Extended Duration Treatment of Tobacco Dependence: A Systematic Review

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ABSTRACT

Introduction

The American Thoracic Society (ATS) developed a clinical practice guideline on initiating pharmacologic treatment in tobacco-dependent adults. Controller pharmacotherapies treat tobacco dependence effectively when taken as prescribed. But relapse after pharmacologic discontinuation is common.

Objective

To evaluate the effectiveness and safety of initiating controller for an extended (>12 week) versus a standard duration (6 – 12 weeks) in tobacco-dependent adults.

Methods

We systematically searched PubMed, EMBASE, CINAHL, and CENTRAL from database inception to December 2021 to identify randomized controlled trials comparing extended versus standard duration of controllers for tobacco dependent adults. We conducted meta-analyses using the Mantel–Haenszel method with random effects model. Outcomes of interest include point prevalent abstinence at 1-year follow up or longer, relapse, adverse events, quality of life, and withdrawal symptoms. Subgroup analyses were conducted according to types of treatment, and duration of extended therapy when feasible. We assessed the certainty of the estimate following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.

Results

We included 13 randomized controlled trials including 8,695 participants that directly compared extended (>12 week) versus standard-duration controller therapy with varenicline, bupropion, or nicotine replacement therapy (NRT). Compared with standard-duration controller therapy, extended-duration controller therapy probably increased abstinence at 1-year follow-up, measured as 7-day point-prevalence abstinence, (RR, 1.18; 95% CI, 1.05 to 1.33, moderate certainty). Extended-duration controller therapy probably reduced relapse compared to standard-duration controller therapy, assessed at 12 to 18 months after initiation of therapy (HR 0.43; 95% CI, 0.29 to 0.64; moderate certainty). Moderate certainty evidence also suggested that extended-duration controller therapy probably did not increase risk of serious adverse events (RR, 1.37; 95% CI, 0.79 to 2.36).

Conclusion

This systematic review supported the recommendation for extended-duration therapy with controllers. Further studies on optimal extended duration are warranted.

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INTRODUCTION

Tobacco dependence is the leading cause of preventable deaths worldwide and remains a pervasive clinical problem in pulmonary practice (1). The Global Burden of Diseases, Injuries, and Risk Factors Study estimated that the age-standardised prevalence of daily smoking was 25.0% for men and 5.4% for women, and smoking accounted for 11.5% of global deaths (6.4 million) in 2015 globally (1). Clinical guidelines have established a clinical practice principle: all patients who use tobacco should receive treatment for their dependence, and not simply be encouraged to stop (2, 3). The American Thoracic Society (ATS) developed clinical practice guideline on initiating pharmacologic treatment in tobacco-dependent adults (4). To develop this guideline, we followed an evidence synthesis and guideline development approach based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology (5-7). We utilized the GRADE Evidence to Decision (EtD) frameworks, which integrate balance between benefits and harms, quality of evidence, patient values and preferences, and cost and resource utilization, etc. in the decision-making process (8, 9). Panel composition, conflict-of-interest management, and guideline review and approval all proceeded in accordance with ATS policies and procedures (10).

This guideline focused on pharmacotherapies. Available pharmacotherapies have been categorized as controllers or relievers, based upon their pharmacokinetics (11). Controllers are expected to have a delayed onset of effect, acting to reduce the frequency and intensity of the impulse to smoke, while relievers are expected to have more acute effects, useful in relieving the impact of cue-induced cravings. Controllers include varenicline, bupropion and nicotine replacement therapy (NRT). Both varenicline and bupropion are prescription only drugs and treatment is initiated in advance of the target quit date. NRT is an over-the-counter treatment. The benefit of controllers compared with placebo or no treatment has been demonstrated in randomized controlled trials (RCTs) (12-14). The studies on controller pharmacotherapies were typically on a duration of 8 to 12 weeks (13).

Controller pharmacotherapies treat tobacco dependence effectively when taken as prescribed and can help smokers make a successful quit attempt. But relapse after pharmacologic discontinuation is common (15). To sustain the positive health effects of quitting, relapse prevention is important. Continuing intervention may reduce relapse rates after a successful completion of an acute treatment phase, and prevent relapse after the hypothesised quit date. Although there has been limited evidence to date, an extended duration of treatment has been effective at modifying sustained abstinence rates in some contexts (16, 17). The ATS guideline panel found guidance on treatment duration to be of critical importance, especially the comparison between extended duration (i.e. >12 weeks) and standard therapy (8 to 12 weeks).

To inform the decision making on relapse prevention, we conducted a systematic review to evaluate the effectiveness and safety of an extended (>12 week) versus a standard duration (6 – 12 weeks) of treatment in tobacco dependent adults when initiating controller medications.

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METHODS

We systematically searched, summarized, and critically appraised the evidence on the extended versus standard duration of controllers for tobacco dependent adults. We reported this review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (18).

Literature Search

We searched PubMed, Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, the National Institute of Health Research Centre for Reviews and Dissemination database, World Health Organization (WHO) International Clinical Trials Registry Platform, and ClinicalTrials.gov from inception to December 2021.

The following concepts were used in search terms: tobacco dependence, controllers including NRT, varenicline, bupropion, and extended treatment. We used the OR Boolean operator to combine the controlled vocabulary (e.g. MeSH, Emtree, including 'exploded' terms) and free-text terms within each concept and used the AND Boolean operator to combine the three concepts. We further used the Scottish Intercollegiate Guidelines Network (SIGN) search filter to identify RCTs. Full search strategies are available in Appendix 1.

