TITLE: Nicotine Replacement Therapy for Smoking Cessation or Reduction: A Review of the Clinical Evidence

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CONTEXT AND POLICY ISSUES

Cigarette smoking is associated with cancer, respiratory disease, and cardiovascular disease. It is reported that 19% of Canadians aged 15 years and older were smokers in 2007.[1] Each year, approximately 45,000 Canadians die from smoking.[1] Cigarette smoking is considered the leading preventable cause of mortality.[2] Smoking cessation reduces the risk of developing and dying from smoking-related diseases.[2] Although approximately 70 percent of smokers plan to quit and over 40 percent of smokers report that they tried to quit, the long-term success rate of any unaided quit attempt is low, with only 3 to 7 percent of smokers who make an attempt still abstinent one year later.[2] With optimal treatment, one-year cessation rates after a single quit attempt can exceed 30 percent.[2]

For most of smokers, smoking is both a learned behavior and a physical addiction to nicotine. The combination of counseling and pharmacologic therapies can produce higher quit rates than either one alone.[3] Pharmacotherapy therapy for smoking cessation, including nicotine replacement therapy (NRT), bupropion, and varenicline, aims to reduce the symptoms of nicotine withdrawal, thereby making it easier for a smoker to stop the habitual use of cigarettes.[3]

In NRT, non-toxic forms of nicotine delivery systems are used to provide nicotine to maintain stimulation of nicotine receptors, thereby eliminating withdrawal symptoms and the sensations of craving for nicotine during a smoking cessation attempt. It has been reported that nicotine products can help people to reduce smoking before quitting smoking.[4] In 2010, CADTH published a health technology assessment (HTA) report on pharmacologic-based strategies for smoking cessation,[1] in which the clinical and cost-effectiveness of NRT products including the nicotine patch, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray and nicotine sublingual tablets were systematically evaluated. The author concluded that all pharmacotherapies including NRT are efficacious in helping the general population quit smoking.[1] Since the publication of that report, newer NRT products such as Nicorette Quick Mist,[5-10] Nicorette Combo Quit,[11] and Nicorette Mini Lozenges[12] have entered the Canadian market. Nicorette QuickMist is a mouth spray and is available in a 1 mg nicotine/spray dose strength.[5-10] Nicorette ComboQuit is a combination of nicotine patches plus nicotine gum.[11] Nicorette Mini Lozenges come in two strengths (2 mg and 4

mg).[12] The 2 mg strength is recommended for smokers who have a first cigarette more than 30 minutes after waking up; the 4 mg lozenge is recommended for those having a first cigarette within 30 minutes of waking up.[12] A smoker's dependence on nicotine can be assessed from the duration of smoking history, the number of cigarettes smoked daily, and how soon the smoker needs to smoke after waking in the morning. The smoker's degree of nicotine dependence predicts the difficulty that the smoker will have in quitting and the intensity of treatment likely to be required.[2] The dosing of most NRT products varies based on the number of cigarettes smoked daily.[3] Nicotine transdermal patches are supplied in different dosages ranging from 5 mg to 15 mg over 16 hours.[1] While there is no standard definition of high dose nicotine product was identified, the high dose of nicotine patch was defined as the dose greater than 22 mg per day.[13-15]

The objective of this review is to evaluate the clinical effectiveness of the newer NRT products including Nicorette QuickMist (or nicotine mouth spray), Nicorette ComboQuit (or combination of patches plus gum) or Nicorette Mini Lozenges (2 mg or 4 mg), use of supratherapeutic doses (high dose) of NRT, and use of NRTs to reduce smoking for those who do not plan to quit.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of newer nicotine replacement products (Nicorette Quick Mist, Nicorette Combo Quit, Nicorette Mini Lozenges) for smoking cessation?

2. What is the clinical evidence for the use of supratherapeutic doses of nicotine replacement therapy?

3. What is the clinical evidence for the use of nicotine replacement products to reduce smoking for those who do not quit?

KEY FINDINGS

No clinical evidence was identified for the NRT products specifically termed as the Nicorette Quick Mist, Nicorette Combo Quit, or Nicorette Mini Lozenges. Limited evidence showed that nicotine mouth spray or the combination of nicotine patch plus gum achieved higher smoking cessation than placebo. Modestly higher smoking cessation rates were observed with high doses nicotine patch compared with standard nicotine patch dose. NRT appears effective in reduction of smoking for those who did not want to quit. However, findings reported in this review should be interpreted with caution due to the potential methodological limitations and clinical heterogeneity of the body evidence. Better designed RCTs in Canadian settings are needed to determine the clinical effectiveness of the newer NRT products or the use of high doses of NRT for smoking cessation, as well as the role of NRT in smoking reduction.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, PubMed, The Cochrane Library (2013, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews and meta-analyses for a broad search of nicotine replacement products. No filters were applied to narrow searches for new

nicotine replacement products, high dose approaches or smoking reduction. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and December 10, 2013

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, and evaluated the full-text publications for the final article selection, according to the selection criteria present in Table 1. We included the studies on nicotine mouth spray or studies of the combination of nicotine patch plus gum even in cases where Nicorette QuickMist or Nicorette Combquit was not specifically mentioned. Any other combination such as patch plus nasal spray[15] or patch plus lozenges[16] are out of the scope of this review.

