allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"…A randomized, multicenter, double-blind, parallel-group, placebo and active-treatment-controlled." Judged to be a low risk of bias.
Blinding of subjective outcomes' assessment?	Low	As above, low risk of bias.

Incomplete outcome data addressed – for efficacy outcomes?	High	"Efficacy data and intent-to-treat analysis…" Completion rate of 213/352 (60.5%), 184/329 (55.9%), and 187/344 (54.4%). High risk of bias with low completion rates.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes of Deaths, SAE, CV deaths, and CV events were reported from the study. High risk of bias as a result of low completion rates.

Study code: Gourlay 1995 - 363

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Low	"A predefined, central, computer generated randomization sequence assigned participants in a 1:1:1 ratio to receive varenicline, bupropion SR, or placebo using a block size of 6, and was stratified by center."
Allocation concealment?	Low	Randomization was centralized.
Blinding of objective outcomes' assessment?	Low	"Participants were randomly assigned to receive active drug or matching placebo administered orally for 12 weeks. […] Participants and investigators were blinded to drug treatment assignments." The abstinent outcomes were both biochemically verified. Additionally, the safety outcomes are objectively defined.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.

Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 629/629 Nicotine patch: 315/315 Placebo: 314/314
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 629/629 Nicotine patch: 315/315 Placebo: 314/314

Study code: Grant 2007 - 381

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Unclear	No method of sequence generation was provided.
Allocation concealment?	Unclear	Method of allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Participants were randomized in a double'blind manner…the control group received identical placebo capsules and was instructed to follow the same medication regimen. Low risk of bias for objective outcomes.
Blinding of subjective outcomes' assessment?	Low	As above, sufficient blinding of placebo vs. medication for Bupropion. Low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	Follow up rates at 6 months follow up was 75%, below 80% completion rate. Judged as a high risk of bias.

Incomplete outcome data addressed – for safety outcomes?	High	Four outcomes of Deaths, SAE, CV deaths and Completed suicide were inferred from the study. Judged a high risk of bias as previous completion rates were below 80%.

Study code: Haggstram 2006 - 205

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	Method used for sequence generation is not provided
Allocation concealment?	Unclear	Method used for allocation concealment is not provided
Blinding of objective outcomes' assessment?	Low	This was a double blind, double dummy placebo controlled study. "Placebo tablets were manufactured […] and were identical to bupropion. Thus, both investigators and patients were blind to the treatment." Additionally, abstinent outcomes were objectively biochemically verified and the safety outcomes assessed were hard endpoints.

Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 104/104 Bupropion: 53/53 Placebo: 51/51
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 104/104 Bupropion: 53/53 Placebo: 51/51

Study code: **Hall 2002 -930**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	Method used for sequence generation is not described.
Allocation concealment?	Unclear	Method for allocation concealment is not described.
Blinding of objective outcomes' assessment?	Low	"We encapsulated both drugs to maintain the patency of the bupropion formulation and to provide a blinded drug. All participants received capsules that were identical in number and appearance." The outcomes assessed in this study are objectively verified.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 121/146 Bupropion and Medical Management: 31/36 Placebo and Medical Management: 31/37 Bupropion and Psychological Intervention: 31/37 Placebo and Psychological Intervention: 28/36 (77.8%) "For all analyses, there were no differences in significance when the data were reanalyzed with missing data coded as smoking."
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 121/146 Bupropion and Medical Management: 31/36 Placebo and Medical Management: 31/37 Bupropion and Psychological Intervention: 31/37 Placebo and Psychological Intervention: 28/36 (77.8%)

Study code: **Hand 2002 - 715**

Item	Authors' Judgment	Description
Adequate sequence generation?	High	"Those who consented were randomised, according to month of entry, to receive either advice and support only (AS) or NRT and advice and support (AS+NRT). […] Because of the simple form of randomization there was one extra month of patients randomised to receive NRT, leading to unequal numbers in the two groups."
Allocation concealment?	Unclear	Method used for allocation concealment is not provided.
Blinding of objective outcomes' assessment?		This was an open design. However the outcomes measured were objectively verified.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 245/245 Advice and support: 109/109 Advice and support + NRT: 136/136
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcomes of interest were assessed as part of this study.

Study code: Hanioka 2010 - 66

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Individuals who were willing to quit smoking were randomly assigned to either an intervention or a non-intervention group." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Disappointment could have led to selective dropout or unwanted changes in behavior. We therefore used a modified random consent design (Kaper et al., 2005); Participants were blinded to the existence of the counterpart experimental group." Blinding approach was not provided and feasible in this study due to the different content of two groups, although the participants were kept blinded to the existence of the counterpart experimental group.

		However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding was not conducted.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"After randomization, those assigned to the intervention group were told in more detail that the study examined the effectiveness of intensive smoking cessation intervention, and those in the non-intervention group were told about the salivary test. Participants in both groups then gave written informed consent to participate." "Participants were counted as smokers if they were lost to follow-up and failed to provide a saliva sample for the intent-to-treat analysis." "During the intervention period, 15 persons were lost to study among the 56 participants." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. By design, the randomized participants gave consent to participate after randomization, so only 62% of those were included in the analysis. Overall, 45% of participants completed the 1-year assessment. Judged a high risk of bias given that the completions rate was far less than 80%.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a high risk of bias.

Study code: Hanson 2001-thesis

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"At the pre-quit visit, participants were randomly assigned in a double-blind manner to receive either the active nicotine patch or the placebo patch." Method for sequence generation was not provided
Allocation concealment?	Unclear	As above, but method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"SmithKline Beecham prepared the active and placebo patches which were identical in appearance."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interest was extracted
Incomplete outcome data addressed – for safety outcomes?	High	"During all visits, adverse clinical events were described as to their nature, severity, duration, action taken, and outcome. " "Of the initial 100 participants, 53% (n=53) completed treatment. Of the active nicotine patch group, 50% (n=25) finished treatment compared to 56% (n=28) of the placebo patch group." Four safety outcome, SAE, was extracted and three (mortality, CV mortality and completed suicide) were inferred 0. All randomized participants were included in the analysis. Given that the completion rates in comparison groups were less than 80% and the approach to handling missing data was not provided, it was judged to be a high risk of bias.

Study code: Harackiewicz 1987 - 372

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"…were randomly assigned to one of four experimental conditions…" Method for sequence generation was not provided
Allocation concealment?	Unclear	As above, but method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The individuals who provided treatment were blind to the content of the self help manuals and did not differentially affect any outcome measures… Interviewers (blind to treatment condition) conducted a smoking history interview and administered several questionnaires." Blinding was not mentioned and probably not feasible in this study due to different contents (combinations) of interventions, although the treatment provider and interviewer were kept blind to the group assignment. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Although 197 patients were originally accepted for the project, 22 failed to return for any follow-up interviews. These patients were excluded from all analyses. Dropout rates did not differ according to condition, and preliminary analyses revealed no differences between dropouts and subjects on any of the psychological measures collected at intake." "All 175 patients were interviewed 6 weeks after intake, and their current smoking status was represented in all data analyses. Those who did not return for later visits were assumed to be smoking." Two efficacy outcomes, CAR at 6 and 12 months were extracted. All randomized 175 participants were included in the study. However, there was no detailed information about the early discontinuations in four groups. It was judged to be a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted

Study code: **Harackiewicz 1988 - 319**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	Method used for sequence generation is not provided.
Allocation concealment?	Unclear	Method used for allocation concealment is not provided
Blinding of objective outcomes' assessment?	Low	The abstinence outcomes are objectively biochemically verified.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed for this study
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 175/197 (88.8%) Nicotine gum: 90/99 (90.9%) Self-help: 47/52 (90.4%) Control: 38/46 (82.6%)
Incomplete outcome data addressed – for safety outcomes?	Low	There were no safety outcomes of interest assessed in this study.

Study code: **Hatsukami 2004 - 151**

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Subjects were assigned randomly using a computer-generated schedule to either sustained-release bupropion or placebo and entered a 6-month treatment phase aimed at reducing the amount of smoking."
Allocation concealment?	Unclear	No mention of the method used for allocation concealment.
Blinding of objective outcomes' assessment?	Low	"[…] performed a double blind, randomized, placebo-controlled multicenter study […]" A placebo matching bupropion was used. The abstinent and safety outcomes were objectively and biochemically verified.
Blinding of subjective outcomes' assessment?	Low	There were no subjective outcomes of interest considered in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 594/594 Bupropion: 295/295 Placebo: 299/299
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 594/594 Bupropion: 295/295 Placebo: 299/299

Study code: Hays 1999-1701

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Subjects were randomly assigned to active patch or placebo, by means of a computer-generated code, in blocks of 20."
Allocation concealment?	Low	"The randomization code was not revealed to any of the investigators tintil completion ofthe study. Packages were sequentially numbered and labeled only with "transdermal nicotine patch." Identical patches for the open label-pay study were labeled in the same fashion."
Blinding of objective outcomes' assessment?	Low	"[…] all subjects enrolled in the placebo-controlled trial were randomly assigned to receive either 22-mg, 24-hour nicotine patch treatment or an identical placebo in a double-blind fashion at the time of their first visit (study entry)." A placebo matching the nicotine patch was used. The abstinent and safety outcomes were objectively and biochemically verified.
Blinding of subjective outcomes' assessment?	Low	There were no subjective outcomes of interest considered in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 643/643 Placebo: 322/322 Active nicotine patch: 321/321
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 643/643 Placebo: 322/322 Active nicotine patch: 321/321

Study code: **Hays 2001 - 423**

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Randomization to the placebo or bupropion groups was computer generated at a central location; the investigators did not know the patient assignments."
Allocation concealment?	Low	"Randomization to the placebo or bupropion groups was computer generated at a central location; the investigators did not know the patient assignments."
Blinding of objective outcomes' assessment?	Low	"All bupropion and placebo pills were identical in shape, size, and color." Additionally, the abstinent and safety outcomes were objectively and biochemically verified.
Blinding of subjective outcomes' assessment?	Low	There were no subjective outcomes of interest considered in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	Overall: 317/429 Bupropion: 159/214 Placebo: 158/215 The percentage completed is slightly lower than 80%. However no information is provided regarding how data missingness was dealt with.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Overall: 317/429 Bupropion: 159/214 Placebo: 158/215 The percentage completed is slightly lower than 80%. However no information is provided regarding how data missingness was dealt with.

Study code: **Herrera 1995-447**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	The method used for randomization was not described.
Allocation concealment?	Unclear	The method used for allocation concealment was not described
Blinding of objective outcomes' assessment?	Low	Method of blinding was not described. However the abstinence outcomes examined are biochemicaly verified and the safety outcomes are objectively captured.
Blinding of subjective outcomes' assessment?	Low	No safety outcomes of interest were examined as part of this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 322/322 Nicotine gum 2 mg:157/157 Nicotine gum 4 mg:87/87 Placebo:78/78
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 322/322 Nicotine gum 2 mg:157/157 Nicotine gum 4 mg:87/87 Placebo:78/78

Study code: **Hertzberg 2001 - 94**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No mention of the method used.
Allocation concealment?	Unclear	No mention of the method used.
Blinding of objective outcomes' assessment?	Low	No mention of the method used. However the abstinent outcome considered and the safety outcomes considered are objectively defined and captured.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 15/15 Bupropion: 10/10 Placebo: 5/5
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 15/15 Bupropion: 10/10 Placebo: 5/5

Study code: **Heydari 2012-268**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No description of the method used.
Allocation concealment?	Unclear	No description of the method used.
Blinding of objective outcomes' assessment?	Low	No mention of the method used. However the abstinent outcome considered and the safety outcomes considered are objectively defined and captured.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	No mention of losses to follow-up.
Incomplete outcome data addressed – for safety outcomes?	Unclear	No mention of losses to follow-up.

Study code: **Hilberink 2011 - 120**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No description of the method used.
Allocation concealment?	Unclear	No description of the method used.
Blinding of objective outcomes' assessment?	Low	No mention of the method used for blinding. However the outcomes of interest examined are either objective in their nature (death) or objectively measured (abstinence).
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 667/697 Usual care: 148/154 Counseling and NRT: 243/252 Counseling and NRT + Bupropion: 276/291
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 697/697 Usual care: 154/154 Counseling and NRT: 252/252 Counseling and NRT + Bupropion: 291/291

Study code: **Hill 1993 - 321**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Random assignment was made, in blocks of approximately 8 to 12 individuals" No description of the method used for sequence generation.
Allocation concealment?	Unclear	No description of the method used.
Blinding of objective outcomes' assessment?	Low	No mention of the method used for blinding. However the outcomes of interest (abstinence) examined are objectively measured.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	Overall: 82/94 Data is not available by group. No mention of dealing with missing data.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Overall: 82/94 Data is not available by group. No mention of dealing with missing data.

Study code: **Hilleman 1994-222**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No description of the method used.
Allocation concealment?	Unclear	No description of the method used.
Blinding of objective outcomes' assessment?	Low	Open label study. Judged as low because the outcomes of interest included are objective endpoints.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcomes of interest were examined in this study.
Incomplete outcome data addressed – for safety outcomes?	\ Low	Overall: 125/140 Fixed dose: 62/69 Tapered dose: 63/71

Study code: **Hjalmarson 1984 - 2835**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No description of the method used.
Allocation concealment?	Unclear	No description of the method used.
Blinding of objective outcomes' assessment?	Low	"All smokers in a group were given the same type of chewing gum, either the standard commercial preparation containing 2 mg of nicotine or a placebo. The placedo gum was flavored with pepper (capsaicin) to imitate the taste of nicotine. […] The gum was distributed by a nurse not involved in the group therapy. Neither she nor any of the therapists knew which chewing gum the subject received." Additionally, the outcomes considered were objectively measured.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 197/206 Nicotine gum: 103/106 Placebo: 94/100
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 197/206 Nicotine gum: 103/106 Placebo: 94/100

Study code: **Hjalmarson 1994 - 2567**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No description of the method used.
Allocation concealment?	Unclear	No description of the method used.
Blinding of objective outcomes' assessment?	Low	"Thus, 248 subjects attended the first session and were randomized to receive either active or placebo spray. This procedure was blind to both subject and therapist. […] The active and placebo sprays were identical in appearance, flavoring, and labeling. The placebo spray contained black pepper oleoresin (piperine) to mimic the localized "stinging" experienced with the administration of nicotine in the nasal passages." Additionally, the outcomes considered were objectively measured.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"The data at 12 months is based on 80% of the original subjects. The remaining 20% of subjects had reported smoking at earlier follow-up assessments." The loss of follow-up was not described by group allocation.
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 223/248 Nicotine:116/125 Placebo:107/123

Study code: **Hjalmarson 1997 -1721**

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Of those interviewed, 285 smokers met the selection criteria and were willing to participate. Of these, 247 came to the first group session, where they received a subject number consecutively. All numbers were on a list for random allocation to medication." It is unclear how the list of random numbers was generated.
Allocation concealment?	Unclear	No description of the method used.
Blinding of objective outcomes' assessment?	Low	"The randomization was blinded to both the participant and the therapist. If there was more than 1 participant from the same household, they were randomized to receive the same treatment." Additionally, the outcomes considered were objectively measured.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Overall: 231/247 Nicotine inhaler: 113/123 Placebo: 118/124
Incomplete outcome data addressed – for safety outcomes?	Low	Overall: 231/247 Nicotine inhaler: 113/123 Placebo: 118/124

Study code: Holt 2005 - 120

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Randomised using a computer generated code"
Allocation concealment?	Unclear	"Neither the study team nor the participant was aware of which treatment had been allocated until the end of the 12 month study period." No description of the method used for allocation concealment.
Blinding of objective outcomes' assessment?	Low	"At the first visit participants who fulfilled the entry criteria were randomised using a computer generated code to either bupropion 150 mg once daily for 3 days, then 150 mg twice daily for 7 weeks, or identical placebo.[…]At the first visit one blinded medication pack was dispensed" Judged as low also because the outcomes of interest included are objective endpoints.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	High	Overall: 78/134 (58.2%) Bupropion: 56/88 (63.6%) Placebo: 22/46 (47.8%)
Incomplete outcome data addressed – for safety outcomes?	High	Overall: 78/134 (58.2%) Bupropion: 56/88 (63.6%) Placebo: 22/46 (47.8%)

Study code: Hughes 1989 - 1300

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No mention of the method used for sequence generation.
Allocation concealment?	Unclear	No mention of the method used for allocation concealment.
Blinding of objective outcomes' assessment?	Low	The placebo was a gum without nicotine that was flavored to match the taste and irritancy of nicotine gum. […] Pharmacists were blind to the contents of the different bins.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	The loss of follow-up was not described.
Incomplete outcome data addressed – for safety outcomes?	Unclear	The loss of follow-up was not described.

Study code: Hughes 1990-1175

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No mention of the method used for sequence generation.
Allocation concealment?	Unclear	No mention of the method used for allocation concealment
Blinding of objective outcomes' assessment?	Low	No mention of the method used for blinding. However, this study was judged as low due to the objectivity of the outcomes considered.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were examined in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcomes of interest were examined in this study.
Incomplete outcome data addressed – for safety outcomes?	Unclear	No description of participants lost to follow-up.

Study code: Hughes 2003 - 946

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No mention of the method used for sequence generation.
Allocation concealment?	Unclear	No mention of the method used for allocation concealment.
Blinding of objective outcomes' assessment?	Low	Investigators mention the use of placebo patch matching the nicotine patch given to the intervention group.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	No description of losses to follow-up.
Incomplete outcome data addressed – for safety outcomes?	Unclear	No description of losses to follow-up.