Study Selection and Inclusion Criteria

We screened the retrieved records with the prespecified inclusion and exclusion criteria. Studies were deemed eligible for inclusion if they were randomised controlled trials, included tobacco dependent adults and compared extended (greater than 12 weeks) versus standard duration (6 to 12 weeks) of controller therapy. Our outcomes of interest included tobacco abstinence at 6 months or longer, serious adverse events (SAEs), change in tobacco use measured by cigarettes per day, relapse, severity of withdrawal, increase or decrease in other substance abuse, and quality of life. For abstinence, we prioritized extracting 7-day point prevalence abstinence, which means abstinence in the 7 days before the follow up measured by biomarkers or self-reported (19). We also extracted prolonged and continuous abstinence when available. Continuous abstinence refers to abstinence between target quit day and the follow-up; while prolonged abstinence refers to sustained abstinence after an initial grace period or to a period of sustained abstinence between two follow-ups(19).

We excluded records if it fulfilled any of the following scenarios: nonoriginal report (e.g., review, commentary, or communication); conference abstracts and structured abstracts; project record; letter/commentary; case reports. We set no restriction on the publication language or publication year.

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Two independent reviewers conducted titles and abstracts screening in duplicate through Endnote. We then obtained full text of eligible studies that were included by either reviewer, and further examined the eligibility. Two reviewers conducted the full-text review in duplicate, with any disagreement resolved by discussion and consensus.

Data Extraction and Quality Assessment

Data were extracted into a form created for the purpose of this systematic review. We extracted the following information: study setting, participant demographics, baseline characteristics, details of the intervention, study design, follow-up, outcome measures, and criteria for risk of bias. To assess the risk-of-bias of included studies, the Cochrane risk-of-bias tool for randomized trials was used (random sequence generation, allocation concealment, blinding of healthcare personnel and patients, attrition, selective report of outcomes)(20).

We contacted the authors of original studies, conference abstracts, and ongoing or unpublished studies to obtain any missing data. Data extraction was performed by two authors independently; disagreements were resolved through discussion and consensus.

Data Analysis

Direct comparison meta-analyses utilized the Mantel–Haenszel method with random effects model (RevMan v5.3, The Nordic Cochrane Centre, Copenhagen). We compared the effectiveness of standard versus extended duration treatment by examining the probabilities of abstinence and relapse. Our primary outcome was 7-day point-prevalent abstinence, measured at 1-year follow up, which was independent of whether treatment had been stopped or not.
For dichotomous outcomes including abstinence, SAEs, relapse, we used relative risk (RR) as effect measure for, while for continuous outcomes such as quality of life, we used mean difference (MD) when the studies reported the same scale and standard mean difference (SMD) if otherwise. In addition, we used hazard ratio (HR) for time to event outcomes (time to relapse). We calculated the point estimates and confidence intervals (95% CI). The Absolute Risk Reduction (ARR) was estimated by multiplying the median of risks observed in control groups by the pooled risk ratio and then presenting the result in terms of anticipated increase or decrease of the effect per 1,000 patients treated.
Heterogeneity between studies was assessed by inspection of similarity between point estimates and overlap of confidence intervals across included studies, Chi-square test and I^2statistic (21). We also conducted subgroup analyses according to the types of treatment, and the duration of extended therapy. To further examine whether treatment duration had an impact on primary outcome (7-day point-prevalent abstinence at 1-year follow up), we conducted subgroup analysis for extended treatment of 1 year or longer and extended treatment of less than 1 year. Funnel plot symmetry was used to assess publication bias when possible (22).

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Certainty of Evidence

Certainty of evidence was appraised using the GRADE approach, in which five domains-risk of bias, indirectness, inconsistency of estimates across studies, imprecision of estimates, and publication bias (5-7)- was applied to downgrade the quality of evidence when necessary. We categorized the certainty in the estimated effects into four levels ranging from very low to high, and prepared summary of findings table (7, 23). We followed a set of standardized statements to interpreting and communicating results of systematic review (24).

Results

Study Characteristics

Figure 1 shows the PRISMA flow diagram for the literature search and screening process. After removing duplicates, we screened 31,59 title and abstract records and identified 13 RCTs that directly compared extended (>12 week) versus standard-duration controller therapy with varenicline, bupropion, or NRT (17, 25-36), with 12 of them in the quantitative synthesis (Figure 1). One study was not included in the meta-analysis,(25) because the eligible outcome in this study was relapse, which was evaluated after week 12, and different from relapse outcome assessed at 12 to 18 months after the initiation of therapy in other studies.

All the included studies were conducted in the USA except three in European countries (25, 26, 30). The studies enrolled between 18 and 2,861 participants. The mean age of participants ranged from 40.3 to 52.4 years old, and the Fagerstrom score at baseline ranged from 4.9 to 7.4. Nine studies were on adult smokers who were otherwise healthy, except two studies recruited participants with schizophrenia (29, 33), one cessation-induced depression mood (28), and one cancer patients (35). Seven studies were on the extended use of NRT(17, 25, 26, 28, 29, 32, 34), four varenicline (30, 33, 35, 36) and two bupropion (27, 31). The extended-duration controller therapy lasted for 12 months for four of the included studies (17, 27, 31, 33), while for other studies the extended therapy ranged from 18 weeks to 9 months (Table 1).

