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Clinical Strategies to Enhance the Efficacy of Nicotine Replacement Therapy for Smoking Cessation: A Review of the Literature

Matthew J. Carpenter, PhD[1,2,*], **Bianca F. Jardin, PhD**[1,2], **Jessica L. Burris, PhD**[1,2], **Amanda R. Mathew, MA**[1], **Robert A. Schnoll, PhD**[3], **Nancy A. Rigotti, MD**[4], and **K. Michael Cummings, PhD, MPH**[1,2]

[1]Medical University of South Carolina, (MUSC), Dept of Psychiatry & Behavioral Sciences, Charleston, SC

[2]MUSC Hollings Cancer Center, Charleston, SC

[3]University of Pennsylvania, Department of Psychiatry, Philadelphia, PA

[4]Harvard Medical School, Department of Medicine, Tobacco Research and Treatment Center, Boston, MA

Abstract

A number of smoking cessation pharmacotherapies have led to increases in quitting and thus to significant benefits to public health. Among existing medications, nicotine replacement therapy (NRT) has been available the longest, has the largest literature base in support, and is the only option for over-the-counter access. While the short term efficacy of NRT is well documented in clinical trials, long term abstinence rates associated with using NRT are modest, as most smokers will relapse. This literature review examines emerging clinical strategies to improve NRT efficacy. After an initial overview of NRT and its FDA-approved indications for use, we review randomized trials in which clinical delivery of NRT was manipulated and tested, in an attempt to enhance efficacy, through a) duration of use (pre-quit and extended use), b) amount of use (high dose and combination NRT), c) tailoring to specific smoker groups (genotype and phenotype), or d) use of NRT for novel purposes (relapse prevention, temporary abstinence, cessation induction). Outcomes vary within and across topic area, and we highlight areas that offer stronger promise. Combination NRT likely represents the most promising strategy moving forward; other clinical strategies offer conflicting evidence but deserve further testing (pre-quit NRT or tailored treatment), or offer potential utility but are in need of further, direct tests. Some areas, though based on a limited set of studies, do not offer great promise (high dose and extended treatment NRT). We conclude with a brief discussion of emergent NRT products (e.g., oral nicotine spray, among others), which may ultimately offer greater efficacy than current formulations. In order to further lower the prevalence of smoking, novel strategies designed to optimize NRT efficacy are needed.

1. Introduction

Nicotine gum was introduced in the U.S. as a prescription medication for smoking cessation in 1984. Since then other forms of nicotine replacement products have been made available worldwide in both prescription and over-the-counter formulations. However, despite the

[*]Corresponding Author: Matthew Carpenter, PhD, Associate Professor, Department of Psychiatry, Clinical Neuroscience, Hollings Cancer Center, Medical University of South Carolina, Ph (843) 876-2436, Fax (843) 876-2344, carpente@musc.edu.

availability of these medications, and the marketing to promote them, the prevalence of smoking has not changed much in the past decade. In the U.S., where broad trend data are available, smoking rates have decreased from 23.3% in 2000 [1] to 19.0% in 2011 [2]. If unchecked, global prevalence of smoking (estimated 23.7%) will remain virtually unchanged in decades to come [3].

Stagnant smoking rates can be linked to two factors: 1) incidence rates for quit attempts have not changed, and 2) low overall use of evidence-based treatment among smokers attempting to quit. U.S. National Health Interview Survey (NHIS) data suggest that only 40% of smokers make a quit attempt annually, a rate that did not change throughout the first decade of the 21st century [4], though more recent reports suggest this statistic may be improving [5]. Among smokers who do make a quit attempt, most evidence, inclusive of studies of smokers beyond the U.S., suggests that use of counseling and pharmacotherapy to quit smoking is modest at best [6–10]. One estimate suggests that almost two-thirds of smokers trying to quit do not use any evidence-based treatment [9]. Pharmacotherapy is particularly under-utilized; across a number of population-based surveys, estimates suggest that only 22–30% of smokers use nicotine replacement therapy (NRT). The availability of varenicline in 2006 appears to have led to wider usage of evidence-based treatment [10, 11], but on the whole, the use of evidence-based pharmacotherapy remains the exception rather than the norm.

