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International Journal of Current Research
Vol. 9, Issue, 10, pp.58492-58501, October, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

NICOTINE REPLACEMENT THERAPY AND SMOKING CESSATION: AN UPDATED SYSTEMATIC REVIEW OF RANDOMIZED CONTROL TRIALS

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ARTICLE INFO

Article History:
Received 06th July, 2017
Received in revised form
23rd August, 2017
Accepted 28th September, 2017
Published online 17th October, 2017

Key words:

Smoking cessation, Abstinence, Nicotine, Nicotine replacement therapy.

ABSTRACT

Background and objective: Smoking cessation is associated with decreased smoking related morbidity and mortality and increased life expectancy. It can be achieved through several pharmacological and non-pharmacological interventions in which nicotine replacement therapy (NRT) is an example that help to replace nicotine from cigarettes, therefore, reducing nicotine withdrawal symptoms and the urge to smoke. The aim of this review is to determine the effectiveness of NRT in enhancing, achieving, and maintaining smoking cessation.

Methods: A literature search was conducted in March 2017 using Medline/PubMed, Science Direct, SCOPUS, TRIP and Google scholar databases, in which randomized trials of NRT and smoking cessation with final follow-up at least 6 months after the start of treatment were selected. Twenty-one eligible trials were identified, in which NRT was compared to placebo, other pharmacotherapy or non-pharmacotherapy and reported abstinence rates. The main outcome measure is self-reported 7-day point of quit rate over study conduction period to assess the specific effect of nicotine replacement therapy among interventional group.

Results: NRT use for at least two weeks is an effective measure in promoting smoking cessation among male and female smokers regardless of the degree of their smoking dependence. Also, NRT use during pregnancy is a safe intervention to enhance smoking cessation among pregnant smokers and is associated with delivery of babies with higher birthweight.

Conclusion: This review concludes that nicotine replacement therapy is an effective, safe intervention to promote and sustain smoking cessation whether used alone or in combination with additional support of pharmacological and non-pharmacological interventions.

Citation: Zainab Mohammed Al Eid, Zahra'a Ibrahim Al Radhi, Fatimah Abbas AlMohammed Saleh and Fatimah Adnan Al Ramadhan, 2017. "Nicotine replacement therapy and smoking cessation: An updated systematic review of randomized control trials", *International Journal of Current Research*, 9, (10), 58492-58501.

INTRODUCTION

Cigarette smoking is the largest modifiable risk factor for human health and a significant cause of morbidity and mortality worldwide (Bergen, 1999 and Jayanthi, 1991). It is estimated that there are approximately 1.1 billion smokers worldwide, of which 900 million are men and 200 million are women with male to female ratio of 2:1 and 7:1 in developed and developing countries, respectively, (Saha, 2007). Cigarette smoking is considered one of the major and powerful risk factors in the development of many health problems, such as atherosclerosis, cardiovascular diseases (CVD), chronic obstructive pulmonary disease (COPD), adverse pregnancy and birth outcomes and cancers, of which lung cancer is of special importance, since it is the leading cause of cancer deaths in males and the second leading cause in females globally (Shammas, 2007; Freund, 1993; Rosenberg, 1985; Ernster, 1988; Coleman, 2012 and Islami, 2015). Cigarette smoking can be considered a chronic disease requiring continuous attention and treatment just like hypertension, diabetes and congestive heart failure (Milani, 1990). Abstinence is of great significance since health benefits of smoking cessation are well documented; it is associated with significant reduction in smoking related CVD, COPD, and lung cancer morbidity and mortality (Taylor, 2002; Wu, 2011). It can be achieved through non-pharmacologic and pharmacologic interventions. Non-pharmacologic intervention consists of smoking cessation counseling sessions, which can be minimal or intensive. Pharmacologic interventions consist of bupropion, vareniclineand nicotine replacement therapy (NRT). Generally, both pharmacotherapies and non-pharmacotherapies are required to significantly influence abstinence rates, however, pharmacotherapies are superior (Milani, 1999; Taylor, 2002; Wu, 2011 and Alberg, 2012).

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NRT is one of the widely used, safe and effective treatment for nicotine dependence; it is the most promising pharmacological intervention studied to date (Alberg, 1999; Bullen, 2010; Hollands, 2013). The main aim of NRT is to temporarily replace nicotine from tobacco, therefore, reducing nicotine withdrawal symptoms and the urge to smoke (Silagy, 2004). It is available in different forms, including nicotine gums, sublingual tablets, lozenges, nasal spray, oral inhaler and transdermal patches, and in different dosage (Milani, 1999; Wadgave, 2016 and Jain, 2013). Typically, it is started when a person stops smoking. However, it can also be used as gradual reduction, pre-cessation or pre-quitting approach in which NRT is used for several weeks prior to quitting (Bullen, 2010; Shiffman, 2009). The aim of this review is to determine whether nicotine replacement therapy, alone or in combination with other modalities, is effective in enhancing, achieving and maintaining long-term smoking abstinence.

MATERIALS AND METHODS

Search strategy for Identification of trials

Reviewers electronically searched the Medline/ PubMed, Science Direct, SCOPUS, TRIP and Google scholar databases using broad search terms (Table 1). Our search was not limited to specific language but was restricted to trials that published from September 2012 up to January 2017 as there was a Cochrane review published about the role of nicotine replacement therapy and smoking cessation in 2006, 2009, and 2012, respectively (Etter, 2006 and Stead, 2012). Titles of results found in each database were screened if it would be appropriate to obtain the full-text paper for the review. A manual searching has been conducted of papers cited in the related publication to ensure that all trials are included in our review.