Risk of Bias

As for risk of bias, all but four studies (25, 28, 35, 36) were classified as low risk of bias for random sequence generation, but only seven studies were low risk of bias for allocation concealment (26, 27, 30, 32-34, 36). In eight studies, personnel and participants were blinded (25-28, 30, 32, 33, 36) but only in four studies outcome assessors were blinded (28, 32, 33, 36). Furthermore, seven studies were considered low risk of bias due to incomplete outcome data (27, 29-31, 33, 34, 36) (Table 1, Appendix 2).

Nine studies (n = 4,962) provided data for the primary analysis of 7-day point-prevalence abstinence at 12 months; five reported SAEs data (*n* = 2,612) and two studies reported relapse data at 12 to 18 months (n=655).

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Effects of Intervention

Abstinence

Figure 2 shows the estimate of treatment effect at 1-year follow-up for extended-duration versus standard-duration controller therapy, and the estimates for subgroups of extended-duration therapies of 12 months and of shorter than 12 months when they were compared with standard-duration therapy. Compared with standard-duration (8 to 12 weeks), extended-duration (24 to 52 weeks) controller therapy probably increased abstinence at 1-year follow-up, measured as 7-day point-prevalent abstinence, (RR, 1.18; 95% CI, 1.05 to 1.33; ARR, 44 more per 1,000 patients; 95% CI, 12 more to 80 more; moderate certainty due to serious risk of bias; Figure 2, Table 2) (17, 27, 30-34). According to the subgroup analysis by the duration of extended therapy, there was no evidence suggesting extended-duration controller therapy of 12 months was superior to extended-duration controller therapy of shorter than 12 months (Figure 2). Subgroup analysis according to types of controllers did not suggest difference (Appendix 3).

However, the effect of extended-duration controller therapy on 7-day point-prevalent abstinence measured after 1-year (between 15 and 18 months) follow up was less certain (RR 1.50, 95% CI 0.91 to 2.47; ARR, 136 more per 1,000 patients; 95% CI, 24 fewer to 399 more; very low quality evidence due to serious risk of bias, inconsistency, and imprecision) (27, 31, 33).

Compared with standard-duration controller therapy, extended-duration controller therapy probably increased continuous abstinence at 1-year follow up (RR 1.14, 95% CI 0.99 to 1.32; ARR, 21 more per 1,000 patients; 95% CI, 1 fewer to 48 more; moderate quality evidence due to serious imprecision; results not shown in forest plot) (17, 26, 27, 30, 33, 34).

Prolonged abstinence at 12 month follow up is probably increased with extended-duration controller therapy (RR 1.19, 95% CI 0.99 to 1.44; ARR, 38 more per 1,000 patients; 95% CI, 2 fewer to 88 more; moderate quality evidence due to serious imprecision; results not shown in forest plot) (17, 32).

Relapse

Pooled estimates from two trials with 655 participants also suggested that 24 to 52 weeks of extended-duration controller therapy probably reduced relapse compared to standard-duration, assessed at 12 to 18 months after initiation of therapy (HR 0.43; 95% CI, 0.29 to 0.64; moderate certainty due to serious imprecision; Figure 3, Table 2) (27, 32, 33).

However, the other study comparing 18 weeks treatment with nicotine patch versus 12 weeks, had a similar rate of relapse after week 12.

Time to relapse was longer following extended versus standard treatment duration (low certainty of evidence) from two trials with 1735 participants (17, 30). However, the estimates from the two studies varied. Schnoll et al reported that participants in the standard treatment of 8 weeks had a mean of 72 days (standard deviation of 62.6) before relapse, fewer than 89 days (standard deviation of 66.5) for those in the extended treatment of 24 or 52 weeks. Another study showed larger difference between median time to the first relapse, with 198 days (95% CI, 159 to 260) for those with 24 weeks of varenicline compared to 87 days (95% CI, 58 to 143) for those with 12 weeks of treatment.

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Serious adverse events
Compared with standard-duration (8 to 12 weeks), extended-duration (24 to 52 weeks) controller therapy probably had a similar risk of SAEs (RR, 1.37; 95% CI, 0.79 to 2.36; ARR, 3 more per 1,000 patients; 95% CI, 2 fewer to 11 more; moderate certainty due to very serious imprecision; Figure 4, Table 2) (30, 32-34).

Other outcomes
Quality of life: One study including 98 participants reported quality of life data. Compared with 12 weeks of standard duration therapy, the quality of life score, measured with Short-Form Health Survey (lower score indicating better quality of life), at 52-week follow up was lower for participants receiving 24 weeks of varenicline therapy (MD, -1.15, 95% CI, -3.75 to 1.45; very low certainty due to serious risk of bias, indirectness, and imprecision; Table 2)(35).

Withdrawal: We have very low certainty evidence on the effect of extended-duration controller therapy on withdrawal symptoms at 13-14 weeks. Assessed as craving and urge to smoke (with a lower score indicating better outcome), the SMD was estimated to be 0.59 lower for those receiving 18 weeks to 24 weeks of extended-duration controller therapy (95% CI, -1.05 to -0.13, very low certainty due to serious risk of bias, inconsistency, and imprecision; Table 2)(28, 30, 36).