To lower the prevalence of smoking further, the public health community will need to prompt more smokers to make more frequent quit attempts, increase the success of attempts made, or both [12]. A number of studies have examined strategies aimed at the first, i.e., to increase quit attempts among smokers reluctant to do so [13–17]. We herein focus on the latter issue; i.e., to examine ways to improve the efficacy of existing treatments for nicotine dependence, with an exclusive focus on pharmacotherapy. We briefly review the medication options for smoking cessation, with a particular focus on nicotine replacement products. Though other medications are approved and efficacious for smoking cessation (briefly noted below), our focus is on NRT, for two reasons. First, NRT has the most extensive literature base of all medications and thus numerous studies have examined ways to improve upon its established efficacy. Second, the only available over-the-counter pharmacotherapy options are NRT (gum, patch, and lozenge), making them the most widely used cessation aids with the greatest capacity for use across the population. Following a brief review of all medication options, the remainder of this article focuses on novel strategies that have been considered to enhance the efficacy of NRT specifically.

Across the world, guidelines for smoking cessation treatment [18, 19; 20] uniformly outline seven front-line medications for smoking cessation. Two non-nicotine products are bupropion and varenicline, and while both offer well-established efficacy [21–29], they are the not a focus of this review. Five NRT products include nicotine patch, gum, lozenge, inhaler and nasal spray. Two meta-analyses have documented their efficacy, relative to placebo [18, 30]. Outcomes are generally consistent across individual products, though these are largely based on indirect (i.e., cross-study) comparisons; few direct trials of active vs. active comparisons exist, and those published have shown similar quit rates [31]. While NRT is consistently shown to almost double the likelihood of successful quitting, the absolute abstinence rates for these medications are modest. For example, these same meta-analyses suggest that six-month quit rates among smokers who use NRT are 20–30%, and these data are remarkably consistent over many trials. Thus, 70–80% of smokers who use these products will relapse, creating what appears to be a glass ceiling of efficacy. This creates a significant challenge to improve upon these rates and make NRT more efficacious and ultimately more effective.

It is important to first understand how nicotine replacement products are currently approved. In the U.S., the Food and Drug Administration (FDA) has approved use of NRT for cessation purposes only. Products are to be initiated at the start of a quit attempt; i.e., to be used only when a person is ready to make a quit attempt and, importantly, discontinued if there is a lapse. They are to be used singularly, though NRT combined with bupropion is acceptable and often advised, with established efficacy. Further, most packaging suggests NRT should be used for a finite and fairly brief period, i.e., up to 12 weeks, after which the smoker should taper and discontinue treatment. The FDA has recently solicited input with regard to these regulations (FDA Docket ID: FDA-2012-N-1148), which suggests, that like other countries, more relaxed standards may be considered. For example, in parts of Europe, NRT is available for adolescents, pregnant smokers, or for purposes of gradual quitting. Though these recent changes have had limited population impact to date [32–34], the trend in Europe and beyond is fewer, not greater, restrictions on NRT. Many have argued that the FDA should revisit current indications for NRT use, in large part due to the growing body of research that has examined alternatives to these regulatory standards. The over-arching purpose of this review is to examine this literature, with a focus on novel, usually off-label use of NRT to further enhance cessation rates beyond established efficacy associated with conventional methods of use. We examine those studies that have directly tested (i.e. randomized controlled trials) the impact of altering NRT delivery through:

1) duration (including studies of pre-quit and extended use treatment)

2) dose (including studies of higher dosing and combination NRT)

3) tailoring (based on specific genotypes or phenotypes)

4) purpose (withdrawal relief during temporary abstinence, relapse prevention, or cessation induction among smokers who are not yet ready to quit)

A number of prior reviews and commentaries have included partial coverage of the topics above [30, 35–39]. At least 17 studies have been published since the most recent of these prior reviews. In addition, several new topic areas have emerged in recent years, most notably tailored therapy to specific sub-groups of smokers. Like most others, however, we have not undertaken a formal meta-analysis, given a) the limited number of studies within a given topic area, and b) the broad methodology across studies.