Selection strategy of studies: Studies were eligible to be included in the review if they were randomized controlled trials (RCT). Other types of studies such as observational, case reports, review, commentaries, letter to editors were excluded. These RCT must meet the following criteria:

- *Males and females'smokers who are trying to quit smoking but cannot abruptly.*
- *The intervention: Nicotine replacement therapy (NRT) including chewing gum transdermal patches, lozenges, oral inhaler.*
- *Participants are willing to use NRT and free from any serious health problems that make NRT contraindicated to be used such as palpitation. Further, studies involved patients as the study group with psychiatric disorders were excluded.*
- *The comparator (the other arm) was placebo, whatever other intervention used for smoking cessation, such as psychological intervention.*
- *Outcomes for abstinence from smoking were reported.*

Studies were excluded if the primary outcome i.e. abstinence from smoking was not reported (Figure 1).

Data extraction

Two reviewers extracted data from the eligible papers using a standardized spreadsheet independently. Any disagreements or discrepancies between both reviewers was resolved by consensus or consultation of a third party. The characteristics of each study were extracted, including first author's name, year of publication, country, study design, period of intervention and primary outcomes in which the trial was performed (Table 2).

Outcome measures

Our primary outcome measure is for self-reported 7-day point of quit rate over study conduction period to assess the specific effect of nicotine replacement therapy among interventional group.Regarding trials that assess the effectiveness of NRT among pregnant women, smoking cessation outcomes extracted at the time of starting using NRT to end of pregnancy or postpartum if reported (Table 2).

Risk of bias assessment

We assessed the quality of methodology applied for each included trial using a scale described by Jadad, *et al*. (Jadad, 1996), for evaluation. This scale is ranging from 0 – 5 and assessing risk of selection bias (randomization), double-blinding, and withdrawal (loss to follow-up) (Table 3).

RESULTS AND DISCUSSION

Our review included 21randomized controlled studieswhich designed to assess the effectiveness of nicotine replacement therapy compared with other interventions use for smoking cessation. [24-45] A Similar number of participants involved in most trials of men and women and four trials recruited only pregnant women. There are four studies that compared NRT with varenicline and one study investigate the effectiveness of NRT over Cytisine. Further, one study investigated hypnotherapy when it is combined with NRT patches.

Effects of nicotine replacement therapy (NRT) intervention for smoking cessation

Effects of nicotine replacement therapy (NRT) alone

A double-blind placebo-controlled clinical trial which was conducted in Netherlands and carried out on 257 smoker male and female adolescent smokers between 12 and 18 years of age, with a mean age of 16 years, who smoked 7 or more cigarettes per day revealed that short-course NRT in the form of nicotine patches is effective in promoting smoking cessation among smokers after 2 weeks of starting the treatment compared to placebo (OR = 2.02, 95% CI = 1.11–3.69), but not end-of-treatment (6 months) cessation. However, highly compliant participants showed significant increase in abstinence rates (OR = 1.09, 95% CI = 1.01–1.17) at the end of treatment compared to low compliant participants (Scherphof, 2013). In a single-blinded randomized controlled trial design, 562 Chinese smokers randomly allocated into two groups with findings showed that no significant difference for giving 2 weeks' free NRT over 1 week's free NRT in quit rate at 6 months and 12 months. Another point is thatgiving 1-week or 2-week supply did not have any measurable effect on determination to quit, 1-week free NRT was enough to encourage motivated smokers to continue to use it for a longer duration as 7-day point prevalence quit rates were not significantly different between two groups, at 6-month (27.5% versus 27.3%; 5 = 0.97) and 12-month (21.1% versus 21.2%; 5 = 0.98) follow-up.