Number of cigarettes: One study including 525 participants reported the number of cigarettes at 52-week follow up, suggesting there may be no decrease in number of cigarettes for 24 to 52 weeks versus 8 weeks of varenicline therapy (MD 0.6 lower, range 1.53 lower to 0.33 higher; low certainty of evidence; Table 2) (17).

Discussion

Main Findings
This is the first systematic review assessing the effectiveness and safety of standard (6-12 week) versus extended (>12 week) duration of controller treatment in tobacco dependent adults who are initiating pharmacological interventions. Nine RCTs suggested a large benefit when comparing 12 weeks or longer controller treatment versus shorter duration, with increased abstinence by 18% (RR = 1.18; 95% CI, 1.05 to 1.33) and decreased relapse rates (HR = 0.43; 95% CI, 029 to 0.64). Four trials demonstrated that when compared with standard duration, extended-duration controller therapy probably does not increase SAEs (RR, 1.37; 95% CI, 0.79 to 2.36). Estimates for effects on abstinence and SAEs above were based on moderate certainty of evidence. Further, low certainty evidence suggested that extended-duration controller therapy likely does not result in a reduction in the number of cigarettes smoked but does result in a delayed time to relapse (ranging from 17 days to 111 days delayed) and slightly better controlled withdrawal symptoms.

Strengths and Limitations
A key strength of this systematic review is its high clinical relevance as we conducted this as a component of a clinical practice guideline, developed with international experts. Patients and clinicians on the panel provided input to our rigorous search strategy. The guideline

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panel also helped identifying potentially relevant unpublished studies renders the likelihood of missing key studies. Patients and frontline clinicians also contributed to identify all the patient-centred outcomes, including abstinence and quality of life, though rarely reported in the literature.

This review is also subject to limitations. The quality of evidence for a number of outcomes was rated low or very low, and there was limited evidence on optimal duration or type of treatment. The certainty of estimated effects for the critical outcomes for the guideline recommendation, including abstinence and SAEs, was ranked as moderate due to risk of bias for cessation outcomes and serious imprecision of estimates relating to SAEs and relapse and the evidence for other outcomes such as quality of life, or withdrawal symptoms was low or very low. Furthermore, our primary outcome was 7-day point-prevalence abstinence measured at 1-year follow up. To examine the impact of extended-treatment duration on this estimate, we conducted subgroup analyses and were not able to find evidence of different effect. However, more studies are needed before we are able to reach conclusion regarding the optimal duration of extended therapy or the optimal duration by controller type interactions. We evaluated the effect of assignment to the interventions at baseline which is the effect of initiating an extended-duration controller therapy or not, rather than the effect of adhering to the interventions, which is, in contrast, the effect of adhering to extended-duration controller therapy or not. It also means that we were unable to examine the association between adherence to pharmacotherapy and effects. Last, there has been changes in the outcome measurement, exhaled carbo monoxide of 7 to 10 in part per million (ppm) was used in early trials(17, 30) as the cutoff value to verify abstinence, while in recent trials, 5 to 6 ppm was used(36). There is no sufficient evidence to assess the impact on treatment effect estimate following the choice of cutoff values.

Implication to Clinical Practice

As a result of the information presented in this review, the ATS guideline panel for whom this systematic review was performed made a strong recommendation for extended duration (> 12 weeks and up to 12 months) over standard duration (≤ 12weeks) of controller treatment when tobacco dependent adults initiate pharmacological treatment. This recommendation goes further than the 2018 American College of Cardiology tobacco-cessation clinical pathway' (37) and the United Kingdom guidance from the National Institute of Health and Clinical Excellence (NICE) (38) which currently recommend at least 3-months of NRT, and 3-6 months of varenicline or bupropion therapy; and up to 12 weeks of treatment with both NRT and varenicline (though does state that for people who have successfully stopped smoking at the end of 12 weeks, an additional 12-weeks of treatment of varenicline may be considered to help maintain abstinence) respectively. The results of our review support that an extended-duration controller therapy should be adopted for patients and clinicians in most instances. Notably, one study was completed and published(36) after the publication of guideline, so the estimates for the primary outcome, 7-day point prevalent abstinence and withdrawal outcome were slightly different from the supporting evidence for the guideline. However, the conclusion was not changed.

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Implication to Research

The current study has shown that extended-duration controller therapy for tobacco dependence is effective and safe to prevent relapse and sustain the positive health effect of cessation, however additional studies of long-term and maintenance therapies are needed. Studies on patient important outcomes such as long-term morbidity or mortality, as well as quality of life data are also needed. Further, there is a lack of evidence regarding optimal treatment durations for patients with other comorbidities such as cancer, or chronic obstructive pulmonary disease, or factors influencing long term treatment adherence. Future research should focus on these areas to identify novel and effective measures for improving maintenance outcomes. Once these data are available, update of guideline and recommendations may be necessary.

Conclusion

Moderate evidence suggested that extended-duration (>12 weeks) controller therapy is beneficial compared to standard (8 to 12 weeks) treatment courses, with increased abstinence, decreased relapse rates, and a similar risk of SAE. This systematic review supported the recommendation for extended over standard duration of controller therapy. Further studies on optimal extended duration are warranted.