A number of topic areas are not included here, but are worthy of mention because they too pertain to the broad themes of how NRT is used and regulated. First, we omit discussion of NRT use among pregnant or adolescent smokers, which FDA labeling currently excludes. Readers interested in the former [40, 41] or the latter [42, 43] are referred elsewhere. Our rationale is that in neither case is NRT used in a different manner or for a different purpose than conventional recommendations. Second, we exclude studies that examine either a) adjunctive behavioral treatment to NRT (e.g., NRT + counseling vs. NRT alone), or b) adjunctive NRT to behavioral treatment (e.g., NRT + counseling vs. counseling alone). Though combined treatment has well-established efficacy [44], provision of NRT within these studies generally conforms to recommended indications for use. Third, we omit all issues regarding policy efforts to enhance use, including pricing, packaging, labeling, and changes to over-the-counter status, as our focus is on clinical strategies that manipulate NRT administration. Such topics are important and relevant to the demand and use of NRT, but are beyond the scope of this review.

To initiate our review, we searched databases in PubMed, CINAHL, EMBase, PsycINFO, Web of Science, and Google Scholar, with broad search terms associated with each topic above (note that these topics do not offer commonly accepted search terms). An initial list of

685 English-based articles was reviewed independently by two authors (BFJ, JLB) for both title and abstract. Articles identified by either author as being potentially relevant (N=113), were combined with additional articles gleaned from reference lists and prior reviews, which were subsequently reviewed for possible inclusion by first three authors. Broad inclusion criteria were as follows: a) relevance to one or more of the four topic areas above, b) use of randomized controlled designs, and c) report of abstinence outcomes at six month follow-up or beyond. This latter criterion is consistent with guidelines for assessment of outcome provided by the Society for Research on Nicotine and Tobacco [45]. Further exclusion criteria per each topic are discussed below. Some topic areas, where an extensive literature base (>10 studies) exists and where prior reviews cover at least 90% of those studies, are kept to a brief discussion, and are noted below. Our final review is based on 39 articles, roughly half of which were conducted in the U.S.

Upon confirmation of study inclusion, co-authors (BFJ, JLB, ARM) separately coded individual studies. Codings for each study were secondarily confirmed by the first author (MJC). Our primary interest was the effect size of treatment at six month follow-up, though we also report outcomes at longer follow-up when available. In rare cases (<5%) where specific abstinence data were not reported, we estimated abstinence rates from graphs with convergence across two raters. Effect sizes are reported as relative risks (% abstinent in experimental group / % abstinent in control group). We opted not to include notation of statistical significance within tables, for several reasons. First, our focus is on clinical, not statistical effects. Many studies were pilot trials and were therefore underpowered to show statistical significance. Second, a moderate number of trials did not report statistical significance for the specific comparison presented below (e.g., groups were collapsed, or statistical testing was performed for some but not all timepoints). It should also be mentioned that individual studies reported outcomes across broad definitions, including continuous and point prevalence abstinence. The definitions and merit of separate abstinence outcomes have been reported elsewhere [45, 46]. In cases where multiple outcomes were reported for the same follow-up period, we chose the more stringent. Thus, within tables below, effect sizes are based on separate and often different definitions of abstinence within each study; it was not possible to standardize the abstinence outcomes across studies prior to the calculation of relative risks. Throughout the discussion below, we caution readers not to make cross-study comparisons of outcomes because of the heterogeneity of methods, which beyond broad range of abstinence definitions include duration of treatment and instructions for use of NRT (e.g., ad libitum vs. a defined daily dose). Rather, our focus is on overall patterns of results across studies.

2. Alternative Duration Treatment

2.1 Pre-Quit NRT

Manufacturer instructions for NRT use recommend initiating use on the day of the quit attempt. Abrupt quit attempts and onset of medication may be unappealing for many smokers, leading some researchers and clinicians to consider gradual lead-in periods prior to a designated quit date. Early exposure to NRT, in advance of a designated quit date, may allow individual smokers to adjust dosage, acclimate to any effects, familiarize themselves with product, gain confidence as the quit date approaches, or reduce reinforcing properties of smoking by providing some/all nicotine intake separately from smoking. Studies below (see also Table I) on pre-quit NRT are organized by the duration of use (2 week, 4 weeks, etc.) prior to the quit attempt. We omit from Table I an early study that examined nicotine gum use for a one week —familiarization period‘ prior to a designated quit date [47], but only reported on short term abstinence, in which rates of sustained abstinence (6 weeks) were not significantly different between familiarization vs. regular use groups (61% vs. 52%, respectively).