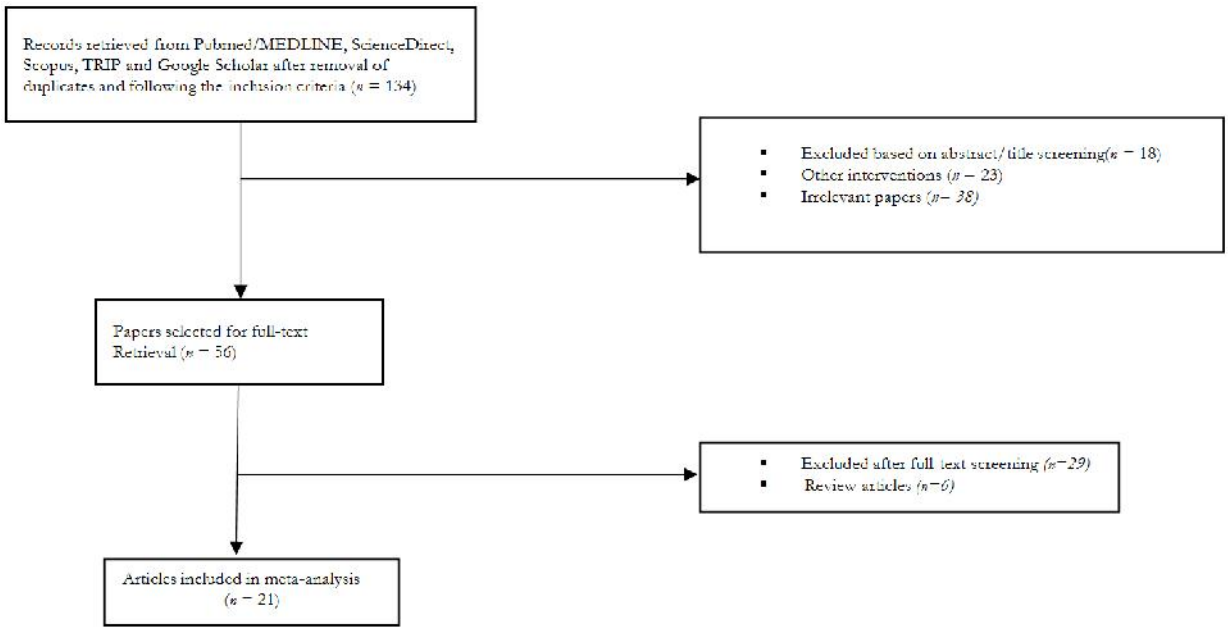

Figure 1. The flow diagram for process of study selection

Table 1. Databases screened

Search terms/key words (used for all databases' searches)	Database and website	Number of records from each database
("nicotine"[MeSH Terms] OR "nicotine"[All Fields]) AND "replacement"[All Fields]) AND ("smoking"[MeSH Terms] OR "smoking"[All Fields]) AND cessation[All Fields].	Medline/Pubmed: www.ncbi.nlm.nih.gov/pubmed/	2,348
	Science Direct: www.sciencedirect.com	729
	SCOPUS: https://www.scopus.com/	3,742
	TRIP database: www.tripdatabase.com/	355
	Google Scholar	7,310

Smoking cessation rate of two weeks was not more effective than 1-week difference between (Abdullah, 2013). Another randomized three-group pretest-posttest trial that is conducted in United States (US) and carried out on participants of young adult age (between 18-30 years of age) showed that smokers who used NRT patches have greater smoking abstinence at 12-weeks (p<.001) and 26-weeks (p<.05) compared to those who didn't, especially if used for more than two weeks (p<.001). Smokers assigned to a self-help booklet or cessation website and heavier smokers were most likely to use NRT (p<.05) which concludes that **t**he use of NRT appeared to be helping the young adults in quitting smoking. Many of them were willing to try NRT. Therefore, NRT should be available to this age group, Strategies should be build and support should be offered for them in order to prevent life-long smoking (Buller, 2014). Further Randomized Clinical Trial conducted in USA by Bock and his colleagues in (2014) on846 participants who were randomly assigned either to motivational rise cure concurrence brief physician advice yet 8 weeks of nicotine alternative remedy (NRT) yet after value care, which consisted about quick health practitioner exhortation and8 weeks about NRT (Bock, 2014).

Caldwell BO *et al* conducted a randomized control trial of 2,286 adult smokers between 18 – 70 years of age who had the desire to quit and smoke ≥9 cigarette per day with Fagerstrom Test of Nicotine Dependence (FTND) score ≥3 were screened, and 1,423 were eligible for randomization. They were randomized to two groups; nicotine oral spray and nicotine patch (active group) and placebo oral spray and nicotine patch (placebo group).

Both groups received 24-hr nicotine transdermal patch for 5 months while the active and placebo groups received 6 months of active (nicotine) and placebo mouth spray. The active group (nicotine oral spray and nicotine patch) showed significantly higher abstinence rate compared to placebo group (placebo oral spray and nicotine patch) at 6 months' follow-up (15.5% vs. 10.6%; p = .006). However, long-term 12-months abstinence rate was of borderline significance; 10.1% in the active group compared with 7.1% in the placebo group, *OR* 1.47 (95% confidence interval [CI] = 1.01–2.12) and p = .045. The addition of 1-mg nicotine oral spray to a nicotine patch significantly increased abstinence at 1, 3, and 6 months compared with placebo mouth spray and a nicotine patch. However, this additional benefit was not significantly different after 6 months. Therefore, the combination of nicotine mouth spray and nicotine patch significantly improve smoking cessation, particularly for the first 6 months, compared to nicotine patch alone, but this effect is not sustained. There are several reasons why such combination failed to improve the abstinence rate after 6 months in this study. First, the presence of substantial number of smokers who had previous attempts to quit and high previous use of NRT (81%). Second, unpleasant taste of nicotine mouth spray. Third, discontinuation of NRT at 6 months. Fourth, less behavioral support and counselling. This study concluded into the addition of nicotine oral spray to nicotine transdermal patch to a group of smokers receiving low level of behavioral support improved early short-term quitting, but the effects is not sustained (Caldwell, 2014). In a trial that enrolled a total of 362 adolescent smokers aged 12 – 18 years who had the desire to quit and smoked ≥7 cigarette per day were eligible for randomization.