Table 1: Selection Criteria

Population	Smokers of any age
Intervention	Q1: Nicorette Quick Mist (or nicotine mouth spray,1 mg/spray), Nicorette Combo Quit (or patch plus gum), or Nicorette Mini Lozenges (2mg or 4mg)[a] Q2: Supratherapeutic doses[b] (or high dose) of nicotine replacement therapy (for example, 2x21mg nicotine patches) Q3: Any nicotine replacement product
Comparator	Placebo, no treatment, other nicotine replacement products
Outcomes	Smoking cessation, smoking reduction, number of quit attempts required, interval between quit attempts, adverse events, abuse potential, product diversion
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials and non-randomized studies

[a]Nicotine mouth spray, the combination of nicotine patch plus gum, and the nicotine lozenges (2mg or 4mg) were included even if the terms of Nicorette Quick Mist, Nicorette Combo Quit or Nicorette Mini Lozenges were not used.
[b]Supratherapeutic dose means above the therapeutic level, or high dose.

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, duplicate data report of one included study or were included in a selected systematic review/meta-analysis.

Critical Appraisal of Individual Studies

The methodological quality of the included systematic review/meta-analyses were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[17] RCTs were assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist 2 (SIGN 50 Checklist 2).[18] A numeric score was not calculated for each study. Instead, the strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 303 citations. Upon screening titles and abstracts, 290 citations were excluded, and 13 potentially relevant articles were retrieved for full-text review. Of the 13 potentially relevant reports, four[16,19-21] did not meet the inclusion criteria. Nine reports[13,15,22-28] are included in this review. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1). Three studies[13,15,25] were systematic reviews. Six were randomized controlled trials. Among the three systematic reviews, one[15] evaluated the clinical effectiveness of both NRT combination of nicotine patch plus nicotine gum and high dose nicotine patch. One[13] reported the clinical effectiveness of high dose nicotine patch use. The third one[25] assessed the clinical effectiveness of NRT in the smoking reduction. Of the six RCTs, one[26] studied the effectiveness and adverse events of nicotine mouth spray; two[22,27] investigated the effectiveness of high dose of nicotine patch in smokers who intended to quit; and three[23,24,28] assessed the role of NRT in the smoking reduction among the smokers who did not want to quit, or did not plan to quit immediately, or failed to achieve smoking cessation from previous NRT.

Summary of Study Characteristics

A summary of the study characteristics can be found in Appendix 2.

1. *What is the clinical effectiveness of newer nicotine replacement products (Nicorette Quick Mist, Nicorette Combo Quit, Nicorette Mini Lozenges) for smoking cessation?*

One systematic review (SR) by Stead et al.[15] assessed the clinical effectiveness of nicotine combination therapy of patch plus gum (not specifically named as Nicorette ComboQuit) and nicotine lozenges (2 mg to 4 mg, not termed as Nicorette Mini-lozenge) compared with placebo. The systematic review was conducted in UK and New Zealand. Three RCTs were included examining nicotine combination therapy, and three RCTs were included for nicotine lozenge (2mg or 4 mg) in the systematic review. In addition to the above SR, one RCT[26] evaluated the clinical effectiveness of nicotine mouth spray (1mg/per spray, but not named as Nicorette QuickMist) compared with placebo. Both arms of the study were also with low-intensity counselling. The trial, including 479 smokers, was conducted in Denmark and Germany with follow-up of 12-weeks. The outcomes were the smoking cessation and adverse events.

2. *What is the clinical evidence for the use of supratherapeutic doses of nicotine replacement therapy?*

Two systematic reviews[13,15] reported the clinical effectiveness of high dose nicotine patch use compared with different doses of nicotine patches. One[15] was conducted in UK and New Zealand, in which eight RCTs were included for the high dose of nicotine patches. Of the eight RCTs, four compared 44 mg doses to standard 22 mg doses (24-hour patches); three compared a 25 mg high dose to 15 mg standard dose (16-hour patches); and one RCT compared a 42 mg high dose to a 21 mg standard dose (24- hour patches). The other systematic review[13] was conducted in Canada, the UK and the USA. Five RCTs examining high dose nicotine patch were included in this SR. High dose was defined as a nicotine patch dose greater than 22 mg per day. In addition to the above two SRs, two RCTs[22,27] compared high dose nicotine transdermal patch with a standard dose of nicotine transdermal patch. One study,[22] conducted in Taiwan, compared nicotine

transdermal patch (31.5 mg/day) with 20.8 mg per day. 184 smokers with schizophrenia were included in the study. Trial duration was 8 weeks. The other study[27] was conducted in the USA and Canada. Eight smokers with a fast rate of nicotine metabolism were included in the trial. The high dose of nicotine patch was defined as the dose equal or greater than 22 mg per day and the standard dose of nicotine patch was defined as the dose less than 21 mg in all included SR[13,15] and RCTs.[22,27] The reported outcomes were smoking cessation and adverse events.

3. *What is the clinical evidence for the use of nicotine replacement products to reduce smoking for those who do not quit?*

One SR[25] and three RCTs[23,24,28] were identified that evaluated the clinical evidence for the use of NRT products to reduce smoking for those who did not intend to quit. The systematic review was conducted in the UK. It included seven RCTs. Of those seven studies, four studies for NRT gum, two for NRT inhaler, and one with free choice of therapy were included. All studies compared NRT with placebo. The outcomes were smoking reduction, smoking cessation and adverse events. Among the three RCTs, one[28] was conducted in USA, one[24] was conducted in the Czech Republic, the UK and France, and the third one[23] was conducted in China. Sample size ranged from 314[24] to 3297.[28] The participants were smokers who did not intend to quit smoking[23,24] or who had failed in previous attempts to quit using NRT,[23] or smokers who wanted gradually to reduce the number of cigarettes until they stop smoking.[28] Trial duration ranged from six months[23,28] to 12 months.[24] The main outcome was smoking reduction, which was defined as ≥50% reduction from baseline in all three studies.

Summary of Critical Appraisal

The strengths and limitations of all included studies are summarized in Appendix 3.