Most randomized trials of pre-quit NRT provide medication for two weeks, after which smokers in both groups receive identical treatment. In the largest trial to date on pre-quit NRT [48], 1,100 quitline users were randomized to receive vouchers for NRT (patch —and/or gum) or not, during a two-week pre-quit period, after which all participants received the same vouchers for eight weeks. NRT vouchers could be redeemed at local pharmacies for a nominal processing fee. There were no between group differences (23% vs. 21%) in point prevalence abstinence rates at six month follow-up. Two studies used a placebo-controlled design to test the effects of pre-quit nicotine patch. In one [49], rates of sustained abstinence after six months were significantly higher in the pre-quit vs. placebo group (22% vs. 12%). In the other [50], there was no significant difference in point prevalence abstinence between the pre-quit and placebo group at six months (21% vs. 13%). A subsequent study by this same study group [51] had a similar design, and randomized smokers within a 2x2 factorial design to pre-quit active vs. placebo patch x pre-quit usual brand vs. low tar/nicotine cigarette smoking. Among those who smoked their usual brand during the pre-quit period, there was 1.5-fold increase in rates of continuous abstinence between active vs. placebo patch; for those smoking low tar/nicotine cigarettes during the pre-quit period, there was over a 3-fold increase in continuous abstinence between active vs. placebo patch. While statistical significance was unreported for each arm of usual brand vs. low tar/nicotine cigarette smoking, there was a main effect reported in favor of pre-quit patch treatment for continuous, but not point prevalence abstinence. A final study of two week pre-quit patch was not placebo controlled but rather compared patch + denicotinized cigarettes vs. switching to light cigarettes [52]. Self-reported quit rates after six months were 28% vs. 21%, respectively (non-significant difference).

Two studies tested four weeks of pre-quit treatment. The first [53] used a 2x2 factorial design of pre-quit patch vs. none x pre-quit active vs. placebo mecamylamine. Among those receiving mecamylamine, 40% vs. 15% of patch vs. no patch participants were continuously abstinent at six months. Among those who did not receive mecamylamine, 20% vs. 15% of patch vs. no patch participants were abstinent. Post-hoc comparisons showed that combined patch + mecamylamine was superior to the pooled effect of the three remaining conditions. Finally, one study tested mail-based provision of pre-quit nicotine gum vs. none [54]. Across a range of range of outcomes and timepoints, there were no significant differences in abstinence.

In sum, with the exception of two studies showing large effects, most evidence suggests a modest impact of pre-quit treatment on long term quit rates. In contrast with a previous review on this topic [30], at least half of the studies we reviewed reported non-significant treatment effects. The differences between outcomes may reflect the varying methodologies of the studies, including types of medication used, instruction provided regarding smoking during pre-quit treatment (e.g., explicit instructions to reduce smoking, switch cigarette brands, or no instruction), and duration of follow-up treatment post quit date. Notably, outcomes do not seem to vary as a function of pre-quit treatment duration. The largest treatment effect was found in the study that provided patch while instructing smokers to switch to lower yield cigarettes [51], which suggests that decreased reinforcement from smoking and/or disruption of normal smoking patterns during the pre-quit period is a possible mechanism by which pre-quit treatment could work. However, a conceptually similar (but smaller) study found no effect for this approach [52]. Finally, it is somewhat surprising that most studies to date have examined pre-quit patch instead of other nicotine formulations that more easily lend themselves to acute withdrawal relief and response to cigarette related cues.