Table 2. Characteristics of included studies

Reference	*Author, year*	*Country*	*Study Design*	NO. of participants	*patient's characteristics*	*Intervention of treatment group*	*Control intervention*	*Follow – up*	*Odd ratio*	*Primary Outcome*
24	Coleman T, *et al*. (2012)	UK	Randomized control trial	1050	Pregnant women (12 to 24 week) between 16-50 years of Age.	Nicotine patch,15 mg/ 16 hours with behavioral cessation support (n=521)	Placebo with behavioral cessation support (n=529)	At 1 month, and at delivery.	unadjusted odds ratio, 1.26; 95% CI, 0.82 to 1.96.	There is no significant increase the rate of abstinencefrom smoking until delivery by adding a nicotine patch (15 mg per 16 hours) to behavioral cessation support for women who smoked during pregnancy.
25	Scherphof CS, et a (2013)	Netherlands	Double-blind placebo-controlled clinical trial.	257	12 - 18 years.	Nicotine Patches (21 mg, 14 mg, and 7 mg) (135)	Placebo patch (21 mg, 14 mg, and 7 mg) (122)	6, 9 weeks	OR = 2.02, 95% CI = 1.11–3.69	NRT is effective in promoting smoking cessation after 2 weeks of treatment among adolescent smokers compared to placebo.
26	Stapleton J, *et al*. (2013)	UK	Open-label randomized controlled trial	1071	Smokers	weekly behavioral support sessions and NRT (418)	weekly behavioral support sessions with bupropion (409) or NRT plusbupropion (244).	1, 6 months	odds ratio = 1.21, 95% confidence interval = 0.883–1.67	There is no significant difference among bupropion, nicotine replacement therapy and their combination when used with behavioral support in smoking cessation.
27	El-Mohandes AE, *et al*. (2013)	USA	Randomized Clinical Trial	52	women ≥18 years, <30 weeks pregnant.	trans-dermal nicotine patches and cognitive behavioral therapy (26, 50%)	cognitive behavioral therapy alone (26, 50 %)	Not reported	Not reported	NRT is effective in promoting smoking cessation among pregnant smokers and is associated with delivery of babies with higher birthweights compared to pregnant smokers who offered only cognitive behavioral therapy.
28	Abdullah A, *et al*. (2013)	Hong Kong	Randomized Controlled Trial	562	Adult healthy Chinese participants, smoking at least 5 cigarettes Daily.	behavioral counseling with free NRT for 1 week (A1=284)	behavioral counseling with free NRT for 2 weeks (A2=278)	At 1 week, 1, 3, 6 and 12 months	At 6 months OR =1.0, 95% CI: 0.7–1.4, P=0.97	No additional advantage of using free NRT for 2 weeks as compared to 1 week usage for smoking cessation.
29	Ramon JM. *et al*. (2014)	Spain	Randomized placebo-controlled trial	341	Age > 18 years and smoking ≥20 cigarettes daily	Patches	varenicline	12 weeks	At 1 month OR=1.24	The combination of nicotine patches and varenicline is not associated with higher abstinence rates at 12 and 24 weeks compared to NRT alone
30	Buller, *et al*. (2014)	USA	Randomized pretest-posttest trial	3,094	between 18 and 30 years old.	Patches	Varenicline	12-week and 26-weeks	Not reported	NRT use for 2 weeks or longer is associated with greater smoking abstinence at 12-week and 26-week follow-up
31	Hsueh K. *et al*. (2014)	Taiwan	Randomized control trial.	587	18 years or older, smoking ≥10 cigarettes per day (CPD)	Patches	varenicline	3, 6, 12, and 36 months	At 36 week OR= 7.94 (95 % CI 1.87–33.74).	An 8-week course of varenicline appears to yield higher abstinence rate up to 3 years than a similar length course of nicotine transdermal patch in routine clinical practicewhere behavioral support is available.
32	Hasan FM., *et al*. (2014)	USA	Randomized control trial	164	Smokers between the ages of 18 and 75 years.	Patches, gum and lozenges	hypnotherapy	1, 2, 4, 8, and 12 weeks	at 26-weeks (RR = 3.6; p = 0.03 and RR = 3.2; p = 0.04, respectively).∗	Hypnotherapy patients were more likely than NRT patients to be nonsmokers at 12 weeks and 26 weeks after hospitalization.
33	Bock BC, *et al*. (2014)	USA	Randomized Clinical Trial	846	Healthy adult smoker (at least 10 cigarettes/day for the past 3 months).	Patches	counseling sessions	1, 2, 6, and 12 months	odds ratio [*OR*] = 1:10, 95% CI = 1:20–1:5	Direct intervention effects on abstinence rates were not significant, after adjusting for model predictors and selection bias.