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The ATS suggested the topic but was not involved in the screening, analysis, and interpretation of the data or in the writing of the paper. The authors retained full control over the conduct and reporting of the paper.

Contribution

RM, YZ, SR, KO, MZ, SP, LCL, IF, SK, FTL, YZ contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: RM, YZ, SR, FTL, YZ drafted the work or revising it critically for important intellectual content; All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare no competing financial interests.

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Table 1. Characteristics of included studies

Study ID	Study characteristics				Population and baseline characteristics						Extended-duration therapy[a]	Standard-duration therapy[a]	Outcomes
	Country	Duration of the study	Health care settings	Types of funding	Population	Number of participants	Age	Male (%)	Number of cigarettes	Fagerstrom score			
Baker 2021	USA	Nov. 2017 to July 2020	Research clinics	Public, and private company	Smokers who used 5 cigarettes per day or more	Total: 1251 Extended: 622 Standard: 629	Mean: 49.1 SD: 11.9	46.0%	Standard duration varenicline Mean: 15.9 SD: 7.6 Standard duration varenicline plus nicotine patch Mean: 16.0 SD: 7.3 Extended varenicline Mean: 16.2 SD: 7.4 Extended varenicline plus nicotine patch Mean: 16.0 SD: 7.7	Standard duration varenicline Mean: 5.1 SD: 2.0 Standard duration varenicline plus nicotine patch Mean: 4.9 SD: 2.0 Extended varenicline Mean: 4.9 SD: 2.0 Extended varenicline plus nicotine patch Mean: 5.0 SD: 2.1	Varenicline monotherapy or varenicline plus nicotine patch for 24 weeks; 60.0% completed treatment	Varenicline monotherapy or varenicline plus nicotine patch for 12 weeks; 60.0% completed treatment	7-day point prevalent abstinence at Month 12, confirmed by exhaled CO (≤5 ppm) Prolonged abstinence at Month 12

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Croghan 2007	USA	Jul. 2001 to Jan. 2003	Oncology practices	Public	Smokers recruited from the general local population (not including cancer patients)	Total: 141 Extended: 71 Standard: 70	Mean: 42.7 SD: 11.56	40%	Mean: 23.5 SD: 10.22	Mean: 5.8; SD: 2.12	bupropion 300mg daily for 12 months; no treatment adherent information	bupropion 300mg daily for 3 months followed by placebo for 9 months; no treatment adherent information	7-day point prevalent abstinence at Months 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15, confirmed by exhaled CO (≤5 ppm)
Dale Horst 2005	USA	Not reported	Local mental health support providers	Public, not-for-profit private organization, and private company	Volunteers with a diagnosis of schizophrenia or schizaffective disorder	Total: 18 Extended: 9 Standard: 8	Mean: 42.5 SD: 10.1 Range: 21-65	52%	Not reported	Mean: 7.4 SD: 1.5 Range: 4-10	NRT patches at doses of 14, 21, or 42mg daily (depending on severity of dependence) for 9 months; no treatment adherent information	NRT patches at doses of 14, 21, or 42 mg daily (depending on severity of dependence) for 3 months, followed by placebo patches for 6 months; no treatment adherent information	7-day point prevalent abstinence at Month 6, confirmed by exhaled CO (≤10 ppm)
Evins 2014	USA	March 2008 to April 2012	Community mental health centres	Public, and private company	Outpatients aged 18-70 with schizophrenia, schizoaffective disorder, or bipolar disorder	Total: 87 Extended: 40 Standard: 47	Extended Mean: 51.4 SD: 9.6 Range: 23-65 Standard Mean: 45.7 SD: 10.3 Range: 23-66	Extended: 60% Standard: 66%	Not reported	Not reported	Varenicline 1mg twice daily for 52 weeks[b]; 33 of 40 participants received treatment	Varenicline 1mg twice daily for 12 weeks[b]; 28 of 47 participants received treatment	7-day point prevalent abstinence at Months 6, 9, 12 and 15, confirmed by exhaled CO (<9 ppm) Relapse
Hays 2001	USA	Not reported	Clinics	private company	Healthy community volunteers	Total: 429 Extended: 214 Standard: 215	Extended Mean: 47.0 SD: 9.7 Range: 20.3-72.7 Standard Mean: 45.4 SD: 9.2	Extended: 45.3% Standard: 52.1%	Extended Mean: 27.3 SD: 10.6 Range: 15-70 Standard Mean: 26.2	Extended Mean: 7.3 SD: 1.5 Standard Mean: 7.1 SD: 1.6	Bupropion 300 mg daily for 52 weeks; 159 of 214 participants completed 104 weeks of study	Bupropion 300 mg daily for 7 weeks; 158 of 215 participants completed 104 weeks of study	7-day point prevalent abstinence at Months 3, 6, 9, 12, and 18, confirmed by exhaled CO (≤10 ppm) Relapse