2.2 Extended Treatment

Nicotine withdrawal occurs shortly after quitting and peaks fairly soon during the course of a quit attempt [55]. However, many smokers continue to report cravings long after quitting [56], and relapse in distant weeks is common [57]. Providing NRT beyond the manufacturers‘ suggested 12-week treatment period may provide additional efficacy. A prior review [30] examined the efficacy of NRT when provided for +/− 8 weeks, but included only one study that directly tested long vs. short term as compared to conventional NRT packaging (more vs. less than 12 weeks). We herein focus only on the latter; i.e., studies that directly test whether extended treatment of NRT results in improved outcomes as compared to more conventional treatment. We have identified four studies that fit this description and have organized discussion below by duration of use (18 weeks, 24 weeks, etc.; Table II). Note we exclude studies of extended NRT vs. extended placebo treatment [58–61], which consistently demonstrate superior efficacy of the former.

One study tested extended treatment of nicotine patch, discontinued either abruptly (at 12 weeks) or gradually (tapered over an additional 6 weeks), but did not include sufficient information to be included in this review [62]. Another trial offered nicotine patch for 18 vs. 10 weeks [63], and though extended treatment resulted in longer latency to relapse, the trial did not report abstinence outcomes beyond 14 weeks, and thus is not included below.

Two trials examined a six-month course of patch. In one [64], smokers were randomized to receive nicotine patch for 24 vs. 8 weeks, with the latter including a placebo control for an additional 16 weeks to equate total treatment duration. Abstinence rates (7 day point prevalence) were significantly higher at six-month follow-up in the extended treatment group (32% vs. 20%). At one year, point prevalence outcomes were equivalent (14%), though rates of prolonged abstinence favored extended treatment (29% vs. 21%). The second study [65] provided patch for 26 vs. 12 weeks (also placebo controlled for an additional 14 weeks). Separate arms for high dose (25mg) and low dose (15mg) patch were also tested for each treatment duration: extended 25mg vs. short 25mg and extended 15mg vs. short 15mg (Table II). Extended and short treatment yielded similar rates of continuous abstinence after six months, within both the high dose group (20% vs. 21%) and low dose group (19% vs. 15%). Comparable results were found at one year.

Two trials examined the availability of nicotine gum [66] or multiple NRT products [67] for up to one year. Within the former, separate study arms included adjunctive counseling vs. medication only, creating two pair-wise comparisons of interest: extended gum vs. no gum, and extended gum + extended counseling vs. extended counseling alone (see Table II). Within the arm that did not receive counseling (i.e., extended gum vs. no gum), there were no differences in 7 day point prevalence abstinence at six month (56% vs. 54%), one year (41% vs. 33%) or two year follow-up (40% vs. 36%). Within the arm that received counseling (i.e., extended gum + extended counseling vs. extended counseling), there were again no differences at six month (59% vs. 58%), one year (48% vs. 55%), or two year follow-up (45% vs. 55%). The authors concluded that extended counseling, but not extended NRT use, increased efficacy. The second trial tested a chronic disease management model [67], in which smokers received counseling plus NRT (choice of multiple products, including combination) for extended duration (one year) vs. not (8 weeks). There were no significant long term differences in abstinence (30% vs. 24% rates of prolonged abstinence). However, in a multivariate logistic model, extended duration treatment resulted in a 74% increase in the odds of successful quitting. Moreover, and consistent with the notion that sustained treatment can facilitate increased quit behavior, extended treatment led to a significant increase in quit attempts and treatment engagement.

In sum, there is weak evidence that extended treatment is more efficacious than standard duration NRT. This weak evidence does not appear to be a consequence of limited power within studies; these are among the larger trials throughout this review. Extended NRT might keep smokers more engaged in the quitting process, but with the exception of one study [64], this has yet to translate into improved abstinence. The lack of strong support for extended NRT is consistent with the evidence that NRT works mainly to help smokers cope with intense cravings, which are at their peak shortly after a quit attempt. Thus, one potential reason for weak efficacy within this literature is that, as cravings lessen over time, the potential of NRT to curb those cravings also lessens, making it less potent to the individual user over time. Another potential issue with extended treatment is the difficulty of maintaining medication compliance over protracted duration. NRT compliance was reported by three studies in Table II. In two [64, 65], patch compliance was below 50% after six months of intended use, and in another [66], average days of gum use was 3 months or less, despite its availability for one year. If extended treatment is to be considered further, one option might be to more closely tailor it to those smokers who endure sustained craving, who may more readily benefit from continued use. If so, strategies to increase medication compliance over the long term would also be worth strong consideration.

