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# A systematic review of studies assessing the association between adherence to smoking cessation medication and treatment success



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# A systematic review of studies assessing the association between adherence to smoking cessation medication and treatment success

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## Abstract

**Aims:** Lack of adherence to smoking cessation medication regimens is assumed to play a significant role in limiting their effectiveness. This study aimed to assess evidence for this assumption.

**Methods:** A systematic search was conducted, supplemented by expert consultation, of articles reporting on randomised trials and observational studies examining the association between adherence to cessation medication and the success of quit attempts. To rule out reverse causality, only studies where adherence was assessed prior to relapse were included. Five studies met the inclusion criteria and results were extracted independently by two researchers. Heterogeneity between studies precluded a pooled analysis of the data.

**Results:** Studies varied widely with regard to both the definition of adherence and outcome measures. Included studies only addressed adherence to nicotine replacement therapy. One study of lozenge use found that amount of medication used between 1 and 2 weeks after the quit date predicted abstinence at 6 weeks (adjusted OR for 'high' versus 'low' lozenge use 1.25; 95% confidence interval (CI) = 1.05-1.50; p<0.02). Similarly, one study found a significant impact of oral nicotine consumption during the first week on abstinence at four weeks (adjusted OR per additional mg/d: 1.05%; CI = 1.01-1.10). Another study found that participants using nicotine replacement therapy for at least five weeks were significantly more likely to self-report continuous abstinence at 6 months. The remaining two studies failed to find a significant effect of treatment duration on outcome at one and two years but had very low power to detect such an effect.

**Conclusions:** There is modest evidence to support the assumption that lack of adherence to nicotine replacement therapy regimens undermines effectiveness in clinical studies.




**Key words:** adherence, cessation, compliance, medication, smoking, success, quitting, nicotine replacement therapy, bupropion, varenicline

## Introduction

Data from numerous randomised controlled trials clearly demonstrate the effectiveness of nicotine replacement therapy (NRT) (1), bupropion (2) and varenicline (3) in promoting long-term abstinence from smoking. However, some population studies suggest that pharmacotherapy may be considerably less effective outside clinical trials (4). One possible explanation for the finding of lower effectiveness in the 'real world' is that many smokers fail to adhere to treatment recommendations, i.e. they tend to take inadequate doses (5, 6) or discontinue treatment early (7). The amount of medication taken is likely to have a moderating effect on the effectiveness of drugs used to assist quit attempts. In randomised controlled trials, great care is being taken to ensure good patient adherence. Nevertheless, a substantial proportion of study participants do not appear to follow dosing instructions: In one early trial on nicotine gum in which patients were advised to use their medication for at least three months, 43% of participants in the active treatment arm stopped taking the gum within 4 weeks (8). Similarly high rates of early discontinuation have been reported for the nicotine patch (9), bupropion (10) and varenicline (11). There is evidence to suggest that adherence to cessation medication is even lower outside clinical trials: In one retrospective survey from the United States, past NRT users who had bought their medication over the counter reported a median treatment duration of 9.8 days (12) which is in contrast with manufacturer recommendations (at least 8 weeks). In one prospective study from China, 84% of participants used NRT for less than 4 weeks, and 44% used it for less than 7 days (13).

There is currently no consensus on what defines adequate adherence in the context of smoking cessation medication. Adherence can be defined as compliance with recommendations on treatment duration or as compliance with a given dosing regimen. A general definition of good adherence to oral medication for the treatment of chronic diseases is use for at least 80% of the recommended duration (14). Due to the diversity regarding the route of administration of medications to support smoking cessation (i.e., nasal, dermal or oral application), a universal criterion for adherence to these drugs is particularly hard to define. As a consequence, studies addressing adherence have used a wide range of definitions, e.g. 'taking at least 1 dose of medication for at least 80% of the treatment days' (15), 'chewing at least 10 pieces of nicotine gum per day' (16), and compliance indices calculated as the proportion of scheduled doses that had actually been taken (17, 18).

Some of the reasons for early termination of cessation medication quoted most frequently in surveys include adverse events (12, 15, 19-21), medication cost (12, 21) and no perceived need to take medication to stop smoking (12, 19, 20). The most important precipitating factor for medication non-adherence, however, is likely to be relapse to smoking. In a recent inter-

net survey on the use of various medications to support a quit attempt (21), 42% of participants stated they had stopped using the nicotine patch because they had relapsed to smoking; the corresponding proportions for other medications were 52% (nicotine gum), 46% (nicotine lozenge/tablet), 54% (nicotine inhaler), 26% (bupropion), and 18% (varenicline). Studies assessing the association between adherence to medication and success of a quit attempt might not yield valid results if non-adherence was not the cause but the consequence of relapse in a substantial proportion of cases. This effect which has also been termed 'reverse causality' (22) is likely to lead to an overestimation of the effect of treatment duration on quitting success as more treatment failures with short durations of treatment would be included in the analysis. This review aims to summarise the available evidence on the association between adherence and abstinence in studies controlling for potential bias due to relapse precipitating discontinuation of medication use.



# Methods

### Search strategy

Online databases (PubMed, WebOfScience, and the Cochrane Tobacco Addiction Group specialized register) were searched up to 28 February 2013 with the terms: 'smoking cessation AND (adherence OR compliance) AND (abstinence OR success)'. An additional search included the terms: '(nicotine replacement OR bupropion OR varenicline) AND (adherence OR compliance)'. Search terms were inclusive in an attempt to locate all studies examining the association between adherence and abstinence. A hand-search of the reference lists of included studies was also carried out, and leading researchers in the field were contacted. Studies identified by these searches were screened for eligibility by two reviewers (T.R. and A.H.), with 98.8% agreement. In six cases, consensus was reached by involving a third reviewer (J.B.) who was blinded to the other reviewers' assessments. Details of the method of data collection, outcome measures, recall period, participant characteristics, sample size, response rate and analysis method were extracted and compiled into a table independently by two researchers (T.R. and A.H). All discrepancies were checked against the study papers, discussed and resolved.

### Inclusion and exclusion criteria

We included primary and secondary analyses of prospective randomised controlled trials and observational studies which specifically addressed the association between medication adherence and abstinence in adult smokers. Due to potential confounding by recall bias, purely retrospective surveys were not included. With regard to pharmacotherapies, only studies

involving the use of nicotine replacement therapy, buproprion or varenicline (used alone or in combination) were included as these are considered first-line treatments in most countries (23, 24). We only included original articles written in English and published in peer-reviewed journals. Review articles, personal communications to editors, commentaries, study protocols, case studies, studies on smoking reduction and studies involving pregnant women or adolescents were excluded.

As outlined above, an important potential confounder in studies assessing the association between treatment adherence and abstinence is relapse leading to non-adherence in which case non-adherence is not the cause but the consequence of relapse. There are two ways to control for this bias:

a) establishing the chronological sequence of non-adherence and relapse during a study

b) assessing adherence during a pre-specified treatment period and determine abstinence only in those who had been continuously abstinent throughout this period

Only studies reporting a valid strategy to control for reverse causality were included in this review.

**Outcome measures**

There was no uniform definition of adherence; most studies used retrospective self-reports of drug use to assess adherence while some interviewed participants daily via an interactive voice response system or established adherence using medication dispensers with an electronic counting device fitted to the bottle cap. Details of the definitions and methods used in individual studies are given in Table 1 and Table S1 (online supplement of this article).

Abstinence was defined as the proportion of participants who achieved point prevalence, 7-day point prevalence or continuous abstinence up to a given time-point. The assessment of abstinence was based on self-report or biochemical validation by exhaled carbon monoxide or salivary cotinine concentrations, and different cut-off values were used in different studies.

**Data analysis**

Due to variation between the studies with regard to the definitions of adherence and abstinence, results could not be pooled statistically. Consequently, the evidence was synthesized in a narrative review.

# Results

### Search results

The electronic literature search yielded 498 articles. For 119 of these, eligibility could not be determined from the abstract so full text versions were retrieved and studied in detail. Thirty further eligible articles were identified through a review of reference lists and one additional article through contacting experts in the field. Of the resulting 150 articles, 37 assessed the association between adherence and abstinence, but only five reported using a strategy to control for potential confounding by reverse causality and were thus included in this review. The authors of one additional study (25) took a different approach to controlling for such confounding in that they adjusted for smoking status during the first three weeks of a trial in a logistic regression of predictors of abstinence at six weeks. In this regard, that study did not meet the inclusion criteria for this review; however, its findings were similar to the results of a study from the same group that was included in this review (22).