Study code: Hughes 2011-955

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No mention of method used for sequence generation.
Allocation concealment?	Unclear	" Clinicians were unaware of the randomization details (e.g., block size) and were blinded as to participant condition." No mention of method used for allocation concealment.
Blinding of objective outcomes' assessment?	Unclear	"Clinicians were unaware of the randomization details (e.g., block size) and were blinded as to participant condition. […]Follow-up phone calls by research assistants blind to study conditions to collect data occurred at 3, 4, 5, and 6 months from study entry. […]No blindness assessment was done." No mention of the method used for blinding.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were assessed in this study.
Incomplete outcome data addressed – for efficacy outcomes?	High	**2 months follow-up** Overall: 153/218 Varenicline: 77/107 Placebo: 76/111 No description at 6 months or longest followup
Incomplete outcome data addressed – for safety outcomes?	High	**2 months follow-up** Overall: 153/218 Varenicline: 77/107 Placebo: 76/111 No description at 6 months or longest followup

Study code: Hurt 1994-595

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No mention of method used for sequence generation.
Allocation concealment?	Unclear	No mention of method used for allocation concealment.
Blinding of objective outcomes' assessment?	Unclear	No mention of method used for blinding.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were considered in this study.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	Overall: 196/240 Nicotine patch: 101/120 Placebo: 95/120 Losses to follow-up are only available for the first 8 weeks (treatment period) and not the longest follow-up, that is 12 months.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Overall: 196/240 Nicotine patch: 101/120 Placebo: 95/120 Losses to follow-up are only available for the first 8 weeks (treatment period) and not the longest follow-up, that is 12 months.

Study code: Hurt 1997 - 1195

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No mention of method used for sequence generation.
Allocation concealment?	Unclear	No mention of method used for allocation concealment.
Blinding of objective outcomes' assessment?	Low	All the tablets were identical in appearance.
Blinding of subjective outcomes' assessment?	Low	No subjective outcomes of interest were considered in this study.
Incomplete outcome data addressed – for efficacy outcomes?	High	"A total of 219 subjects (148 during the treatment phase and 71 subsequently) did not complete the 12-month study. […]The rate of completion of the study increased with the dose and was 57 percent, 65 percent, 64 percent, and 71 percent for the placebo, 100-mg, 150-mg, and 300-mg groups, respectively."
Incomplete outcome data addressed – for safety outcomes?	High	"A total of 219 subjects (148 during the treatment phase and 71 subsequently) did not complete the 12-month study. […]The rate of completion of the study increased with the dose and was 57 percent, 65 percent, 64 percent, and 71 percent for the placebo, 100-mg, 150-mg, and 300-mg groups, respectively."

Study code: Hurt 1990-1529

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The subjects were assigned randomly to receive either an active nicotine patch…or a placebo patch…" Method of sequence generation was not provided.
Allocation concealment?	Unclear	Method of allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The placebo patch was the same size and shape but contained no nicotine" "In all cases, the nurse was unaware of the treatment assignment." The second part of the study was not blinded and was based on smoking status and initial patch assignment. Blinding approach was provided and appropriate. Although this study included an open label period, the concern that blinding might be broken should not bias the

		objective outcomes which were all based on robust clinical or laboratory evidences.
Blinding of subjective outcomes' assessment?	Unclear	As above, however the risk of bias for subjective outcome assessment was unclear as the participants may be aware influenced in the second half of the study as it's open label.
Incomplete outcome data addressed – for efficacy outcomes?	High	"When all 70 subjects were analyzed on the basis of their initial assignment (intent-to-treat), at 6 weeks". CAR at 6 months was measured and only 8 of 70 subjects dropped out in the first 6 weeks due to reaction, hospitalization and enrolled in other studies. However, the information about the early discontinuations during the 6-month study was not provided. Final 6 months CAR was evaluated based on those assigned in second phase (not randomized). Judged a high risk due to intent-to-treat analysis not conducted at 6 months CAR.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety data of interest was extracted or inferred.

Study code: Jamrozik 1984 - 794

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	High	"A randomized, placebo controlled trial of nicotine chewing…" "Patients who agreed to study were allocated to the next available of 10 alphabetical codes for Tx from a list kept in each practice. The codes were balanced to give equal numbers of patients receiving either the active gum containing 2 mg buffered ……" Judged to be high risk as allocation was given as patients were seen. This study seemed to adopt a stratified randomization approach. However, the method of sequence generation was not provided.
Allocation concealment?	Unclear	Concealment from patients and the clinical staff is unclear, although code was stored at the clinic but unclear as to how it was stored.
Blinding of objective outcomes' assessment?	Low	"…receiving either the active gum containing 2 mg buffered nicotine per tablet or a placebo identical in appearance and packaging." "No one doctor or member of staff was likely to see sufficient numbers of patients to be able to break the 10 code system. " Physician for home visits also remained blind to the Tx allocation.

Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained through identical packaging of nicotine or placebo gum.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Data was collected from all participants except for 3 (out of 200) who had moved and were untraceable." CAR at 6 months was measured using intent-to-treat analysis. Judged to be low risk due to the high completion rate of 99% (197/200).
Incomplete outcome data addressed – for safety outcomes?	Low	No safety data was extracted or inferred.

Study code: Jarvik 1984 - 790

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The subjects were randomly assigned to nicotine and placebo gum groups, and the study was double-blind." Although it states randomly assigned, no details are given on methods of sequence generation.
Allocation concealment?	Unclear	Method of allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Judge to have a low risk of bias due to a double blind study design.
Blinding of subjective outcomes' assessment?	Unclear	No details were given on the blinding beyond the design.
Incomplete outcome data addressed – for efficacy outcomes?	Low	PPA at 12 months was reported for both groups and analysis was completed by intent-to-treat with no reported loss to follow up as 48/48 participants were measured at 12 month follow up.

Incomplete outcome data addressed – for safety outcomes?	Low	No safety data was extracted or inferred.

Study code: Jarvis 1982 - 537

Item	Authors' Judgment	Description
Adequate sequence generation?	High	"…116 subjects were entered into the trial…were treated in groups of 10, taken in order from the waiting list, each group being allocated at random to receive either the active or placebo gum." Judged to be high risk as group randomization through selection of next individuals on the waiting list has a higher risk of bias.
Allocation concealment?	Unclear	Allocation concealment was not described.
Blinding of objective outcomes' assessment?	Low	"Therapists and subjects were blind to the allocation." "The placebo gum contained 1 mg nicotine and its biological availability was reduced by the lack of an alkaline buffer…designed to mimic the nicotine taste…" Due to a double blind design and identical taste between the gums, judged to be low risk.
Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained through identical taste of the placebo gum.

Incomplete outcome data addressed – for efficacy outcomes?	Low	At 12 month follow up, all three measurements of PPA, PAR and CAR were measured by an intent-to-treat analysis. Out of 58 patients, 6 from each group were not validated with a roughly 90% completion rate. Judged to be low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	Safety data was inferred through the study.

Study code: Jensen 1990 - 831

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Five hundred and seventeen smokers were randomized to 24 smaller groups and each group was randomly allocated to treatment." Method of sequence generation not provided.
Allocation concealment?	Unclear	As above, no method of allocation concealment was provided.
Blinding of objective outcomes' assessment?	Low	"The study was not blind because the daily consumption of silver acetate had to be restricted to a maximum of six pieces to avoid risk of argyria." Although this study was not blind, the concern that participants may be influenced should not bias the objective outcomes which were all based on robust clinical or laboratory evidences.
Blinding of subjective outcomes' assessment?	High	As above, there is a high risk of bias for the subjective outcomes as the trial was not blinded.

Incomplete outcome data addressed – for efficacy outcomes?	Low	The CAR was recorded and verified at 6 and 12 months follow up. Of the 517 enrolled in the study, 21 were lost to follow up with a final intent-to-treat analysis of 496/517 (96%). Judged to be low risk due to high completion rate and intent-to-treat analysis.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Jorenby 1999 - 685

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Unclear	"The subjects were randomly assigned to one of four treatments with use of an unequal cell design…randomization was not balanced within sites." Unclear as sequence generation was not fully described and randomization not balanced.
Allocation concealment?	Unclear	As above, no details on methods of allocation concealment were stated.
Blinding of objective outcomes' assessment?	Low	The study was conducted as a double blind, placebo controlled study. The objective outcomes were judged to be low risk due to the robust clinical or laboratory evidences.
Blinding of subjective outcomes' assessment?	Unclear	As above, however judged to be unclear as there is potential for bias if the blinding was ineffective.
Incomplete outcome data addressed – for efficacy outcomes?	High	"A total of 311 subjects (34.8%) discontinued treatment: 177 left the study and provided no additional information, whereas 134 stopped taking the medication but participated in follow up assessments. Due to the low completion rates in this study, judged to

		be a high risk.
Incomplete outcome data addressed – for safety outcomes?	High	SAE were explained and the data extracted. However, judged a high risk of bias as above.

Study code: Jorenby 2006 - 56

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	The study design was a randomized, double blind, placebo controlled trial. "Participants were randomly assigned to 1 of the 3 treatment groups in a double-blind manner. Randomization was completed centrally by using a computer-generated list and sites used an electronic system to assign participants to treatment." Judged to be an effective method of sequence generation and a low risk.
Allocation concealment?	Low	To maintain the study blind, each participant randomized to treatment was dispensed 2 folders of study medication each week… Folders for all participants (regardless of treatment assignment) were identical throughout the treatment phase." Judged to be low risk due to centrally randomized computer methods of sequence generation and identical folders used for dispensing medications.
Blinding of objective outcomes' assessment?	Low	The study was a double blind method and each participant received their medication/placebo in identical packaging. Judged to be a low risk of bias.

Blinding of subjective outcomes' assessment?	Low	As above, judged to be a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Overall study completion rates at week 52 were 70% (240 participants) in the varenicline group, 65% (221 participants) in the bupropion SR group, and 60% (204 participants) in the placebo group." CAR and PPA were measured at 6 and 12 month follow up visits. Judged to be a high risk of bias as completion rate was only 70%.
Incomplete outcome data addressed – for safety outcomes?	Low	Mortality was reported as 0, SAE was reported twelve times in the various groups, and CV mortality was also reported.

Study code: Joseph 1996 - 1792

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Low	This study is "…a randomized, double-blind, placebo controlled trial with… a computer-generated schedule to randomly assign patients to the study groups in blocks of 10." Judged to be a low risk of bias due to computer based sequence generation.
Allocation concealment?	Unclear	No methods of allocation concealment were provided.
Blinding of objective outcomes' assessment?	Low	"Subjects in the placebo group were given placebo patches of identical size, appearance, and odor." Judged to be a low level of risk due to comprehensive blinding procedures.
Blinding of subjective outcomes' assessment?	Low	As above, little risk of bias due to effective blinding.

Incomplete outcome data addressed – for efficacy outcomes?	High	"Because some subjects discontinued therapy on their own, we also analyzed the data considering only subjects who used patches according to the study protocol. At the week 6 visit, 73 percent of the subjects in the nicotine group were wearing patches, as compared with 56 percent in the placebo group." PPA was measured at 6 months follow up but due to the analysis only considering those who completed the study, there's a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Two safety outcomes of mortality and SAE were clearly outlined. However, due to a low completion rate in the study, there is a high risk of bias.

Study code: Kalman 2011 - 111

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Urn randomization was used to allocate 144 participants to medication condition (Stout et al., 1994). Four variables were included in the urn randomization: (1) gender; (2) severity of nicotine dependence (high vs. low); (3) depressive symptoms (high vs. low); and (4) substance use history (alcohol dependence only vs. alcohol dependence plus at least one other drug dependence)." Judged to be a low risk of bias through this method of sequence generation.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Participants were randomly assigned to bupropion or placebo for 8 weeks… Active and placebo medications were identical in appearance." Low risk of bias due to robust clinical or laboratory measurements.
Blinding of subjective outcomes' assessment?	Low	As above, the subjective outcomes were not biased due to proper blinding of the groups.

Incomplete outcome data addressed – for efficacy outcomes?	High	"In a modified intent-to-treat analysis, data were analyzed for the 130 participants who received at least one dose of study medication. Fourteen participants who dropped out before receiving any study medication were not included in the analyses. Completion rates at the 7-, 11- and 24-week follow-ups were 86%, 74% and 65%, respectively." PPA and PAR measurements were taken at 6 months follow up. Judged to be a high risk of bias due to low completion rates.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Killen 1997 - 663

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"A total of 424 smokers were randomized in a 2 X 2 factorial experiment. Assignment to the patch condition was double-blind." Method of sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned but could potentially be feasible due to a nicotine patch and placebo controlled study design. Judged as a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidence, which should not be biased even if it is an open label study.
Blinding of subjective outcomes' assessment?	Unclear	As above, unclear as to if there is bias or not in the blinding as it was not sufficiently outlined.

Incomplete outcome data addressed – for efficacy outcomes?	High	"Of self-reported nonsmokers. 75% and 69% provided biochemical confirmation at 6 and 12 months, respectively; these rates did not differ by treatment group. As noted, those failing to provide confirmation were reclassified as smokers." PPA and PAR was measured at 6 months as well as PPA measured at 12 months. Judged to be high risk of bias as completion rates are low.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Killen 1999 - 226

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Unclear	"Assignment to treatment dose was double-blind." No method of sequence generation was reported.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Details of blinding were not described beyond mentioning the design as a double blind trial. Judged as a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	High	"At the 12-month follow-up, participants were asked to guess their treatment assignment. Fifty-nine percent of those receiving the 15-mg dose guessed correctly compared with 34% of those assigned to the 25-mg dose: *2(2, N* = 390) = 8.67, *p<.* 05." Judged to be a high risk of bias as there was a significant difference between the two arms guessing their treatment assignment.

Incomplete outcome data addressed – for efficacy outcomes?	Low	"Of self-reported nonsmokers, 86% and 85% provided biochemical confirmation of their abstinence at 6 and 12 months; these rates did not differ by treatment group." PPA was measured at 6 and 12 months follow up. Judged to be a low risk of bias as completion rate was sufficient and all participants included in analysis.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcomes, SAE, was extracted, while two others, including death and CV death were inferred 0. As above, judged a low risk of bias.

Study code: Killen 2004 - 729

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Assignment to treatment condition was double-blind." No method of sequence generation was reported.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding was only mentioned as a double blind design and not described further. Judged a low risk of bias due to robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Low	"Participants were asked to guess their treatment assignment at Week 10. Only 30% (28 of 92) of those in the patch plus placebo condition and 31% (26 of 83) of those receiving patch plus bupropion guessed their assignment correctly." Judged a low risk of bias as maintenance of blinding was very similar across both treatment arms.

Incomplete outcome data addressed – for efficacy outcomes?	High	PPA was measured at 6 months follow up after treatment. The number assessed at 6 months was 70 out of 108 (64.8%) and 64 out of 103 (62.1%) for the placebo and bupropion, respectively. Judged to be a high risk of bias due to low response rates in both groups.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Kornitzer 1995 - 41

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Low	"Subjects were allocated a number and treatment plan following a randomized list generated by a computer program. The investigator and the subjects were completely blind concerning treatment." Judged low risk of bias as sequence generation was sufficient.
Allocation concealment?	Low	"Sealed code envelopes were held by the principal investigator to be broken in the event of a real emergency. In fact, unblinding was never requested during the whole study." Judged a low risk of bias as allocation concealment adequately maintained double blinding.
Blinding of objective outcomes' assessment?	Low	Low risk of bias due to effective blinding and robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Low	"…Corresponding placebo patches were identical in appearance and packaging." The use of sealed envelopes as well as the blinding of treatment medications was sufficient. Therefore, the

		study has a low risk of bias for subjective outcomes.
Incomplete outcome data addressed – for efficacy outcomes?	High	CAR was measured at 6 and 12 months follow up. The completion rates were 121 out of 149 (81.2%), 105 out of 150 (70%) and 45 out of 75 (60%). The analysis after 12 months was intent-to-treat. However, there is a high risk of bias due to low completion rates.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Kralikova 2009 – 433

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"This was a double-blind, placebo controlled trial with parallel groups…" Unclear as sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Our study differed from previous trials because smokers could choose one of two NRT products, gum or inhaler, and were given opportunity to quit or reduce." Judged to be a low risk of bias as the objective outcomes are based on robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	High	As above, judged to be a high risk of bias as selection of treatment may bias the blinding of subjective outcomes in the study.
Incomplete outcome data addressed – for efficacy outcomes?	High	The CAR and PPA were both measured at 12 months follow up with an intent-to-treat analysis. 68% in active group and 67% in the placebo group were still using the product daily at 9 months. Vs. 41% and 34%, respectively, in the inhaler group. The main reason for not using

		treatment was “did not need it” in both groups.” Judged to be high risk of bias as the completion rate was very low in all groups in the study.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Lacasse 2008 - 1215

Item	Authors’ Judgment	Description
Adequate sequence generation?	Unclear	“Design was randomized trial…” Method of sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes’ assessment?	Low	“In order to minimize bias, the 6 and 12 month follow-up outcomes were assessed using a short standardized and closed questionnaire by a research assistant who did not know the patients’ group allocation.” Low risk of bias as the objective outcomes is based on robust clinical or laboratory evidence.
Blinding of subjective outcomes’ assessment?	Unclear	As above, unclear as to if there is bias or not in the blinding as it was not sufficiently outlined.
Incomplete outcome data addressed – for efficacy outcomes?	Low	PPA was measured at 12 months follow-up. The completion rate for the intervention arm was 85 out of 99 (85.9%) and 86 out of 97 (88.7%) for the usual care arm. Judged to have a low risk of bias as the completion rate

		was high.
Incomplete outcome data addressed – for safety outcomes?	Low	The safety outcomes of deaths and CV deaths were reported from the study. Judged to be a low risk of bias as the study had a high completion rate and low loss to follow-up.

Study code: Leischow 1996 - 364

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"A single-site, randomized, double-blind, placebo-controlled design was used. At the prequit visit, subjects were sequentially and randomly assigned to either the nicotine- or placebo-inhaler treatment groups. The randomization code was generated by computer." Judged to be low risk of bias as sequence generation was done by a computer.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	As above, the study design is a randomized, double-blind, placebo-controlled design. Low risk of bias as the objective outcomes is based on robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.

Incomplete outcome data addressed – for efficacy outcomes?	High	CAR was recorded at 6 and 12 months follow up. "At month 12, 24% of nicotine-inhaler and 8% of placebo inhaler subjects remained in the trial." Due to a very low completion rate in the study, risk of bias is judged to be high.
Incomplete outcome data addressed – for safety outcomes?	High	Three safety outcomes of Death, SAE and CV deaths were inferred. Judged a high risk of bias given that the safety data was all inferred 0, the completion rates were lower than 80%, and the statistical methods for safety data were not provided.

