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Smoking cessation strategies in patients with chronic obstructive pulmonary disease

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Running head

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Abstract

Background

Smoking cessation is the cornerstone of treatment of chronic obstructive pulmonary disease (COPD) patients. This systematic review evaluates the effectiveness of behavioural and pharmacological smoking cessation strategies in COPD patients.

Methods

Medline was searched from January 2002 to October 2011. Randomized controlled trials, evaluating the effect of smoking cessation interventions for COPD patients, published in English, were selected. Methodological quality of included trials was assessed with the Delphi List by two reviewers independently. Relative risks of smoking cessation of intervention compared to controls were calculated.

Results

Eight studies met the inclusion criteria. Heterogeneity was observed for study population, the intervention strategy, the follow up period and the outcome. According to the Delphi List methodological quality scores, five studies were considered to be of acceptable quality. Pharmacological therapy combined with behavioural counselling was more effective than each strategy separately. In COPD patients, the intensity of counselling did not seem to influence the results, nor did the choice of drug therapy make a difference.

Conclusions

This systematic review makes clear that in COPD patients, pharmacological therapy combined with behavioural counselling is more effective than each strategy separately. The intensity of counselling nor the type of anti-smoking drug made a difference.

Key words

Behavioural therapy

Smoking cessation

Systematic review

Tobacco use cessation

Pharmacotherapy

Pulmonary disease, chronic obstructive

Abbreviation list

CO	Carbon monoxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
FEV1	Forced expiratory volume in 1 second
GP	General practitioner
GOLD	Global Initiative for chronic Obstructive Lung Disease
MIS	Minimal Intervention Strategy
ng/ml	Nanogram per milliliter
NRT	Nicotine replacement therapy
Ppm	Parts per million
RCT	Randomized controlled trial
RR	Relative risk
SST	Smoke Stop Therapy
95%CI	95% confidence interval

Introduction

The single most common cause of chronic obstructive pulmonary disease (COPD) is cigarette smoking.[1] About 15-20% of smokers develop COPD[2,3] and approximately 37% of the COPD patients are current smokers.[4] Because almost all patients with COPD smoke or have smoked in the past, they are also at increased risk for developing lung cancer[5] as well as cardiovascular diseases, e.g. coronary, peripheral and cerebral artery diseases, and an eventually higher cardiovascular mortality rate.[6-8]

Smoking cessation,[9-11] as well as pharmacological treatment of COPD,[12] improve symptoms and quality of life. However, only smoking cessation substantially changes the clinical course of COPD by reducing the rate of decline of pulmonary function and all-cause mortality.[9,13,14] Additionally, smoking cessation reduces the risk of developing and eventually dying from lung cancer, cardiovascular disease, and other tobacco related illnesses.[15,16] Patients with COPD therefore have a greater and more urgent need to stop smoking than the average smoker. For this the European Respiratory Society Task Force guidelines for smoking cessation in patients with respiratory disease recommend integration of smoking cessation treatment into the management of the patients' condition.[17,18] However, COPD patients are far more resistant to smoking cessation treatment than 'healthy' smokers, partly because of higher age, higher pack-year history, and stronger physical dependence on nicotine.[19] Because COPD patients have a higher risk for depressive symptoms,[20-23][20,24,25] smoking cessation attempts may be less successful and proportion of relapses may be higher.[21,23]

In 2002 van der Meer *et al.* conducted a Cochrane review to determine the effectiveness of smoking cessation interventions in COPD patients, concluding that a combination of psychosocial and pharmacological interventions is superior to no treatment or to psychological interventions alone.[21] They recommended more randomized controlled trials, investigating whether tailoring interventions to the needs of COPD patients improves quit rates in these patients.