### Description of included studies

All five articles assessed the association between NRT use and abstinence; this research aim was explicitly stated in three studies (22, 26, 27) and addressed in sub-group analyses in the other two (28, 29). Two articles presented secondary analyses of randomised controlled trials (22, 27), and two articles provided data from prospective observational studies (26, 28). The only article reporting original results of a randomised controlled trial referred to a study of nicotine gum versus placebo in addition to nicotine patch treatment in a small sample (n = 96) of alcohol-dependent smokers in an early phase of out-patient alcohol treatment (29).

One study was conducted in the United Kingdom (27), one in the United States (29), one enrolled patients in both countries (22), and the two remaining studies were from Switzerland (26) and Germany (28), respectively. Baseline sample sizes ranged from 92 to 1,030, study populations were predominantly white, the mean/median age of participants ranged from 40 to 47 years, 29% to 54% of participants were female, and the mean/median number of cigarettes smoked daily ranged from 20 to 25. The length of follow-up ranged from four weeks to two years. Each study took a different approach to measuring adherence (see below). Smoking outcome was assessed as continuous abstinence and validated by exhaled carbon monoxide (CO) in four of the five studies (22, 26, 27, 29). The association between adherence and abstinence was assessed by means of a logistic regression in four and by a $\chi^2$ test in one study (28).

Details of the 37 articles addressing the association between adherence and abstinence but not controlling for relapse as a cause for non-adherence are provided in Table S1 in the online supplement to this article. Information on included studies is summarised in Table 1.

**Summary of the evidence**

Due to the heterogeneity of the studies discussed above, this section provides short narrative summaries of the five included studies.

1. Shiffman (22) conducted a secondary analysis of a randomised controlled trial of nicotine lozenges versus placebo in 1,030 smokers. Participants were instructed to use lozenges for 6 weeks. Adherence to study medication was monitored daily during the first two weeks of the trial, using an interactive voice response system. In the absence of an *a priori* definition of adherence, study participants were categorised as 'high' lozenge users or 'low' lozenge users based on a median split of the entire cohort. The mean number of lozenges used per day was 10.2 $\pm$ 2.5 in the 'high' users group and 5.1 $\pm$ 1.9 in the 'low' users group. Smoking outcome was defined as continuous 28-day abstinence, validated by exhaled CO at 6 weeks. In order to control for confounding by non-adherence due to relapse, the analysis (logistic regression) only included participants that had remained abstinent for the first two weeks of the trial (i.e. the period during which adherence was monitored daily). Thus, a dichotomised parameter of lozenge use during the first two weeks was examined as a predictor of continuous abstinence at six weeks in those who had been randomised to active treatment and who had not relapsed during the first two weeks (sample size not reported). The odds of continuous abstinence were significantly higher for 'high' lozenge users in both the unadjusted model (OR 1.60; 95% confidence interval (CI): 1.13-2.27; p<0.009) and a model adjusting for gender and numbers of cigarettes smoked at study entry (OR 1.25; CI = 1.05-1.50; p<0.02). When entered as a continuous variable, each additional lozenge per day significantly increased the odds of achieving abstinence by 10% (4-16%) in both the unadjusted and the adjusted model.

2. Hollands et al. (27) report the results of a secondary analysis of data from a randomised controlled trial in a primary care setting. All participants received a nicotine patch (dose tailored to the number of cigarettes smoked per day) and additional oral NRT. Participants were randomised to have their oral dose calculated based on (a) their genotype (presence/absence of a specific mutation; see (30) for details) or (b) their level of nicotine dependence as measured by the Fagerström Test of Nicotine Dependence (FTND (31)). Adherence during the first trial week was operationalised as NRT consumption and measured in mg/d. Smoking outcome was defined as 4-week abstinence, validated by exhaled CO. In order to control for confounding by non-adherence due to relapse, the

analysis (logistic regression) only included participants that had remained abstinent for the first trial week. Thus, a continuous measure of NRT use during the first week was examined as a predictor of continuous abstinence at four weeks in those who had not relapsed during the first week (n = 285). The odds of abstinence increased by 5% (CI = 1-10%) per additional mg/d in a model adjusting for various confounders, including nicotine dependence and treatment arm of the randomised trial.

3. Cooney et al. (29) randomised 96 alcohol-dependent smokers in an early phase of outpatient alcohol treatment (two study sites) to nicotine gum versus placebo on top of a 12-week course of nicotine patches. Participants were encouraged to use between 6 and 20 pieces of gum per day. There was no *a priori* definition of adherence; medication use was assessed two weeks after the target quit date by eliciting a 7-day retrospective report of gum use during patient interviews. The frequency of gum use at two weeks was entered into logistic regressions of predictors of continuous abstinence (validated by exhaled CO) at 3, 6 and 12 months. In order to control for confounding by non-adherence due to relapse, the final analysis only included participants that had remained abstinent during the first two weeks (n = 37). After adjusting for educational level, depression score, nicotine dependence and study site, more frequent use of study medication (gum or placebo) during the second week of the first two treatment weeks increased the odds of continuous abstinence at 3, 6 and 12 months by 4% (CI = 1% to 6%; p = 0.008), 4% (1% to 8%; p = 0.045) and 3% (-3% to 10%; p = 0.364), respectively.

4. Raupach et al. (28) followed up 369 participants of a hospital-based smoking cessation programme for 6 months who had been encouraged to purchase NRT themselves. Participants provided self-reports of continuous abstinence and treatment duration at the six-month telephone follow-up. In the absence of an *a priori* definition of adherence, this study considered a minimum treatment duration of five weeks to indicate good adherence. In order to control for confounding by non-adherence due to relapse, analysis of the association between adherence and abstinence was restricted to those who had either remained abstinent or relapsed only after discontinuing medication use (n = 127). Within this sub-group, self-reported continuous abstinence rate at 6 months was significantly higher if medication had been used for at least five weeks (61.0% vs. 42.6%; p = 0.039).

5. Schneider et al. (26) followed up 92 smokers who were provided with nicotine nasal spray to be used ad libitum for up to 18 months. During the first month of the study, spray use was monitored using a metered-dose inhaler fitted with an electronic device recording the date and time of each use. There was no *a priori* definition of adherence, and continuous abstinence from the end of the first month was assessed and validated by ex-

haled CO at a clinic visit two years after study entry. The methods report that in order to control for confounding by non-adherence due to relapse, only participants who had remained abstinent during the first month (n = 48) were included in the final analysis. In the multiple regression, median daily consumption of nasal spray was not predictive of continuous abstinence at 2 years (no ORs provided). It should be noted that the reporting in the results was brief and without exact figures, which meant there was no numerical confirmation of the stated methods that the analysis would be limited to the appropriate subgroup.

# Discussion

### Main findings of this review

The results of this review indicate that there is a substantial lack of high-quality studies assessing the association between treatment adherence and subsequent quitting success. The two studies with the most rigorous control for confounding by reverse causality (22, 27) both found a significant effect of the amount of medication taken and quit rates at four to six weeks. The only other study reporting a significant effect on continuous 6-month abstinence (28) was limited by its observational design, a lack of biochemical validation of smoking status and potential confounding by participant motivation and recall bias. The two remaining studies which did not find significant effects after one (29) and two (26) years appeared underpowered as sample sizes were small. Since all five studies that met our inclusion criteria addressed adherence to NRT products, no conclusions can currently be drawn on the association between adherence and treatment success for other first-line treatments such as bupropion and varenicline, or combinations of treatments.

### Strengths and limitations

In order to ensure the inclusion of all relevant articles, two independent reviewers assessed all publications identified by an extensive search of the literature. Agreement between reviewers was high, and all discrepancies were resolved by involving a third independent reviewer. We used conservative inclusion criteria in order to restrict this review to studies with relatively rigid methodology. This led to the exclusion of one study (25) that did not control for reverse causality in the way set out in our criteria but produced similar results as a comparable study with a larger sample size.

Only original articles written in English were included in this review. A total of 25 Pubmed citations were excluded due to their being written in Spanish (n = 9), German (n = 8), Polish

(n = 3), French (n = 2), Dutch (n = 1), Turkish (n = 1), or Japanese (n = 1). Six of these were review articles and had to be excluded for that reason, and one was a commentary. The abstracts of the remaining 18 articles were screened, and none of these assessed abstinence in relation to medication adherence. Thus, exclusion of articles not written in English is unlikely to have confounded our results.