Study code: Lerman 2004 - 426

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Low	" Randomization was determined by using a computer-generated randomization scheme operated by a senior data manager; stratification was done by study site." Judged to be low risk of bias through sequence generation methods of using a computer.
Allocation concealment?	High	"Allocation to treatment could not be concealed from the counselors or the study assistants who delivered the medication to patients after preparation at the research pharmacy." High risk of bias as no concealment took place.
Blinding of objective outcomes' assessment?	Low	"This was a randomized, open-label clinical trial of transdermal nicotine versus nicotine nasal spray for smoking cessation." Low risk of bias as the objective outcomes is based on robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	High	As above, the study design was open label which has a high risk of bias.

Incomplete outcome data addressed – for efficacy outcomes?	Low	PPA and CAR were both measured at 6 months follow up. The completion rate for transdermal was 144 out of 175 (82.3%) and 155 out of 175 (88.6%) for nasal spray. Judged to be a low risk of bias for efficacy outcomes due to a high completion rate in the study and an intent-to-treat analysis.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Levine 2010 - 543

Item	Authors' Judgment	Description
Adequate sequence generation?	High	"Eligible women were randomly assigned, in blocks of 8 to 17, to standard or concerns." Judged to be a high risk of bias as randomization was conducted by blocks of participants.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Bupropion hydrochloride sustained release, 150 mg, or placebo was administered daily for the first 2 days and twice daily for the remainder of the 26 week treatment." Low risk of bias as the objective outcomes is based on robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Low	As above, the blinding was maintained through the double-blinding design of the study.
Incomplete outcome data addressed – for efficacy outcomes?	High	PPA and PAR were recorded at both 6 and 12 month follow up periods and intent-to-treat analysis was conducted. The completion rates at 12 months of the concerns arm was 94 out of 193 (48.7%) and 74 out of 156 (47.4%) for the standard arm.

		Judged to be a high risk of bias as the completion rate of the study was well below 80%.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Lewis 1998 - 296

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"The patient was randomized to either the MC condition or a patch condition using a predetermined computer-generated randomization code." Judged to be a low risk of bias as the method of sequence generation was deemed adequate.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Sets of patches were given to participants based on their treatment arm and placebo patches are identical in appearance to the active patches. Low risk of bias for objective outcomes based on robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Low	"Both patients and study staff were blinded with respect to patch dose." Judged to be low risk of bias as the design was double-blind and treatments were identical in appearance.

Incomplete outcome data addressed – for efficacy outcomes?	Low	PPA was recorded at 6 months follow-up and an intent-to-treat analysis was conducted. No further efficacy outcomes or completion rates were reported but due to the design of the study being conducted on admitted patients within the hospital, judged to be a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	Three safety outcomes of Death, SAE and CV deaths were inferred from the study as 0. Due to the above mentioned lack of efficacy outcome reporting, judged to have a low risk of bias.

Study code: Malcolm 1980 - 295

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"One hundred and ninety four were randomly allocated into three groups…" Method of sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The trial was double blind between the gum groups." "The placebo gums were spiced with capsicum to produce a similar pungent taste." Judged to have a low risk of bias due to robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Low	As above, a low risk of bias due to double blinding as well as identical characteristics of the gum between both arms.
Incomplete outcome data addressed – for efficacy outcomes?	Low	CAR at 6 months follow up was reported. No further efficacy outcomes or completion rates were available. Judged to be a low risk of bias.

Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Marshall 1985 - 1397

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Patients were assigned randomly to two groups, on receipt of their post card." No method of sequence generation is provided.
Allocation concealment?	Unclear	Method of allocation concealment is not provided.
Blinding of objective outcomes' assessment?	Low	Low risk of bias due to robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	High	No methods of blinding were provided. The two intervention groups received different levels of contact from the physician and started off with either a pink paper (low contact) or white paper (high contact). Judged to be a high risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	CAR was measured at 12 months follow-up. "Only 7 people, all in the low contact group, could not be contacted in the follow up, all being classified as failures." Judged to be a low risk of bias due to a high risk of completion rate of 193 out of 200 (96.5%) participants.

Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: McCarthy 2008 - 717

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Staff who screened and enrolled participants were unaware of the experimental condition to be assigned. Randomization via random number list was not blocked."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Study pills, which looked identical in the placebo and active medication conditions, were packaged in containers labeled with participant identification numbers prior to participant enrollment." Judged low risk of bias due to effective blinding and robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Low	As above, blinding of subjective outcomes is deemed to be effective.
Incomplete outcome data addressed – for efficacy outcomes?	High	PPA and PAR were collected at 6 and 12 month follow-up. At 12 month follow-up, 292 out of 463 (63.1%) people completed the measurements. Judged a high risk of bias due to low completion rates.

Incomplete outcome data addressed – for safety outcomes?	High	Death and CV deaths were inferred from the study, However, judged to be a high risk of bias due to the low completion rates mentioned above.

Study code: Molyneux 2003 - 484

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Patients were randomized to one of three treatment groups following enrolment using a list generated for each centre, allocating equally in random permuted blocks of nine." Method of sequence generation judged to be adequate and a low risk of bias.
Allocation concealment?	Unclear	Method of allocation concealment is not provided.
Blinding of objective outcomes' assessment?	Low	As above, patients were randomized to three treatment groups but no further information on blinding methods were provided. Judged to be a low risk of bias for objective outcomes due to robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Unclear	As above, not enough information is provided about blinding of subjective outcomes.

Incomplete outcome data addressed – for efficacy outcomes?	High	PPA and CAR were measured at 12 month follow up and an intent-to-treat analysis was conducted. At 12 months, the completion rate for all three arms was 41 out of 92 (44.6%) for usual care, 41 out of 91 (45.1%) for counseling alone, and 44 out of 91 (48.4%) for NRT/counseling. Judged to be a high risk of bias as the completion rates are well below 80%.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Moolchan 2005 - e407

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"For this double blind study, adolescents were randomized to 1 of 3 groups according to an algorithm held by the National Institute on Drug Abuse Pharmacy…" Judged to be a low risk of bias for sequence generation.
Allocation concealment?	Low	As above, concealment on allocation by the National Institute on Drug Abuse Pharmacy is deemed to be sufficient and therefore, a low risk of bias.
Blinding of objective outcomes' assessment?	Low	"Because both the patch and gum are used commonly, the 3 groups included (1) active patch and placebo gum, (2) active gum and placebo patch, (3) placebo gum and placebo patch." Judged to be a low risk of bias.
Blinding of subjective outcomes' assessment?	Low	As above, effective blinding in the study gives a low risk of bias for subjective outcomes.

Incomplete outcome data addressed – for efficacy outcomes?	High	PPA was measured at 6 months follow up. "The proportions of randomized participants who completed the study were 41.3% (19 of 46 subjects) for the gum group, 52.9% (18 of 34 subjects) for the patch group, and 40.0% (16 of 40 subjects) for the placebo group." Judged to be high risk of bias with completion rates well below 80%.
Incomplete outcome data addressed – for safety outcomes?	High	Three safety outcomes of Deaths, SAE, and CV deaths were inferred from the study. However, judged to be a high risk of bias due to the above low rates of completion.

Study code: Muramoto 2007-1068

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Low	"Active study medication and identical-appearing placebo were prepackaged into 3 sets of identical-appearing blister cards in accordance with a computer-generated randomization list."
Allocation concealment?	Low	"At the baseline/prequit visit, a research assistant assigned the subject the next treatment number (and associated blister cards) in sequence."
Blinding of objective outcomes' assessment?	Low	In addition to the above, "Study subjects and researchers remained blind to treatment group assignment throughout the study. To evaluate the success of blinding, subjects were asked to guess their treatment group at the end of treatment (week 6)."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias for the subjective outcomes assessment.

Incomplete outcome data addressed – for efficacy outcomes?	High	Efficacy outcome of PPA at 6 months was extracted. All randomized participants received the assigned treatment and were included in the analysis.64.8% (68/105), 63.5% (66/104), and 57.3% (59/103) of participants in bupropion hydrochloride SR150mg/d, bupropion hydrochloride SR 300 mg/d , and placebo groups, respectively, completed the 26-week assessment. Judged a high risk of bias given that the completion rates were all much less than 80%.
Incomplete outcome data addressed – for safety outcomes?	High	Two safety outcomes (SAE and suicidal ideation) were extracted. Three safety outcomes were inferred 0 (death, CV death, and completed suicide). Judged a high risk of bias given that the completion rates were all much less than 80%.

Study code: Myung 2007-1065

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"All the eligible subjects were randomly assigned to receive either nicotine patches or placebo patches according to one of two schedules provided by the computerized randomized plan generator… This entire random allocation sequence was conducted by a third person and remained unknown until the interventions were blindly assigned to the two groups by the third person."
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	In addition to the above, "The placebo patch group was given identical- appearing patches using the same method as that used for the nicotine patch group."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias for the subjective outcomes assessment.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interest was extracted.
Incomplete outcome data addressed – for safety outcomes?	Low	"No subject was dropped out; all the subjects who were not present at the time of the scheduled visit were interviewed by telephone." One safety outcomes, SAE, was extracted; while three (mortality, CV mortality and completed suicide) inferred 0. All randomized participants in each group seemed to be included in the analysis and completed 12-month follow-up. Judged a low risk of bias.

Study code: Nakamura 2007-1040

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"At the baseline visit, a computer-generated list of random numbers was used to assign subjects to receive 12 weeks of treatment with varenicline 0.25 mg BID, 0.5 mg BID, or 1 mg BID or placebo."
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	"This randomized, double-blind, placebo-controlled study investigated…" Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was ineffective.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding approach was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Participants with missing data for a single clinic visit were considered abstinent from smoking for the visit if they were CO-confirmed abstinent for the visits immediately preceding and following the missed visit. Participants missing data for more than one visit in a 4-week endpoint evaluation period (Weeks 4–7 or 9–12) during the treatment phase were coded as smokers for that endpoint. Participants who withdrew from the study or were lost to follow-up were considered smokers for the remainder of the study, regardless of their smoking status at their last recorded visit. For the 7-day point prevalence of abstinence, participants with a missing response were considered smokers for that 7-day period and missing CO confirmation was imputed as above." Efficacy outcomes of CAR and PPA at each of 6 and 12 months were extracted. All randomized participants were included in the analysis, except for 3 in varenicline and 5 in placebo group not receiving the assigned treatment. 63% (100/160) and 56% (89/160) of participants in the varenicline and placebo groups, respectively, completed the 52-week assessment. Judged a high risk of bias given the completion rates were well less than 80%.
Incomplete outcome data addressed – for safety outcomes?	High	Two safety outcomes, SAE, mortality and CV events, were reported; while three (mortality, CV mortality and completed suicide) inferred 0. As above, judged a high risk of bias given the low completion rates.

Study code: Niaura 1994 - 70

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"This study employed a 2*2 randomized factorial design. Subjects were stratified on the basis of high or low scores on the original version of the Fagerstrom Tolerance Questionnaire (FTQ: 6)….." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned and probably not feasible due to the different interventions- nicotine gum use or no gum. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if it is an open label study.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Follow-up rates overall were good, with 92.5% (160/173) of the subjects providing information at 6 months and 86.7% (150/173) of subjects providing information at 12 months." "The conservative intent-to-treat principle was adopted for the analyses, counting all individuals who did not provide outcome information as smokers." Efficacy outcomes of CAR and PPA at 6 and 12 months were extracted. All randomized participants were included in the analysis. Judged a low risk of bias given the high overall completion rates at 6 and 12 months.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Niaura 1999 - 685

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects then signed a quit smoking contract and were informed that in subsequent sessions they would be randomized to different treatments for relapse prevention..." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Counselors were kept blind to the relapse prevention conditions to which subjects were assigned." "Even though the therapists could not be kept blind to which condition each subject was assigned therapists did not appear to be biased in favor of a particular treatment, as they were equally confident across conditions at the end-of-treatment of subjects' chances of maintaining abstinence during the follow-up (Ms range from 2.9 to 3.5) and there were no therapist effects on treatment outcome at any follow-up point." Blinding was not mentioned and probably not feasible due to the different combinations of interventions, although at some points, the therapists were kept blind and the blinding seemed to be maintained. Judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if it is an open label study.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"…subjects who were lost to follow-up for any reason were coded as smoking in analyses using these status points." "Subject attrition at each follow-up was minimal (between 2% and 20% at any one point), and there were no significant differences in attrition at any point between any of the treatment conditions. A total of 126 subjects completed treatment (98% of the original sample; n=98 completed > 50% of treatment sessions) and 80% (n=103) completed the 12-month follow-up." Efficacy outcomes of PPA at 6 and 12 months were extracted. All randomized participants were included in the analysis. Judged a low risk of bias given that the overall completion rates at 6 and 12 months were no less than 80%.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Niaura 2008 - 1931

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"A computer-generated randomization list was created by Pfizer using randomly permuted blocks and a pseudo-random number generator. At the baseline visit, qualified participants were assigned in a 1: 1 ratio to varenicline treatment or placebo in the numerical order that they were accepted to the study."
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was ineffective.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"The primary efficacy analyses of the primary and secondary end points (CAR at weeks 9–12, 9–24, and 9–52, and 7-day PP) were conducted in the nicotine-dependent group (all subjects who received ≥1 dose of study medication and had a TDS score ≥5);... Efficacy analyses were also conducted in the total group… " The abstinence rates were only reported for nicotine-dependent groups. Efficacy outcomes of CAR and PPA at each of 6 and 12 months were extracted. All randomized nicotine-dependent participants were included in the analysis, except for one in the 0.5mg BID group who did not receive the assigned treatment. 81.3% (104/128), 80.6% (104/129), and 79.0% (103/130) and 89.0% (115/129) of participants in the varenicline 0.25mg BID, 0.5mg BID, 1mg BID and placebo groups, respectively, completed the 52-week assessment. Judged an unclear risk of bias in this respect given that only 83% (516/569) of the total randomized (nicotine-dependent participants) were followed up, among whom the overall completion rate was roughly about 80%.
Incomplete outcome data addressed – for safety outcomes?	Low	"…the primary tolerability analyses were conducted in the total group (all subjects who received ≥1 dose of study medication, regardless of TDS score)." Three safety outcomes, including SAE, mortality, CV mortality and completed suicide) were reported. Judged a low risk of bias given the completion rates in each group were roughly greater than 80%.

Study code: Nides 2006 - 1561

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"This randomized, multicenter, double-blind, parallel- group, placebo- and active-controlled phase 2 clinical trial was conducted at 7 US sites from February 21, 2000, to January 3, 2003. Before the start of the study, a randomization list was computer generated using a method of randomly permuted blocks and a pseudorandom number generator. Investigators assigned medication to subjects in numerical order of acceptance into the study."
Allocation concealment?	Low	As above, the randomization list for 7 sites was presumably conducted by a central unit, with which the allocation should be concealed.
Blinding of objective outcomes' assessment?	Low	"Randomized subjects received 1 of 3 varenicline tartrate dose regimens (0.3mgonce daily, 1.0mgonce daily, or 1.0mgtwice daily), sustained-release bupropion hydrochloride (150mgtwice daily), or matched placebo. Varenicline doses were selected on the basis of tolerability data from phase 1 studies, and subjects were dosed for 6 weeks, receiving blinded placebo during week 7 to preserve treatment blinding." As above, judged a low risk of bias for the objective outcomes assessment as the blinding is maintained by the matched placebo and regimen.
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias for the subjective outcomes assessment.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Subjects who dropped out for any reason were considered to be smokers at all subsequent time points." "Analyses are reported here for the all subjects population (those who reported taking ≥1 dose of study medication) for each treatment group vs placebo." The abstinence rates of CAR at 6 and 12 months were extracted. All randomized were included in the analysis, except for 2, 2, 2, 2 and 3 in varenicline 0.3 mg/d, 1 mg/d, 2 mg/d, bupropion 300 mg/d and placebo group, respectively, not receiving any medication. None of those 5 groups attained more than 80% completion rate for 52-week assessment, ranging from 51.6% to 61.1%. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	"The AEs were recorded during each weekly visit. Serious AEs were reported from randomization through 30 days after the last dose of study medication. Those AEs that occurred after 30 days were reported if the investigator considered them related to the study medication." Five safety outcomes, including SAE, CV event, mortality, CV mortality and completed suicide) were reported. As above, judged a high risk of bias given the low completion rates in each group.

Study code: Nollen 2007 - 911

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Sequential enrollment continued until 500 participants were randomized. Randomization codes were computer generated by the study statistician in blocks of 20."
Allocation concealment?	Low	"Duffel bags were numbered and prestuffed, based on the randomization code, with a 4-week supply of 21mg transdermal nicotine patches and the respective educational materials by nonintervention staff." Combining both descriptions the on randomization process, the allocation was presumably concealed.
Blinding of objective outcomes' assessment?	Low	"This was an investigator-blinded trial of 500 African American smokers who were randomly assigned to receive a targeted smoking cessation videotape and guide or a standard care videotape and guide." "Duffel bags were numbered and prestuffed, based on the randomization code, with a 4-week supply of 21mg transdermal nicotine patches and the respective educational materials by nonintervention staff."
Blinding of subjective outcomes' assessment?	Unclear	As above, the participants were not blinded. The subjective outcomes might probably be influenced by the participants' knowledge of the allocated interventions after assignment if the blinding was not conducted. However, the different interventions between two groups were about the contents of video and guide. It is not clear if participants would be able to distinguish different materials. Judged un unclear risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"All statistical analyses were performed on an intention-to-treat basis. Following from intent-to-treat principles, participants who withdrew or were lost to follow-up were imputed as smokers." "Of the 500 participants, 333 (66.6%) attended their Week 4 visit, and 328 (65.6%) attended their Month 6 visit… No other demographic differences were found between participants who returned or were lost to follow-up at Week 4 or Month 6." The abstinence rate of PPA at 6 months was extracted. All randomized were included in the analysis. The 6-month overall completion rate was far less than 80%. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, CV event, mortality and completed suicide) were inferred. As above, judged a high risk of bias given the low overall completion rate. In addition, the statistical and assessment strategy for safety outcomes were not provided.