3. Increased NRT Dose

3.1 Higher Dosing NRT

The rationale behind higher dose NRT is based on the premise that nicotine withdrawal during a quit attempt will be attenuated more effectively to the extent that nicotine has been more adequately replaced. Several studies show higher dose NRT relieves withdrawal and craving, and may even improve concentration and emotion regulation after quitting [68–70]. We include herein studies that compare higher dose NRT formulations (all studies used patch) to conventional dosage of NRT (up to 21mg); some studies included placebo comparisons but those groups are not discussed here. Among higher vs. standard dose studies that met inclusion criteria, almost all examined 44mg vs. 21mg patch. Thus, our discussion below, as well Table III, summarizes the findings accordingly. This section does not include those studies that tailored NRT dosage to baseline smoking level (or dependence); those studies are discussed elsewhere in this review. Also not included below is a forthcoming trial of 42mg vs. 21mg patch [71], based solely on smokers who quickly metabolize nicotine (as a proof of concept trial, outcomes were reported only after eight weeks of treatment). Thus, the studies reviewed here include those that administered a blanket dosage (higher vs. standard) to smokers within each group, regardless of dependence level. However, a common eligibility criterion across almost all studies was a higher level of smoking upon study entry, on the assumption that such treatments would generally not be indicated for lower level smokers. Thus, we secondarily order our discussion below by this eligibility criterion.

One study [72] used stratified randomization to provide light, moderate, and heavy smokers either 44mg, 22mg, or 11mg nicotine patch (placebo included as well, but not discussed here). Six month 7-day point prevalence abstinence rates in each of these groups respectively, were 78%, 54%, and 59%, and 12 month abstinence rates were 67%, 35%, and 41% (significance not reported). Outcomes were not reported separately by baseline smoking level. Another study [73] tested 44mg vs. 22mg patch, but also randomized smokers to receive minimal counseling, individual counseling, or group counseling (six cell factorial design). Collapsing across counseling groups, six month point prevalence abstinence rates were slightly lower in the higher dose (27%) compared to the lower dose groups (29%). A third study of 42mg vs. 21mg patch was based on smokers with a history of alcohol dependence who were at least two months abstinent from alcohol upon study entry [74]. At all the timepoints evaluated, abstinence outcomes were more favorable among

smokers receiving the lower dose product (17% vs. 9% at both six and nine months), though none of these differences reach statistical significance. Finally, a large (N=1039) multi-site trial of heavy smokers tested 42mg vs. 35mg vs. 21mg patch [75]. Continuous abstinence rates across each of these groups were 26%, 20%, and 20% at six months, and 19%, 9%, and 13% at one year. Although the omnibus test for dosage (across all groups, including a placebo group) was significant for all timepoints, none of the pair-wise comparisons between active dosage groups reached statistical significance.

Two studies examined 25mg vs. 15mg patch [65, 76], though it may be debated whether the former truly represents increased doses of NRT. In the first [65], smokers were randomized to receive 25mg or 15mg patch, for either 12 or 26 weeks. Note this study is also summarized above in Section 2.2. Sustained abstinence rates at six months favored the high dose patch, but only when delivered for 12 weeks (21% vs. 15%), and not for 26 weeks (20% vs. 19%). Comparable results were found at one-year follow-up. Finally, in a study of heavy smokers who were randomized to receive 25mg or 15mg patch [76], 16% and 14% achieved 7-day point prevalence abstinence at six months, respectively; 14% were abstinent in both groups at one year, and 10% were abstinent in both groups at both six and 12 months (i.e., repeated point prevalence). Finally we should note that one study of 25mg vs. 15mg patch [62] is not included in this review, because smokers only received high dose patch if they had failed at the lower dose.

In sum, the findings on higher dose NRT show mixed evidence of support for the hypothesis that higher dosages of NRT work better than standard dose formulations, at least in regards to the nicotine patch. The findings from high dose studies (42–44mg) were generally comparable to those of moderately high dose studies (25mg). Of the four tests of 44mg patch, only two found small to moderate effects. Of these, one was restricted to heavy smokers [75] and the other was not [72]. Of the two studies of 25mg patch, the one study to demonstrate an effect was inclusive of moderate smokers (15 cigarettes per day). Thus, one interpretation is that success will be moderated by the amount of replacement the smoker receives. Taken one step further, this also suggests that baseline dependence could moderate the effects of higher dose NRT.