During the last decade, the attitude of physicians towards smoking has changed. More attention has been drawn to the biomedical aetiology of tobacco addiction, perceiving tobacco addiction more as a neuropsychological disease instead of simply an unhealthy lifestyle.[26] Awareness of the importance of quit smoking medication has not only increased among health professionals, but also among responsible persons in most western governments. New laws have been introduced, banning smoking from public places in Europe,

Australia, Canada, and the US, and in addition, the public opinion towards smoking has shifted to 'not done'.[27-29]

The aforementioned changes might have affected the randomized controlled trials on smoking cessation intervention programs tailored to the needs of COPD patients. In order to facilitate implementation of the newest insights in smoking cessation treatment of COPD patients, the aim of this systematic review was to investigate the efficacy and effectiveness of different behavioural and pharmacological smoking cessation strategies in COPD patients since 2002.

Methods

Search strategy

Medline was searched from January 2002 to October the 20th 2011. Keywords (MeSH terms and text words) describing the study population were: chronic obstructive pulmonary disease, chronic obstructive lung disease, COLD, emphysem*, bronchit*, COPD, emphysema, chronic obstructive airway disease. Keywords describing smoking cessation interventions were: smoking, smoking cessation, tobacco, tobacco use cessation, tobacco use disorder, nicotine, cessation intervention, smoking cessation program, quit*, smok*, cessation. All these were combined with keywords referring to outcome: abstain*, abstin*, abstinence, abstination, quit*, stop*, cessat*, ceas*. To identify randomized controlled trials validated search terms for Medline searches were used.[30] The search was limited to articles published in English or Dutch. For determining additional studies, reference lists of review articles and included studies were scrutinized.[21,31-35]

Study selection

Abstracts of identified publications were screened for eligibility. If potentially relevant abstracts didn't provide enough information, full papers were retrieved. Studies were selected by applying the following inclusion criteria: 1. COPD patients; 2. randomized controlled trial; 3. Evaluation of smoking cessation intervention; 4. published in English or Dutch.

Data extraction and quality assessment

A structured data extraction was performed, focussing on design, setting, type of intervention, patient

characteristics, outcome measures and results. Methodological quality of included studies were rated, applying the Delphi List.[36] Items were scored 'yes', 'no' or 'don't know'. Only items that were assessed with 'yes' were given a score of one point. A total score for overall methodological quality of maximum nine points was obtained by applying equal weights to all items. For the definition of 'acceptable methodological quality', an arbitrary but generally accepted cut-off value of five points or more was used.

If enough data were available in the original article, i.e. absolute numbers of smoking cessation in each treatment group, the relative risks (RR) with corresponding 95% confidence intervals were calculated by determining the rate of smoking cessation in both the treated group and the untreated group. When both point prevalence and continuous abstinence were provided, only continuous abstinence was reported.

Two reviewers (MW and EvR) independently screened and selected the publications, as well as extracted data and assessed methodological quality. Consensus was used to resolve disagreement. If consensus could not be reached, a third reviewer (AS), was consulted.

Results

Identification of studies

Results of the search strategy are presented in Figure 1. In total, 8 randomized controlled trials (11 publications) were included.[9,25,37-45] As these studies were very heterogeneous regarding to study population, type of intervention, duration of follow up, and outcome measure, no pooling of data was carried out. Characteristics of the included studies and of the participants within each study are shown in table 1 and 2, respectively.

Methodological assessment

According to the Delphi List methodological quality scores, five studies were considered to be of acceptable quality (≥5 points, table 1). The scores for methodological quality varied between 3 and 9 points. The study of Wagena *et al.* had a maximum score of 9 points, indicating a low probability of bias. Most prevalent methodological shortcomings were absence of blinding of care provider, patient and outcome assessor, and lack of concealment of randomization method. All studies used biochemical validation to confirm self-reported smoking cessation (table 1). The 3 studies that did not have an acceptable quality score (>5 points) presented

the following shortcomings: none of the 3 studies concealed the treatment allocation, or blinded the care provider, patient and outcome assessor. Besides, in the studies of Christenhusz *et al.* and Hilberink *et al.* the groups were not comparable at baseline. In addition, Christenhusz *et al.* did not use an intention-to-treat analyses and Wilson *et al.* did not provide point estimates of smoking cessation.