Another limitation of this review is that we were unable to conduct quantitative quality assessments of the included studies. This was due to the fact that there are currently no universally accepted quality criteria for the type of studies included in this review; available tools to assess the quality of such studies have been criticised for their low reliability (32, 33). Instead, we used our field-specific expertise to provide qualitative judgments on the quality of included studies. Only two of the five included studies reported results from randomised-controlled trials; however, these were derived from secondary analyses. Thus, the association between adherence and abstinence was not a primary endpoint of these studies. The remaining three studies enrolled specific patient groups (i.e., alcohol-dependent smokers or smokers highly motivated to quit who reported to a university-based cessation clinic) which limits the generalisability of their findings to a general smoker population. Sample size was below 100 in two studies, and drop-out rates approached 50% in one study. Finally, four of the five studies did not use an a priori definition of adherence. In summary, the quality of included studies was low to moderate, and more well-designed studies are clearly needed.

Interpretation of the available evidence is further hampered by the lack of a universal definition of adherence and a consensus on how to control for reverse causality. Recently, it has been suggested to report adherence as the percentage of prescribed amount or to directly calculate medication intake (27). Excluding participants who stopped using NRT because they abandoned their quit attempt (28) would be desirable but can only be done if all relevant data are available. The alternative approach taken by some authors (i.e. relating adherence during a short interval at the beginning of a trial to abstinence at a later stage) is more problematic as it does not account for (non-)adherence between the initial adherence period and the time when the quit attempt ended. While one study on medium-term abstinence retrospectively assessed adherence throughout the entire treatment phase (28), the two other small studies assessing abstinence at one (29) or two years (26) only controlled for reverse causality during the first 2-4 weeks of the treatment phase. Thus, even in these studies, a residual bias arising from reverse causality cannot be excluded.

**Suggestions for future research**

The definitions of adherence used in these studies were not primarily based on theoretical considerations including the mode of action of pharmacotherapies but mainly derived *post*

*hoc* from the data (e.g., median split of the number of lozenges taken per day or an arbitrary cut-off of at least 5 weeks of treatment). The fact that relapse tends to occur early during a quit attempt (34) suggests that the first weeks of treatment are most important, but no firm conclusions can be drawn from the available literature. Identification of a minimum treatment duration (or amount of medication taken per day) for pharmacotherapy to be effective is important in order to design interventions that may increase adherence (35-38). Ideally, such interventions would be informed by an analysis of modifiable predictors of adherence.

Despite the lack of a universal (and clinically meaningful) definition of good adherence, a number of studies have reported on predictors of adherence. These studies used various designs including secondary analyses of randomised controlled trial data (19), prospective observations (13) and retrospective surveys (20, 39). Factors that were found to be associated with better adherence by most studies included male gender (13), more advanced age (13, 15, 19, 20), higher self-efficacy (19, 40), lower smoking rate at study entry (15), and more intensive concomitant counselling (41). However, since non-adherence may be precipitated by relapse in up to 50% of cases (21), these might reflect characteristics associated with higher odds of successful quit attempts regardless of medication adherence. In fact, most of the predictors listed above have been found to independently increase quit rates in a number of studies (42).

In conclusion, we found some evidence in studies of nicotine replacement therapy that low rates of adherence may be limiting effectiveness in clinical trials. These findings need to be confirmed using more rigorous methods (e.g. by assessing adherence using medication dispenser systems with an electronic monitoring device (37) up to a pre-defined follow-up point or the end of a quit attempt). They also need to be extended to other stop smoking medications and to use of stop smoking medicines outside of clinical studies.



**Declarations of interest**

TR has received honoraria from Pfizer®, Novartis®, Glaxo Smith Kline®, Astra Zeneca® and Roche® as a speaker in activities related to continuing medical education and smoking cessation. RW undertakes consultancy and research for and receives travel funds and hospitality from manufacturers of medications for smoking cessation. He also undertakes training for smoking cessation advisors and has a share of a patent for a novel nicotine delivery device. JB, AH and LB have no competing interests.

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## Tables

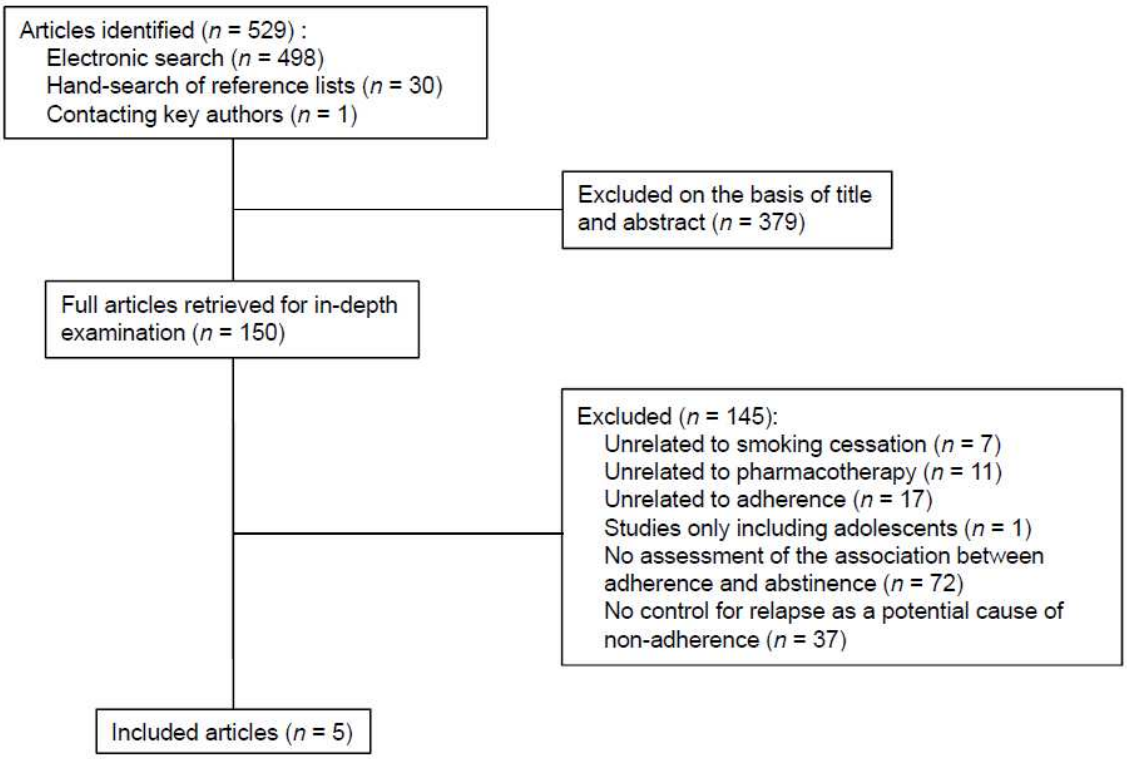
| ID | Country, Year and Study Population | Participant characteristics | Study design | Length of follow-up[a] | Methods of recruitment | Definitions and measurements | | Sample size | | Analysis method (incl. control of confounders) | Main findings regarding the association between adherence and abstinence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | adherence | success | Baseline | Follow-up | | |
| (22) | Countries: United Kingdom & USA<br>Year of study: not reported<br>Population: participants of a smoking cessation trial who were abstinent during the first two weeks | mean age: 43.3 ± 12.1 yrs<br>55% women<br>94% white<br>mean cig/d: 21.0 ± 10.0<br>mean FTND: 4.1 ± 2.4 | secondary analysis of an RCT of nicotine lozenges (2 or 4 mg) vs. placebo | 6 weeks | not reported | adherence during the first 2 weeks was monitored daily (IVR system)<br>definition of adherence: 'high lozenge use' based on a median split of all participants; group means: 10.2 ± 2.5 vs. 5.1 ± 1.9 lozenges per day | continuous 28-day abstinence at week 6, validated by CO<10 ppm | 1030 of which 612 received verum and 418 placebo | 1020 | logistic regression for predictors of 28-day abstinence at week 6, adjusted for gender and cig/d<br>control for relapse: exclusion of participants who had smoked during the first 2 study weeks | OR of abstinence for high vs. low lozenge use (participants in the verum group only):<br>- unadjusted: 1.60 (1.13-2.27)<br>- adjusted: 1.25 (1.05-1.50)<br>OR of abstinence per additional lozenge/day:<br>- unadjusted: 1.10 (1.04-1.16)<br>- adjusted: 1.10 (1.04-1.16)<br>significant treatment-by-adherence interaction |
| (27) | Country: United Kingdom<br>Year of study: 2007-2009<br>Population: smokers ≥10/d | mean age ~47 yrs<br>~54% women<br>~90% white<br>~21 cig/d<br>mean FTND ~5.5 | RCT of different ways to tailor oral NRT in addition to NRT patches and counselling | 4 weeks | Patients attending one of 29 primary care practices in Birmingham & Bristol were directly approached | Consumption (mg/d) during the first week was measured by self-report and pill counts and recorded in daily diaries<br>Adherence = proportion of prescribed dose | Self-reported 4-week abstinence, validated by CO<10 ppm | 633 | 285 | logistic regression for predictors of 4-week abstinence, adjusted for trial arm, genotype, cig/d, FTND, length of previous quit attempts<br>control for relapse: exclusion of participants who had smoked during the first study week | OR of abstinence per additional mg/d consumed:<br>- unadjusted: 1.03 (0.99-1.07)<br>- adjusted: 1.05 (1.01-1.10) |
| (29) | Country: USA<br>Year of study: 2004-2007<br>Population: patients with a diagnosis of alcohol abuse/ dependence and smoking ≥15/d | mean age ~45 yrs<br>~29% women<br>~90% white<br>~25.5 cig/d<br>mean FTND ~6 | RCT of nicotine gum vs. placebo in addition to a patch and behavioural therapy | 3, 6 and 12 months | radio & newspaper advertisements referrals from a substance abuse clinic | no a priori definition of adherence<br>measurement: 7-day retrospective report of the frequency of gum use, assessed 2 wks after target quit date | self-reported continuous abstinence at all time points, validated by CO <10 ppm | 96 of which 45 received verum | follow-up data based on the verum group (n = 45):<br>3 months: 37<br>6 months: 32<br>12 months: 30 | logistic regression for continuous abstinence at different time-points, adjusted for education level, depression score, FTND and study site;<br>control for relapse: Assessment of adherence at 2 weeks included only those who were still abstinent (n = 37) | adjusted ORs for continuous abstinence at...<br>- 3 months: 1.04 (1.01-1.06)<br>- 6 months: 1.04 (1.01-1.08)<br>- 12 months: 1.03 (0.97-1.10) |
| (28) | Country: Germany<br>Year of study: 2003-2006<br>Population: smokers (general population and hospital staff) | median age: 45 yrs<br>58.8% women<br>median cid/g: 20<br>median FTND: 5 | prospective observational study of a hospital-based smoking cessation clinic; participants self-selected to use NRT | 6 months | local newspaper articles, posters and flyers | no a priori definition of adherence | self-reported continuous 6-month abstinence; no biochemical validation | 369 of which 182 self-selected to use NRT | 127 participants used NRT and did not relapse before stopping NRT | $\chi^2$ test<br>control for relapse: participants who relapsed before stopping NRT were excluded | continuous 6-month abstinence rates for NRT use >35 days vs. <35 days: 61.0% vs. 42.6%; p=0.039 |
| (26) | Country: Switzerland<br>Year of study: 1996-1997<br>Population: smokers ≥15/d | median age: 40 yrs<br>46.7% women<br>median cig/d: 25<br>median FTND: 5 | prospective observational study of prolonged use (up to 18 months) of nicotine nasal spray | 24 months | referrals to the smoking cessation unit and advertisements in a hospital | no a priori definition of adherence<br>MDIlog: adherence was only assessed for the first month | self-reported continuous abstinence from mo 1 to mo 24, validated by CO<10 ppm | 92 | 82 of which 48 were 'totally abstinent' after 1 month | multiple logistic regression for predictors of abstinence<br>control for relapse: pts. who smoked at 1 mo were excluded | Median daily consumption of nasal spray was not predictive of abstinence (no ORs provided). |