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34	Tulloch H., *et al*. (2014)	Canada	Randomized, controlled trial.	737	_	Patches	varenicline, counseling sessions	8 follow-up appointments over 12 months	Not reported.	Abstinence rates at 5 and 52 weeks was not higher among smokers receiving combined NRT and varenicline compared to those receiving NRT or varenicline alone.
35	Caldwell BO *et al*. (2014)	*New Zealand*	Randomized controlled trial	1,423	Healthy adult smokers between 18 – 70 years of age who smoke ≥9 cigarettes per day.	nicotine patches and nicotine oral spray	Seven hundred and seven received placebo spray and nicotine patch	At 6 and 12 months	*OR* 1.47 (95% confidence interval [CI] = 1.01–2.12)	The addition of nicotine oral spray to nicotine transdermal patch to a group of smokers receiving low level of behavioral support improved early short-term quitting, but the effects is not sustained.
36	Scherphof CS *et al*. (2014)	Netherlands	Randomized controlled trial	362	Adolescent between 12 and 18 years of age who smoked ≥7 cigarettes per day.	nicotine patch (n=182)	placebo patch (n=180)	At 6 and 12 months	*OR* = 0.64, 95% CI = 0.21, 1.93.	Nicotine replacement therapy in the form of nicotine transdermal patch failed to achieve smoking cessation at 6 and 12-month follow-up among adolescent smokers.
37	Walker N *et al*. (2014)	New Zealand	Parallel, randomized, controlled trial	1310	Adult smokers ≥18 years who smoked daily	Nicotine patch, gum, lozenges or combined nicotine gum and lozenges (n= 655)	Cytisine (n= 655)	At 1, 2, and 6-months	At 6-months follow-up: Risk difference = 1.5, 95% CI= (-3.5 to 6.5) $p = 0.594$	Cytisine was effective for continuous smoking cessation and superior to that of NRT at 1-month, 2-months and 6-months.
38	Berlin I *et al*. (2014)	France	Randomized controlled multicenter trial	402	Pregnant smokers ≥18 years of age and between 12 and 20 weeks' gestation.	Nicotine patch (n=203)	Placebo patch (n=199)	Monthly from the quit day up to the time of delivery	*OR* = 1.08, 95% CI= 0.45 to 2.60, with a *p* value of 0.87. Birth weight: $p = 0.41$	Treatment of pregnant smokers with nicotine patches did not increase either smoking cessation rates or birth weights despite adjustment of nicotine dose.
39	Xiao D *et al*. (2014)	China	Randomized controlled trial	300	Healthy adult smokers ≥18 years of age, smoked ≥10 cigarettes per day.	Nicotine patch (n=150)	nicotine gum (n=150)	At 6-months (week 24)	Not reported.	NRT is well tolerated by and results in significantly higher abstinence rate among Chinese smokers.
40	Schnoll RA., *et al* (2015)	USA	Randomized controlled trial	525	Adults ≥18 years or older, to smoke at least 10 cigarettes per day	transdermal nicotine patch	Placebo	At 6-months (24 week)	Not reported	6-month smoking cessation rates can be increased significantly with 24 weeks compared with 8 weeks of nicotine patch use.
41	Gray K m. *et al* . (2015)	USA	Randomized controlled trial	(N=140).	ages 18-45 and averaging ≥10 cigarettes per day for at least 6 months	Nicotine patches	varenicline tablets and placebo patches (n=67)	two-week end-of-treatment abstinence for primary outcomes	2.7 (1.3-6.0), p=0.011	Favored of varenicline regarding its abstinence
42	Baker T. , *et al*. (2016)	USA	Randomized trial	1086	mean age 48 years, mean of 17 cigarettes smoked/day	Nicotine patches	varenicline only	abstinence at 26 weeks	(−3.3, 95% CI: −9.1 to 2.6)	There is insignificant difference in biochemically confirmed rates of smoking abstinence at 26 weeks among smokers receiving varenicline, nicotine patch or combined NRT
43	Tulloch H. ,*et al*. (2016)	Canada	Randomized, controlled trial	1700	Mean age 48 years	The NRT patches (21 mg daily)	VR 1 mg twice daily for up to 24 weeks	5-52 weeks	1.84 vs 2.01 respectively	Smokers receiving combined/extended NRT showed higher success of quitting compared to NRT monotherapy.
44	Vaz L., *et al*. (2016)	UK	Randomized controlled trial.	1050	Mean age 24 years	Patches	placebo	At 1 month	[*OR*] 1.11,	Pregnant smokers who were adherent to NRT had greater abstinence rates at the time of delivery compared to placebo.
45	Cunningham JA. ,*et al*. (2016)	Canada	Single-blinded randomized clinical trial	2093	Mean age 48 years	Patches	No intervention.	30-day smoking abstinence at 6 months	2.65 vs 2.85	The use of nicotine patches for 5 weeks is associated with higher rate of self-reported and biochemically validated abstinence

They were randomized to either a nicotine patch group (182 participants) or a placebo patch group (180 participants). Both groups received an information meeting followed by a 6- or 9-week treatment. Th Resultsat 6-month follow-up, 8.1% of participants (18 adolescent smokers) reported self-abstinence in the nicotine patch group and 5.7% (7 adolescent smokers) in placebo patch group (*OR* = 1.54, 95% CI = 0.57, 4.16). At 12-month follow-up, biochemically validated abstinent rate was 4.4% and 6.6% in nicotine and placebo patch groups, respectively (*OR* = 0.64, 95% CI = 0.21, 1.93). Therefore, there is no significant effect of nicotine patch on self-reported abstinence rate at 6-months and biochemically validated abstinence rate at 12-months neither after considering compliance nor after adjusting for covariates. As the short- and long-term effects of nicotine patch on abstinence rate among highly compliant adolescent participants was not confirmed in the extended follow-up assessments indicating that nicotine patches unable to help adolescents remain abstinent. The difference in effectiveness of NRT between adolescents and adults suggests the presence of essential factors which affect the process of smoking cessation among the two groups.

groups. The point prevalence abstinence ranged in nicotine patch group was 8% – 12.5% and 8% – 9.5% in the placebo patch group without statistically significant differences. As interpretation for results of this study, the abstinence rates among pregnant smokers did not increase even after a relatively high daily doseof nicotine patch, which was administered with a relatively high self-reported compliancerate during the second and thirdtrimester. Also, smoking abstinence was unrelated to the level of nicotine substitution as evident by the nicotine substitution rate, suggesting the presence of other factors that may determine smoking abstinence in pregnant smokers. Non-changed birth weight and other birth characteristics in nicotine patch group was a probable consequence of the lack of efficacy for abstinence compared to placebo patch group. The dose adjustment schedule after relapses, mostly occurred by week 2 after quit date did not increase the efficacy of the nicotine patches. Therefore, Treatment of pregnant smokers with nicotine patches did not increase either smoking cessation rates or birth weights despite adjustment of nicotine dose (Berlin, 2014).