Behavioural intervention

Borglykke *et al.* showed that patients hospitalized with symptoms of acute exacerbation of COPD who participated in an smoking cessation group, significantly more often stopped smoking after 1 year (29.8%), compared to hospitalized patients who only received information on the benefits of smoking cessation (12.7%, relative risk (RR), 2.3 95% confidence interval (CI) 1.3-4.2). [45]

Combining a pharmacological and behavioural intervention

Added value of a pharmacological intervention

Tashkin *et al.* evaluated the effect of varenicline treatment compared to placebo. [46,47] After 1 year, the use of varenicline (18.5%) resulted in significantly higher continuous abstinence rates (RR 3.3, 95%CI 1.9-5.9) compared to placebo (5.6%).

Wagena *et al.* evaluated the smoking cessation effect of bupropion or nortriptyline.[25] Out of the 225 participants 44% were “at risk for” COPD (GOLD 0).[46] After six months, the use of bupropion (28%) as well as nortriptyline (25%) resulted in higher prolonged abstinence rates compared to placebo (15%). Only the difference between bupropion and placebo reached statistical significance (RR 1.91, 95%CI 1.04-3.50). Bupropion and nortriptyline were equally effective (RR 1.12, 95%CI 0.67-1.86).

Additional value of a combined intervention

Kotz *et al.* evaluated the effect of confrontational counselling and regular counselling, both combined with nortriptyline, compared to usual care. Compared to usual care, regular counselling with nortriptyline (11.6%) as well as confrontational counselling with nortriptyline (11.2%) increased the prolonged abstinence rates after 1 year, although not statistically significant, compared to usual care (5.9%), RR 2.1, 95%CI 0.7-5.8, and RR 1.9,

CI95% 0.7-5.6, respectively. Confrontational counselling and regular counselling plus nortriptyline were equally effective (RR 1.0, 95%CI 0.5-2.0).

Hilberink *et al.* evaluated the effect of a behavioural intervention combined with nicotine replacement therapy (NRT) alone or with NRT plus bupropion, compared to usual care, in patients with a clinical diagnosis of COPD.[41,42,48] The point prevalence of abstinence after 1 year was non-significantly higher in both intervention groups (NRT group: 7.4%, NRT + bupropion group: 7.6%) than in the usual care group (3.4%), RR 2.2, 95%CI 0.8-5.8, RR 2.3, 95%CI 0.9-5.9, respectively.

Factorial design evaluating both a behavioural and pharmacological intervention

Tønnesen *et al.* evaluated the efficacy of nicotine sublingual tablet or placebo combined with either high or low behavioural support.[9] After one year, significantly higher quit rates were observed in the group using sublingual nicotine tablets (14%) compared to placebo (5%, RR 2.60, 95%CI 1.29-5.24). However, no significant difference in sustained abstinence rate between the groups receiving low (9%) or high behavioural support (10%), RR 1.12, 95%CI 0.60-2.09, was observed.

Behavioural intervention combined with free pharmacotherapy

Christenhusz *et al.* evaluated the effect of "SmokeStopTherapy" (SST) with free bupropion compared to the Minimal Intervention Strategy (MIS).[43,44] The SST group received bupropion for free, while in the control group pharmacological support was recommended, but voluntary and at the patient's costs. After 12 months, the continuous abstinence rate was significantly higher in the SST group (19% vs. 9%, RR 2.22, 95%CI 1.06-4.65).

Wilson *et al.* evaluated whether an intensive individual or group behavioural intervention increased smoking cessation rates compared to usual care. As only 91 hospital outpatients participated, the number of patients in each subgroup was small. The trial failed to find a statistically significant difference between the treatment groups, as after one year none of the patients achieved complete smoking cessation.