Study code: Okuyemi 2007 - 43

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"This study was a 6-month cluster-randomized trial in which 20 public housing and section 8 developments (HDs) were randomly assigned to…" "Housing developments were stratified by elderly versus nonelderly (i.e., "family") developments, as determined by the Kansas City (Kansas and Missouri) Housing Authorities, and randomization occurred within each stratum." Method for sequence generation was not provided.
Allocation concealment?	Low	"Study personnel remained blinded to randomization at the time of the health fair." "Treatment assignment was revealed to the research staff only after each health fair was completed. A timed e-mail was sent to the study coordinator at 6:00 p.m. after each health fair was complete along with a sealed envelope containing the randomization code. Sequential enrollment continued until 20 HDs were randomized, of which 10 were randomized to the smoking cessation arm and 10 to the comparison arm."
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned and probably not feasible due to the different contents of intervention combinations. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was not conducted.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes were likely to be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"All analyses were conducted under the intention-to-treat principle." One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in analysis. However, 78% (84/107) and 71% (47/66) of the participants in [**Nicotine gum + Motivation counseling and education materials on smoking cession**] and [**Motivation counseling and education materials on fruits and vegetables**] group completed the 6-month assessment, respectively. Judged a high risk of bias given that the completion rates were less than 80% and that the information about the early discontinuations in two groups was not provided.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Oncken 2007-296 + Oncken 2006-1141

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"A total of 152 women were randomized to double-blind treatment using a 3:5 treatment assignment, which resulted in 57 women being assigned to use the nicotine patch and 95 women assigned to use the placebo patch. The randomization schedule was chosen to yield an approximately equal number of abstainers in each group during the active treatment phase, making it possible to evaluate the effects of nicotine versus placebo on bone turnover." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was ineffective.
Blinding of subjective outcomes' assessment?	High	"The majority (52%) of the nicotine group believed correctly that they had received the nicotine patch, and the majority (61%) of the placebo group believed correctly that they have received the placebo... The association between treatment group and the accuracy of the belief concerning treatment group was significant ($X^2_{(2)}$ =15.61, p<.001)." Blinding approach was not provided and blinding did not seem appropriately maintained. Judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was conducted ineffectively.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"If there was a discrepancy between subject report and CO level, the subject was coded as a smoker for that visit. In addition, the subject was considered a smoker for any missed visits." "From the original sample, 119 women (78.3%) completed the visit 8 assessment (47 were from the nicotine group and 72 from the placebo group, a ratio of .65, similar to the ratio of .63 at randomization)." Two abstinence outcomes, PPA and PAR at 16 months, were extracted. It seemed that all randomized participants were included in analysis. However, 82% (47/57) and 76% (72/95) of the participants in [nicotine patch + intensive group counseling] and [placebo patch + intensive group counseling] group completed the 16-month assessment, respectively. Judged an unclear risk of bias given that the completion rates were marginal to 80% and that the information about the early discontinuations and the approach to handling missing data were not provided.
Incomplete outcome data addressed –	Unclear	Two safety outcomes, SAE and CV event, were extracted; while three (mortality, CV mortality and completed suicide) inferred 0. As above, judged an unclear risk of bias.

for safety outcomes?		

Study code: Oncken 2006-1571

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Eligible subjects were randomly assigned to 1 of 5 groups at the baseline visit…" Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"…a 12-week, multicenter, double-blind, placebo-controlled, randomized study with weekly visits, followed by a 40-week assessment after discontinuation of the regimen." "Subjects and investigators were blinded to the study drug treatment assignment. Subjects were not encouraged to guess their treatment assignment and were encouraged to eat prior to varenicline intake and to take the medication with 240 mL of water." Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was ineffective.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was conducted ineffectively.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Subjects who withdrew or were lost to follow-up were assumed to be smokers for the remainder of the study." "Subjects completing the 12-week study ranged from 70.8% to 76.9% for the varenicline groups compared with 55.8% for placebo. Of subjects completing the treatment phase, 87.5% (n=344 from the varenicline groups and n=54 from the placebo group) signed another consent to enter the 40-week extension study. Of these, 309 (n=269 from the varenicline groups and n=40 from the placebo group) completed the week 52 visit." Three abstinence outcomes, PPA and 6 at 12 months and CAR at 12 months were extracted. All randomized participants were included in analysis. However, less than 80% of the participants completed the 12-week treatment and further less completed the 12-month assessment (ranging from 31% to 59%). Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Six safety outcomes, including SAE, CV event, mortality, CV mortality, suicidal ideation and completed suicide were extracted As above, judged a high risk of bias.

Study code: Ortega 2011 - 3

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"…were randomized, assigning each to one of the branches of the study, using a computerized algorithm according to whether they received NRT or not."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding not mentioned and probably not feasible due to different combing forms of interventions. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was not conducted.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely to be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"The state of the smoker 12 months after being discharged from the hospital was confirmed in 588 patients (82%) of those who had declined to participate in the study and in 1,640 (89%) of the randomized subjects. The lack of information or the loss to follow-up of the patients was considered a relapse in tobacco habit in the analysis of the results." One abstinence outcome, CAR at 12 months, was extracted. All randomized participants were included in the analysis. The overall completion rate of 89% was quite high, although the numbers and reasons of the early discontinuations in each arm were not provided. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Pack 2008 - 237

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The present study was an effectiveness study with a 2 (medication conditions) x 2 (psychosocial interventions) design. Participants were randomized to receive either…" "Randomization was done in 13 blocks of 36 participants, blocked by gender. Gender was used as a blocking variable because of hypothesized gender differences in response to nicotine replacement therapy." "Four hundred eight participants were randomized into 4 groups." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding not mentioned and probably not feasible in this study due to different combing forms of interventions. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding was not conducted.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely to be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Participants lost to follow-up at any point were considered as relapsed and analyzed as continuing smokers using an intent-to-treat analysis." "Overall follow-up rates at 8 weeks, 6 months, and 12 months were 64.0%, 72.8%, and 69.9%, respectively, with little variation between groups." Two abstinence outcomes, PPA at 6 and 12 months, were extracted. All randomized participants were included in the analysis. The reported data was collapsed across the Quit Line and Self-Help conditions due to no omnibus differences between counseling conditions and no interactions between groups (4-group to 2-group comparison). However, the overall completion rates at 6 and 12 months were less than 80%, which might probably bias the outcome estimate.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome, SAE, was reported, but not attributable to groups. No safety outcome of interest was extracted or inferred.

Study code: Paoletti 1996 - 643

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Smokers with cotinine plasma values ≤ 250 ng·mL^{-1} were randomly assigned to placebo (LC-P; n=60) or to 15 mg nicotine patch (LC-15; n=60). Smokers with cotinine plasma values >250 ng·mL^{-1} were randomly assigned to 15 mg nicotine patch (HC-15; n=90) or to 25 mg nicotine patch (HC-25; n=87)." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Therefore, to preserve blindness throughout the period of treatment, all subjects used two patches…" "The placebo patches did not contain nicotine and were identical in size, colour and other characteristics to the active ones; and, therefore, blindness of the study was maintained."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Finally, subjects who did not return for the scheduled visits and were lost to follow up were defined as "drop-outs." "The number of drop-outs increased through the follow-up, as expected, and they are considered as, "failures" for the analyses to estimate the success in the groups of treatment." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. At 26- and 52-week visits, 53% (158/297) and 67% (200/297) withdrew from the study, respectively. Judged a high risk of bias given that the overall completion rates were well below 80% and that the information of early discontinuations from each group was not provided.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a high risk of bias given the low completion rates and the lack of information.

Study code: Piper 2007 - 947

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Randomization was conducted in double-blind fashion using blocked randomization within each of the 10 cohorts." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	As above, but the blinding approach was not provided. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding was not conducted properly.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes would probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted properly.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Participants who could not be reached at follow-up were considered to be smoking for the purposes of follow-up analyses." "All analyses were intent-to-treat unless otherwise noted." Two abstinence outcomes, PPA at 6 and 12 months, were extracted. All randomized participants were included in the analysis. Thirty-one, 36 and 31 of participants in [bupropion + nicotine gum], [bupropion + placebo gum] and [2 placebos], respectively, early discontinued from the study. Overall, 73% (444/608) of the participants completed the 6 months assessment and 69% (417/608) completed the 12 months assessments. Judged a high risk of bias given that the overall completion rates were less than 80% and that the information of the early discontinuations was not provided.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a high risk of bias given the low completion rates and the lack of information.

Study code: Piper 2009-1253

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Randomization was double-blind and used a blocked randomization scheme with gender and self-reported race (white/non-white) as the blocking variables." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"There were five distinct placebo conditions, matched to each of the active treatment conditions (i.e., placebo bupropion, placebo lozenge, placebo patch, placebo patch + lozenge and placebo bupropion + lozenge… Staff did not know to which type(s) of medication i.e., patch, pill, and/or lozenge) a participant would be assigned until the moment of randomization, and study staff were blinded to whether the medication was active or placebo." "There were no statistically significant differences amongst the placebo conditions in 7-day point-prevalence outcomes at 1 week, end of treatment (EOT) or 6-months post-quit. Therefore, for all subsequent analyses, the placebo conditions were combined into a unified placebo condition."
Blinding of subjective outcomes' assessment?	Unclear	As above, blinding was maintained by using the matched placebos corresponding to the active drugs. However, three active drugs had different dose forms and a dummy approach did not seem to be conducted. Participants' or assessors' knowledge (preference) of the allocated form of drug after assignment would probably affect the subjective outcomes' assessment. Judged an unclear risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"All analyses were conducted using the intent-to-treat principle such that all smokers who were randomized to a treatment were included in the analyses and individuals with missing data were considered to be smoking." One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in the analysis. Overall, 94% (1414/1504) of the participants completed the 6-month assessment, with each groups' completion rates being higher than 92%. Judged a low risk of bias given the high completion rates.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV event and CV mortality were extracted; while one safety outcome, completed suicide, was inferred 0. As above, judged a low risk of bias given the high completion rates.

Study code: Pirie 1992 - 1238

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No method of sequence generation was provided.
Allocation concealment?	Unclear	Method of allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Low risk of bias as the study contained robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Unclear	No further information was given on the blinding of subjective outcomes, resulting in an unclear risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Completion rates were 98.3% ad 6 months and 98.1% at 12 months follow up. PPA and CAR were measured at both 6 and 12 months. Low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcomes were extracted or inferred.

Study code: Planer 2011-1055

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"In a double-blind, randomized controlled trial…" Method for sequence generation was not provided.
Allocation concealment?	Low	"Numbered study bottles were supplied by the study coordinator and remained concealed from the patients and medical staff."
Blinding of objective outcomes' assessment?	Low	"Participants were randomized to bupropion SR (hereinafter, bupropion group) or identical placebo."
Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained by using the identical placebo.

Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interested was available.
Incomplete outcome data addressed – for safety outcomes?	Low	"Primary efficacy and safety analyses were performed on an intent-to-treat basis." "Clinical and safety outcomes were all-cause mortality and any hospitalization at 1 year…Secondary safety outcomes included the event of an ACS or any chest pain during follow-up, adverse effects attributed to study medication, and change in blood pressure or body mass index (BMI)." Five safety outcomes, including SAE, mortality, CV event, CV mortality and completed suicide were extracted; while one, SAE, was inferred 0. As cited, all randomized participants were included in the analysis. Except for one participant in placebo group withdrawing from the study, all completed the follow-up assessment. Judged a low risk of bias given the high completion rate.

Study code: Prapavessis 2007-1416

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Participants from both conditions (i.e., EX and CBT) were then further randomised into two treatment conditions: those who received nicotine replacement therapy (NRT patches) and those who did not. This randomization procedure created four conditions: EX+nicotine patch; EX+no nicotine patch; CBT+nicotine patch and CBT+no nicotine patch." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned and probably not feasible due to the different combined interventions. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if it was an open label study.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Analyses were conducted by intent to treat which was based on the 121 participants who started the program." "At the 12-month follow-up, 77.4% of the CBT and 60.3% of the EX participants returned (p=.05)." Efficacy outcomes of CAR and PPA at 12 months were extracted. Except for 21 participants who dropped out within the preliminary session, all randomized participants were included in the analysis. The overall completion rate at 12 months was less than and the drop-out numbers were significantly different. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted

Study code: Puska 1979-141

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Participants to the courses were individually randomly allocated to the two groups at the beginning of each course." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Only Nicorette ® containing 4 mg of nicotine was used as active preparate. Placebo chewing gum was made to resemble active Nicorette ® in taste. People were asked to have a piece of chewing gum when they felt the urge to smoke--both during the course and afterwards as long as felt necessary. Neither the subjects nor the course leaders were aware who received active and who placebo gum."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interest was extracted.
Incomplete outcome data addressed – for safety outcomes?	High	"The amount of drop-out from the course (29%) was slightly smaller than the amount of drop-out from the similar courses without the trial (33%). The drop-outs did not differ much between the active and placebo groups;" Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were inferred 0. All randomized participants were included in the analysis. With 29% of the participants early discontinuing from the study, 72% (84/116) and 67% (76/113) in nicotine chewing and placebo group completed the half year follow-up assessment, respectively. Judged a high risk of bias given the low completion rate.

Study code: Puska 1995-231

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The subjects were randomly allocated to one of two groups…" Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The study was carried out in a strictly double blind fashion." "The gum only group received identical placebo patches. "
Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained by using the identical placebo.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Success was defined as continuously lapse-free abstinence after week 1 verified with a CO level in expired air of less than 10 ppm at all visits after week 1.""All subjects were included in the assessment of outcome." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. The respective completion rates in [nicotine patch + nicotine gum] and [placebo patch + nicotine gum] group were 77% (115/150) and 71% (107/150) at 6 months, and 70% (105/150) and 61% (92/150) at 12 months. Judged a high risk of bias given the less-than-80% completion rates and the lack of information regarding the early discontinuations.
Incomplete outcome data addressed – for safety outcomes?	High	"For safety assessment the subjects were asked at each visit about possible adverse events." Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were inferred 0. As above, judged a high risk of bias given the less-than-80% completion rates and the lack of information regarding the early discontinuations.

Study code: Ray 2007-1237

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The trial was an open-label randomized clinical trial of two forms of NRT for smoking cessation." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	As above, this was an open-label trial. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even in an open-label trial.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely to be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment in an open-label trial.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Of the 374 participants in the intent-to-treat analysis, 94% completed the EOT assessment and 95% completed the 6-month assessment." "Consistent with recommendations, we presumed that those who failed to complete the follow-up, or failed to provide a sample for biochemical verification, had relapsed…" One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in the analysis and the overall completion rate at 6 months was well greater than 80%. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Registered 2001 - 1

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	No method of sequence generation was provided.
Allocation concealment?	Unclear	Method of allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"A multi-center, double blind, placebo controlled, randomized, parallel group…." Bupropion and placebo followed same dosage regimen for the same duration during the study. Low risk of bias.
Blinding of subjective outcomes' assessment?	Low	As above, low risk of bias as the subjective outcomes were sufficiently blinded with placebo regimen and dosage as well as the double blind study design.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	CAR was measured at 6 and 12 months. Unclear as to what the completion rates for the study were.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Five safety outcomes for Deaths, SAE, CV deaths, CV events and Completed suicides were extracted from the study. Unclear as to the completion rates and the resulting risk of bias.

Study code: Reid 2008 - 68

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Randomization was computer generated, using permuted blocks of six, stratified by site and sex."
Allocation concealment?	Low	"A study statistician, who had no other contact with site study staff, performed the randomization, and staff were blind as to stratification and block size strategies."
Blinding of objective outcomes' assessment?	Low	Low risk of bias due to robust clinical or laboratory evidence.
Blinding of subjective outcomes' assessment?	Low	As above, randomization was blinded sufficiently and study sessions were done in closed group format to maintain blinding. Low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	PPA was measured at 6 months follow up. Completion rate was 142/153 (92.8%) for the SC group and 68/72 (94.4%) for the TAU group. Low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcomes were extracted or inferred.

Study code: Rennard 2006-555

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"This double-blind, parallel group, randomized, multicenter study" Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Subjects were randomized to receive either 10-mg nicotine inhaler (Nicotrol/Nicorette, Pfizer Consumer Healthcare) or a matched placebo inhaler identical to the active treatment with the nicotine excluded. Both inhalers included 1mg of menthol. The inhalers could be used ad libitum, with a recommended dose of 6–12 cartridges per day, for up to 12 months."

Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained by the use of identical inhaler and regimen.
Incomplete outcome data addressed – for efficacy outcomes?	High	"The primary analysis was performed on an intention-to-treat basis and included all subjects who were randomized and received medication. Subjects who withdrew early or were lost to follow-up were classified as failures." "A total of 154 subjects (89 active, 65 placebo) completed the 15-month study. Thus, 275 subjects dropped out during the study (126 active, 149 placebo)." Two abstinence outcomes, PPA at 6 and 15 months, were extracted. All randomized participants were included in the analysis. 41% (89/215) of the participants in nicotine inhaler group and 30% (65/214) of those in placebo inhaler group completed the 15-month assessment. Judged a high risk of bias given that the completion rates were both well below 80%.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcome, SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a high risk of bias given the very low completion rates.