Table 3. Risk of bias assessment

References	Study	Randomization.	Double-blinding.	Withdraw (drop out).
24	Coleman, *et al*. (2012)	++	0	0
25	Scherphof CS., *et al* (2013)	++	++	+
26	Stapleton J., *et al* (2013)	++	0	0
27	El-Mohandes AE., *et al*. (2013)	++	++	+
28	Abdullah A, *et al*. (2013)	++	+	0
29	Roman JM *et al*. (2013)	++	++	0
30	Buller *et al*. (2014)	++	0	+
31	Hsueh *et al*. (2014)	++	0	0
32	Hasan FM *et al*. (2014)	++	0	+
33	Bock B C *et al*. (2014)	++	+	+
34	Tulloch H *et al* (2014)	++	++	0
35	Caldwell BO *et al*. (2014)	++	++	+
36	Scherphof CS *et al* (2014)	++	++	+
37	Walker N *et al* (2014)	++	0	+
38	Berlin I *et al*. (2014)	++	++	+
39	Xiao D *et al*	++	0	+
40	Schnoll RA *et al* (2015)	++	0	+
41	Gray K m. *et al* (2015)	++	++	+
42	Baker T *et al*. (2016)	++	0	+
43	Tulloch H *et al* (2016)	++	+	+
44	Vaz L *et al*. (2016)	+	+	0
45	Cunningham JA *et al*. (2016)	++	+	+

This study concluded thatnicotine replacement therapy in the form of nicotine transdermal patch failed to achieve smoking cessation at 6 and 12-month follow-up among adolescent smokers (Scherphof,, 2014). A randomized control trialof 476 pregnant smokers ≥18 years (median age of 29.25 years) and between 12 and 20 weeks' gestation, who were motivated to quit and smoked ≥5 cigarettes per daywere screened, and 402 were eligible for randomization. Two-hundred and three participants received nicotine patches, and 199 participants received placebo patches. Both groups received brief behavioral support and smoking cessation counselling. They were followed-up monthly form the quit day up to the time of delivery. The results of eleven participants (5.5%) in nicotine patch group and ten (5.1%) in placebo patch group achieved complete smoking abstinence from the quit day up to the last visit before delivery, which was statistically insignificant (*OR* = 1.08, 95% CI=0.45 to 2.60, with a *p* value of 0.87). The mean birth weight in the nicotine patch group was 3065 g and 3015 g in the placebo patch group, which was also statistically insignificant ($p = 0.41$). The median time to the first lapse (first cigarette smoked after target quit day) was 15 days in both

Another trial of300 healthy healthcare professionals ≥18 years of age, who wanted to quit, smoked ≥10 cigarettes per day and had smoked for at least 3 years were randomly assigned to either nicotine gum or nicotine patch. A hundred and fifty participants received nicotine patches, and another 150 participants received nicotine gum, those who smoked ≤20 cigarettes per day received 2 mg gum, and those who smoked >20 cigarettes per day received 4 mg gum. Treatment continued for 12 weeks and all participants received brief behavioral support and smoking cessation counselling throughout the treatment period. They were followed-up weekly either via telephone call or clinic visit. The resultat 24-week follow-up, carbon monoxide verified continuous abstinence rate was 17%. The highest abstinence rate (20.9%) was among participant received 2 mg gum; corresponding rates with 4 mg gum and patchwere 15.6% and 15.3%, respectively. The point prevalence rate was 35%, being 37.2% in 2 mg gum group, 25% in 4 mg gum group, and 38% in patch group. Thirty-eight percent of participants had reduced their daily cigarette consumption by at least 50% compared to baseline. Nicotine replacement therapy was well tolerated by study

subjects, who were highly compliant, and no serious side-effects were reported. NRT is well tolerated by and results in significantly higher abstinence rate among Chinese smokers (Xiao, 2014). A trial conducted which randomized 525 treatment-seeking smokers to 8 (as standard), 24 (as extended), or 52 weeks (as maintenance) of nicotine patch treatment to compare each period for promoting tobacco abstinence which results of 21.7% of participants at 24 weeks were abstinent which was significant comparing to participants on standard arm i.e. 8 weeks as (odds ratio [OR], 1.70 [95% CI, 1.03-2.81]; P = .04). this duration has not been proved to be associated with any adverse effects which indicates to the safety of long term use of nicotine patch treatment, although no significant difference in efficacy beyond 24 weeks (Schnoll, 2015). In a randomized trial of the 2093 participants who were sent nicotine patches showed self-reported abstinence rates significantlyhigher among participants whowere sent nicotine patches by mail compared with the control group at 6-month (38 [9.8%]of 389 vs 15 [3.6%] of 415; OR, 2.89; 95%CI, 1.56-5.34;*P* = .001)and 8-week (37 [8.7%] of 427 vs 11 [2.5%] of 436; OR, 3.67; 95%CI, 1.84-7.29; *P* < .001) follow-ups which provides the evidence of the effectiveness of mailed nicotine patches without behavioral support to promote tobacco cessation (Cunningham, 2016).