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							Range: 20.2-71.9		SD: 9.6 Range: 15-70				
NCT 01756885[c]	USA	Not reported	Not reported	Not reported	Smokers diagnosed with cancer	Total: 207 Extended: 105 Standard: 102	Extended Mean: 58.0 SD: 9.4 Standard Mean: 60.0 SD: 9.5	Extended: 43.8% Standard: 54.9%	Not reported	Extended Mean: 4.4 SD: 2.1 Standard Mean: 4.6 SD: 2.2	varenicline 1mg twice daily for 24 weeks, and smoking cessation counseling[b]; 79 of 105 participants completed study	varenicline 1mg twice daily for 12 weeks followed placebo for 12 weeks, and smoking cessation counseling[b]; 79 of 102 participants completed study	7-day point prevalent abstinence at Weeks 24 and 52, confirmed by exhaled CO (<10 ppm) Continuous abstinence at Weeks 24 and 52 Serious adverse events Quality of life measured with SF-12 (Higher score indicates worse quality of life)
Pomerleau 2003	USA	Not reported	Local community	Not reported	Smokers from local community	Total: 55 Extended: 30 Standard: 25	Extended Mean: 38.7 SD: 10.5 Standard Mean: 42.4 SD: 11.0	Extended: 33% Standard: 68%	Extended Mean: 24.2 SD: 8.6 Standard Mean: 22.0 SD: 8.7	Extended Mean: 6.1 SD: 2.4 Standard Mean: 5.6 SD: 1.5	NRT patch 21mg daily for 14 weeks, followed by 4 weeks of tapering period; no treatment adherent information	NRT patch 21mg daily for 6 weeks, followed by 4 weeks of tapering period; no treatment adherent information	Continuous abstinence at Week 18, confirmed by exhaled CO (≤10 ppm) Withdrawal symptoms measured by DSM-IV withdrawal Symptomatology (depressed mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, excessive hunger)

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													and craving for a cigarette
Schlam 2016	USA	Jun. 2010-Nov. 2013	Primary care clinics	Public	Smokers attending cliinics	Total: 544 Extended: 275 Standard: 269	Extended Mean: 46.9 SD: 12.2 Standard Mean: 45.4 SD: 13.3	Extended: 41.1% Standard: 40.9%	Extended Mean: 19.0 SD: 9.0 Standard Mean: 18.2 SD: 8.5	Extended Mean: 4.9 SD: 2.3 Standard Mean: 4.8 SD: 2.2	NRT patches at doses of 7, 14, and 21 mg daily (depending on severity of dependence) for 26 weeks + nicotine gum; 133 of 275 participants received all treatment	NRT patches at doses of 7, 14, and 21 mg daily (depending on severity of dependence) for 8 weeks + nicotine gum; 172 of 269 participants received all treatment	7-day point prevalent abstinence at Months 6 and 12, measured by self-report Continuous abstinence at Months 6 and 12 Serious adverse events
Schnoll 2015	USA	Jun. 2009 - Apr. 2014	community	Public	Smokers in Philadelphia and Chicago	Total: 525 Extended: 345 Standard: 180	Mean: 46.4 SD: 12.1	Extended: 49.0% Standard: 50.0%	Mean: 17.1 SD: 8.4	Mean: 5.1 SD: 2.0	NRT patch 21mg daily for 24 weeks or 52 weeks; 107 of 172 participants randomized to 52 weeks of treatment and 123 of 173 participants randomized to 24 weeks of treatment received treatment	NRT patch 21mg daily for 8 weeks; 148 of 180 participants randomized to 8 weeks of treatment received treatment	7-day point prevalent abstinence at Weeks 24 and 52, confirmed by exhaled CO (≤10 ppm) Continuous and prolonged abstinence at Weeks 24 and 52 Relapse
Schnoll 2010	USA	Oct. 2004-Mar. 2008	Not reported	Public	Smokers recruited via advertisements	Total: 568 Extended: 282 Standard: 286	Extended Mean: 44.8 SD: 10.2 Standard Mean: 44.9 SD: 10.4	Extended: 55.7% Standard: 54.9%	Extended Mean: 21.1 SD: 9.5 Standard Mean: 21.3	Extended Mean: 5.2 SD: 2.2 Standard Mean: 5.3 SD: 2.1	NRT patch 21mg daily for 24 weeks; 212 of 286 participants were available at	NRT patch 21mg daily for 8 weeks, followed by placebo for 16 weeks; 218 of 282	7-day point prevalent abstinence at Weeks 24 and 52, confirmed by exhaled CO (≤10 ppm)

									SD: 9.0		week 24 assessment	participants were available at week 24 assessment	Continuous and prolonged abstinence at Weeks 24 and 52 Serious adverse events Relapse
Stapleton 1995	United Kingdom	Not reported	General practice	Not reported	Heavy smokers aged 20-60	Total: 800 Extended: 400 Standard: 400	Extended Mean: 40.3 SD: 9.9 Standard Mean: 41.5 SD: 10.2	Extended: 41.9% Standard: 44.8%	Extended Mean: 23.6 SD: 6.9 Standard Mean: 24.2 SD: 7.6	Not reported	NRT patch of 25mg in high dose arm and 15mg in low dose arm for 12 weeks, followed by gradual withdrawal for 6 weeks; compliance rate was 61% at week 12	NRT patch of 25mg in high dose arm and 15mg in low dose arm for 12 weeks, followed by abrupt withdrawal; compliance rate was 61% at week 12	Relapse measured after week 12
Tonnesen 1999	17 European countries	Jan. 1994-Nov. 1995	Chest clinics	Not reported	Smokers from general population	Total: 2861 Extended: 715 in both high dose and low dose arms Standard: 715 in high dose arm, 716 in low dose arm	Extended Mean: 40 in both high dose and low dose arms SD: 10 in both high dose and low dose arms Standard Mean: 41 in both high dose and low dose arms SD: 10 in both high dose and low dose arms	Extended: 52% in both high dose and low dose arms Standard: 53% in high dose arm, 51% in low dose arm	Extended Mean: 28 in high dose arm, 26 in low dose arm SD: 11 in high dose arm, 10 in low dose arm Standard Mean: 26 in high dose arm, 27 in low dose arm SD: 9 in high dose arm, 10 %	Extended Mean: 5.6 in both high dose and low dose arms SD: 2.1 in both high dose and low dose arms Standard Mean: 5.6 in high dose arm, 5.4 in low dose arm SD: 2.1 in both high dose and low dose arms	NRT patch of 25mg in high dose arm and 15mg in low dose arm for 22 weeks, followed by 10mg in both arms for 4 weeks; attendance rate was 36% at week 26	NRT patch of 25mg in high dose arm and 15mg in low dose arm for 8 weeks, followed by 10mg in both arms for 4 weeks; attendance rate was 55% at week 12	Continuous abstinence at Weeks 12, 26 and 52, confirmed by exhaled CO (<10 ppm)