Study code: Rennard 2012- 343

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"A predefined, central, computer-generated randomization sequence assigned subjects in a 3:1 ratio to receive either varenicline or placebo (block size: 4, stratified by center)"
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	"Those randomized to placebo received matched placebo dosing with identical appearance to varenicline." "In order to preserve the blind of the investigative centers, subjects, and sponsor, no unblinded data listings and tables were produced, other than for the Data Monitoring Committee, until data from the non-treatment follow-up period had been entered into a database and cleaned."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"The primary efficacy analysis population was all subjects randomized to treatment. Subjects who discontinued the study were assumed to be smokers from the point of discontinuation to end of study." "In total, 493 subjects were randomized to varenicline and 166 to placebo and were included in the efficacy analysis. Of these, 486 in the varenicline group and 165 in the placebo group received at least one dose of medication and were included in the safety analysis." "Study completion rates were similar for both study groups: 86.2% (n = 425) for varenicline and 84.9% (n = 141) for placebo." Two abstinence outcomes, PPA and CAR at 6 months, were extracted. All randomized participants were included in the analysis. The completion rates in both groups exceeded 80% and the reasons for early discontinuations seem parallel. The missing data would not bias the efficacy outcome estimate under the conservative approach where the subjects who discontinued the study were considered as smokers.
Incomplete outcome data addressed – for safety outcomes?	Low	"In total, 493 subjects were randomized to varenicline and 166 to placebo and were included in the efficacy analysis. Of these, 486 in the varenicline group and 165 in the placebo group received at least one dose of medication and were included in the safety analysis." Six safety outcomes, including SAE, mortality, CV events, CV mortality, suicidal ideation, and completed suicide were extracted. As above, judged a low risk of bias given the higher-than-80% completion rates and seemingly balanced missing data.

Study code: Richmond 1993-187

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"All patients were allocated according to random weekly assignment to one of three intervention groups... This method of patient allocation was viewed as less disruptive to the routine of general practice than a daily change of intervention group or individual random assignment." It is not clear how random weekly assignment was conducted.
Allocation concealment?	Unclear	As above, judged an unclear risk of bias.
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned and probably not feasible due to the different combined interventions. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if it was an open label study.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Of the 450 study patients, 132 (29%) fully participated in the study as planned and did not miss any of the scheduled visits. For Groups SBCN and SBC, this included 59 (30% of the 200) and 39 (26% of the 150) respectively, who attended the treatment and all subsequent visits." Four abstinence outcomes, PPA and CAR at each of 6 and 12 months, were extracted. All randomized participants were included in efficacy analysis. Given the low rates of full participants, the completion rate of 12-month efficacy assessment would likely be lower than 80%. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted.

Study code: Richmond 1994-130, Richmond 1997-27,617, Richmond 2007-282

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Treatment and control patches were arranged in random order by Mario Merrell Dow, Sydney, then issued sequentially to patients as they attended." Method for sequence generation was not provided.
Allocation concealment?	Low	As above, a central randomization was adopted and judged a low risk of bias.
Blinding of objective outcomes' assessment?	Low	"Subjects, counsellors and the principal investigators were blinded as to which patch the subjects received during treatment and follow up." "Subjects in the placebo group received patches which contained 1 mg nicotine in order to mimic the odour of the active patch."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Outcomes were determined on an intent-to-treat basis, with participants who failed to attend sessions of the program or brief visits for assessment at any point being regarded as continuing smokers." "The dropout rate at six months was 18% of subjects in the active patch group and 50% of those in the placebo group (χ^2=33.6; P<0.001)." Seven abstinence outcomes, including PPA and CAR at each of 6 and 12 months, CAR at 2 and 3 years, and PAR at 12 months, were extracted. All randomized participants were included in efficacy analysis. Given the significantly lower completion rate in placebo group at 6-month, it was judged to be a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were inferred 0. As above, judged a high risk of bias.

Study code: Rigotti 2006-1080

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Using a computer program, the study statistician generated a sequence of randomly-permuted blocks of 4 within strata formed by study site and daily cigarette consumption (<10 vs >10)."
Allocation concealment?	Low	"The study pharmacist used this sequence, concealed from enrollment staff, to assign participants to study arm. Subjects and study personnel, except the statistician and pharmacist, were blind to treatment assignment.
Blinding of objective outcomes' assessment?	Low	"Subjects were randomly assigned to sustained-release bupropion or identical placebo."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Primary efficacy and safety analyses were done on an intention- to-treat basis. Subjects who died before follow-up at 3 months (n=1) or 12 months (n=2) were excluded from efficacy analyses but included in safety analyses." Two abstinence outcomes, PPA and CAR at 6 months, were extracted. All randomized participants were included in efficacy analysis, except for 3 in each of bupropion and placebo group not receiving any medication and 2 in placebo group who die before the 12-month assessment. 67% (85/127) and 63% (80/127) of randomized participants in bupropion SR and placebo group completed the study, respectively. Judged a high risk of bias given that less than 80% completed the study and the approach to handling missing data were not provided.
Incomplete outcome data addressed – for safety outcomes?	High	Five safety outcomes, including SAE, mortality, CV mortality CV event and completed suicide, were extracted. All randomized participants were included in the safety analysis except for those 6 not taking any medication. Judged a high risk of bias given the low completion rates and the lack of approach to handling the missing data.

Study code: Rigotti 2010 - 221

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"The study sponsor conducted the randomization centrally using a computer-generated list that prespecified the order of treatment allocation."
Allocation concealment?	Low	"Study sites obtained treatment group assignments with a Web-based or telephone system." A central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	"A multicenter, randomized, double-blind, placebo-controlled trial" Participants were randomly assigned to take varenicline or placebo for 12 weeks and were followed up to week 52 in a blinded posttreatment phase" "Eligible participants were randomly assigned, stratified by study site, to varenicline … or to an identical placebo regimen." "Reported or observed cardiovascular events or deaths resulting from any cause were reviewed separately and adjudicated under blinded conditions by an independent event committee made up of 3 board-certified cardiologists who used a standard events manual."
Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Efficacy outcomes were assessed with an intention-to-treat analysis that included all randomized participants. Individuals who discontinued study participation or were lost to follow-up were counted as smokers from the time of study discontinuation." Four abstinence outcomes, PPA and CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. Both completion rates of varenicline (85.1%, 302/355) and placebo group (80.5%, 289/359) exceeded 80%. The missing data would not bias the efficacy outcome estimate under the conservative approach where the subjects who discontinued the study were considered as smokers.
Incomplete outcome data addressed – for safety outcomes?	Low	"Safety outcomes were assessed among participants who took at least 1 dose of study drug." Seven safety outcomes, including SAE, mortality, CV events, CV mortality, suicidal ideation, aggression and completed suicide were extracted. Two participants in varenicline and 9 in placebo group did not take any medication and therefore were not included in the safety analysis. As above, judged a low risk of bias given that the completion rates in both groups were greater than 80%. The amount of missing data would probably not bias the safety outcome estimate.

Study code: Rovina 2009 - 279

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects were randomly assigned to attend one of the four following smoking cessation programs for 19 weeks:" Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"This was an open-label study that recruited smokers from the Smoking Cessation Clinic…" An open label study, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"All subjects who discontinued treatment or were lost during the follow-up period were classified as failures." "…205 took part in the study. All of them completed treatment, while 184 (90%) completed the 12-month follow-up." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. Judged a low risk of bias given that the overall completion rate of 12-month assessment was well above 80%. The missing data should not bias the efficacy outcome estimate under the conservative approach where the subjects who discontinued the study were considered as smokers.
Incomplete outcome data addressed – for safety outcomes?	Low	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a low risk of bias given the high overall completion rate.

Study code: Russell 1993-1308 & Stapleton 1995-31

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The study had a double blind, placebo controlled, parallel group design with two thirds of subjects randomly allocated to active patches and one third to placebo patches." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The placebo patches were identical in size and appearance but contained no nicotine. A new patch was applied each morning to a dry, non-hairy area on the upper arm, trunk, buttock, or thigh and removed before going to bed." "Again both subjects and their doctors or nurses were blind to whether the dose increase was real or placebo. Criteria for offering an extra patch were…"
Blinding of subjective outcomes' assessment?	Low	As above, but judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"The main criterion of success was self reported complete abstinence from week 3 to one year, validated by a carbon monoxide concentration 6, 12, 26, and 52. Outcome was intention to treat basis with failure to attend for validation at any point being counted as a lapse to smoking." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. However, there was no information about the early discontinuations. Judged an unclear risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Unclear	"Analysis of side effects was based on all subjects (383 wearing active patches, 184 wearing placebo) who provided ratings at least once." Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged an unclear risk of bias given the lack of information about the early discontinuations.

Study code: Sachs 1993 - 1881

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects were sequentially and randomly assigned to receive either active or placebo patch treatment." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"A single-site, randomized, double-blind, outpatient, parallel-group, placebo-controlled trial…" Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which would not be biased if the blinding was not maintained properly.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was conducted ineffectively.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"Subjects who used any other smoking cessation aids (behavioral or pharmacological), did not return for their follow-up visits, or were unavailable for follow-up were classified as smokers." "The reason for subject dropout before the end of the trial was ascertained using a standard checklist." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. Although the dropout reasons were planned to be followed and ascertained, only the dropouts due to the adverse events were reported in the publication. Judged an unclear risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Unclear	"At each study visit, subjects were asked in an unprompted fashion by project personnel to describe any intercurrent symptoms, adverse experiences, or any other problems they might have had, whether or not they thought they were attributed to their use of the assigned patch." Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged an unclear risk of bias given the insufficient information about the early discontinuations.

Study code: Schmitz 2007-699

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The final sample of participants completing intake assessment and fulfilling all eligibility criteria (N=154) were randomly assigned to one of the four treatment groups using an urn procedure." Method for sequence generation was not provided.
Allocation concealment?	Low	"Investigators and research staff were blind to the randomization codes, which were kept by a faculty member independent of the research and treatment team."
Blinding of objective outcomes' assessment?	Low	"Sustained-release bupropion (300 mg/day; 150 mg/day for 3 days, followed by 150 mg twice daily) or matching unmarked placebo tablets were packaged in MEMS by the pharmacist and dispensed weekly by the nurse in double-blind fashion. Participants were told to take one tablet (150 mg) in the morning and one tablet (150 mg) in the evening with at least 8 hours, but not more than 12 hours, between doses." Also from the text, the two forms of psychotherapy, cognitive-behavior therapy and supportive therapy, were conducted in group therapy sessions and under the same schedule. The differences were only about the underlying theories and derived techniques.
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	Two abstinence outcomes, PPA at 6 and 12 months, were extracted. All randomized participants were included in the analysis, except for 4, 3, 2 and 1 in [placebo + supportive therapy], [placebo + cognitive-behavioral therapy] [bupropion + supportive therapy] and [bupropion + cognitive-behavioral therapy] group, respectively, not taking any treatment. The respective completion rates at 6 and 12 months were 35% (13/37) and 43% (16/37) in [placebo + supportive therapy] group, 46% (18/39) and 49% (19/39) in [placebo + cognitive-behavioral therapy] group, 38% (14/37) and 43% (16/37) in [bupropion + supportive therapy] group, and 37% (15/41) and 46% (19/41) in [bupropion + cognitive-behavioral therapy] group. Judged a high risk of bias given the low completion rates across the groups in which the missing data might be likely to bias the final outcome estimate.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Schneider 1983- 253

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"One hundred subjects were randomly assigned to nicotine or placebo gum conditions with concomitant individual therapy provided." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	**"**The main study consisted of a double-blind comparison of nicotine and placebo gum in a clinic-support setting.**" "** The placebo for this study was supplied and manufactured by the same groups. It is similar in appearance, texture and taste to the active gum.**"**
Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained by using placebo indifferent from nicotine gum.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	Two abstinence outcomes, PPA at 6 and 12 months, were extracted. All randomized participants were included in efficacy analysis. However, there was no information about whether all the included participants completed the 6- and 12-month assessment. The statistical strategy to handling missing data was not provided, either. Judged an unclear risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were extracted. As above, judged an unclear risk of bias.

Study code: Schneider 1995 – 1671

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects were randomly assigned to conditions and the trial was double-blind." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	A double-blind study but no blinding approach was described. However, drug blinding was tested: "In terms of identifying drug, active subjects thought they received active drug 76% of the time while 47% of placebo subjects guessed placebo. Conversely, 53% of placebo subjects thought they received active and 24% of active subjects thought they received placebo. These determinations are not broken down by length of time in the trial." It seemed that the blinding was maintained throughout the study.
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	Four abstinence outcomes, PPA and CAR at each of 6 and 12 months, were extracted. All randomized participants were included in efficacy analysis. However, there was no information about whether all the included participants completed the 6- and 12-month assessment. The statistical strategy to handling missing data was not provided, either. Judged an unclear risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were extracted. As above, judged an unclear risk of bias.

Study code: Schneider 1996 - 1293

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"A computer generated randomization list was prepared by the manufacturers."
Allocation concealment?	Low	"An independent "randomizer" packaged drug from the list. Subjects and all personnel connected with the trial (including the PI) were kept blind."
Blinding of objective outcomes' assessment?	Low	A double-blind study where the active and placebo inhaler seemed to be identical in every aspect except that "Each active inhaler contains 10 mg of nicotine and 1 mg of menthol. The menthol is added to decrease irritancy from nicotine. The placebo inhaler contains only menthol." The regimen of both arms was the same.
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"Number of subjects varied at each visit due to drop-outs but included those who slipped." Four abstinence outcomes, CAR at each of 6 and 12 months, were extracted. All randomized participants were included in efficacy analysis. However, there was no information about whether all the included participants completed the 6-month assessment, although there seemed to be some participants early withdrawing from the study. The statistical strategy to handling missing data was not provided, either. Judged an unclear risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were extracted. As above, judged an unclear risk of bias.

Study code: Schnoll 2010-144

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"…we randomly assigned participants at week -2 by using a computer-based randomization table provided by a statistician who used Stata, version 8 (StataCorp, College Station, Texas) and a computer program overseen by the database manager. A nonstratified randomization scheme was generated by sampling without replacement and by using small blocks of 20 participants."
Allocation concealment?	Low	As above, a central randomization was conducted. In addition, "Participants and all research personnel except the database manager blinded to randomization."
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned but judged a low risk of bias given that all outcomes assessments are objective and the appropriateness of blinding won't bias the outcome assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias. The blinding was easy to break for the group where participants used nicotine patch for the first 8 weeks, then placebo patch for the following 16 weeks.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Seven-day point prevalence abstinence is self-reported nonsmoking for 7 days before the assessment, verified by carbon monoxide level (≤10 ppm). We assumed that participants had smoked if they were lost to follow-up, could not provide a carbon monoxide sample, or had carbon monoxide levels greater than 10 ppm." "Completion rates at week 24 were higher for extended versus standard therapy (91% vs. 83%; P = 0.007), but completion rates at week 52 were similar for extended and standard therapy (83% vs. 79%; P = 0.23)." Five abstinence outcomes, CAR and PPA at each of 6 and 12 months and PAR at 6 months, were extracted. All randomized participants were included in efficacy analysis, except that 1 in the standard group and 6 in the extended group were found ineligible after randomization and did not take any medication. Although around 80% of the participants stayed in the study at week 52, both groups had less than 80% of those completing the 24- and 52-week efficacy assessments. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Unclear	Five safety outcomes, including SAE, mortality, CV mortality, CV event and completed suicide, were extracted. As above, judged an unclear risk of bias given that around 80% of the participants stayed in the study at week 52 but the approach to handling missing data was not provided.

Study code: Schnoll 2010-237

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Randomization was coordinated by FCCC and was stratified at each site." Method for sequence generation not provided.
Allocation concealment?	Unclear	As above, a central randomization was adopted.
Blinding of objective outcomes' assessment?	Low	"This was an open-label, randomized, Phase 4, effectiveness trial." An open trial but judged a low risk of bias given that all outcomes assessments are objective and the lack of blinding won't bias the outcome assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"…subjects who failed to complete assessments, failed to provide a breath sample, or provided a carbon monoxide (CO) sample ≥10ppm were considered smokers." "Nine individuals either withdrew from the study prior to treatment or were found to be ineligible after randomization and were removed from the intent-to-treat (ITT) sample. The final ITT sample was 642 (321/arm)." One abstinence outcome, PPA at 6 month, was extracted. All randomized participants were included in efficacy analysis, except for 9 who did not meet inclusion criteria and did not take any medication. 57% (182/321) and 52% (167/321) of participants in nicotine patch and nicotine lozenge group completed the study, respectively. Judged a high risk of bias given the completion rate of efficacy assessment. The approach to handling the missing data was not provided, either.
Incomplete outcome data addressed – for safety outcomes?	High	Five safety outcomes, including SAE, mortality, CV mortality, CV event and completed suicide, were extracted. As above, judged a high risk of bias given the low completion rates the lack of an approach to handling missing data.

Study code: Schnoll 2010-811

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"...patients were randomized to bupropion or placebo for 9 weeks." Method for sequence generation not provided.
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes' assessment?	Low	"This was a double-blind, placebo-controlled trial." Blinding approach not provided. However, judged a low risk of bias given that all outcomes assessments are objective and the appropriateness of blinding won't bias the outcome assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Analysis was based on intent-to-treat, with those with missing data at Week 12 and 27 data presumed to be smokers." "There was no significant difference across treatment arms in the rate of completion of Week 12 (bupropion = 74%; placebo = 81%; p = .17) or Week 27 (bupropion = 65%; placebo = 72%; p = .23) assessments." One abstinence outcome, PPA at 6 month, was extracted. All randomized participants were included in the analysis, except for 1 without any known reason. Judged a high risk of bias given that the completion rates at 27 weeks in both groups are lower than 80%. The conservative approach to regarding the participants with missing data as smokers could not justify the risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were extracted. As above, judged a high risk of bias given the low completion rates and the lack of an approach to handling missing data.

Study code: Schuurmans 2004 - 634

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Randomization was performed with a computer generated list that allocated to placebo (n = 100) or to active pre-treatment (n = 100)."
Allocation concealment?	Low	"Numbering of identical boxes containing patches was carried out prior to the study by a person not involved in the study. The treatment code was broken only after the last follow-up visit had been completed and the data recorded."
Blinding of objective outcomes' assessment?	Low	"This was a double-blind randomized study with parallel groups." Blinding approach was not provided. However, judged a low risk of bias given that all outcomes assessments are objective and the appropriateness of blinding won't bias the outcome assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"An intention-to-treat analysis was performed." One abstinence outcome, CAR at 6 month, was extracted. All randomized participants were included in the analysis. 73% (73/100) and 71% (71/100) of participants in pre-treatment nicotine patch and placebo patch group completed the 26-week assessment. Judge a high risk of bias given the lower-than-80% completion rates and the lack of an approach to handling missing data.
Incomplete outcome data addressed – for safety outcomes?	High	"Analysis of adverse events was performed for all follow-up visits after the quit date." One safety outcome, death was extracted; while one, SAE, inferred as 0. As above, judged a high risk of bias given the low completion rates and the lack of an approach to handling missing data.