**Table 1:** Characteristics of included studies. yrs, years; cig/d, cigarettes per day; FTND, Fagerström Test of Nicotine Dependence; RCT, randomised controlled trial; NRT, nicotine replacement therapy; MDILog, metered-dose inhaler chronolog; IVR, interactive voice response; CO, carbon monoxide; ppm, parts per million; PP, point prevalence; pts, patients; OR, odds ratio

[a] Unless otherwise stated, length of follow-up refers to the time point used to establish the association between adherence and abstinence

## Figures

**Figure 1:** Flowchart of the study selection and exclusion process



**Supporting information**

Additional Supporting Information may be found in the online version of this article:

Table S1: Characteristics of studies which were excluded due to a lack of control for confounding by non-adherence due to relapse. yrs, years; cig/d, cigarettes per day; FTND, Fagerström Test of Nicotine Dependence; RCT, randomised controlled trial; NRT, nicotine replacement therapy; MDILog, metered-dose inhaler chronolog; IVR, interactive voice response; CO, carbon monoxide; ppm, parts per million; PP, point prevalence; pts, patients; OR, odds ratio

Appendix S1: Systematic review protocol

| ID | Country, Year and Study Population | Participant characteristics | Design & data collection | Recall period / length of follow-up | Methods of recruitment | Definitions | | Sample size | | Analysis method (incl. control of confounders) | Main findings regarding the association between adherence and abstinence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | adherence | success | Baseline | Follow-up | | |
| [1] | USA<br>before 1999<br>smokers (≥20/d)<br>participating in a university-based cessation clinic | 38.7 ± 10.2 yrs<br>53.5% women<br>62.4% Caucas.<br>26.4 ± 10.3 cig/d<br>FTND 6.7 ± 1.5 | 8-week patch Tx plus three levels of support (random.)<br>questionnaires on withdrawal, motivation (URICA), self-efficacy | week 9 and week 26<br><br>timeline follow-back (TLFB) method | University campus notices, newspaper ads, 'word of mouth | continuously wearing the assigned patch at the recommended patch dose in the instructed manner for the entire 24-h time period<br><br>dichotomised measure of adherence = patch use for more than the median number of days | self-report (TLFB) of abstinence of unspecified duration, validated by CO<10 ppm | 101 (34/34/33 in the 3 groups) | "11 to 12 treatment drop-outs", a majority of whom were smoking at the 9- and 26-week follow-up! | correlation analysis and logistic regression for predictors of abstinence<br>no specific control for non-adherence due to relapse | **Week 9:** correlation patch use / smoking: r=-0.50; p<0.0005; dichotomised adherence / abstinence: unadjusted OR 23.44 (6.51-84.39); adjusted OR 3.22 (0.94-11.07)<br>**Week 26:** correlation patch use / smoking: r=-0.34; p=0.002; dichotomised adherence / abstinence: unadjusted OR 4.25 (1.28-14.12); adjusted OR 1.43 (0.33-6.18) |
| [2] | Australia, Canada, United Kingdom, USA<br>2006-2008<br>smokers or recent quitters who had used medication in the previous year | 45.5 ± 13.0 yrs<br>60.5% women<br>17.5 ± 9.2 cig/d<br>NRT use: 80.5% (of these: OTC 68.3%)<br>BUP/VAR use: 19.5% | ITC Four-Country Survey (CAN, UK, USA, and AUS), computer-assisted telephone interviews Waves 5 & 6 (10/06-2/08), including only follow-ups that had been recruited at least one wave before | 12 months preceding the interview (retrospective) | recruitment of smokers using random-digit dialling | ≥8 weeks of treatment with NRT, BUP or VAR (sub-groups: <1 wk, 1-2 wks, 2-4 wks, 4-8 wks, ≥8 wks)<br>NRT: adequate dose: ≥ 10 pcs/d | self-reported 6-month continuous abstinence; no biochemical validation | 1219 (920 relapsers, 299 successful quitters) | use duration data available for 1118 subjects;<br>smoking outcome data available for 548 subjects; of these, 22.6% achieved 6-mo cont. abstin., but 201 were excluded (discontin. due to relapse) | multiple logistic regression for predictors of abstinence; all subjects who recalled having discontinued due to relapse were excluded (risk of recall bias) | adjusted ORs for continuous abstinence at 6 mo (data for n = 347):<br>- non-adherence: 0.16 (0.08-0.31)<br>- 'not needed' vs other reasons: 3.26 (1.75-6.07) |
| [3] | USA<br>2006-2007<br>smokers ≥10/d | 47.3 ± 10.9 yrs<br>66.8% women<br>89.6% white<br>19.7 ± 8.2 cig/d<br>FTND 5.0 ± 2.1 | secondary analysis of the COMPASS Trial (**VAR**):<br>smokers who set a quit date were mailed one 28-day supply of VAR; three levels of support (random.) | telephone interviews at baseline, 21 days, 12 weeks, and 6 months post target quit date | brochures placed in health plan–owned clinics, physician referrals, Quit For Life Program | 4 self-report indices:<br>a) days taken (dichotomised: ≥80% of prescribed amount)<br>b) taken for 7 days before TQD<br>c) taken for 7 days after TQD<br>d) Medication Adherence Questionnaire (intentional vs. unintentional non-adherence) | self-reported 7-day PP; no biochemical validation | 1161 | 893 to 1161 (depending on the adherence index examined);<br>strange: the mother paper reports a 6-month sample size of 892 | logistic regression for predictors of 6-month continuous abstinence (using the 4 adherences indices)<br>$\chi^2$ Test for assoc. btw. dichotomised adherence and 7-day PP at 6 months<br>no specific control for non-adherence due to relapse | unadjusted ORs for 7-day PP at 6 months per 1 SD increase in the independent variable:<br>a) 1.81 (1.56-2.09)<br>b) 1.15 (1.00-1.33)<br>c) 1.24 (1.07-1.44)<br>d) less intentional non-adherence: 1.23 (1.07-1.41)<br><br>prevalence of 7-day PP at 6 months: 52.2% (adherent) vs. 25.4% (non-adherent); p<0.0001 |
| [4] | USA<br>2003-2005<br>smokers ≥10/d | 42.7 ± 11.5 yrs<br>51.8% women<br>81.9% white<br>22.6 ± 9.3 cid/d<br>FTND 5.4 ± 2.1 | secondary analysis of an RCT of message framing for smoking cessation in addition to **BUP** | timeline follow-back (TLFB) method<br><br>maximum follow-up 26 weeks | newspaper and radio ads, press releases, mailings to physicians, Internet | Percentage adherence = number of cap openings / 95 * 100<br><br>"Treatment completion" is mentioned but not defined | self-reported 7-d PP at 6, 12 and 26 weeks, validated by CO ≤10 ppm | 249 | 249 | linear and logistic regression, adjusted for message framing (i.e., rando group)<br>no specific control for non-adherence due to relapse | ORs of quitting at various time-points, by mean percentage of cap openings:<br>- 6-wk cont. abst.: 0.96 (0.95-0.98)<br>- 7-d PP at 6 wks: 0.96 (0.95-0.97)<br>- 7-d PP at 12 wks: 0.97 (0.96-0.99)<br>- 7-d PP at 26 wks: 0.97 (0.95-0.99) |
| [5] | USA<br>2003-2005<br>smokers ≥10/d | 42.9 ± 11.6 yrs<br>44.0% women<br>81.6% white<br>21.6 ± 9.1 cid/d<br>FTND 5.3 ± 2.1 | secondary analysis of 2 RCTs of **VAR/BUP/PLC** for smoking cessation | 12 weeks | media advertising | "completer": subjects who took ≥1 dose of medication for ≥80% of the treatment days | self-reported abstinence wks 9-12, validated by CO ≤10 ppm | 2045 (692 VAR, 669 BUP, 684 PLC) | 2045 | logistic regression for predictors of abstinence<br>no specific control for non-adherence due to relapse | positive correlation between adherence to treatment and tobacco abstinence with no significant treatment-by-adherence interaction (data presented in a |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | during the 12-week treatment period | | | | | figure; no ORs reported) |