The selected systematic reviews[13,15,25] were considered moderate to high quality methodologically because they met most of the AMSTAR criteria including comprehensive database searches, a thorough process of study selection and data extraction, assessment of the risk bias of the individual studies, and appropriate outcome measurement, appropriate data synthesis and assessment of the heterogeneity. The main potential limitations include that the methodological quality of included studies was not considered in the analysis,[13,15,25] the list of excluded studies were not provided,[13,25] and the potential for publication bias was reported in two SRs[13,15] and not assessed in the third SR.[25]

The methodological quality of the six RCT reports[22-24,26-28] was considered moderate. The main strengths were that research questions were well described in all studies; baseline characteristics were well reported and comparable between intervention and control groups; the only difference between groups was the NRT treatment under investigation; key outcome measurements (such as smoking cessation) were standard and valid; and intention to treat (ITT) analyses were performed. Three RCTs [23,24,26] were reported with adequate power to detect the treatment group difference. The main limitations were that the randomization method was not clearly described,[22-24,27] allocation concealment was not reported,[22-24,27,28] a single blind process was applied,[23] and the dropout rates were very high even though they were comparable in both treatment and control arms.[26,28] The main reason for discontinuation from the study was reported lack of willingness to continue the study[26] or failure to achieve the smoking cessation.[28] No adequate power to detect the treatment difference was reported in one RCT.[27] Whether the trial was power enough to detect the difference were not reported in two RCTs.[22,28]

Summary of Findings

The main findings of the included studies are summarized in Appendix 4.

1. *What is the clinical effectiveness of newer nicotine replacement products (Nicorette Quick Mist, Nicorette Combo Quit, Nicorette Mini Lozenges) for smoking cessation?*

No clinical evidence was identified for the NRT products specifically termed as Nicorette Quick Mist, Nicorette Combo Quit or Nicorette Mini Lozenges. The findings from the trials for nicotine mouth spray, the combination of nicotine patch plus gum, or nicotine lozenge (2 mg or 4 mg) are summarized below.

Nicotine mouth spray

One RCT[26] investigated the efficacy of the nicotine mouth spray in smoking cessation. It was reported that nicotine mouth spray (NMS) yielded significantly higher smoking cessation rates (26%) than placebo (16%) from week 2 until week 6 (relative risk [RR] 1.62, 95% confidence interval [CI], 1.09 to 2.41), week 24 (16% versus 7%; RR: 2.30, 95% CI, 1.23 to 4.30), and week 52 (14% versus 6%; RR: 2.48, 95% CI, 1.24 to 4.94). Most adverse events were mild to moderate. The overall rate of treatment-related adverse events was 87% with nicotine mouth spray versus 71% with placebo. The most common treatment-related adverse events were hiccups, throat irritation, nausea, dyspepsia, mouth irritation, salivary hypersecretion, burning sensation in the mouth, and constipation. Withdrew due to adverse events (WDAE) was 9% of smokers on nicotine mouth spray compared to 8% on placebo. The authors indicated that nicotine mouth spray delivered significantly higher 6-, 24- and 52-week continuous abstinence rates than placebo.

Combination of nicotine patch plus gum

The systematic review by Stead et al.[15] reported that statistically significant more smokers achieved cessation in the combination therapy of patch plus gum compared with patch alone. The pooled relative risk for smoking cessation (based on two RCTs including 395 smokers) was 1.75, 95% CI, 1.04 to 2.94 in favor of combination therapy. Numerically more (but not statistically significantly more) smokers achieved smoking cessation in the patch plus gum therapy group compared that in the gum therapy alone. The relative risk (95%CI) was 1.38 (0.88 to 2.17). The authors suggested that there is evidence of benefit from combining the nicotine patch with gum compared to use of a single form patch or gum.

Nicotine lozenges (2 mg or 4 mg)

In the systematic review,[15] Stead et al. examined the effectiveness of lozenges (2 mg or 4 mg) compared with nicotine patch (<21mg) for smoking cessation. Based on three RCTs including 1707 smokers, the pooled relative risk (95%CI) was 0.94 (0.79 to 1.12). No statistically significantly significance in terms of cessation rate was found between lozenges (2 or 4 mg) and nicotine patch (<21mg).

2. *What is the clinical evidence for the use of supratherapeutic doses of nicotine replacement therapy?*

In the systematic review by Stead et al.,[15] it was reported that for nicotine patch 44 mg for 24 hours compared with nicotine patch 22 mg for 24 hours, the pooled relative risk (95%CI) for smoking

cessation was 1.08 (0.89 to 1.32) (based on 4 RCTs, 1188 smokers); comparing 42 mg with 21 mg for 24 hours the relative risk (95%CI) was 1.12 (0.82 to 1.53) (based on 1 RCT, 467 smokers); comparing 25 mg with 15 mg for 16 hours, the relative risk (95%CI) was 1.19 (1.00 to 1.41) (based on 3 RCTs, 3446 smokers). In total, based on eight RCTs including 5101 smokers, smokers with high dose patches (>22mg) achieved statistically significant more smoking cessation than that in standard dose patches (RR [95%CI]: 1.14 [1.01 to 1.29]). Similar results were also reported in the systematic review by Mills,[13](RR [95%CI]: 1.23 [1.05, 1.46]) (see Appendix 4).

In the RCT by Chen et al.,[22] it was reported that 7-day prevalence of smoking cessation was 1% for high dose (31.2mg) and 4% for standard dose group (20.8 mg), respectively, in smokers with schizophrenia. In the RCT by Schnoll et al.,[27] the 7-day cessation rate was 30% and 23% for high dose and standard dose respectively (odds ratio [OR] [95%CI] 1.52 [0.57 to 4.07] P = 0.41) in smokers with a faster rate of nicotine metabolism.