Study code: Segnan 1991 - 239

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"At that time, the GPs were to offer recruitment to all eligible subjects who came to their office, following a predetermined randomized sequence of the four interventions…and blocked treatment-allocation was based on a sequence of random numbers" Method for sequence generation not provided.
Allocation concealment?	Low	"A package of closed, numbered envelopes containing the material pertaining to the interventions was provided to each GP at the beginning of the study. The envelopes were indistinguishable from the outside... The research staff checked physicians' compliance with the procedure for assignment by comparing envelope numbers and dates of recruitment."
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned and probably not feasible in this study due to different combination of interventions. However, judged a low risk of bias given that all outcomes assessments are objective and the appropriateness of blinding won't bias the outcome assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Two subjects could not be traced at one-year follow-up because of death, and six because of serious illnesses. Exclusion of these subjects from the analysis does not change the results. " Two abstinence outcomes, PPA at 6 and 12 month, were extracted. All randomized participants were included in the analysis. Overall, 99% (917/923) completed the 12-month efficacy assessment. Judged a low risk of bias given the high overall completion rate.
Incomplete outcome data addressed – for safety outcomes?	Low	None of safety outcome of interest was extracted or inferred.

Study code: Shiffman 2002-1267

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"...smokers returned to the study site and were randomized to receive the active or the placebo lozenges, ..." Method for sequence generation not provided.
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes' assessment?	Low	"… a randomized, double-blind, placebo-controlled parallel clinical trial…" Blinding approach was not provided. However, judged a low risk of bias given that all outcomes assessments are objective and the appropriateness of blinding won't bias the outcome assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not effectively conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"At each visit, participants who failed to maintain abstinence (assessed by self-report or results of carbon monoxide verification) were continued and followed up." "At each visit after week 2, participants who had smoked were discontinued; only continuous abstainers were retained and followed up. Participants who did not appear for a visit were counted as treatment failures." Two abstinence outcomes, CAR at 6 and 12 month, were extracted. By study design, only abstainers were staying in the study and followed up. Although the overall completion rate of efficacy assessment at 24 weeks (20%) was far less than 80%, it was judged a low risk of bias by the efficacy outcome definition and measurement.
Incomplete outcome data addressed – for safety outcomes?	High	"We also compared the percentage of participants in the active treatment and placebo groups who reported AEs." Two safety outcomes, SAE and mortality, were extracted; while two, CV mortality and completed suicide, inferred 0. All randomized participants were included in the safety analysis (Intent-to-Treat Population, from Table 5). However by study design, more than 80% of participants early discontinued from the study and were not followed up. There was no information about how the study handled the missing data, either. Judged a high risk of bias.

Study code: Shiffman 2009-96

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Using a 1:1 computer-generated randomization scheme, balanced across study sites and generated separately for the 2-and 4-mg groups, participants were randomized on a double blind basis to receive active or placebo gum..."
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes' assessment?	Low	"…a randomized double-blind placebo-controlled clinical trial to test the efficacy of nicotine gum (versus placebo) in assisting cessation through gradual reduction." Blinding approach was not provided. However, judged a low risk of bias given that all outcomes assessments are objective and the appropriateness of blinding won't bias the outcome assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Study visits were used to monitor for participants' achievement of initial abstinence. Participants who reported abstinence for at least a day, as verified by CO at ≤ 10 ppm (average of two measurements), were considered to have achieved initial abstinence…. participants who did not achieve initial abstinence after this time were excused from the remainder of the study and counted as treatment failures in subsequent analyses. Participants who achieved initial abstinence were scheduled for a follow-up visit 28–35 days after their first day of abstinence to assess 28-day continuous abstinence." Two abstinence outcomes, CAR at 6 and 12 month, were extracted. By study design that only abstainers were followed up, 66, 86 and 88 in placebo, nicotine gum 2mg and 4 mg group stayed in the study and, among them, 88%, 87% and 89% completed the 6-month efficacy assessment, respectively. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	"Participants with verified 28-day continuous abstinence were counted as successes on the primary outcome and scheduled for a follow-up visit 6 months from the beginning of treatment, at which time they reported on their smoking, gum use, and adverse events." Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were inferred 0. Per study design, more than 90% of participants early discontinued from the study and were not followed up. There was no information about how the study handled the missing data, either.

Study code: Simon 2004-1797

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"We assigned participants to the 2 study arms by using a computer algorithm to generate a random list of treatment assignments."
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes' assessment?	Low	"Participants randomized to the control arm of the study received an identical course of placebo. All study personnel engaged in providing interventions to participants were blinded to treatment assignment." Blinding approach (identical course only) did not seem sufficient to maintain the blinding of bupropion and placebo. However, judged a low risk of bias given that all outcomes assessments are objective and the appropriateness of blinding won't bias the outcome assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Of the 244 participants enrolled, 3 (1%) were lost to follow-up (all randomized to the placebo arm) and an additional 5 participants (2%) died during the study (2 bupropion-and 3 placebo-treated subjects). After excluding the 5 participants who died during the course of the study, 239 subjects were available for analysis" One abstinence outcome, CAR at 6 month, was extracted. All randomized participants were included in the analysis, except for 5 participants died during the study. Overall, 96% (236/244) completed the 12-month assessment. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome, mortality was referred; while SAE, inferred 0). As above, judged a low risk of bias given the high completion rate at the 12-month assessment.

Study code: Simon 2009 - 663

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"We assigned participants to the two study arms by using a computer algorithm to generate a random list of treatment assignments."
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes' assessment?	Low	"Participants randomized to the control arm of the study received an identical-appearing placebo. All study personnel engaged in providing interventions to participants were blinded to treatment assignment." "A greater number of participants randomized to the bupropion arm were able to correctly guess their treatment assignment: 45% for bupropion versus 22% for placebo (p = .10)."
Blinding of subjective outcomes' assessment?	Low	Although there are significantly greater number of participants randomized to the bupropion arm were able to correctly guess their treatment assignment, it was judged a low risk of bias given that the blinding approach was considered appropriate.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"We used an intention-to- treat analysis as the principal method to compare smoking cessation rates in the two treatment arms." "Of the 85 participants enrolled, 2 died during the study (1 bupropion and 1 placebo subject); thus, 83 subjects were available for the intention-to-treat analysis (see Figure 1). The two participants lost to follow-up and the seven participants who dropped out of the study were considered smokers in analyses that required biochemical or spousal confirmation of quitting." One abstinence outcome, CAR at 6 month, was extracted. All randomized participants were included in the analysis, except for 1 in each of [bupropion + counseling] and [placebo + counseling] group died during the study. 90% (38/42) in [bupropion + counseling] and 84% (36/43) in [placebo + counseling] completed the 6-month assessment. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	"We monitored side effects of the study medications during the telephone calls that took place at weeks 1, 3, 5, and 7 of follow-up." "Medical problems, such as coronary disease, chronic obstructive pulmonary disease (COPD), vascular disease, diabetes mellitus, hypertension, and tobacco-related malignancy (i.e., cancer of the lung, bladder, kidney, oropharynx, or larynx), were recorded based on participant interviews and, when available, chart review." Two safety outcomes, including SAE and mortality, were extracted. Although the safety assessment seemed to only focus on the 7-week treatment period, it was judged to be a low risk of bias given the low completion rates.

Study code: Sonderskov 1997-309

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"... 522 gave informed consent and were randomized by means of randomized sequential treatment packages." Method for sequence generation not provided.
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes' assessment?	Low	"To ensure that the nicotine and placebo patches were identical in terms of color and odor, the placebo patches contained a pharmacologically negligible amount of nicotine." "The blinding procedure was not broken until all main results were tabulated."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interested was available.
Incomplete outcome data addressed – for safety outcomes?	Low	"Participants lost to follow-up (n = 19) were classified as smokers." "The results were analyzed according to the "intention to treat" principle…" One safety outcomes, SAE, was extracted; while 3, including mortality, CV mortality and completed suicide, were inferred 0. All randomized participants were included in the analysis and, overall, 96% (503/522) of those completed the 26-week assessment. Judged a low risk of bias given the high completion rate.

Study code: Stein 2006-599

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"… randomization and group assignment occurred. The study interventionist then performed either the minimal or the maximal treatment. " Method for sequence generation not provided.
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes' assessment?	Low	"Follow-up research assessments were performed at 1, 3 and 6 months after study enrollment by research assistants blinded to participant group assignment." Blinding was not mentioned and probably infeasible in this study due to the different interventions in two groups, although blinding for assessor was maintained. However, judged a low risk of bias given that objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Our primary analysis used an intent-to-treat approach, with missing individuals presumed to have continued or resumed smoking." One abstinence outcome, PPA at 6 month, was extracted. All randomized participants were included in the analysis. In both comparison groups, the completion rate at 6-month assessments exceeded 80%. Judged a low risk of bias given that the amount of missing data would probably not bias the effect estimate.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Steinberg 2009 - 447

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"We created computer-generated randomization tables by using block sizes of 4 by the 4 combinations of cigarette consumption (< 20 cigarettes/d or ≥ 20 cigarettes/d) and severity of medical illness (moderate [cardiovascular risk factors or tobacco caused symptoms] or severe [cardiovascular disease, cancer, or chronic pulmonary disease])."
Allocation concealment?	Low	"The research nurse called a staff member (unaffiliated with the study) to record the participant on the randomization table, and he or she relayed back the treatment assignment. The assignment was not revealed to the nurse until after the participant was randomly assigned."
Blinding of objective outcomes' assessment?	Low	"…we did not blind treatment assignment…" An open label study but judged a low risk of bias given that objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding design should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Analyses were conducted on an intention-to-treat basis with participants who were lost to follow-up (patch alone [n=13] and combination therapy [n=18]) classified as still smoking." "Overall, 24% (31 of 127) of participants were lost to follow-up by 26 weeks (20% [13 of 64] in the patch alone group and 28% [18 of 63] in the combination group; P= 0.28)." One abstinence outcome, PPA at 6 month, was extracted. All randomized participants were included in the analysis. Judged a high risk of bias given that the completion rates at 26 weeks in both groups are lower than 80%. The conservative approach to regarding the participants with missing data as smokers could not justify the risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Five safety outcomes, including SAE, mortality, CV mortality, CV event and completed suicide, were extracted. As above, judged a high risk of bias given the low completion rates and the lack of an approach to handling missing data.

Study code: Steinberg 2011 - 1127

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Subjects were randomized in a 1:1 ratio through a centralized telephone randomization process by the study statistician and hospital research pharmacist." Sequence generation judged to be a low risk of bias.
Allocation concealment?	Unclear	Method of allocation concealment is not provided.
Blinding of objective outcomes' assessment?	Low	"The subject, research nurse, and treatment staff were blinded to treatment assignment." Judged to be a low risk of bias.
Blinding of subjective outcomes' assessment?	Low	As above, description of sufficient blinding and placebo control was provided. Judged to be a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	Longest follow up was 24 weeks, no reported 6 or 12 month follow-up. Completion rates were 22/40 (55%) for the varenicline arm and 21 out of 39 (54%) for the placebo arm. Judged to be a high risk of bias for efficacy outcomes.
Incomplete outcome data addressed – for safety outcomes?	High	Five safety outcomes were reported for the study, Deaths, SAE, CV deaths, CV events, and Completed suicide. Judged to be a high risk of bias as completion rates are well below 80%.

Study code: Sutherland 1992 - 324

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"They drew a card marked A or P for allocation to active or placebo group, respectively."
Allocation concealment?	Unclear	Method of allocation concealment is not provided.
Blinding of objective outcomes' assessment?	Low	"Subjects and therapists were blind to spray assignment…The placebo spray contained black pepper oleo resin (piperine) to mimic the sensation of nicotine in the nasal spray." Very effective methods of binding for the objective outcomes.
Blinding of subjective outcomes' assessment?	Low	As above, effective methods of blinding of subjective outcomes result in low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	Both CAR and PAR were measured at 6 and 12 months follow-up. "On average, 96% in the active group and 95% in the placebo group were followed up at each of the five occasions." Judged as a low risk of bias due to a high rate of completion.
Incomplete outcome data addressed – for safety outcomes?	Low	Safety outcome of CV events was reported and 4 other outcomes of Deaths, SAE, CV deaths, and Completed suicide were all inferred. Judged to be a low risk of bias.

Study code: Sutton 1987 - 1210

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	" Of these (interested in smoking cessation), a randomly selected 270 were sent a personal invitation from the chief medical officer to take part in a program…the remaing 64 smokers were not sent an invitation and became a randomized no-intervention control group." Method of sequence generation is not provided.
Allocation concealment?	Unclear	Method of allocation concealment is not provided.
Blinding of objective outcomes' assessment?	Low	"There was a small amount of contamination between groups in that four members of the control group asked for and were given treatment." Judged as a low risk of bias due to robust clinical or

		laboratory evidence.
Blinding of subjective outcomes' assessment?	High	Judged to be a high risk of bias as there was contamination between treatment and controls.
Incomplete outcome data addressed – for efficacy outcomes?	Low	PAR and CAR were measured at 12 months follow-up. "All but three of the 334 cigarette smokers were contacted, a follow-up rate of 99 per cent, although 31 were not seen in person." A completion rate of 303/334 (90.7%) . Judged to be low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome was extracted or inferred.

Study code: Swan 2003 - 2337

Item	**Authors' Judgment**	**Description**
Adequate sequence generation?	Low	"…The participants were randomly assigned to treatment group by a procedure built into the study database that used a random-number generator. The computer code for the procedure calculated probabilities of group assignment…" Judged to be a sufficient method of sequence generation and a low risk of bias
Allocation concealment?	Unclear	Method of allocation concealment is not provided.
Blinding of objective outcomes' assessment?	Low	"In actual practice setting, patients are prescribed active medication and know the dose they are prescribed. Therefore, to maintain fidelity with actual practice, the study did not include a placebo control group and was not blinded." "Participants randomized to the 150 mg groups were prescribed 1 pill per day; those randomized to the 300 mg group were prescribed 1 pill twice per day." Low risk of bias for objective outcomes.
Blinding of subjective outcomes'	High	As above, no blinding occurred and the dosages of the pills differ between the two treatment arms, leaving room

assessment?		for bias. Judged to be a high risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"At 12 months, 223 participants (14.6%) did not complete the follow-up." "…This study was conducted in an actual practice setting and relied entirely on telephone and mailed interaction between study participants and project staff…" Measurements of efficacy outcomes were not recorded or extracted due to no biochemical verification. Judged as a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	Two safety outcomes of Deaths and CV deaths were extracted at 0 and SAE as well as Completed suicide were inferred. As above, low risk of bias due to high response rates.

Study code: Tashkin 2001 – 1571

Item	**Authors' Judgment**	Description
Adequate sequence generation?	Low	"Randomisation was done according to a randomisation code provided by GlaxoWellcome, using block sizes of four stratified by centre. Within each block of four, two participants were assigned placebo and two bupropion SR." Method for sequence generation not provided.
Allocation concealment?	Low	In addition to the above, "The randomisation codes were kept at the study sites during the trial and we instructed investigators to break the code only for a medical emergency."
Blinding of objective outcomes' assessment?	Low	Eligible individuals were randomly assigned bupropion SR 150 mg once daily for days 1–3, followed by 150 mg twice daily for days 4–84, or matching placebo in a 1/1 ratio.
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"We did all analyses on the intention-to-treat population, which consisted of patients who took at least one dose of study medication. All participants who withdrew from the study were taken to be smokers thereafter." Two abstinence outcomes, PPA and CAR at each of 6 months, were extracted. All randomized participants were included in the analysis. With 126 participants early discontinuing from the study, 73% (149/204) and 65% (129/200) of the participants in bupropion and placebo group completed the 6-month assessment, respectively. Judged a high risk of bias given that the lower-than-80% completion rates. The conservative approach to regarding the participants with missing data as smokers could not justify the risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	"The frequency and nature of adverse events were recorded at each clinic visit during the treatment phase." Two safety outcomes (SAE and CV event) were extracted; while 3 (mortality, CV mortality and completed) extracted. In addition to the low completion rates described above, the study seemed to only observe participants' safety during the 12-week treatment. The approach to handling missing safety data was not provided, either. Judged a high risk of bias.

Study code: Tashkin 2011 – 591

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Eligible participants were randomized at the baseline visit to receive either varenicline (0.5 mg once daily for 3 days, 0.5 mg bid for 4 days, then 1.0 mg bid, for a total of 12 weeks) or placebo (with identical regimen)." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding approach was only about the identical regimen but not about the blinding of 2 drugs. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Participants who discontinued the study were assumed to be smokers from the point of discontinuation through the end of study. The primary and secondary end points in all randomized participants who took at least one dose of study medication were analyzed…" Four abstinence outcomes, PPA and CAR at each of 6 and 12 months, were extracted. All randomized participants were included in the analysis, except for 2 in varenicline and 3 in placebo group not receiving any medication.70% (176/250) and 62% (157/254) of the participants in varenicline and placebo group completed the study, respectively. Judged a high risk of bias given that the lower-than-80% completion rates. The conservative approach to regarding the participants with missing data as smokers could not justify the risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	"Safety data were assessed in all participants who received study medication. These data were evaluated according to the incidence and type of AEs and SAEs; the incidence of abnormal laboratory parameters; and the change from baseline in laboratory parameters, vital signs, and body weight." Six safety outcomes, including SAE, mortality, CV mortality, CV event, suicidal ideation, completed suicide and aggression, were extracted. As above, judged a high risk of bias given the low completion rates and the lack of an approach to handling missing safety data.