| [6] | China<br>2000-2002<br>smokers attending a Smoking Cessation Health Centre | 85% aged 20-59<br>20% women<br>72% smoked >10/d<br>43% with FTND≥5 | Prospective observational study 8/00-1/02; the cessation service (including a 1-wk supply of NRT) was free | follow-up interviews including self-administered questionnaires at 1, 3 and 12 months<br>NRT use was asked about at 3 months retrospectively | subjects reporting to the centre via phone or in person were invited to participate | NRT use for ≥4wks during the first 3 months (self-report at 3 months) | self-reported 7-d PP at 12 months; no biochemical validation | 1186 of which 89% received a prescription for NRT →1051 | 3 months: 889<br>12 months: 698 | logistic regression for predictors of abstinence<br>no specific control for non-adherence due to relapse | ORs for 7-d PP at 12 mo:<br>- adherence to NRT: 1.97 (1.35-2.88)<br>- higher personal income: 1.82 (1.38-2.41)<br>- perceived health status as good: 1.48 (1.09-2.02)<br>- confidence in the ability to quit: 1.53 (1.16-2.02) |
| [7] | USA<br>1992<br>elderly smokers (65-74 yrs) | 69.3 ± 2.7 yrs<br>75.2% women<br>92.2% white<br>no data on baseline smoking due to an error | telephone survey; inclusion during the first quarter of 1992 | telephone interview 6 months after NRT use (retrospective) | Patients filing new claims for nicotine patches through the PACE program were invited | no a priori definition of adherence | self-reported PP at 6 months; no biochemical validation | 1070 of which 940 turned out to be eligible | 871 pts. completed the interview | T test to compare quitters and non-quitters regarding the duration of NRT patch use<br>no specific control for non-adherence due to relapse | duration of patch use in quitters vs. non-quitters: 48.4 ± 31.9 days vs. 32.0 ± 33.1 days (p<0.001) |
| [8] | United Kingdom<br>2007-2008<br>adults who had received prescriptions for varenicline | mean age 46.5 yrs<br>60.6% women | THIN database: mailed questionnaire survey | approximately 6 months, retrospective | data extraction (random sample) from an existing database | no a priori definition of adherence | self-reported 7-d PP at approximately 6 months; no biochemical validation | 915 | 193 | univariate logistic regression for predictors of 6-month abstinence; no specific control for non-adherence due to relapse | ORs of abstinence for various treatment durations (ref: <2 weeks):<br>- 2-4 wks: 2.0 (0.6-6.1)<br>- 5-8 wks: 5.4 (1.9-15.9)<br>- 9-12 wks: 11.0 (3.9-31.1)<br>- >12 wks: 7.6 (2.0-28.8) |
| [9] | Country: USA<br>Year of study: not reported<br>Population: smokers | mean age: 42.8 ± 11.5 yrs<br>52.6% women<br>87.3% white<br>mean cig/d: 25.2 ± 11.3 | secondary analysis of an RCT of nicotine patches vs. placebo under simulated over-the-counter conditions | 6 weeks | not reported | adherence during wks 1-3 was captured in a patient diary<br>definition of adherence:<br>a) patch use for ≥20 of 21 treatment days (post-hoc definition)<br>b) linear measure | self-reported 7-d PP at 6 weeks, validated by CO<10 ppm | 567 | 371 | logistic regression for predictors of abstinence at 6 weeks<br>control for relapse: The model controlled for smoking status during weeks 1-3 | OR of abstinence in adherent vs. non-adherent subjects (active group only): 3.25 (1.30-8.09); 53.2% vs. 21.5%<br>significant treatment-by-adherence interaction<br>similar results when a linear measure of adherence was used |
| [10] | USA<br>1992<br>patients who received a nicotine patch prescription | mean age ~40 yrs<br>57% women | Telephone interviews between 9/92 and 11/92 | between 3 and 10 months (not specified), retrospective | data extraction from an existing database | no a priori definition of adherence | self-reported PP at the time of the interview; no biochemical validation | eligible: 404 | completed the interview: 284; subsample used: 260 | within-group comparison (non-smokers) using T and $\chi^2$ tests;<br>no specific control for non-adherence due to relapse | Nonsmokers were more likely to have used the patch longer than shorter (5-level variable) and to report having used the patch every day as compared to less frequently (3-level variable) |
| [11] | Sweden<br>before 1984<br>no further information | mean age: 40.7 yrs<br>56% women<br>mean cig/d: 19.0<br>mean FTND: 6.3 | RCT of long vs. short support and gum vs. no gum (2x2 design) | mailed questionnaire or phone call at 6 & 12 months | enrolment through participating physicians | "arbitrary criterion": chewing ≥10 pieces per day | self-reported PP at 6 and 12 months, validated by CO≤4 ppm at 6 mo in a subsample (n = 26) | 151 | 145 | descriptive analysis<br>no specific control for non-adherence due to relapse | PP at 12 mo for adherent vs. non-adherent pts: 30% vs. 22% |
| [12] | USA<br>before 1989<br>smokers ≥1 pack/day | mean age ~42 yrs<br>~53% women<br>~27 cig/d<br>mean FTND ~6.5 | RCT of behavioural Tx vs. 'education' and fixed vs. ad lib gum (2x2 design); the treatment phase lasted 11 weeks | 6 months | newspaper ads | compliance index: pieces chewed / pieces scheduled<br>An index of >0.6 was considered 'sufficient' | self-reported 48-h PP, validated by CO<8 ppm at 10 wks and by saliva cotinine <10 ng/ml at 6 months | 107 | 89 of which 82 provided data at 6 months | descriptive analysis<br>no specific control for non-adherence due to relapse | "Average gum use did not correlate significantly with any outcome variable" (no data provided, except for a subgroup analysis for n = 10 with no p values in Table 2) |
| [13] | Italy<br>2007-2008<br>smokers motivated to quit | 51.1 ± 10.7 yrs<br>56.3% women<br>22.8 ± 8.8 cig/d<br>mean FTND ~5.5 | non-randomised trial of **VAR** vs. PLC (self-selection) in addition to a 6-wk group cessation course | 12, 26 and 52 weeks | outpatient clinic | taking VAR for 12 weeks | self-reported PP, validated by CO<10 ppm in 22 subjects at 12 months | 112 | 110 of which 48 self-selected to take VAR and were included in the analysis | propensity score matching (to account for self-selection)<br>$\chi^2$ test<br>no specific control for non-adherence due to | PP at 12 months: 62.5% (adherent) vs. 53.1% (non-adherent); p=0.381 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | relapse | |
| [14] | USA<br>2003-2006<br>heavy drinking<br>smokers ≥10/d | 41.5 ± 12.0 yrs<br>45% women<br>90.7% white<br>21.3 ± 9.4 cig/d<br>FTND 5.0 ± 2.2 | RCT of adding a brief alcohol intervention to a 4-week individual smoking cessation treatment; all pts. received NRT patches | maximum follow-up 26 weeks | community bulletin boards, newspaper & radio ads | Percent days of using patch during was used as the index of compliance with nicotine patch | self-reported 7-d PP, validated by CO≤10 ppm and saliva cotinine ≤15 ng/ml at 16 & 26 weeks | 236 | 2 wks: 222<br>8 wks: 220<br>16 wks: 213<br>26 wks: 222 | GEE models predicting 7-d PP<br>no specific control for non-adherence due to relapse | OR of quitting for greater adherence: 2.23; p <0.0001 (no 95% CI provided) |
| [15] | USA<br>2001-2004<br>smokers ≥10/d | 46.1% women<br>86% white | RCT of extended BUP vs. PLC following an 11-wk programme with BUP + NRT | Last clinic visit at week 25; telephone follow-up (IVR system) until 52 months | Internet, newspaper &radio ads, local organizations (12/01-3/04) | positive answer to the questions "Are you wearing a patch now" and "Have you taken your pill this morning?"<br>no clear definition of adherence | self-reported PP, validated by CO<10 ppm at 52 weeks (special appointment for self-reported non-smokers) | 362 | 362 | logistic regression<br>no specific control for non-adherence due to relapse | OR of quitting for more frequent use of study medication (including placebo) at...<br>- 25 wks: 1.7 (1.5-2.0)<br>- 52 wks: 1.61 (1.4-1.9) |
| [16] | USA<br>before 2007<br>female smokers ≥10/d | 47.8 ± 9.3 yrs<br>100% women<br>70.1% white<br>21.4 ± 9.2 cig/d<br>FTND 5.8 ± 2.3 | RCT of **BUP** vs. PLC and CBT vs. support (2x2 design) | 12 months, but the association between adherence and abstinence was only assessed at 7 weeks (EOT) | radio, television and print ads | MEMS: adherence = taking 2 doses/d<br>Adherence score = days of adherence / 42 days of Tx | self-reported 7-d PP, validated by CO and salivary cotinine <15 ng/ml | 154 | EOT: 81<br>3 mo: 69<br>6 mo: 60<br>9 mo: 69<br>12 mo: 70 | logistic regression for predictors of abstinence at 7 weeks<br>no specific control for non-adherence due to relapse | For participants receiving BUP, adherence<br>levels did not predict abstinence rates at EOT |