Discussion

This is the first systematic review since 2002, evaluating the efficacy and effectiveness of pharmacological and behavioural smoking cessation interventions in COPD patients. Eight studies fulfilled the inclusion criteria. Results of the included studies indicate that pharmacological therapy, combined with behavioural counselling,

is still the most effective smoking cessation strategy for COPD patients. The intensity of counselling did not seem to influence the results. Neither did the choice of drug therapy make a difference. These findings are in line with the results of the Cochrane review of Van der Meer *et al*.[21] published in 2002.

Compared to the review of van der Meer *et al*., the studies included in our review were of higher methodological quality; in the review of van der Meer *et al.* only two of the five included studies (40%) had five or more "yes" scores on the Delphi List, compared to 63% (5 out of 8) in this review. Studies included in the review of van der Meer *et al.* only determined the effectiveness of NRT and bupropion, while this review as well included studies investigating the newer drugs varenicline and nortriptyline. Another difference is that the behavioral interventions in this review are more tailored to the needs of the COPD patient compared to the behavioral interventions included in the review of van der Meer.

Pharmacological interventions

Four of the included studies mainly evaluated the effect of pharmacological treatments. Pharmacological support with bupropion, nortriptyline, NRT or varenicline, results in higher smoking cessation rates, compared with placebo, an effect also seen in non COPD smokers.[9,25,38,41,42,47] Importantly, none of the RCT's showed a significant difference in smoking cessation rates between different drugs. This is in contrast to studies in smokers without COPD. Studies comparing drugs and a meta-analysis suggests that varenicline would be more effective for smoking cessation than the antidepressants nortriptyline and bupropion, and NRT,[49,50] while bupropion, nortriptyline and NRT were equally effective.[51] Interestingly, a recent meta-analysis of Shah *et al.* showed that combining NRT with one of the other agents resulted in significantly higher abstinence rates if compared with any of the monotherapies in non COPD smokers.[52]

Behavioural interventions

Four of the included studies evaluated the effect of a behavioural intervention. Tønnesen found no significant difference in abstinence rates between low or high behavioural support, possibly because of too much similarity of the two regimens.[9] Both Chistenhusz and Borglykke showed that group therapy increases smoking cessation rates in COPD patients.[43-45] Counselling combined with pharmacotherapy was more effective than usual care in the studies of Hilberink and Kotz.[39-42] However, these results were not

statistically significant, which may be due to the high treatment standard of usual care and low statistical power of the studies.

In non COPD smokers, results of different studies and meta-analysis suggests that all behavioural interventions are more effective when combined with pharmacotherapy to accomplish smoking cessation. A recent study of Hoogendoorn *et al.* compared the costs of intensive counselling and pharmacotherapy. They showed that compared with usual care, intensive counselling and pharmacotherapy resulted in low costs per quality adjusted life year gained, and pharmacotherapy was cost saving compared to intensive counselling.[34]

Limitations

Interpretation of the results of the studies was challenging. First, only five out of eight studies were of acceptable methodological quality, applying a well-accepted cut-off value of five points or more to the Delphi List. Next, the numbers of patients included in the studies were small, resulting in broad confidence intervals. Furthermore, different types of outcome measures were used, making it impossible to directly compare study results. Besides, the bigger part of the studies failed to detect a statistically significant difference between the various smoking cessation strategies and usual care stop smoking guidance; this may be due to the high standard of usual care nowadays. Lastly, no clear uniform definition of COPD was provided.

Recommendations

Compared to the review of van der Meer *et al*. the studies included in this 2002-2011 review are of higher methodological quality, are investigating more different and newer drug therapies and the behavioral interventions were more tailored to the needs of the COPD patients. However, in order to be able to identify optimal smoking cessation strategies for patients with COPD, we would like to propose some recommendations. First, more high-quality, well-powered randomized controlled trials with a minimal follow up of one year, and continuous abstinence from target quit date as primary outcome measure should be performed. In order to obtain high quality, randomised controlled trials should be performed according to the Consolidated Standards of Reporting Trials (CONSORT) statements in future research.[53] Second, to realize uniformity between smoking cessation studies, the duration of follow up should be minimally one year, and continuous abstinence from target quit date should be used as primary outcome measure. West *et al.*

proposed six standard criteria to realize uniformity between smoking cessation studies: the 'Russell Standard'.[54] We recommend the use of these criteria to enable meaningful comparison between studies.