Effects of nicotine replacement therapy (NRT) compared or in combination with other interventions

NRT and Bupropion: One open-label randomized controlled trial that was conducted in United Kingdome and carried out on 1071 smokers'adult male and female smokerswith an average age of 40.8 years showed that the use of NRT alone or in combination with other medications (bupropion)to study the efficacy of NRT, bupropion or their combination on smoking cessation which concluded that there is no significant difference on the effectiveness of smoking cessation (OR = 1.21, 95% CI = 0.883–1.67) (Stapleton, 2013).

NRT and Varenicline

Another randomized placebo-controlled trial included 341 smokers who smoked 20 or more per day received a 12-week course of varenicline and an 11-week course of either the placebo patch orthe active patch and behavioral support. The outcome of this study was abstinence for 2 weeks duration continuously showed that combined treatment of nicotine patches and varenicline was not associated with greater continuous abstinence rates compared to NRT alone at 12 weeks (39.1% versus 31.8%; odds ratio (OR) 1.24; 95% confidence interval (CI) 0.8 to 2.6) and 24 weeks (32.8% versus 28.2%; OR 1.17; 95% CI 0.4 to 1.9). the study concluded that the abstinence rates with the use of varenicline monotherapy improved more than the use of varenicline with the nicotine patch in combination at 12 and 24 weeks (Roman, 2014). Another randomized control trials conducted by Hsueh K. and his colleagues (2014) in Taiwan which recruited 587 smokers shows maintenance of abstinence as an advantage for varenicline, OR= 7.94 (95 % CI 1.87–33.74). Abstinence rates were higher for participants on varenicline than with those who used NRT alone,however, because the varenicline group started with a higher abstinence rate at 3 months, this means that they had a slightly lower relapse rate between then and 36 months. The odds of relapse between 3 months and 36 months were non-significantly higher for the NRT group than the varenicline group (OR=1.68, p=0.12) (Coleman, 2012). A randomized clinical trial conducted on 737 smokers found that there is no significant difference in the abstinence rate found between smokers who used combined NRT and varenicline treatment and those who used NRT or varenicline alone (Tulloch, 2014). Results of another Double-blind randomized trials on 140Female smokers, ages 18-45 and averaging ≥10 cigarettes per day for at least 6 monthssuggest that both varenicline and extended and combination NRT enhance success in the short-term of quitting with no clear evidence for quit rates in the long-term in comparison to NRT monotherapy astwo-week end of treatment for nicotine patch participants 17.8% whereas for varenicline participants 37.7% by 17.8% (odds ratio [OR] (95% confidence interval [CI]) 2.7 (1.3-6.0), p=0.011) and for 1 week and 4 week, abstinence results were favored varenicline respectively (Hsueh, 2014). Anotherrandomized clinical trialamong 1086 smokers who were randomized with follow up of 12-month randomly assigned into three groups: 1) nicotine patch only (n=241); 2) varenicline only (including 1 pre-quit week; n=424); and 3) C-NRT (nicotine patch + nicotine lozenge; n=421) results in no significant differences among these three pharmacotherapies on any of the 26 or 52-week abstinence variance (Cunningham, 2015).

A trial of 737 smokers randomized as follow: NRT (n = 245) received 10 weeks of patches (21 mg daily maximum), NRT+ (n = 245) received patches (35 mg daily maximum) and gum or inhaler for up to 22 weeks, and VR (n = 247) received 1 mg twice daily for up to 24 weeks.The continuous abstinence rate for weeks 5–52 were 10.0 %, 12.4 %, and 15.3 % in the NRT, NRT+, and VR groups, respectively. Among all of them, initial cessation was established but for Varenicline the abstinence was remarkable in the medium term. However, none of them have increased cessation rate in the long-term in compare to NRT alone (Tulloch, 2016).

NRT versus Hypnotherapy

Compared to the NRT group, A study conducted on 164 patients receiving hypnotherapy with results shown that those patients were more likely to abstain from smoking at 12 and 26 weeks after hospitalization. At 12 weeks, 43.9% of patients in hypnotherapy group were self-reported nonsmokers compared to 28.2% of patients that received NRT. Smoking abstinence rates in the group receiving hypnotherapy plus NRT were similar to those observed in those receiving hypnotherapy alone. Participants randomized to the hypnotherapy group tended to have higher smoking abstinence rates at 12 and 26 weeks of follow-up compared to those randomized to the NRT control group ($p = 0.14$ and $p = 0.06$, respectively). Similarly, participants randomized to the ''NRT plus hypnotherapy'' group tended to have higher smoking abstinence rates at 12 ($p = 0.08$) and 26 weeks of follow-up compared to those randomized to the NRT control group ($p = 0.10$). There was no difference in smoking abstinence rates at 26 weeks between participants in the observed ''self-quit'' group and participants in any of the three treatment groups (*p*-values range from 0.34 to 0.50). Although not significantly different, verified smoking cessation rates at 26-weeks post-hospitalization also tended to be higher in cardiac patients as compared to pulmonary patients (34.1% vs. 20.0%; $p = 0.07$) (Tulloch, 2016).