3. *What is the clinical evidence for the use of nicotine replacement products to reduce smoking for those who do not quit?*

One systematic review[23] evaluated the smoking reduction effectiveness of NRT. Seven placebo controlled RCTs (four used NRT gum, two used inhaler, and one used free choice of therapy) were included in the systematic review. It was found that 7% of smokers receiving NRT attained sustained abstinence for six months, twice the rate of those receiving placebo (RR [fixed effects model] 2.06; 95% CI, 1.34 to 3.15; RR [random effects model] 1.99; 95% CI,1.01, 3.91, based on five RCTs). The number needed to treat was 29. Compared with placebo, the relative risk (95%CI) for smoking reduction (defined as less than 50% of baseline) in NRT from week 6 to the end of follow-up (up to 26 months) was 3.84 (2.32 to 6.35) in favor of NRT. No statistically significant difference in adverse events was identified between NRT and placebo in terms of death, serious adverse events, and discontinuation because of adverse events (see Appendix 4). The authors concluded that NRT is effective in achieving sustained smoking abstinence for smokers who have no intention or are unable to attempt an abrupt quit. The authors also acknowledged that regular behavioral support was used in most of the included RCTs; therefore, the smoking reduction effectiveness of NRT without regular behavioral support needs to be further examined.

In the RCT conducted in 2012, Lam et al.[23] reported that smokers in the NRT group obtained a statistically significantly higher self-reported smoking cessation rate (OR [95%CI] 1.81 [1.14 to 2.88] but no statistically significance was observed in the CO-validated rate (by an expired carbon monoxide level of <9 ppm and a urinary cotinine level of <115 ng/ml) at six months (RR [95%CI]: 1.87 [0.96 to 3.7]). The relative risk (95%CI) for self-reported smoking reduction rate (≥50%) of daily cigarette consumption in NRT compare with control was 3.0 (2.16 to 4.15) in favor of NRT. The author concluded that smoking reduction counselling together with NRT was effective in achieving smoking reduction and complete cessation for smokers who were not ready to quit.

In RCT by Kralikova et al.,[24] it was reported that sustained abstinence rates at 4 months were 20% in the NRT group (10 mg nicotine inhaler or 4 mg nicotine gum) and 9% in the placebo group (*P* = 0.009). Sustained abstinence rates at 12 months were 19% and 9% in the NRT and placebo groups respectively (*P* = 0.019). Smoking reduction did not differ between the groups with the reduction rate 17% vs. 18% in NRT and placebo group respectively. The author concluded that NRT resulted in a significantly higher smoking quit rate than placebo.

In the third RCT,[28] Shiffman et al. found that smokers on nicotine gum were significantly more likely to achieve cessation at 6 months (for 2 mg gum: OR 1.80; for 4 mg gum: OR 5.96)

compared with placebo. During the reduction phase (in the first two weeks), smoking reduction rate was found to be 19% vs. 11% (OR [95%CI]: 1.81 [1.49, 2.21]). The author concluded that smokers who wish to quit smoking by gradual reduction can increase their success by using nicotine gum to facilitate reduction and cessation.

Limitations

The overall methodological quality of the included SRs was moderate to high. The main methodological limitation of RCTs were that the randomization method and allocation concealment were not clearly reported in four RCTs[22-24,27] and the drop-out was very high in two RCTs.[26,28] The major limitations of the overall body evidence are discussed as follows: Firstly, the follow-up duration in the selected SRs[13,15,25] and trial durations of the included RCTs[22-24,26-28] varied, which could contribute to the inconsistency of the findings. Secondly, there was some clinical heterogeneity of the smokers included in selected SRs or RCTs, such as some were healthy smokers without other medical conditions, some were alcohol-dependent smokers,[13,29] some were smokers with a faster rate of nicotine metabolism,[27] and some were smokers with schizophrenia. Thirdly, the degree of the nicotine dependence (that is the number of cigarettes smoked daily) varied from minimum number of daily cigarettes equal or great than one[26] to equal or greater than 15.[24] Since heavy smokers might face more of a challenge to achieve smoking cessation and are likely to require more intense treatment such as high dose or longer treatment,[2] the degree of nicotine dependence of smoker will be an important factor to be considered in the interpreting the findings across the body evidence. Fourthly, the definition of carbon monoxide validated smoking cessation was not consistent, such as the smoking cessation was confirmed as carbon monoxide level of less than 9 ppm in one RCT,[23] but it was defined as less than 10ppm in other studies.[22,24,26] The validated carbon monoxide level was not reported in remaining two RCTs.[27,28] Fifthly, the majority of the trials included a co-intervention, such as counselling or behavioral support, but the degree of counselling varied. Therefore, the actual effect of NRT without counselling was not clear. Lastly, the evidence obtained from trials outside Canada may not be transferable to Canadian setting due to the potential cultural, social, and economic differences.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No clinical evidence was identified for the NRT products specifically termed as Nicorette Quick Mist, Nicorette Combo Quit or Nicorette Mini Lozenges. However, limited evidence showed that nicotine mouth spray or the combination of nicotine patch plus gum achieved higher smoking cessation than placebo. No statistically significant difference were found between nicotine Lozenge 2mg or 4mg) with nicotine patch. Statistically significant higher smoking cessation rates, despite the modest effect size, were observed with high dose nicotine patches (>22mg) compared with standard dose nicotine patch use (<22mg). NRT appears effective in the smoking reduction for those smokers who did not want to quit, failed from previous NRT, or intended to quit smoking gradually. No statistically significant different adverse events were identified among various NRT products. However, due to the methodological limitations and clinical heterogeneity of the body evidence, the findings identified in this review should be interpreted with caution. Better designed RCTs in Canadian settings are needed to determine the clinical effectiveness of the newer NRT products (Nicorette Quick Mist, Nicorette Combo Quit, Nicorette Mini Lozenges) or the use of supratherapeutic doses of nicotine for smoking cessation, and NRT's role in the smoking reduction for those who do not intend to quit.