Subsequently, we would like to recommend a meta-analysis of individual patient data (individual data analysis) of RCT's, in order to identify subgroups of patients with COPD with specific patient characteristics, e.g. pack years of smoking, age, gender, comorbidities, and number of quit attempts, that might benefit from various smoking cessation strategies.[55] Smoking COPD patients are known to be a difficult target for smoking cessation, being more resistant to smoking cessation therapies. In order to amplify the development of patient tailored smoking cessation strategies, it would be very useful to identify the characteristics of smokers with COPD and to evaluate how these characteristics may affect smoking cessation strategies; e.g. COPD patients have a higher risk for depressive symptoms and COPD smokers who are depressed at the same time, may benefit more from anti-depressant smoking cessation therapy. Finally, we recommend to integrate smoking cessation treatment into the regular COPD care, to lower barriers for smoking cessation treatment and to advocate a proactive role of physicians in motivating COPD patients to quit smoking.[18]

Conclusions

To conclude, results of this 2002-2011 systematic review of smoking cessation strategies for patients with COPD indicate that pharmacological therapy, in addition to behavioural counselling, is the most effective smoking cessation strategy for COPD patients. In contrast to non COPD smokers, neither the intensity of counselling nor the type of anti-smoking drug made a significant difference in stop smoking results. Patients with COPD, being more resistant to smoking cessation therapies, could benefit significantly from smoking cessation, as smoking cessation is currently the only evidenced based intervention to change the clinical course of the disease. Further research should focus on identifying subgroups that benefit most of patient-tailored smoking cessation strategies.

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Tables & figures

Figure 1. Flowchart showing results of the search strategy.

Table 2. Characteristics of participants.

Author, year	Patients, n	Age, m (SD)	Male, n (%)	Definition of COPD	FEV1 (% pred.), m (SD)
Wagena 2005[25]	I1: 86 I2: 80 C: 89	I1: 51.1 (8.3) I2: 51.2 (9.1) C: 51.3 (8.4)	I1: 34 (40%) I2: 44 (55%) C: 46 (52%)	GOLD criteria, stage 0 (at risk for) included[46]	I1: 86.3 (21.0) I2: 83.1 (21.7) C: 87.4 (23.0)
Tønnesen 2006[9]	I1: 95 I2: 90 I3: 97 C: 88	I1: 59.2 (10.3) I2: 61.3 (9.6) I3: 61.2 (9.4) C: 62.5 (9.3)	I1: 45 (47%) I2: 46 (51%) I3: 46 (47%) C: 40 (46%)	Post-bronchodilator FEV1/FVC < 70% FEV1 <90% pred.	I1: 55.1 (15.4) I2: 53.4 (19.4) I3: 58.2 (17.8) C: 56.0 (19.1)
Christenhusz 2007[43,44]	I: 114 C: 111	I: 57.0 (8.4) C: 59.6 (8.5)	I: 55 (48%) C: 63 (57%)	FEV1 <69% of pred.*	I: 65.6 (27.4) C: 62.8 (25.7)
Wilson 2008[37]	I1: 27 I2: 29 C: 35	I1: 61.0 (8) I2: 60.4 (9) C: 61.4 (8)	I1: 14 (52%) I2: 12 (41%) C: 18 (51%)	FEV1/FVC < 0.7 FEV1 < 80% pred.**	I1: 52.1 (20) I2: 54.6 (23) C: 54.3 (20)
Borglykke 2008[45]	I:121 C: 102	I: 65 C: 67	I: 42 (35%) C: 37 (36%)	Patients having symptoms of COPD	Not available
Kotz 2009[39]	I1: 116 I2: 112 C: 68	I1: 53.8 (7.0) I2: 54.9 (8.0) C: 53.0 (7.6)	I1: 71 (61%) I2: 74 (66%) C: 40 (59%)	Post-broncholidator FEV1/FVC<70% FEV1 ≥ 50% pred.	I1: 80.5 (14.7) I2: 83.7 (16.8) C: 79.7 (14.0)
Tashkin 2011[38]	I: 248 C: 251	I: 57.2 (9.1) C: 57.1 (9.0)	I: 155 (63%) C: 156 (62%)	Post-bronchodilator FEV1/FVC < 70% FEV1 ≥ 50% pred.	I: 70.8 (17.0) C 69.1 (16.9)
Hilberink 2011[41,42]	I1: 243 I2: 276 C: 148	I1: 58.0 (12.2) I2: 60.7 (11.2) C: 60.1 (11.5)	I1: 113 (47%) I2: 132 (48%) C: 82 (55%)	Clinical criteria by GP	Not available