| [17] | USA<br>2001-2003<br>smokers treated at a tobacco dependence clinic | 44 ± ?? yrs<br>61% women<br>71% Caucas.<br>22 ± ?? cig/d | retrospective cohort analysis of smokers using ≥1 form of NRT | 4-wk data were collected at visits or by phone<br>26-wk data were collected by phone or mail | not described | no a priori definition of adherence | self-reported 7-d PP at 4 and 26 weeks, validated by CO<10 ppm in a subsample (n=255) at 4 weeks | 790 | 26 wks: 626 (dropouts were considered to be smoking and not using NRT) | $\chi^2$ test<br>no specific control for non-adherence due to relapse after 4 weeks | 7-d PP at 6 months in those using NRT for ≥6 mo vs. <6mo: 65% vs. 27%; p<0.001 (subgroup of those who were abstinent at 4 wks: 82% vs. 52%; p<0.01) |
| [18] | United Kingdom<br>before 1987<br>smokers working in a retailing company | 34.3 ± 10.6 yrs<br>70% women<br>15.5 ± 7.6 cig/d | quasi-randomised trial of a 2-session cessation programme (of 334 interested smokers, only 270 were invited, and 172 of these took part)<br>NRT had to be purchased | 12 months | mailing of invitation letters to employees | use of >1 box of nicotine gum (105 pieces) | self-reported continuous 12-month abstinence (lenient or strict definition), validated by CO<10 ppm | 334 | 12 mo: 331 were interviewed, but only 303 in person | descriptive analysis<br>no specific control for non-adherence due to relapse | 12-month continuous abstinence rates in those using >105 pieces of gum vs. those using ≤ 105 pieces: 19% vs. 9% (no p value given) |
| [19] | United Kingdom<br>before 1988<br>smokers working in four companies | 40 ± ?? yrs<br>43% women<br>19 ± ?? yrs | quasi-randomised trial of a 3-month cessation programme<br>NRT had to be purchased | 12 months | participants of an earlier trial of videos to support quitting | use of >1 box of nicotine gum (105 pieces) | self-reported PP at 12 months, validated by CO<10 ppm | 161 (79 interv., 82 control) of which 32 entered the programme | 161 | descriptive analysis<br>no specific control for non-adherence due to relapse | no significant association between amount of gum used and abstinence |
| [20] | USA<br>before 2000<br>smokers ≥10/d | mean age ~46 yrs<br>~46% women<br>~87% white<br>~25.5 cig/d | RCT of 2 different doses of paroxetine or PLC in addition to nicotine patches | 4, 10 and 26 weeks (interactive voice response system) and clinic visits in those who claimed to be abstinent) | newspaper ad | no a priori definition of adherence | self-reported 7-d PP at 10 & 26 wks, validated by CO <9 ppm and saliva cotinine <20 ng/ml | 224 | 224 | logistic regression for the association between the number of affirmative statements on adherence on the telephone and abstinence at 4 weeks | OR of abstinence at 4 weeks for more affirmative statements: 3.27 (2.0-5.2) |
| [21] | USA<br>before 1992<br>smokers (50% were employees of the hospital where the study was conducted) | 38.9 ± 8.9 yrs<br>66.6% women<br>28.4 ± 12.5 cig/d<br>FTND 6.6 ± 1.7 | observational study of voluntary NRT use in a 10-session group cessation programme | 6 months | hospital publications | subjects completed a questionnaire on gum use 3 wks after TQD<br>adherence = used as recommended | self-reported PP at 6 mo, validated by CO (no cut-off provided) | 36 | 36 | T tests, $\chi^2$ tests<br>no specific control for non-adherence due to relapse | abstinence rates in adherent vs. non-adherent subjects: 50% vs. 83% (n.s.) |
| [22] | USA<br>2003-2004<br>African-American light smokers (≤10/d) | 45.1 ± 10.7 yrs<br>66.9% women<br>7.6 ± 3.2 cig/d | secondary analysis of an RCT (name: 'KIS'; full name not provided) of health educ. vs. MI and nicotine gum | weeks 1, 3, 6, 8, and 26 | not reported | use of ≥75% of the prescribed dose | self-reported 7-d PP at 26 wks, validated by saliva cotinine≤20 ng/ml | 755 of which 378 were randomised to verum (gum) | week 26: 637<br>662 were included in the adherence analyses | descriptive analyses and multiple logistic regression for predictors of abstinence<br>no specific control for | abstinence rates at 26 wks for adherent vs. non-adherent subjects: 9.5% vs. 16.7% (no p value given)<br><br>adjusted OR of quitting for adher- |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | vs. PLC (2x2 design); 3/03-6/04 | | | | | | | non-adherence due to relapse | ence to study medication (including placebo) at 26 wks: 0.50 (0.28-0.87) |
| [23] | USA<br>before 1995<br>smokers | 42.2 ± 9.7 yrs<br>51% women<br>33.0 ± 10.6 cig/d<br>FTND 7.8 ± 1.5 | RCT of 4 gum use durations (0 / 7 / 15 / 30 pcs/d) in addition to minimal support | up to 24 weeks | newspaper and radio ads | no a priori definition of adherence; gum use was assessed by self-report | CO≤10 ppm | 177 | 177 | ANOVA (4 groups)<br>no specific control for non-adherence due to relapse | no overall effect of gum-group assignment on abstinence |
| [24] | United Kingdom<br>1980<br>smokers who were offered NRT gum | mean age: 40 yrs<br>56% women<br>mean cig/d: 17.9 | subgroup analysis of a cessation intervention trial | 4 and 12 months | not reported | Categorical variable 'gum use': 0 / 1-14 pcs / 15-105 pcs / >105 pcs | self-reported PP at 4 & 12 mo, validated by CO in a subsample at 12 months | 679 | 474 | logistic regression for predictors of abstinence<br>no specific control for non-adherence due to relapse | Use of >105 pcs/d was associated with significantly higher 4-mo and 12-mo abstinence rates that use of ≤105 pcs/d.<br>ORs are not reported |
| [25] | USA<br>1989-1990<br>highly-dependent smokers (FTND≥7) | mean age ~40 yrs<br>42.8% women<br>97% Caucas.<br>mean FTND ~8.4 | RCT of 2 doses of nicotine gum (4 / 2 mg) vs. PLC in addition to a minimal intervention; 5/89-5/90 | 6 weeks | not reported | using an average of ≥9 pcs/d | continuous 28-day abstinence at week 6, validated by CO<10 ppm | 563 | 216 | 4-wk abstinence was calculated separately for adherent and non-adherent pts. in the three groups but were only compared between groups | abstinence rates in adherent subjects: 56% (4 mg) / 33% (2 mg) / 33% (PLC); p = 0.0016 (no sign. difference in non-adherent subjects) |
| [26] | USA<br>before 1999<br>heavy smokers (>25/d) | mean age ~47 yrs<br>41.4% women<br>~82.5% white<br>mean cig/d ~36 | RCT of 25 mg vs. 15 mg nicotine patches (6 weeks) in addition to self-help material | 2 mo (clinic visit) 6 & 12 months (phone visit) | newspaper ads | adherence was assessed at 1, 2, 4 & 6 wks (IVR system) definition of adherence: positive answer to the question "Are you wearing a patch now?" | self-reported 7-d PP at various time-points, validated by CO<9 ppm and saliva cotinine <20 ng/ml at 2 months | 408 | IVR calls:<br>wk 1: ~380<br>wk 2: ~370<br>wk 4: ~350<br>wk 6: ~290 | $\chi^2$ Test comparing adherent and non-adherent subjects<br>no specific control for non-adherence due to relapse | validated abstinence rates at 2 months in adherent vs. non-adherent subjects: 28% vs. 11% (p<0.001) |
| [27] | USA<br>before 2007<br>female smokers ≥10/d | 42.1 ± 10.0 yrs<br>100% women<br>61.8% Caucas.<br>20.8 ± 8.8 cig/d<br>FTND 5.0 ± 2.5 | RCT of using MEMS feedback to increase adherence to a 7-wk course of **BUP** | 6 weeks | not reported | MEMS: a) dose adherence =taking 2 doses per day; b) full adherence = 2 doses per day, 8-12 h apart The intervention group received an intervention to increase adherence! | self-reported 7-d PP at 3 & 6 weeks, validated by CO (no specific information provided) | 55 (intervention 27, control 28) | 24 overall | effect sizes expressed in terms of multiple regression coefficients<br>no specific control for non-adherence due to relapse | At 3 & 6 wks, both types of adherence were associated with higher abstinence rates (all p<0.05) |