Study code: Transdermal Nicotine Study Group 1991 - 3133

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"In trial 1, five centers enrolled 513 patients who were randomized to one of four treatments: 21-, 14-, or 7-mg transdermal nicotine or placebo. Trial 2 enrolled 422 patients at four centers and was identical to trial 1 except that the 7-mg transdermal nicotine dose was omitted." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Two parallel, 6-week, multicenter, double-blind trials (trials 1 and 2) and an 18-week continuation trial (trial 3) were conducted." "Placebo systems contained nicotine in the drug reservoir to mimic the odor of active systems but delivered less than 1 mg of nicotine in 24 hours." "Because concordance between married subjects could bias results, married partners were assigned (randomly) to identical study regimens. Only one partner chosen randomly, however, was included for analysis."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"A total of nine subjects (1%) were excluded from further analysis because of major protocol violations." "Overall, 250 patients (27%) withdrew from the study prematurely, 151 patients (23%) receiving active treatment and 99 patients (37%) receiving placebo (P<.001)…. Significantly fewer patients receiving active treatment than placebo withdrew due to lack of efficacy." One abstinence outcome, CAR at 6 months, was extracted. After pooling trial 1 and 2, it seemed that not all randomized participants were included in the analysis (table 3), with 13, 21 and 18 participants in nicotine patch 21 mg, nicotine patch 14 mg and placebo patch group were lost, respectively, and the related information was partly provided. In addition, the completion rates of three groups were less than 80%. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcome, SAE, mortality, CV mortality and completed suicide were inferred 0. As above, judged a high risk of bias.

Study code: Tonnesen 1988 - 15

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"On the basis of age, sex, cigarette consumption, and health status, each participant was assigned to one of 32 lists, 16 for the high-dependence group and 16 for the medium-or-low dependence group; the subjects on each list were then randomly assigned to treatment in blocks of two." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"This double-blind placebo-controlled dose-response study..." ""The placebo gum, 2-mg nicotine gum, and 4-mg nicotine gum, manufactured and supplied by A. B. Leo, Sweden, did not differ in appearance. The 2-mg and 4-mg nicotine gum contained nicotine bound to a resin (for "slow release"), a hydrocarbonate buffer (which increased buccal absorption of the nicotine), and sorbitol (190 mg). The placebo gum contained capsaicin to simulate the taste of nicotine. "
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"All subjects who attended the first group counseling session were included in our calculation of the results of this study, even though some were absent from sessions and some did not use the nicotine gum at all. In computing results, we counted only subjects who completely abstained from smoking and whose carbon monoxide concentration was below 6 ppm as nonsmokers. " "Only 2 of the 173 subjects were lost to follow-up." Three abstinence outcomes, CAR at 6, 12 and 24 months, were extracted. All randomized participants were included in the analysis. Overall, 99% (171/173) of the randomized participants completed the study. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	One safety outcome, SAE, was extracted and three (mortality, CV mortality and completed suicide) were inferred 0. As above, judged a high risk of bias.

Study code: Tonnesen 1988 - 17

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"One hundred and seventy-two persons who returned a questionnaire by mail were randomly allocated to 2 mg nicotine gum (62), 4 mg gum (54), or to a control group (56)." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The study was open, and in each group some used 2 mg and some 4 mg gum. We told them that we did not expect any difference in the effect of 2 and 4 mg pieces of gum as there was no upper limit to the number of pieces of gums used daily." An open label study, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Six persons (5.2%) in the gum group and six persons (10.7%) in the control group did not respond to follow-up. All were considered failures. " Three abstinence outcomes, PPA at 6, 12 and 22 months, were extracted. All randomized participants were included in the analysis. Overall, 93% (160/172) of the randomized participants completed the follow-up. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were inferred 0. As above, judged a low risk of bias given the high overall completion rate.

Study code: Tonnesen 1991 - 311+Tonnesen 1992-241+Mikkelsen 1994 95

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"The subjects were sequentially and randomly assigned to either active treatment or placebo according to a computer-generated randomization code. Patches were packaged and labeled with consecutive numbers. "
Allocation concealment?	Unclear	As above, the group allocation should be concealed.
Blinding of objective outcomes' assessment?	Low	"The placebo patches were identical to the active patches in appearance, packaging, and labe3ling, but contained no nicotine. " "Fifty-eight percent of the subjects with the placebo patch and 78 percent of those with the nicotine patch correctly guessed which treatment they had received. However, there was no significant difference in outcome between those who identified the treatment correctly and those who did not. "
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"All 289 subjects who attended the first session were included in the assessment of outcome. …Success was defined as a statement that smoking had ceased, verified by a concentration of carbon monoxide of 10 ppm or less in expired air at all sessions after the first week. " "Three subjects were completely lost to follow-up after 26 weeks." Four abstinence outcomes, CAR at 12 months, and PAR at 1, 2 and 3 years, were extracted. All randomized participants were included in the analysis. The overall completion rate for the 12-month study was as high as 99% (286/289). Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	Two safety outcomes, including SAE and mortality, were extracted. As above, judged a low risk of bias although the safety assessment seemed to only cover the 12-week treatment period.

Study code: Tonnesen 1993 - 1268

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"The subjects were randomly assigned to either active nicotine inhaler or placebo inhaler treatment. The randomization code for assignment to either active or placebo inhaler was generated by a computer program. "
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The placebo inhaler contained only the additive and was identical in appearance to the active inhaler." "At the 1-year follow-up 232 subjects were asked if they knew what treatment they had received. Forty-six percent on active treatment and 58% on placebo identified the treatment correctly, 13% on active treatment and 15% on placebo guessed wrong, and 42% on active treatment and 27% on placebo did not know which treatment they had received."
Blinding of subjective outcomes' assessment?	Low	As above, the blinding was maintained through the study and confirmed in the end of study. Judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"All 286 subjects attending the first session were included in the calculation of continuous smoking abstinence." "Six subjects were unavailable for follow-up, and seven subjects were excluded because of protocol violation." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. The overall completion rate for the 12-month study was as high as 95% (273/286). Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome, SAE, was extracted, and three (mortality, CV mortality and completed suicide) were extracted. As above, judged a low risk of bias given the high overall completion rate.

Study code: Tonnesen 1996 - 1619

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"This was an open randomized study with active NNS. " Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	An open label study and the blinding were infeasible due to the different treatment schedules (*ad libitum* use versus fixed schedule). However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Subjects lost to follow-up were assumed to be smokers. All randomized subjects were included in the outcome calculations." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. It is not clear whether all participants were followed up at 6 and 12 months. However from Table 4, it seemed that the participants continuously discontinuously withdrew in 6-week treatment. At 6 weeks, 48% (43/89) of the randomized participants were observed for side effects of nicotine nasal spray use. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were extracted. As above, judged a high risk of bias given the low overall completion rate.

Study code: Tonnesen 1999 - 238

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"A computer-generated allocation list was prepared centrally and allocated subjects to treatment numbers. Randomization, which was stratified only by centre, took place at enrolment day in each centre. The five treatment groups were balanced in equal numbers within centres. "
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	"Active and placebo patches were identical in appearance and packaging. In order to maintain blinding, all subjects continued to use two patches for a total of 26 weeks i.e. active patches were replaced with placebo patches in the short duration groups. To gradually taper the nicotine patch dose by the same fraction for both the high and standard dose and also because of the two patch sizes available in the study, the tapering doses were 25±15±10 mg and 15±10±10 mg."
Blinding of subjective outcomes' assessment?	Low	As above, the blinding was maintained through the study. Judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Subjects were classified as failures in cases of a missing CO verification, a missing visit, or use of other nicotine containing products. Subjects who did not attend a scheduled visit in spite of two requests to do so were also considered failures." "The rate of attendance decreased with time: 2,815 (78%) smokers attended at 4 weeks, whereas 2,367 (66%), 1,965 (55%), 1,506 (42%), 1,271 (36%), and 1,792 (50%) attended the study at weeks 8, 12, 22, 26 and 52, respectively. An extra effort was made to get subjects to return at the twelve-month follow-up." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants were included in the analysis. The overall completion rates for the 6- and 12-month study were less than 80% with varied reasons. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Three safety outcomes, including mortality, CV mortality and completed suicide, were extracted. As above, judged a low risk of bias given the low overall completion rates.

Study code: Tonnesen 2000 - 717

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Subjects included in the study were allocated to 1 of 4 treatment arms by a computer-generated list with random numbers. "
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"This was an open randomized study." An open label study and the blinding were infeasible due to the different forms of treatments. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"When the subjects relapsed, most would not attend the clinic again, resulting in an attendance rate of 68% after 2 weeks, 43% after 6 weeks, 28% after 12 weeks, and 11% after 1 yr. Most of those who did not show up at the follow up studies were contacted by telephone and almost all had relapsed and were smoking again." Three abstinence outcomes, CAR at 6 and 12 months and PPA at 12 months, were extracted. All randomized participants were included in the analysis. However, less-than-28% and 11% of the randomized participants completed the 6- and 12-month assessment, respectively. Judged a high risk of bias given the low overall completion rate. The approach to handling missing data was not provided, either.
Incomplete outcome data addressed – for safety outcomes?	Low	No safety outcome of interest was extracted or inferred.

Study code: Tonnesen 2003-184

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Subjects eligible for enrolment were randomized in a 3 : 1 ratio to receive bupropion SR 150 mg twice daily or placebo throughout the 7-week treatment phase." "GlaxoSmithKline created a randomization schedule in a 3: 1 bupropion: placebo ratio. Each centre received a lwast with treatment numbers and subjects were consecutively assigned a treatment number at the baseline visit."
Allocation concealment?	Low	As above, a central randomization was conducted and the allocation concealed.
Blinding of objective outcomes' assessment?	Low	"GlaxoSmithKline supplied bupropion SR 150 mg and placebo-to-match tablets for oral administration as white, film-coated tablets. The tablets were manufactured and packed in bottles by GlaxoWellcome, Zebulon, North Carolina, USA. Bupropion SR 150 mg or placebo were administered once daily during days 1–3 of the 7-week treatment phase and then twice daily for the remainder of the treatment phase. Medication and all visits were free of charge."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Premature discontinuation from the study (treatment and follow-up phases) was greater for placebo (43%) than for bupropion SR (33%). Primary reasons for discontinuation were adverse events (8% bupropion SR vs. 6% placebo), consent withdrawn (10% bupropion SR vs. 16% placebo) and lost to follow-up (9% bupropion SR vs. 12% placebo). A total of 457 subjects (65%) – 355 in bupropion SR group and 102 in placebo group – attended the 1-year visit." Four abstinence outcomes, CAR and PPA at each of 6 and 12 months, were extracted, respectively. All randomized participants were included in the analysis. However, the overall completion rate of 65% was less than 80%. The approach to handling missing data was not provided Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Two safety outcome, SAE and mortality, were extracted. As above, judged a high risk of bias given the low overall completion rate.

Study code: Tonnesen 2006-334

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Patients were allocated to one of the four treatment groups using a block randomization list at each center. " Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The placebo tablets were identical in appearance to the active tablet but contained 3 μ of capsaicin and no nicotine."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"The analysis of treatment effect was calculated on an intention-to-treat basis, with subjects who withdrew regarded as failures and included in the outcome analyses." "At the 1-year visit, 288 patients were followed up: 114 patients attended a clinic visit, and 174 patients were contacted by telephone (Fig 1). Eighty-two patients (22%) were not available for follow-up;" "As there was no statistical interaction between treatments, ie, no effect modification between behavioral support and sublingual medication for all outcome measures…" Three abstinence outcomes, PPA at 6 and 12 months and CAR at 12 months, were extracted. All randomized participants were included in the analysis. Overall, 31% (114/370) of the randomized participants completed the 12-month assessment. Judged a high risk of bias given that low overall completion rate. The approach to handling missing data was not provided, either.
Incomplete outcome data addressed – for safety outcomes?	High	Two safety outcomes, SAE and mortality, were extracted by the medication groups (nicotine sublingual tablet vs. placebo). As above, judged a high risk of bias given the low overall completion rate.

Study code: Tonnesen 2012-548

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Allocation to treatment group was based on a subject randomization list stratified by study site. The supply or resupply of study medication to a subject was determined via an interactive voice response system involving a dispenser pack number randomization list. Both randomisation lists were computer-generated and were devised by the Biometrics and Clinical Data Systems Department, McNeil-PPC, Inc., Fort Washington, PA, USA. "
Allocation concealment?	Low	As above, a central randomization was conducted.
Blinding of objective outcomes' assessment?	Low	"All study medications were manufactured by McNeil AB, Helsingborg, Sweden. The NMS (1 mg of nicotine per spray after priming) and placebo spray contained 150 metered spray doses for administration into the mouth. The nicotine solution was clear to weakly opalescent, colourless to light yellow, with a peppermint scent. The placebo was identical in appearance, but contained capsaicin instead of nicotine to mimic the taste of nicotine."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Any subject who missed the visit(s) at week(s) 8, 16 and/or 20, or for some other reason had missing CO value(s) at one or more of these visits, was not regarded a treatment failure if the subject was verified continuously abstinent at a later visit." "All randomised subjects received study medication and were included in both the full (intention-to-treat) and safety analysis sets." Three abstinence outcomes, CAR at 6 and 12 months and PPA at 12 months, were extracted. All randomized participants were analyzed. 47% (75/161) and 53% (167/318) of participants in placebo and nicotine mouth spray group completed the study, respectively. Judged a high risk of bias given the completion rates were lower than 80%.
Incomplete outcome data addressed – for safety outcomes?	High	Three safety outcomes, SAE, mortality and CV mortality, were extracted. As above, judged a high risk of bias given the completion rates were lower than 80%. The approach to handling the missing data was not provided, either.

Study code: Tonstad 2003 - 946

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Participants were then randomised in a 1:1 ratio to receive either bupropion SR (150 mg/day on days 1–3; 150 mg twice daily on days 4–49) or placebo during the 7-week treatment phase." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"We performed a multicentre, randomised, double blind, placebo-controlled study in subjects from 28 centres across 10 countries." Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was conducted ineffectively.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Subjects with missing investigator assessments were assumed to be smokers at that visit." "After 52 weeks, 120 (38%) patients receiving bupropion SR and 155 (50%) receiving placebo had prematurely discontinued treatment." Four abstinence outcomes, PPA and CAR at 6 and 12 months, were extracted, respectively. All randomized participants were included in the analysis, except for 2 in bupropion group and 1 in placebo group not taking any medication. The 12-month completion rates in two arms were less than 80%. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	"Vital signs were recorded throughout the study, and adverse events were recorded throughout the treatment phase and up to week 9. All serious adverse events were collected throughout the treatment phase, after which only serious adverse events related to study medication were recorded." Three safety outcomes, SAE, mortality and CV events, were extracted. As described, the safety observation did not cover the whole study period and the approach to handling the missing data was not provided. In addition, the completion rates were lower than 80%. Judged a high risk of bias.

Study code: Tsai 2007 - 1027

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Eligible subjects were randomized, using the method of randomly permuted blocks (block size = 4), and assigned to receive varenicline or placebo in a ratio of 1:1. Investigators obtained subject identification numbers and study drug assignments via a Web- and telephone-based drug management system that assigned subjects at the baseline visit in the order in which they were deemed eligible for treatment. Knowledge of treatment assignments was withheld from those directly involved with the operation of the study, including study subjects, study investigators and their staffs, and sponsor personnel involved in clinical operations."
Allocation concealment?	Low	As above, central randomization was conducted and the allocation was concealed.
Blinding of objective outcomes' assessment?	Low	"A randomized, double-blind, placebo-controlled, multicenter clinical trial." Blinding approach was not provide, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was conducted ineffectively.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Analyses of efficacy were conducted on all subjects who received ≥1 dose, including partial doses, of ran randomized study medication… Subjects who dropped out of the study were classified as nonresponders for the remainder of the study." Two abstinence outcomes, PPA and CAR (from 9 to 24 weeks) at 6 months, were extracted. All randomized participants were included in the analysis. 95% (120/126) and 94% (117/124) of the randomized participants in varenicline and placebo group completed the 6-month assessment, respectively. Judged a low risk of bias given the very high completion rates.
Incomplete outcome data addressed – for safety outcomes?	Low	"All observed or self reported adverse events (AEs) were recorded on case-report forms and followed up until resolved or to the study end. The severity, duration, date of onset, action taken, and the suspected relationship to study drug of all AEs were recorded at each visit. AEs at any dose that resulted in death, were life threatening, required hospitalization, or resulted in significant disability were classified as serious AEs." One safety outcomes, SAE, was extracted, while three (mortality, CV mortality and completed suicide) inferred 0. As above, judged a low risk of bias given the very high completion rates.

Study code: Tsukahara 2010 - 771

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"They were randomized within 4 weeks by computer in a 1:1 ratio… Based on the smoking population of Japan (40% of males, 12% of females), randomization was conducted with a male: female ratio of 3:1."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"This was a randomized controlled open comparative trial of varenicline vs nicotine patch in adult smokers." An open trial, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interested was available.
Incomplete outcome data addressed – for safety outcomes?	Low	"The primary endpoint of this trial was the incidence of smoking cessation in the 2 groups at weeks 9-12 and weeks 9-24, and the safety and withdrawal symptoms, including stress, at weeks 12." "…adverse effects, including the results of laboratory examinations, were monitored." Four safety outcomes, including SAE, mortality, CV mortality and completed suicide were inferred 0. All randomized participants seemed to be included in the analysis. Two in each of varenicline and nicotine patch group dropped out during the followed up. Both groups had the completion rate of 88% for the 24-week safety assessment. Judged a low risk of bias.

Study code: Uyar 2007 - 922

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Members were randomly allocated to nicotine patch, bupropion and control group." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned and probably not feasible in this stud due to different forms of treatments. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Declaration of quitting and CO levels less than 10 ppm was accepted as success criteria. Smoking at least one cigarette per day was regarded as failure." "Four patients discontinued bupropion treatment because of oral aphthac (n=1), hallucination (n=1) and sexual dysfunction (n=2). Whereas one patient discontinued nicotine patch therapy due to oral aphthac formation." One abstinence outcome, PPA at 6 months, was extracted. All randomized participants seemed to be included in the analysis. 92% (46/50), 98% (49/50), and 100% (31/31) of participants in nicotine patch, bupropion SR and placebo group completed the 6-month assessment. Judged a low risk of bias given the high completion rates.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome, CV events, was extracted, whereas four (SAE, mortality, CV mortality, and completed suicide) inferred 0. As described, judged a low risk of bias given the high completion rates.