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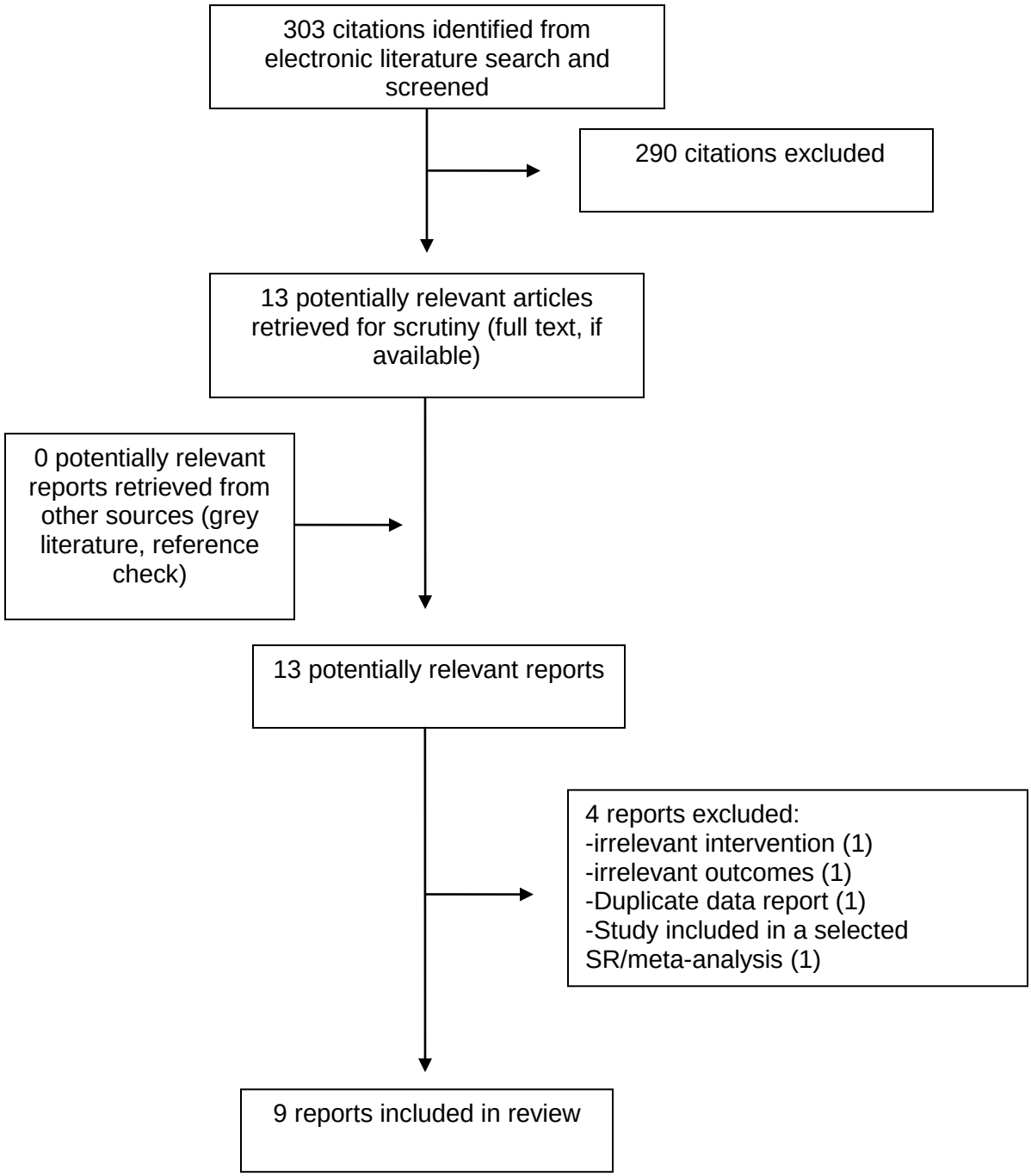
30. Supplementary table III: characteristics of high dose versus standard dose nicotine patch therapy studies. Supplementary material for: Mills EJ, Wu P, Lockhart I, Thorlund K, Puhan M, Ebbert JO. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. Ann Med. 2012 Sep;44(6):588-97. 2012.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Length of Study	Patient Characteristics, Sample Size	Intervention	Comparators	Main Outcomes
Systematic review/Meta-analysis					
Stead LF[15] 2012, UK, New Zealand	SR of RCTs	Smokers ● N= 8 RCTs for high dose patch; ●N=3 RCTs for combination of patch and gum[a] ●N=3 RCTs for lozenge (2 mg to 4 mg)[b]	●High dose nicotine transdermal patch ● Combination of patch plus gum ●Nicotine lozenge	●Standard dose nicotine patch (vs. high dose) ●Other NRTs(vs. combination) ●Placebo or other NRTs (vs. nicotine lozenge)	●Smoking cessation ●Adverse events
Mills EJ[13] 2012, Multi-nations (Canada, UK and USA)	SR of RCTs[c]	Smokers ●N= 5 RCTs for high dose patch ●N=2 RCTs for combination of patch and gum [d]	●High dose nicotine transdermal patch ●combination of patch and gum	●Standard dose nicotine patch (vs. high dose) ●Other NRTs(vs. combination)	●Smoking cessation
Moore D [25] 2009, UK	SR of RCTs	Smokers (without intention to quit) N=7 RCTs	NRT gum (4 RCTs) NRT inhaler (2 RCTs) Free choice of therapy (1 RCT)	Placebo	●Smoking cessation ●Smoking reduction ●Adverse events
Randomized controlled trials					
Chen HK [22] 2013, Taiwan	RCT Duration: 8 weeks	Smokers (daily smoker, minimum cigarettes number not reported) in patients with schizophrenia N=184	Nicotine transdermal patch 31.5mg/d for week 1-4 20.8 mg/d for week 5-8	Nicotine transdermal patch 20.8 mg/d for 8 weeks	●Smoking cessation ●Smoking reduction
Schnoll RA [27] 2013, USA and Canada	RCT Duration: 8 weeks	Smokers(≥ 10 cigarettes/d) with a faster rate of nicotine metabolism N=87	Nicotine transdermal patch 42 mg/d for 7 days	Nicotine transdermal patch 21 mg/d for 7 days	●Smoking cessation ●Adverse events
Tonnesen P [26] 2012, Denmark. and Germany	RCT Duration: 12 weeks	Smokers (>= 1 cigarette/d) N=479	Nicotine mouth Spary[e] (with low-intensity counselling)	Placebo (with low-intensity counselling)	Smoking cessation Adverse events WDAE
Lam TH[23] 2012 P.R. China, USA	RCT Duration: 6 months	Smokers (≥ 2 cigarettes/d) not willing to quit smoking or failed in previous attempts to quit using NRT N=1154	NRT plus counselling	counselling	●Self-reported 7-day point-prevalence tobacco abstinence ●validated quit rate ●Self-reported reduction rate (≥50%) of cigarette consumption[f]
Kralikova E [24] 2009 Czech Republic, UK	RCT Treatment duration: 9 months	Smokers ((≥ 15 cigarettes/d) not willing to quit smoking	Nicotine gum (4 mg) or inhaler (10 mg)	Placebo gum or placebo inhaler	At 12 months ●Smoking reduction ((≥50%) of daily cigarette