| [28] | USA<br>2009-2010<br>black smokers >10/d | 46.8 ± 11.3 yrs<br>62.5% women<br>100% black<br>16.3 ± 5.4 cig/d | RCT of adherence support vs. usual care in addition to a 12-wk course of **VAR**; 3/09-8/09 | 12 weeks | not reported | adherence was assessed by pill counts and is expressed as a percentage | self-reported 7-d PP at 12 wks, validated by saliva cotinine <20 ng/ml | 72 | 4 weeks: 60<br>8 weeks: 57<br>12 weeks: 61 | $\chi^2$ test<br>no specific control for non-adherence due to relapse | adherence in quitters vs. relapsers at 12 weeks: 95.8% vs. 80.8%; p<0.05 |
| [29] | USA<br>2004<br>homeless smokers | mean age ~44 yrs<br>~39.1% women<br>~30% white<br>mean cig/d ~15<br>mean FTND ~4 | RCT of two different counselling formats in addition to NRT (self-selection of patch or gum); 2/04-12/04 | 26 weeks (association between adherence & abstinence was only assessed at 8 weeks) | flyers distributed at 13 homeless service facilities | adherence to patch: 1 patch/d<br>adherence to gum: according to a tailored dosing schedule (no details provided) | self-reported 7-d PP at 26 wks, validated by CO<10 ppm and saliva cotinine ≤20 ng/ml | 46 | 28 | $\chi^2$ test (presumably)<br>no specific control for non-adherence due to relapse | abstinence rates at 8 wks for use of ≥4 vs. <4 patches/wk: 33.3% vs. 10.5%; p=0.3 (This information is only given in the abstract, not in the paper) |
| [30] | USA<br>1989<br>highly-dependent smokers (FTND≥7) | mean age ~43 yrs<br>44% women<br>~91% white | RCT of 3 doses of nicotine gum (4 / 2 / 0.5 mg) | 1, 2, 4 and 6 weeks after TQD | newspaper ads | pts. were instructed to use 12 pcs/d and to complete a usage diary | continuous 28-day abstinence at week 6, validated by CO<8 ppm | 90 | 90 | Mann-Whitney test<br>no specific control for non-adherence due to relapse | At 6 weeks, abstinent subjects had used significantly more gum than relapsers (10.9 ± 2.1 vs. 9.7 ± 1.6 pcs/d; p < 0.03); this effect was driven by a significant finding in the 4 mg group |
| [31] | Denmark<br>before 1993<br>smokers ≥10/d | mean age ~39 yrs<br>~60% women<br>mean cig/d ~20<br>mean FTND ~7.3 | RCT of nicotine inhaler vs. PLC | 12 months (association between adherence & abstinence was only assessed at 6 weeks) | newspaper ads | pts. were instructed to use 2-10 inhalers/d and to complete a usage diary for the first 3 wks of the trial | self-reported continuous abstinence at 12 months, validated by CO<10 ppm | 286 | 12 months: 273 | logistic regression for predictors of abstinence at 6 weeks<br>no specific control for non-adherence due to relapse | In the active group, abstinent subjects at week 6 had used more inhalers/d than relapsers (p=0.008)<br>OR of abstinence at 6 weeks for number of inhalers used: 1.41 (no CI provided) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [32] | Malaysia<br>2009-2010<br>smokers working at two public universities | 35.9 ± 10.9 yrs<br>0% women | observational study of a behavioural intervention and free NRT; 11/09-6/10 | 8 weeks | invitation letter and e-mail, Health screenings, 'Wellness Day' | NRT use for ≥2 weeks | validated by CO<10 ppm | 185 | not reported | logistic regression for predictors of abstinence at 2 months<br>no specific control for non-adherence due to relapse | According to the abstract, adherence to NRT was a univariate predictor of cessation (p<0.001). Apparently, adherence was not entered in the multivariate model. |
| [33] | USA<br>2005-2008<br>smokers ≥10 cig/d with attention-deficit/ hyperactivity disorder | 37.8 ± 10.0 yrs<br>43.5% women<br>82.6% white<br>19.9 ± 7.7 cig/d<br>FTND 5.5 ± 2.2 | secondary analysis of an RCT of methylphenidate or PLC in addition to nicotine patches and counselling; 12/05-1/08 | 10 weeks | advertising, letters to clinic patients, networking with community professionals | self-reported patch adherence: number of patches used divided by the number dispensed | a) prolonged abstinence during weeks 7-10 (i.e. not smoking on 7 consecutive days or at least once per week for 2 consecutive weeks)<br>b) self-reported continuous abstinence weeks 7 through 10, validated by CO (no cut-off provided)<br>c) self-reported 7-d PP at 10 weeks | 255 | not reported | mediation model to assess relationships between thoughts about abstinence (predictors), adherence (mediator) and abstinence (outcome); bootstrapped logistic regression<br>no specific control for non-adherence due to relapse | When factoring out predictor variables, the mediator variable 'patch adherence' was positively associated with all three outcomes (regression coefficients around 0.3). |
| [34] | Korea<br>2007-2009<br>smokers attending a smoking cessation clinic | mean age ~48 yrs<br>0% women<br>median cig/d: 20<br>median FTND: 5 | retrospective analysis of smokers receiving VAR as part of a cessation programme (9/07-12/09) | 6 months | not reported | no a priori definition of adherence; no description of adherence measurement (presumably self-report) | self-reported 6-month continuous rate, validated by CO (no cut-off provided) | 87 | 78 | logistic regression for predictors of 6-month continuous abstinence<br>no specific control for non-adherence due to relapse | unadjusted OR of abstinence per additional week of medication use: 1.123 (1.032-1.222)<br>adjusted OR: 1.172 (1.052-1.305) |
| [35] | USA<br>before 2004<br>smokers ≥10 cig/d | 43.3% women | RCT of three intensities of cognitive-behavioural support in addition to free nicotine patches | 7 weeks,<br>6 months,<br>12 months | subjects were directly approached by primary care providers | three levels of adherence (self-report at 7 weeks):<br>- full: using all patches<br>- partial: using most or some patches<br>- none: using a bit or none of the patches | self-reported 7-d PP at 7 wks, 6 months and 12 months, validated by CO <10 ppm | 619 | 7 weeks: 485<br>6 months: not reported<br>12 months: not reported | logistic regression for predictors of abstinence<br>no specific control for non-adherence due to relapse | OR of abstinence in fully adherent (vs. all other groups) subjects:<br>- 7 weeks: 1.71 (1.14–2.58)<br>- 6 months: 2.47 (1.56–3.91)<br>- 12 months: 2.12 (1.34–3.37) |
| [36] | USA<br>before 1997<br>smokers | mean age ~44 yrs<br>49.5% women<br>~82% white<br>mean cig/d ~23 | secondary analysis of an RCT (2 x 2 factorial design) of nicotine patch (21 mg) vs. PLC and self-help with vs. without video | 2, 6 and 12 months | newspaper ads | current patch use was assessed via telephone at 24 hrs, 1 week, 1 month and 2 months. Full compliance was defined as answering 'yes' at all assessments | self-reported 7-d PP at 2, 6 and 12 months, validated by CO <9 ppm and saliva cotinine <20 ng/ml | 424 | 6 months: 410<br>12 months: 410 | Cox proportional hazard analysis of time to relapse with compliance status entered as an independent variabe | Patch compliance status entered the model at 2 months (p<0.001), 6 months (p<0.001) and 12 months (p<0.001). |
| [37] | United Kingdom<br>2001-2003<br>smokers attending Stop Smoking Services | 44 ± 12.7 yrs<br>57% women<br>91% white<br>22.2 ± 9.5 cig/d<br>FTND 5.8 ± 2.1 | prospective observational study including smokers setting a quit date and using BUP; 1/01-12/03 | 4 weeks | not reported | no a priori definition of adherence; BUP use was assessed by self-report | self-reported 14-d PP four weeks after the quit date, validated by CO <10 ppm | 388 | 388 | $\chi^2$ test<br>no specific control for non-adherence due to relapse | 14-d PP at four weeks depending on BUP use in the week prior to the quit date: 44% (≥14 tablets) vs. 32% (<14 tablets); p = 0.26 |