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									in low dose arm				
Tonsad 2006	7 countries including USA	Apr. 2003-Feb. 2004	medical clinics	Private company	Cigarette smokers 18-75 years	Total: 1210 Extended: 603 Standard: 607	Extended Mean: 45.4 SD: 10.4 Standard Mean: 45.3 SD: 10.4	Extended: 49.8% Standard: 51.7%	Extended Mean: 20.7 SD: 7.3 Standard Mean: 20.7 SD: 7.5	Extended Mean: 5.43 SD: 1.96 Standard Mean: 5.35 SD: 1.98	Varenicline 1mg twice daily for 24 weeks[b]; 555 of 603 participants completed treatment	Varenicline 1mg twice daily for 12 weeks, followed by placebo for 12 weeks[b]; 510 of 607 participants completed treatment	7-day point prevalent abstinence at Weeks 24 and 52, confirmed by exhaled CO (≤10 ppm) Continuous abstinence at Weeks 24, 36, and 52 Serious adverse events Relapse Withdrawal symptoms measured by MNWS

Abbreviations: CO, carbon monoxide; SD, standard deviation; SF-12, The Short-Form Health Survey; MNWS, Minnesota Nicotine Withdrawal Scale

[a] We reported the number of participants who received treatment if the information was available, or the number of participants who completed the study if otherwise as substitute of treatment compliance.

[b] In the first week, the dose of varenicline was up titrated, 0.5mg daily for 3 days, followed by 0.5mg twice daily for 4 days.

[c] Information was extracted according to results on clinical trial registry because no full text was available.

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Table 2. Summary of findings table

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard duration	Risk difference with extended duration (greater than 12-week)
7-day point prevalent abstinence at 1 year assessed with: Self report + exhaled carbon monoxide concentration verification follow up: mean 1 years	3711 (8 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 1.22** (1.07 to 1.39)	242 per 1,000	**53 more per 1,000** (17 more to 94 more)
7-day point prevalent abstinence at 1 year assessed with: Self report + exhaled carbon monoxide concentration verification follow up: after 1 years (15 to 18 months)	657 (3 RCTs)	⊕⊕◯◯ LOW[b]	**RR 1.50** (0.91 to 2.47)	271 per 1,000	**136 more per 1,000** (24 fewer to 399 more)
Continuous abstinence at 1 year assessed with: Self report + exhaled carbon monoxide concentration verification follow up: mean 1 years	5680 (7 RCTs)	⊕⊕⊕◯ MODERATE[c]	**RR 1.14** (0.99 to 1.32)	149 per 1,000	**21 more per 1,000** (1 fewer to 48 more)
Prolonged abstinence at 1-year assessed with: Self report + exhaled carbon monoxide concentration verification follow up: mean 1 years	1093 (2 RCTs)	⊕⊕⊕◯ MODERATE[d]	**RR 1.33** (1.07 to 1.66)	207 per 1,000	**68 more per 1,000** (14 more to 136 more)
Relapse follow up: range 12 months to 18 months[l]	328 (3 RCTs)	⊕⊕⊕◯ MODERATE[e]	**HR 0.43** (0.29 to 0.64)	-	**-**
Time to relapse follow up: 1 years[n]	1735 (2 RCTs)	⊕⊕◯◯ LOW[f]	-	The mean time to relapse was **0** days	MD **22.03 days more** (10.81 more to 33.24 more)[p]
Serious adverse event	2612 (5 RCTs)	⊕⊕⊕◯ MODERATE[g]	**RR 1.37** (0.79 to 2.36)	8 per 1,000	**3 more per 1,000** (2 fewer to 11 more)