First Author, Publication Year, Country	Study Design, Length of Study	Patient Characteristics, Sample Size	Intervention	Comparators	Main Outcomes
and France	Follow-up: to 12 months	N=314			consumption[f] ●Smoking cessation
Shiffman S[28] 2009, USA	RCT Treatment Duration: 8 weeks	Smokers (minimum cigarettes number not reported) willing gradually reducing the number of cigarettes until they stop smoking N=3297	Nicotine gum (2 mg or 4mg)	Placebo	●Smoking reduction (≥50%) of daily cigarette consumption[f] ●Smoking cessation

d=day(s); WDAE=Withdrew due to adverse events;
[a] Combination of nicotine patch plus gum is included in this review because Nicorette Combo Quit consists of nicotine patch and gum , and no evidence was identified for the NRT specifically termed as Nicorette Combo Quit
[b] Nicotine lozenge (2 mg or 4 mg) is included in this review because the strength of Nicorette Mini Lozenges are 2 mg or 4 mg, and no evidence was identified for the NRT specifically termed as Nicorette Mini Lozenges
[c] Included only RCTs with at least 3 months posttarget quit date (TQD) with biochemical confirmation of smoking abstinence
[d]However, the two studies of combination of nicotine patch plus nicotine gum included in the SR by Mills[13] were already reported in the SR by Stead et al[15]. And also there was no pooled data. Therefore, only the high dose info was extracted in this review.
[e]Nicotine mouth spray is included in this review because Nicorette Quick Mist is a nicotine mouth spray, and no evidence was identified for the NRT specifically termed as Nicorette Quick Mist.
[f]Smoking reduction defined as ≥50% less of daily cigarette consumption versus baseline.

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year	Strengths	Limitations
Systematic review / meta-analysis assessed with AMSTAR check list		
Stead LF[15] 2012, UK, New Zealand	• Research questions and selection criteria were defined and presented • Comprehensive literature search based on pre-defined criteria • Two independent investigators performed data extraction • List of included and excluded studies provided • Quality assessment of the included studies was described • Methods used to combine the findings were clearly reported • Conflict of interests declared	• One investigator performed study selection • Whether the quality of included studies was considered in the analysis and conclusion was not clearly indicated • Potential publication bias
Mills EJ[13] 2012, Multi-nations (Canada, UK and USA)	• Research questions and selection criteria were defined and presented • Comprehensive literature search based on pre-defined criteria • Two independent investigators performed study selection, and data extraction • List of included studies provided[29,30] • Quality assessment of the included studies was described • Methods used to combine the findings were clearly reported • Conflict of interests declared	• List of excluded studies not provided • Whether the quality of included studies was considered in the analysis and conclusion was not clearly indicated • Potential publication bias
Moore D[25] 2009, UK	• Research questions and selection criteria were defined and presented • Comprehensive literature search based on pre-defined criteria • Two independent investigators performed study selection • One investigator performed data extraction and the second investigator checked the data • List of included studies provided • Quality assessment of the included studies was described • Methods used to combine the findings were clearly reported • Conflict of interests declared	• List of excluded studies not provided • Whether the quality of included studies was considered in the analysis and conclusion was not clearly indicated • Publication bias was not assessed
Randomized controlled trials assessed with SIGN 50 Check list 2		
Chen HK[22] 2013, Taiwan	• Research question was clearly defined • Double blinding process was described • Key patient characteristics at baseline were comparable in the treatment and control groups • Only difference between groups was treatment under investigation • Key outcome measurement was standard, valid and reliable • ITT analysis performed	• Randomization method was not clearly described • Allocation concealment was not reported • Drop-out rates were high in both arms (19.6% vs. 22.8%) • Whether the results across all centers were comparable were not addressed