N: absolute number, m: mean, SD: standard deviation, I: intervention group, C: control group, COPD: chronic obstructive pulmonary disease, GP: general practitioner, FEV1: forced expiratory volume in 1 second, % of pred.: percentage of predicted, * moderate or severe COPD according to American Thoracic Society criteria[56], ** COPD according to National Institute for Health and Clinical Excellence (NICE) guidelines[57].

Optional additional table (website) Quality assessment based on the Delphi List.[36] Items of the Delphi List were scored 'yes', 'no' or 'don't know'. Only items that were assessed with 'yes' were given a score of 1 point. A total score for overall methodological quality of maximum 9 points was obtained by applying equal weights to all items. "?" denotes unclear, + denotes yes, - denotes no.

Author	Randomization method	Concealment treatment allocation	Similarity groups at baseline	Eligibility criteria specified	Blinding outcome assessor	Blinding care provider	Blinding patient	Outcome: point estimates and measures of variability	Intention to treat analysis	Total score
Wagena[25]	+	+	+	+	+	+	+	+	+	9
Tønnesen[9]	+	?	+	+	?	-	-	+	+	5
Christenhusz[43,44]	+	?	-	+	?	-	-	+	-	3
Wilson[37]	+	?	+	+	?	-	-	-	+	4
Borglykke[45]	+	-	+	+	?	-	?	+	+	5
Kotz[39]	+	+	+	+	?	?	+	+	+	7
Tashkin[38]	+	?	+	+	?	?	+	+	+	6
Hilberink[41,42]	+	?	-	+	?	-	-	+	+	4

Table 1. Characteristics of studies.