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Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard duration	Risk difference with extended duration (greater than 12-week)
Quality of life assessed with: The Short-Form Health Survey (SF-12) (Higher score indicates worse quality of life) Scale from: 12 to 47 follow up: 52 weeks	98 (1 RCT)	⨁◯◯◯ VERY LOW[h]	-	-	MD **1.15 lower** (3.75 lower to 1.45 higher)
Withdrawal assessed with: craving and urge to smoke; low scores indicates better outcome follow up: range 13 weeks to 14 weeks[q]	1186 (2 RCTs)	⨁◯◯◯ VERY LOW[i]	-	-	SMD **1.54 lower** (3.94 lower to 0.85 higher)
Withdrawal assessed with: Minnesota Nicotine Withdrawal Scale, urge to smoke; lower score indicates better outcome Scale from: 0 to 4 follow up: 25 weeks	967 (1 RCT)	⨁⨁◯◯ LOW[j]	-	-	MD **0.27 lower** (0.44 lower to 0.1 lower)
Number of cigarette follow up: mean 1 years	525 (1 RCT)	⨁⨁◯◯ LOW[k]	-	-	MD **0.6 lower** (1.53 lower to 0.33 higher)

a. Downgraded by one level for serious risk of bias. For included studies, Schnoll 2015 and Schlam 2016 were open label trials, and in Schnoll 2015 no placebo was used. It was unclear whether Croghan 2007 was a trial with participants, healthcare personnels, and outcome assessors blinded. If we excluding three studies (Schnoll 2015, Schlam 2016, and Croghan 2007), the lower limit of confidence interval would be 1.02, suggesting only a small benefit of extended treatment. It means if we excluded open label studies, the estimate would be imprecise.
b. Downgraded by two levels due to serious risk of bias and inconsistency. Croghan 2007 was a trial with participants, healthcare personnels, and outcome assessors blinded. The meta-analysis combined estimates from three studies, with varied point estimates, and little overlap between confidence intervals. The I2 was 68%.
c. Downgraded by one level for serious imprecision. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the benefit of extended treatment will be different. The absolute effect of extended treatment could be more abstinence or less abstinence. Though studies includign Schnoll 2015 and Schlam 2016 were judged to be high risk of bias. The studies with low risk of bias reported similar estimates as the studies with high risk of bias. Sensitivity analysis suggested excluding these studies had little impact on the pooled estimate.
d. Downgraded by one level for serious risk of bias. Schnoll 2015 was an open label trial and no placebo was used.
e. Downgraded by one level for serious imprecision. The pooled estimate was based on two studies (Evins 2014, Schnoll 2010) with 328 patients. The total sample size was 662.
f. Downgraded by two levels for serious risk of bias and inconsistency. Schnoll 2015 was an open label trial and no placebo was used. In Schnoll 2015, relapse was defined as 7 consecutive days of self-reported smoking from the cessation date to weeks 24 and 52 after a 2-week grace period, while in Tonstad 2006, relpase was measured by the strict criterion of a single "puff." The estimates of difference in time to relapse between group were so different between the two studies (Schnoll 2015 and Tonstad 2006): 17 days and 111 days. Schnoll 2015 used nicotine patch while Tonstad 2006 was on varenicline. But it is unclear the type of medication was the reason of inconsistency.
g. Downgraded by one level for serious imprecision. The confidence interval includes 1, indicating if we consider lower or the upper limit of the confidence interval, the conclusion on the safety of extended treatment will be different. The number of events was small.

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h. Downgraded by three levels due to serious risk of bias, indirectness, and imprecision. The estimate was based on one single study, NCT01756885. In this study, 47 of 105 participants in the extended treatment group and 51 of 102 in the standard duration group provided the quality of life data. The high proportion of loss to follow up and missing participant data may cause an imbalance in prognosis factors between groups. Furthermore, we have limited information (only from trial registry) to fully assess the risk of bias for this study. This is a study on smoking cancer patients and the sample size was small.

i. Downgraded by three levels due to serious risk of bias, inconsistency, and imprecision. There was no details reported on the randomization process for Pomerleau 2003. In Tonstad 2006, though this study used intention to treat analysis strategy, the study was considered at high risk of bias for "withdrawal symptom", because the loss to follow up was different between groups (499 in extended treatment group and 468 participants in the control group). Though both suggested extended use of medication can decrease the withdrawal symptom, the two studies (Pomerleau 2003 and Tonstad 2006) showed different effect estimates. The two studies used different measurement tools (craving score and Minnesota Nicotine Withdrawal Scale), and were on different medications (nicotine patch versus varenicline), and used different length of extended treatment. The source of inconsistency was unclear. In Pomerleau 2003, the craving was measured with a scale of 0 to 5, with 5 indicating the greatest severity. In Tonstad 2006, the urge to smoke was measured with Minnesota Nicotine Withdrawal Scale, with a range of 0 to 4. Lower score indicates better outcomes in both scales. The confidence interval includes 0, indicating the effect of extended treatment on the withdrawal symptom is inconclusive.

j. Downgraded by two levels due to serious risk of bias and imprecision. In Tonstad 2006, though this study used intention to treat analysis strategy, the study was considered at high risk of bias for "withdrawal symptom", because the loss to follow up was different between groups (499 in extended treatment group and 468 participants in the control group). The difference between group was small, though the minimal clinical important difference is unclear, it was unlikely to be clinically important.

k. Downgraded by two levels due to serious risk of bias and imprecision. Schlam 2016 was an open label study. The confidence interval included 0, indicating the extended treatment may not decrease the number of cigarettes compared with standard duration. Furthermore, the difference may not be clinically important.

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Figure Legends

Figure 1 – PRISMA diagram of included studies

Figure 2 – Meta-analysis of point prevalent abstinence at 12 months

Figure 3 – Meta-analysis of relapse at 12-18 months after initiation of therapy

Figure 4 – Meta-analysis of serious adverse events

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