First Author, Publication Year	Strengths	Limitations
Schnoll RA[27] 2013, USA and Canada	• Research question was clearly defined • Key patient characteristics at baseline were comparable in the treatment and control groups • Only difference between groups was treatment under investigation • Key outcome measurement was standard, valid and reliable • ITT analysis performed • Drop-out rate comparable in both arms	• Randomization method was not clearly described • Allocation concealment was not reported • Blinding process was not clearly described • Whether the results across all centers were comparable were not addressed
Tonnesen P[26] 2012, Denmark. and Germany	• Research question was clearly defined • Randomization method was clearly described • Allocation concealment was reported • Double blind was described • Key patient characteristics at baseline were comparable in the treatment and control groups • Only difference between groups was treatment under investigation • Key outcome measurement was standard, valid and reliable • ITT analysis performed	• Drop-out rate were high in both arms (NRT vs. placebo: 47.5%% vs. 53.4%) • Whether the results across all centers were comparable were not addressed
Lam TH[23] 2012 P.R. China, USA	• Research question was clearly defined • Key patient characteristics at baseline are comparable in the treatment and control groups • Only difference between groups was treatment under investigation • Key outcome measurement was standard, valid and reliable • ITT analysis performed • Drop-out rate were low and comparable in both arms (5.8% vs. 4.4%)	• Randomization method was not clearly described • Allocation concealment was not reported • Single blind process • Whether the results across all centers were comparable were not addressed
Kralikova E[24] 2009 Czech Republic, UK and France	• Research question was clearly defined • Double blinding process • Key patient characteristics at baseline were comparable in the treatment and control groups • Only difference between groups was treatment under investigation • ITT analysis performed	• Randomization method was not clearly described • Allocation concealment was not reported • Drop-out not reported • Whether the results across all centers were comparable were not addressed
Shiffman S[28] 2009, USA	• Research question was clearly defined • Randomization method was clearly described • Double blinding process • Key patient characteristics at baseline were comparable in the treatment and control groups • Only difference between groups was treatment under investigation • Key outcome measurement was standard, valid and reliable • ITT analysis performed	• Allocation concealment was not clearly reported • High drop-out rate (NRT vs. placebo: 95% vs. 91% for 2mg, 98% vs. 91% for 4mg) • Whether the results across all centers were comparable were not addressed

AMSTAR=A Measurement Tool to Assess the Methodological Quality of Systematic Reviews; ITT=intention to treat; NRT=nicotine replacement therapy; SIGN=Scottish Intercollegiate Guidelines Network.

APPENDIX 4: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Author's Conclusions
Systematic review/meta-analysis		
Stead LF[15] 2012, UK, New Zealand	Smoking cessation at maximum follow-up (6 mos. to 12 mos.) ●**Combination of patch with gum** RR(95%CI): *Patch plus gum versus patch alone (2 RCTs, 395 smokers)* 1.75 (1.04, 2.94) *Patch plus gum versus gum alone (1 RCT, 300 smokers)* 1.38 (0.88, 2.17) ●**Lozenge (2 - 4 mg) versus patch (<21mg)** (3 RCT, 1707 smokers) 0.94 (0.79, 1.12) ●**High dose patch vs. standard dose patch** RR(95%CI): *44 mg vs. 22 mg for 24h (4 RCTs, 1188 smokers)* 1.08 (0.89, 1.32) *42 mg vs. 21 mg for 24 h (1RCT, 467 smokers)* 1.12 (0.82, 1.53) *25 mg vs. 15 mg for 16 h (3 RCTs, 3446 smokers)* 1.19 (1.00, 1.41) Total: high dose vs. standard dose patches: 1.14(1.01, 1.29) (8 RCTs, 5101 smokers) Adverse events: Not extractable	*On page 24*: "There is evidence of benefit from combining the nicotine patch with an acute dosing type (e.g. gum) to allow ad lib dosing compared to use of a single form."
Mills EJ[13] 2012, Multi-nations (Canada, UK and USA)	●Smoking cessation at up to 12 mos. follow-up ●**High dose patch (>22mg) vs. standard dose patch (≤22mg)** RR(95%CI): At 4 weeks: 1.22 (1.11, 1.34) (4 RCTs, 3197 smokers) At 3 months: 1.09 (0.84, 1.43) (3 RCTs, 3466 smokers) At 6 months: 1.16 (0.99, 1.37) (5 RCTs, 3605 smokers) At 4 12 months: 1.23 (1.05, 1.46) (4 RCTs, 3499 smokers) ●**Combination of patch with gum**[a] No pooled data. Not extractable	*On page 589:* Key messages: "… High-dose nicotine replacement therapy (NRT) and combination NRT are advocated as offering increased treatment effects. However, the effectiveness of all available treatments, relative to each other, is not known…"
Moore D[25] 2009, UK	NRT vs. placebo ●Smoking cessation at 6 months: RR(95%CI) (five RCTs, 1833 smokers) NRT vs. placebo: 2.06 (1.34, 3.15) (fixed effects model); 1.99 (1.01, 3.91 (random effects model); NNT: 29 ●Smoking reduction from week 6 to 12 mos.: 3.84 (2.32 to 6.35) (6 RCTs, 2233 smokers) ●Adverse events: OR (95%CI) Death: 1.00 (0.25 ,4.02) SAE : 1.16 (0.79 to 1.50) WDAE: 1.25 (0.64, 2.51) Nausea:1.69 (1.21, 2.36)	*On page 1*: "Available trials indicate that nicotine replacement therapy is an effective intervention in achieving sustained smoking abstinence for smokers who have no intention or are unable to attempt an abrupt quit. Most of the evidence, however, comes from trials with regular behavioral support and monitoring and it is unclear whether using nicotine replacement therapy without regular contact would be as effective."
Randomized controlled trials		
Chen HK[22] 2013, Taiwan	●Smoking cessation[b] 1% vs. 4% (high dose vs. low dose) ●Smoking reduction 3 less cigarettes on average in high	*On page 263:* "In summary, among a cohort of chronic institutionalized schizophrenic