Study	Methods - Setting - Country - Design	Duration of - Exposure - Follow up	Intervention	Partici-pants, N	Primary endpoint and biochemical validation technique	Results N (%)	 RR (95% CI)	Score on Delphi List[36]
Wagena 2005[25]	- population based - The Netherlands - RCT, double blind, placebo controlled	- 12 wk - 6 mo	I1: bupropion I2: nortriptyline C: placebo All groups: individual face-to-face counseling + supportive telephone calls	255	- prolonged abstinence, wk 4 to 26 - validation: urinary cotinine <60 ng/ml	I1: 24/86 (27.9%) I2: 20/80 (25.0%) C3: 13/89 (14.6%)	I1 vs. C **1.9 (1.0-3.5)** I2 vs. C 1.7 (0.9-3.2) I1 vs. I2 1.1 (0.7-1.9)	9
Tønnesen 2006[9]	- hospital outpatients - Denmark - RCT, placebo controlled	- 1 yr - 1 yr	I1: nicotine sublingual tablet + low support I2: nicotine sublingual tablet + high support I3: placebo sublingual tablet + high support C: placebo sublingual tablet + low support	370	- sustained abstinence, wk 2 to 52 - validation: CO-measurement <10 ppm	NRT vs. placebo: NRT: 26/185 (14.1%) Placebo: 10/185 (5.4%) high vs. low support: High: 19/187 (10.2%) Low: 17/183 (9.3%)	**2.6 (1.3-5.2)** 1.1 (0.6-2.0)	5
Christenhusz 2007[43,44]	- hospital outpatients - The Netherlands - RCT	- 3 mo - 1 yr	I: SmokeStopTherapy (SST) = group and individual counseling, telephone contacts, free bupropion C: MIS for lung patients	225	- continuous abstinence, 1 yr - validation: salivary cotinine <20 ng/ml	I: 20/114 (17.5%) C: 9/111 (8.1%)	**2.2 (1.0-4.5)**	3
Wilson 2008[37]	- hospital outpatients - Ireland - RCT	- 5 wk - 1 yr	C: usual care, brief advice to stop smoking I1: individual support, 5 individual sessions with nurse + free NRT offered I2: group support, brief advice to stop smoking + 5 group sessions with nurse + free NRT offered	91	- complete cessation, 1 yr - validation: CO-measurement ≤10 ppm + salivary cotinine ≤10 ng/ml	C: 0 I1: 0 I2: 0	NS	4
Borglykke 2008[45]	- hospitalized patients - Danmark - RCT	- 5 wk - 1 yr	C: no additional intervention I: participation in smoking cessation group, weekly 2 hour sessions, 5 weeks All groups: information on benefit of smoking cessation at admission	223	- point abstinence, 1 yr - validation: carbohemoglobin measurement <2%	C:13/102 (12.7%) I: 36/121 (29.8%)	**2.3 (1.3-4.2)**	5

Study	Methods - Setting - Country - Design	Duration of - Exposure - Follow up	Intervention	Participants, N	Primary endpoint and biochemical validation technique	Results N (%)	 RR (95% CI)	Score on Delphi List[36]
Kotz 2009[39]	- population based - The Netherlands - RCT	- 4 wk - 1 yr	C: usual care I1: confrontational counseling by nurse + nortriptyline I2: health education and promotion by nurse + nortriptyline	296	- prolonged abstinence wk 5 to 52 - urinary cotinine <50 ng/ml	C: 4/68 (5.9%) I1: 13/116 (11.2%) I2: 13/112 (11.6%)	I1 vs. I2 1.0 (0.5-2.0) I1 vs. C 1.9 (0.7-5.6) I2 vs. C 2.0 (0.7-5.8)	7
Tashkin 2011[38]	- hospital outpatients - United States, Spain, France, Italy - RCT	- 12 wk - 1 yr	C: Placebo I: Varenicline All groups: educational booklet, brief counseling sessions at telephone call (n=6) and clinic visits (n=19)	499	- continuous abstinence, 1 yr - validation: CO measurement ≤10 ppm	I: 46/248 (18.5%) C: 14/251 (5.6%)	**3.3 (1.9-5.9)**	6
Hilberink 2011[41,42]	- GP practices - The Netherlands - cluster RCT	- depending on motivational stage - 1 yr	I1: counseling strategy + NRT I2: counseling strategy + NRT + bupropion C: usual care Counseling strategy: intensified MIS according to motivational stage	667	- point prevalence, 1 yr - validation: urinary cotinine lever <50 ng/ml	I1: 18/243 (7.4%) I2: 21/276 (7.6%) C: 5/148 (3.4%)	I2 vs. I1 1.0 (0.6-1.9) I1 vs. C 2.2 (0.8-5.8) I2 vs. C 2.3 (0.9-5.9)	4

N: absolute number, 95%CI: 95% confidence interval, I: intervention group, C: control group, GP: general practitioner, wk: weeks, mo: months, yr: years, RR: relative risk, NRT: nicotine replacement therapy, NS: not significant, ppm: parts per million, ng/ml: nanogram per milliliter, RCT: randomized controlled trial, CO: carbon monoxide, MIS: minimal intervention strategy