Table S1: Characteristics of studies which were excluded due to a lack of control for confounding by non-adherence due to relapse

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# Appendix

## SYSTEMATIC REVIEW PROTOCOL

## A systematic review of studies assessing the association between adherence to smoking cessation medication and treatment success

A number of studies suggest an association between the dose of cessation medication (i.e., daily dose or duration of use) and abstinence from smoking. There are two possible explanations for this finding: (1) Adherence to dosing regimens could be causally related to higher abstinence rates (i.e., non-adherence is a risk factor for failing to quit). (2) Patients who relapse may stop taking their medication. Thus, relapse during the study period could precipitate non-adherence in which case a reverse causality must be assumed (i.e., relapse precipitates non-adherence). Studies aimed at demonstrating that continuous abstinence is causally linked to medication adherence need to control for confounding by reverse causality. This can be done by either excluding all participants who relapsed before stopping their medication or by assessing adherence during a pre-specified treatment period and determine abstinence only in those subjects who had been continuously abstinent throughout this period.



*Review Questions*

Is there an association between adherence to cessation medication and continuous abstinence from smoking if reverse causality is being controlled for?

*Search terms*

Smoking cessation AND (adherence OR compliance) AND (abstinence OR success); (nicotine replacement OR bupropion OR varenicline) AND (adherence OR compliance)

The search terms are deliberately inclusive so that papers are not missed.

*Databases searched*
Pubmed, WebOfScience, the Cochrane Tobacco Addiction Group specialized register

*Hand search*
Reference lists of included studies

*Researchers contacted for knowledge of unpublished data/ongoing studies*
- Professor Jonathan Foulds

*Study Selection Criteria*
*Inclusion criteria*
- General population sample (i.e. not recruited for particular clinical conditions)
- Adult participants (≥18 years of age)
- First-line treatments (nicotine replacement therapy, bupropion, varenicline) alone or in combination
- Prospective design
- Specifically examining the association between medication adherence and continuous abstinence from smoking
- Published in peer-reviewed journals
- Written in English
- specific analysis controlling for reverse causality

*Exclusion criteria*
- Retrospective surveys (risk of confounding by recall bias)
- Review articles
- personal communications to editors
- commentaries
- study protocols
- case studies
- studies on smoking reduction
- studies involving pregnant women and adolescents

*Search procedure*
The lead reviewer will select studies for inclusion in the review. A second reviewer will independently screen all papers for suitability (using the study eligibility for review form).

*Data to be extracted*
- Study design
- Study sample and selection
- Outcome definition and measures
- Recall period
- Response rate
- Analysis

*Data extraction strategy*
Details of the studies agreed to be eligible for the review will be extracted and compiled into tables by the lead researcher and double-checked. All details in the table will be examined by a second reviewer highlighting any errors in extraction or

discrepancies in interpretation between the reviewers. Any discrepancies will be discussed and resolved with the opinion of the other reviewers where necessary.

## Study Eligibility for Review Form

**General Information**

Pubmed ID:

Study Title:

Author contact details:

Identification number in the systematic review:

Identification of reviewer:

**Study Characteristics**
*Verification of study eligibility*

1) General population sample ☐
2) Adult participants ( e.g. ≥ 18 years) ☐
3) First-line treatments (NRT, bupropion, varenicline) ☐
4) Prospective design ☐
5) Specifically examining the association between medication adherence and continuous abstinence from smoking ☐
6) Written in English ☐

Notes:

Table 1: Characteristics of studies examining the association between medication adherence and quitting success

| ID | Country, Year and Study Population | Participant characteristics | Design & data collection | Recall period / length of follow-up | Methods of recruitment | Definitions | | Sample size | | Analysis method (incl. control of confounders) | Main findings regarding the association between adherence and abstinence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | adherence | success | Baseline | Follow-up | | |
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**Tables of outcome**

Data will be extracted and entered into the table by the lead reviewer and also independently by a second reviewer. Any discrepancies will be recorded, discussed and resolved.

Table 1: Studies examining the association between adherence and continuous abstinence and controlling for reverse causation.

Table 2: Studies examining the association between adherence and continuous abstinence without controlling for reverse causation.

**NOTES:**

- If more than one definition of success is examined (e.g. 1 week abstinence and 6 months abstinence) the longest length of abstinence that was linked to adherence data will be included in the study (i.e. 6 months).
- Where the association has been examined over multiple countries, the combined data-set will be used where available in preference to those that examine the association within each country individually.

**Systematic review – second reviewer guide**

1. Search through the 483 titles and abstracts and extract those that are eligible for the study. Please also note the reference of the studies that you required a full-text document to ascertain if eligible. Please use the following codes to record the reasons for exclusion:

| | |
|---|---|
| 1 | not written in English |
| 2 | no original data – review article |
| 3 | no original data – personal communications, commentaries, case reports, study protocols, replies to other articles or "patient pages" |
| 4 | unrelated to smoking cessation (but other conditions or smoking reduction) |
| 5 | unrelated to pharmacotherapy |
| 6 | unrelated to adherence |
| 7 | including adolescents or pregnant women |
| 8 | other (e.g., no specific research question related to the association between adherence and quitting success / predictors of adherence) |
| 10 | no control for reverse causation |

2. Check that you agree with all details entered in the Table (i.e. summary of included studies). Alter using track changes 1) any incorrect details, 2) details not needed, and 3) add anything missed that might be relevant

    - Note any factors which you feel would be important to include in quality assessment of the studies.

Thank you!