First Author, Publication Year	Main Study Findings	Author's Conclusions
	dose than those in the low-dose group (p = 0.005) However, it was not significant (p = 0.35) in a repeated measures analysis of variance.	patients, smoking cessation and reduction outcomes were not correlated with NRT dose, and the cessation rate was much lower than rates in similar studies. It indicates that long-term hospitalized schizophrenic patients have more difficulties with quitting smoking. More effective integrative smoking cessation programs should be addressed for these patients."
Schnoll RA[27] 2013, USA and Canada	High dose patch vs. low dose patch ●Smoking cessation[c] %, OR(95%CI), p value <u>After one week treatment:</u> I day cessation 75% vs. 58 %; 3.21 (1.12, 9.24); p = 0 .03 7-day cessation 50% vs. 35%; OR = 2.02 (0.82, 4.94); p = 0.13. <u>After 8-week treatment:</u> I day cessation 46% vs. 30%; 2.32 (0.92, 5.92); p = 0.08. 7-day cessation 30% vs. 23%; 1.52 (0.57, 4.07); p = 0.41. ●SAEs: 2% vs. 0% (high dose vs. standard dose)	*On page 348:* "Further examination of the efficacy of 42 mg nicotine patch therapy for fast metabolizers of nicotine is warranted."
Tonnesen P[26] 2012, Denmark. and Germany	Nicotine mouth spray vs. placebo ●Smoking cessation[b] %; RR(95%CI) Week 6: 26% vs. 16%; 1.62 (1.09, 2.41) Week 24: 16% vs. 7%; 2.30, (1.23, 4.30) Week 52 14% vs 6%; 2.48 (1.24, 4.94) ●SAEs: 4% vs. 5% ●Overall TRAEs: 87% vs. 71% WDAE: 9 % vs. 8%	*On page 548: It was reported that* "Nicotine mouth spray delivered significantly higher 6-, 24- and 52-week continuous abstinence rates than placebo."
Lam TH[23] 2012 P.R. China, USA	NRT vs. control OR(95%CI) at 6 months ●Self-reported 7-day point-prevalence tobacco abstinence 1.81 (1.14, 2.88) ●Validated quit rate at month 6: 1.87(0.96, 3.7)[d] ●Self-reported reduction rate (≥50%) of daily cigarette consumption: 3.0(2.16, 4.15)	*On page 8:* "Smoking reduction counselling together with NRT was effective in achieving smoking reduction and complete cessation for smokers who were not ready to quit..."
Kralikova E[24] 2009 Czech Republic, UK and France	NRT vs. placebo (%) ●**Smoking reduction:** Sustained reduction from week 6 to month 4: 22% vs. 11%; p value: NR Sustained reduction from month 6 to month 12: 17% vs. 18%; p value: NR ●**Smoking abstinence(validated)[b]** -Sustained abstinence from week 6 to month 4: 20% vs. 9%; p value: 0.009 -Sustained abstinence from month 6 to month 12: 19% vs. 9%; p = 0.019 -Point prevalence abstinence at month 4	*On page 1:* "In conclusion, treatment with 10 mg nicotine inhaler or 4 mg nicotine chewing gum resulted in a significantly higher abstinence rate than placebo. In addition a large number of smokers managed to reduce their cigarette consumption by more than 50% compared to baseline."

First Author, Publication Year	Main Study Findings	Author's Conclusions
	26 % vs. 13%; *p* = 0.009 -Point prevalence abstinence at month 12 22% vs. 11%; *p* = 0.016	
Shiffman S[28] 2009, USA	Nicotine gum vs. placebo OR(95%CI) ●Smoke reduction at 2 weeks 19% vs. 11% OR (95%CI): 1.81(1.49, 2.21) 2 mg gum: greater reduction in number of cigarettes in gum than those in placebo (NS) 4 mg gum: greater reduction in number of cigarettes in gum than those in placebo (p<0.001)) ●6 month continuous smoke abstinence[c] Overall: 6% vs. 2%, OR(95%CI): 2.86(1.93, 4.24) 2 mg gum group: 1.80 (1.1, 2.9) 4 mg gum group: 5.96 (2.9, 12.2) ●AEs such as nausea, hiccups, and heartburn (nicotine gum vs. placebo) 48% vs. 37 (*p* < 0.001)	*On page 96:* "These findings demonstrate that smokers who wish to quit smoking by gradual reduction can increase their success by using nicotine gum to facilitate reduction and cessation."

AE=adverse events; h=hour (s); MOs=months; NNT= number to treat; NR=not reported; NS=not statistically significant; OR=Odds Ratio; RR=Relative risk; SAE =serious adverse events; TRAEs= treatment related adverse events; WDAE=withdrew due to adverse events; 95%CI=95% confidence interval.

[a]The two studies of combination of nicotine patch plus nicotine gum included in the SR by Mills[13] were already reported in the SR by Stead et al[15]. And also there was no pooled data.

[b] confirmed by expired carbon monoxide (CO) readings of <10 ppm.

[c] validated CO level was not reported.

[d] Smoking quitting was confirmed by a CO level of <9 ppm and a urinary cotinine level of <115 ng/ml.