NRT versus Cytisine: In a study of11,071 adult smokers ≥18 years with an average of 38.1 years who were motivated to quit and smoked an average of 19.15 cigarettes per day were

screened and 1,310 were eligible for randomization. Six-hundred and fifty-five participants received 25-day course of cytisine tablets and 655 8-week course of NRT (patches, gums, lozenges, or combined gums and lozenges). Both groups received brie telephone-based behavioral support and counselling. The primary outcome was self-reported continuous abstinence at 1 month while secondary outcome self-reported continuous abstinence at 2-months and 6-months which results of continuous smoking abstinence at 1 month which was 40% and 31% for participants receiving cytisine and NRT, respectively (Risk difference = 8.9, 95% CI= 3.7 to 14.1, p = <0.001) with nearly comparable results at 2-months and 6-months, except that 6-months results were statistically insignificant. Therefore, cytisine was effective for continuous smoking cessation and superior to that of NRT at 1-month, 2-months and 6-months. However, self-reported side-effects, mainly nausea and vomiting and sleep disorders, was higher among cytisine group (31%) than NRT group (20%) over 6-months period which concluded that cytisine is an effective and superior smoking cessation measure compared to NRT. It can be regarded as a first-line treatment for smoking dependence (Walke, 2014). As dependent smokers who had the desire to quit cytisine was superior to NRT to achieve smoking cessation. However, self-reported side-effects were twice as common in cytisine group than NRT group. Compliance in both group was modest, but time to relapse was delayed in cytisine group.

In specific population

Pregnant women: A randomized controlled trial of 1050 smoker pregnant women participants who were 16 to 50 years of age and with 12 to 24 of gestational age received nicotine patch (15 mg/ 16 hours) or placebo randomly beside behavioral cessation supportrevealed nonsignificant difference in biochemically validated prolonged abstinence rate at delivery among nicotine-replacement group (9.4%) and placebo group (7.6%) [OR for abstinence with nicotine-replacement therapy, 1.26; 95% CI, 0.82 to 1.96]. However, the biochemically validated abstinence rate was significantly greater in the nicotine replacement group than in placebo group at 1 month (21.3% vs. 11.7%; odds ratio, 2.05; 95% CI, 1.46 to 2.88). Mean birthweight, rates of preterm birth, low birthweight, were similar in the two groups (Coleman, 2012).
Another randomized double-blinded trial that involved 52 pregnant smoker women desire to quit, received either cognitive behavioral therapy alone or combined with NRT. Women receiving both the NRT and CBT had abstinence rates higher than women receiving CBT only. Also, participants in Group 1 gave birth with higher gestational age (39.4 weeks) compared to Group 2 (38.4 weeks) (p = 0.02), and delivered babies with higher mean birthweights (3,203 g) compared to Group 2 (2,997 g) (p = 0.18). However, there was no difference in the prematurity rate in both groups (El-Mohandes, 2013; Abdullah, 2013). Ina placebo randomized controlled trial that investigates the adherence of 1050 pregnant women to NRT patch which was great, a likely hypothesis is that NRT patches, if usedsufficiently, may be effective for smoking cessation in pregnancy (Vaz, 2016). These four clinical trials have been included in our systematic review demonstrating the role of NRT in smoking cessation among pregnant women. All of them showed that there is a significant role of NRT in smoking cessation. The studies that were comparing the effect of NRT and behavioral intervention (CBT) demonstrate that participant who were receiving both NRT and CBT have much more significant quit rate compared to those receiving CBT alone. All of the trials in this review chose the trans-dermal nicotine patch, since it is the only form of NRT that is FDA approved for use during pregnancy. The other forms (gum, inhaler, lozenge) are not. Some of the studies concluded that younger women, those with fewer depressive symptoms, and smoking less number of cigarettes have better smoking quit rates (Coleman, 2012; El-Mohandes, 2013; Vaz, 2016). Some limitations to this systematic review do exist.The potential for publication bias cannot be excluded. It is therefore possible that there are some unpublished trials, with less favorable results, that we have not identified despite our efforts to do so. Further research is needed for direct comparison between different form of NRT alone and their doses and durations. In addition, combined form of NRT and/or other pharmacotherapies such varenicline and cytisine.

Conclusion

This review concludes that the use of NRT, mainly nicotine patches, for promoting smoking abstinence is effective even in pregnant women. Giving birth with higher gestational age and with the higher birthweight babies are the benefit from NRT during pregnancy beside smoking abstinence. Long-term abstinence was achieved with NRT, however, non-full smoking cessation achieved by reducing the number of cigarettes smoked per day. Moreover, the effectiveness of such therapy is increased as NRT combined with other medication specifically varenicline. We recommend that more studies should be done regarding the effectiveness of NRT among adolescent smokers because there is controversy between the studies that was conducted on adolescent; one showed that NRT is effective while the other showed it is not effective. Further researches is needed to be conducted to clarify these treatment modalities' effectiveness and investigate the proper dose and duration of pharmacotherapies through longer and larger trials are still needed.

Conflict of interest：No conflict of interest

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