Study code: Wagena 2005-2286

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Randomization was done according to a computer-generated randomization list provided by the pharmacist of Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands, stratified for COPD severity, using blocks of 33. Patients were stratified based on the definition provided by the European Respiratory Society."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Our study was a blinded, placebo-controlled, double-dummy randomized trial." "Pharmacin BV, Zwijndrecht, the Netherlands, produced placebo bupropion and placebo nortriptyline and film coated the placebo and active bupropion tablets to maintain the patency of the bupropion formulation." "All statistical analyses were done with blinding maintained." "A panel of 3 judges (including P.G.K.) concluded that placebo bupropion and placebo nortriptyline matched the active formulations perfectly in appearance…At both time points, participants could not distinguish between bupropion SR and nortriptyline treatments. Blinding of the study staff (nurses, counselors, main investigator, and outcome assessor) was not evaluated."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"Participants lost to follow-up were considered to be smokers in the intention-to-treat analysis." Two abstinence outcomes, PPA and CAR at 6 months, were extracted. All randomized participants were included in the analysis. 88% (76/86) and 87% (77/89) of the participants in bupropion SR and placebo group completed the 26-week assessment. The reasons for the early discontinuations in two groups also seem parallel. Judged a low risk of bias.
Incomplete outcome data addressed – for safety outcomes?	Low	Four safety outcomes, including SAE, mortality, CV mortality, and completed suicide, were extracted. As above, judged a low risk of bias.

Study code: Wallstrom 2000 - 1161

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Subjects were randomized to receive either active or placebo treatment using a computer program."
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The placebo tablet used was identical in appearance to the active tablet but contained only capsaicin 3 l g." "All medication was dispensed by staff who were not involved in treating the subjects." "Treatment groups were revealed after the study was completed."
Blinding of subjective outcomes' assessment?	High	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"The primary efficacy evaluation was an intent-to-treat analysis." Two abstinence outcomes, CAR at 6 and 12 months, were extracted. All randomized participants, including 3 in nicotine sublingual tablet and 4 in placebo group not taking any medication. Overall, 99% (245/247) of the randomized participants completed the 12-month assessment. Judged a low risk of bias given the very high completion rates.
Incomplete outcome data addressed – for safety outcomes?	Low	"Adverse events were also recorded at each visit, elicited using open-ended general questions." Two safety outcome, SAE and CV events, were extracted; while three (mortality, CV mortality, and completed suicide) inferred 0. As above, judged a low risk of bias given the very high completion rate.

Study code: Wang 2009 - 384

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"…eligible subjects were randomized to treatment with varenicline 1 mg bd or placebo in a 1: 1 ratio." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The 24-week, randomized, double-blind, placebo controlled trial…" Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was ineffective.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"All pre-specified primary and key secondary efficacy analyses were intention-to-treat with the primary analysis population defined as all subjects (across the three countries) who were randomized and received at least one dose, even a partial dose, of randomized study medication, irrespective of their smoking cessation outcome or whether they had missing data. In the case of a missed visit or visits a subject was considered a responder if, at their next visit (at which time they were required to demonstrate an expired CO level ≤ 10 p.p.m.), they reported that since their last visit/contact they had neither smoked nor used (i) nicotine products if the missed visit(s) occurred between weeks 9 and 12 or (ii) tobacco products if the missed visit(s) occurred between weeks 13 and 24. In these subjects, missing CO data were inferred to be ≤ 10 p.p.m. and therefore did not dwasqualify the subject as a responder if all other criteria were met." One abstinence outcomes, CAR at 6 months, was extracted. All randomized participants were included in the analysis. 97% (160/165) and 96% (161/168) of the randomized participants in varenicline and placebo group completed the 6-month assessment, respectively. Judged a low risk of bias given the very high completion rates.
Incomplete outcome data addressed – for safety outcomes?	Low	"The incidence and severity of all observed or reported AE were recorded and followed up until resolution or the end of the study. These included adverse drug reactions, illnesses with onset during the study and exacerbation of previous illnesses. Any clinically significant changes in physical examination findings and relevant clinical laboratory test findings were recorded as AE." Four safety outcome, SAE, mortality, CV mortality, and completed suicide) were extracted. As above, judged a low

		risk of bias given the very high completion rate.

Study code: Ward 2012 -394

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Patients were then allocated to treatment using random permuted blocks stratified according to clinic and patient gender."
Allocation concealment?	Low	"Allocation assignments were contained in opaque, sequentially-numbered envelopes and were maintained in the biostatistics unit of the SCTS, a facility geographically separated from the clinics. A statistician, not otherwise involved in the trial, made each allocation after receiving a request from a cessation coordinator, prepared the treatment package, including patches, and had it delivered to the clinic."
Blinding of objective outcomes' assessment?	Low	"Patients, interventionists and data collectors were blind to allocation." "Prior to their use, placebo and nicotine patches were compared by 10 independent judges who rated the shape, size, color and packaging of the two types of patches as identical and were not able to correctly identify the patch type other than by chance."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Analyses were performed on an intention-to-treat basis, with individuals with missing outcome data or self-reported abstinence not confirmed by carbon monoxide at any follow-up point classified as not quit." Four abstinence outcomes, CAR and PAR at each of 6 and 12 months, were extracted. All randomized participants were analyzed, including 5 in placebo and 4 in nicotine patch group not receiving intervention. 67% (90/135) and 71% (95/135) of participants in placebo and nicotine patch group completed the study, respectively. Judged a high risk of bias given the completion rates were lower than 80%. The approach to handling missing data was provided for efficacy outcome but not for safety outcomes. In addition, all safety outcomes were inferred as zero events.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality, and completed suicide) were inferred 0. As above, judged a high risk of bias given the less-than-80% completion rates. The approach to handling missing data for safety outcomes was not provided, either.

Study code: Warner 2005-1138

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Randomization was performed using two stratification factors: baseline smoking rate (10 –20, 21–40, or ≥ 41 cigarettes/day) and anticipated type of surgery (inpatient *vs.* outpatient). For each stratum, a randomization schedule was generated by the Mayo Division of Biostatistics using a block size of four."
Allocation concealment?	Low	"Using these randomization schedules, study patches were packaged according to strata-specific subject identification numbers by personnel without subject contact. At the time of enrollment, group assignment was determined by assignment of the next sequential subject identification number for the appropriate strata. All parties were blinded to treatment assignment."
Blinding of objective outcomes' assessment?	Low	"…subjects were randomly assigned to receive either active nicotine patches or placebo patches, which could not be distinguished by appearance."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interested was available.
Incomplete outcome data addressed – for safety outcomes?	Low	One safety outcome, SAE, was extracted, and three (mortality, CV mortality, and completed suicide) were inferred 0. All randomized participants were included in the analysis, except for 2 in placebo and 3 in nicotine patch group not receiving any intervention. 86% (51/59) and 85% (53/62) of the randomized participants completed the 180-day postoperative assessment. Judged a low risk of bias given that the completion rates in two groups were higher than 80%.

Study code: Wennike 2003-1395

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"A total of 411 smokers attended the entry visit and were randomized to receive either active gum (n=205) or placebo (n=206)" Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The placebo gum was similar in appearance and taste, but contained no nicotine."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	High	"The primary analysis was an intention-to-treat analysis that included all subjects who were randomized and received medication. Dropouts were regarded as treatment failures. The primary analysis included abstainers." "Of these, 169 subjects (41%) attended the 12-month visit and 153 (37%) completed the 24-month study." Two abstinence outcomes, PPA at 12 and 24 months, were extracted. All randomized participants were analyzed. Overall, 41% and 37% of the randomized participants completed the 12- and 24-month assessment, respectively. The completion rates were lower than 80%. The information for the early discontinuations was not provided by groups and the risk of bias cannot be justified. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	Three safety outcomes, mortality, CV mortality and completed suicide, were inferred 0. In addition to the above, the approach to handling missing data of safety outcomes was not provided. Judged a high risk of bias.

Study code: Westman 1993 - 1917

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Using simple randomization, the subjects were assigned to active or placebo treatment groups." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"Placebo patches looked and smelled like active nicotine patches." "At all times, the subjects and study staff were masked to the treatment assignments." "The adequacy of subject blinding was assessed at the 6-week visit…. In this way, both groups were correct about half of the time, and active group subjects were no more likely to be correct than placebo group subjects."
Blinding of subjective outcomes' assessment?	Low	As above, blinding was maintained through the treatment period and assessed in the end of treatment. Judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"Continuous abstinence at 6 months was defined as self-report of zero cigarettes per day since the 3-month visit, verified by carbon monoxide levels of less than 8 ppm at the 6-month visit. Dropouts were contacted by telephone to determine smoking status. " One abstinence outcome, CAR at 6 months, was extracted. All randomized participants were included in the analysis, except for one in nicotine patch group who "used nicotine gum throughout the study and was excluded from the abstinence analysis." The completion rates and reasons for the early discontinuations at 6 months were not provided, but 84% and 79% in the nicotine patch and placebo group returned at 6 weeks, respectively. Judged an unclear risk of bias given all the uncertainties.
Incomplete outcome data addressed – for safety outcomes?	High	"Blood pressure, pulse, weight, and adverse effects were assessed at the 4-week and 6-week visits." Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were inferred 0. In addition to the unknown completion rates at 6 months and the lack of approach to handling missing, the safety assessments seemed to be conducted only at 4 and 6 weeks, which cannot be inferred to those of 6 months. Judged a high risk of bias.

Study code: Williams 2007-793

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"In this double-blind, multicenter clinical trial, subjects were randomized in a ratio of 2: 1 to varenicline 1 mg twice daily (BID) or placebo." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was ineffective.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Subjects who discontinued the study before week 52 had an early termination visit." "All analyses included all randomized subjects who took at least one dose of study medication…. Subjects who either missed a visit or whose nicotine use data were missing at a visit were considered smokers for that visit, and smokers who discontinued the study were considered smokers for subsequent visits regardless of their smoking status at their last recorded visit." Three abstinence outcomes, PPA at 24, 52, and 53 weeks, were extracted. All randomized participants were included in the analysis. 53.8% (135/251) and 46.8% (59/126) completed the 52-week assessment. Judged a high risk of bias given the less-than-80% completion rates.
Incomplete outcome data addressed – for safety outcomes?	High	"At each visit after screening, observed or reported adverse events (AEs), concomitant medications, and vital signs (i.e., blood pressure and pulse rate) were documented." Five safety outcomes, including SAE, mortality, CV events, CV mortality and completed suicide, were inferred 0. In addition to the low completion rates, the approach to handling missing was not provided. Judged a high risk of bias.

Study code: Williams 2012-654+ Pfizer 2011

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Subjects were randomized (2:1) to varenicline or placebo." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"The study was blinded to subjects, sponsors, investigators, and raters." Blinding approach was not provided. However, judged a low risk of bias the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was not conducted effectively.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	Unclear	"An intention-to-treat approach was used for all analyses analysis." "Overall, 98 of 128 patients completed the study, with no statistically significant difference between the treatment groups (varenicline, 73%; placebo, 86%; *P* =.12)" One abstinence outcome, PPA at 6 months, was extracted. All randomized participants were included in the analysis, except for one participant in varenicline group not returning to take any medication. The completion rates in overall study population and varenicline group were close to 80%, with no statistically significant difference between two groups. Judged an unclear risk of bias given the lack of an approach to handling missing data.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including suicidal ideation, mortality, CV mortality and completed suicide were extracted from the publication. The data for SAE was extracted from the website of Clincaltrial.gov., where the total number of patients reporting SAE was 9 instead of 10 in the publication. In addition to the above concerns, it was judged a high risk of bias.

Study code: Wittchen 2011-28

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Assignment to treatment conditions was randomized through use of the patient questionnaire, which was available in four different colors presented in a randomized order (generated by the study center). These questionnaires were distributed consecutively to all attending patients on the target days by nurses."
Allocation concealment?	High	As above. Judged a high risk of bias given that researchers and participants would have known the treatment assignment by the color they have.
Blinding of objective outcomes' assessment?	Low	Blinding was not mentioned and probably not feasible in this study due to the different combined forms of treatments. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, the lack of blinding approach should not bias the assessments.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes were likely influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted..
Incomplete outcome data addressed – for efficacy outcomes?	Low	No efficacy outcome of interested was available.
Incomplete outcome data addressed – for safety outcomes?	High	"All participants who received at least one dose of study medication were included in the safety analysis." One safety outcome, SAE, was extracted, while three (mortality, CV mortality and completed suicide) inferred 0. All randomized participants were included in safety analysis. 59% (64/108), 51% (52/105), 51% (89/175) and 58% (47/81) of randomized participants in bupropion+CBT, NRT+CBT, CBT and MI group completed the study, respectively. Judged a high risk of bias given the completion rates were lower than 80%. The approach to handling missing data for safety outcomes was not provided.

Study code: Wong 2012-755

Item	Authors' Judgment	Description
Adequate sequence generation?	Low	"Smokers were randomly assigned to receive varenicline (Pfizer Inc., Kirkland, Quebec, Canada) or matching placebo using a computer-generated randomization list at each center. A stratified randomization with blocks of 40, based on the smoker's stage of change, was employed because the stage of change may predict successful abstinence from smoking."
Allocation concealment?	Low	"The patient assignments were placed into sequentially numbered, opaque sealed envelopes, and were kept by an independent research pharmacist at each center who was not involved with patient care or outcome assessments." "The patients, healthcare personnel, and research staff were blinded to the randomization throughout the study period."
Blinding of objective outcomes' assessment?	Low	"Smokers were randomly assigned to receive varenicline (Pfizer Inc., Kirkland, Quebec, Canada) or matching placebo…For each patient, the research pharmacist opened the envelope and provided the research coordinator with the medication or placebo (lactose, identical in appearance) according to the randomization schedule."
Blinding of subjective outcomes' assessment?	Low	As above, judged a low risk of bias.
Incomplete outcome data addressed – for efficacy outcomes?	Low	"An intention-to-treat analysis was performed. Patients who discontinued treatment or discontinued follow-up were considered smokers." Two abstinence outcomes, PPA at 6 and 12 months, were extracted. All randomized participants were included in efficacy and safety analysis. 88% (119/135) and 89% (134/151) of participants in placebo and varenicline group completed the study, respectively. Judged a low risk of bias given the completion rates were high and the missing data won't significantly bias the outcome estimate.
Incomplete outcome data addressed – for safety outcomes?	Low	Three safety outcomes, including SAE, mortality and CV events, were extracted, As above, judge a low risk of bias given the high completion rates.

Study code: Zellweger 2005 - 240

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"Participants were randomized in a 3:1 ratio to receive bupropion SR…." Method for sequence generation was not provided.
Allocation concealment?	Unclear	Method for allocation concealment was not provided.
Blinding of objective outcomes' assessment?	Low	"This was a multicenter, randomized, double-blind, placebo-controlled study conducted at 26 centers in 12 countries." Blinding approach was not provided, but judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased even if the blinding approach was ineffective.
Blinding of subjective outcomes' assessment?	Unclear	As above, but judged an unclear risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted effectively.
Incomplete outcome data addressed – for efficacy outcomes?	High	"Analyses were performed on the intent-to-treat (ITT) population. The ITT population was to include all participants who took at least one dose of study medication, but this had to be modified due to data irregularities from one site as described in results below. All participants with missing investigator's assessments of smoking status, or who discontinued the study, were considered as smokers." "Subjects from one center (n=20) were excluded from efficacy analyses due to audit irregularities." "Overall, 25% of participants in both groups withdrew from the study prematurely (up to 52 weeks). During the treatment phase, 18% of the bupropion subjects and 17% of the placebo subjects prematurely withdrew from the study." Three abstinence outcomes, PPA at 6 and 12 months and CAR at 6 months, were extracted. All randomized participants were included in efficacy analysis, except for 3 not taking medication (1 in bupropion SR and 2 in placebo group) and 20 (16 in bupropion SR and 4 in placebo group) for the reason of audit irregularities. Overall, less than 75% of the randomized participants completed the study. Judged a high risk of bias.
Incomplete outcome data addressed – for safety outcomes?	High	"Vital signs were monitored and recorded throughout the study. Adverse events (AEs) were recorded during the treatment phase, and all serious adverse events (SAEs) were collected throughout the treatment and follow-up phases." Two safety outcome, SAE and CV events, was extracted, and 3 (mortality, CV events and completed suicide) were inferred 0. As above, judge a high risk of bias given the less-than-80% completion rates.

Study code: Zernig 2008-2024

Item	Authors' Judgment	Description
Adequate sequence generation?	Unclear	"The study was designed as a randomized controlled clinical trial …." Method for sequence generation was not provided.
Allocation concealment?	Low	"Treatment allocation concealment was obtained in the following manner: a technician (K.Z.) at the Experimental Psychiatry Unit of the Medical University Innsbruck used a randomization list provided by the study statistician (G.K.) to print out treatment allocation slips, put the slips into sequentially numbered opaque envelopes and sealed the envelopes. These sealed envelopes were mailed to the interview centre in Graz, were used strictly according to their sequence number and were broken by the interviewer only after the participant had given her/his written consent."
Blinding of objective outcomes' assessment?	Low	Blinding seemed infeasible in this study due to the different forms of treatments. However, judged a low risk of bias given that the objective outcomes were all based on robust clinical or laboratory evidences, which should not be biased.
Blinding of subjective outcomes' assessment?	High	As above, but judged a high risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted.
Incomplete outcome data addressed – for efficacy outcomes?	High	"…the final intention-to-treat (ITT) sample consisted of 413 participants in the bupropion and 366 participants in the psychotherapy group." Four abstinence outcomes, PPA and CAR at 6 and 12 months, were extracted. All randomized participants were included in efficacy analysis, including 159 in bupropion SR and 7 in psychotherapy group rejecting the treatments. 55% (227/413) and 98% (358/366) of randomized participants in bupropion SR and psychotherapy group completed the study, respectively. Judged a high risk of bias given the significantly different discontinuations from two groups.
Incomplete outcome data addressed – for safety outcomes?	High	Four safety outcomes, including SAE, mortality, CV mortality and completed suicide, were extracted. As above, judged a high risk of bias.