While several of the studies listed in Table III conducted post hoc sensitivity analyses to examine the efficacy of high dose NRT among sub-groups of smokers, two separate studies (not included in Table III) were a priori designed with this question in mind. In one [77], smokers who were rated as high or low in dependence were randomized (stratified) to receive 21mg vs. 42mg patch. In addition to the dependence phenotype, this study also examined a genotype for likelihood of quitting success‘ an additional potential moderator of smoking cessation. There was a significant three-way interaction between patch dosage, dependence phenotype, and quit-success genotype, such that high dose NRT resulted in higher rates of continuous abstinence (through 10 weeks) among high dependent smokers with low quit-success genotypes. However, the higher dose patch resulted in lower abstinence rates for less dependent smokers with the same genotype. The authors concluded that personalized treatment, in which NRT dose is tailored to individual smokers, may enhance quitting success. In a separate study [78], smokers high in dependence (high baseline cotinine values) were randomized to receive either 25mg or 15mg patch, while those low in dependence were randomized to receive 15mg or placebo patch. Sustained abstinence rates in the high dependence group after one year were comparable between treatment groups (11% for 15mg vs. 9% for 25mg). This issue of tailoring NRT to specific geno/phenotypes is further discussed below, Section 4.

3.2 Combination NRT

Most studies of combined NRT are based on patch + gum or lozenge. The rationale for this combination, presented in detail elsewhere [37], is at least twofold. First, combination NRT delivers greater amounts of nicotine than single products. However, given the modest outcomes from higher dose NRT studies, this rationale alone is insufficient. Second, whereas nicotine patch provides a steady dose of nicotine throughout the day, products like gum and lozenge allow for acute nicotine delivery, affording smokers the opportunity to address situation-induced cravings to smoke [79, 80]. Given that both tonic and phasic craving influence smoking [81], different modes of nicotine delivery may be more effective than single formulations alone. Most [82–85], but not all [86] studies show that combined NRT, relative to single formulations, effectively controls withdrawal and craving.

Several, prior narrative reviews or meta-analyses have examined the efficacy of combination therapy, and particularly combination NRT [37–39]. At least three new studies have been published since these prior reviews. Results from randomized trials that tested combination vs. monotherapy are presented below, and summarized in Table IV, each ordered by type of product used. Not included below is a trial of combination NRT (patch + inhaler) compared to brief advice to quit alone (i.e., control group not monotherapy), tested among hospital patients, which demonstrated short, but not long term efficacy [87]. Also not included is a test of triple medication (patch + inhaler + bupropion), which is not a pure test of combination NRT per se [88].

Two recent randomized trials with similar methods tested combination (patch + lozenge) vs. single NRT. One was an efficacy trial [89], and the other an effectiveness trial based in primary care clinics [90]. In the former, combined NRT treatment resulted in superior abstinence rates, compared to an aggregate effect across all monotherapies (including separate groups of patch, lozenge, and bupropion only), both at the end of 8 weeks of treatment (54% patch + lozenge vs. 45% patch vs. 40% lozenge) and at 6 month follow-up (40% patch + lozenge vs. 34% patch vs. 34% lozenge). Post-hoc analyses suggested a clear benefit of reduced craving as a function of combined patch + lozenge, relative to monotherapy [91]. A comparative effectiveness trial from the same group [90] used an open label design and resulted in generally similar outcomes, though with lower absolute rates of abstinence than the preceding trial, a result common in efficacy vs. effectiveness trials. Six-month point prevalence abstinence rates were 27% in the combined patch + lozenge group, compared to 20% in the lozenge and 18% in the patch alone groups. Survival analyses indicated that combined treatment produced significantly longer time to relapse than did either monotherapy group.

Three studies tested gum + patch, one in comparison to gum alone [92], and two in comparison to patch alone [93, 94]. The first [92] showed superior efficacy for combined treatment at 12 week follow-up (39% vs. 28%) but not at 6 months (27% vs. 21%) or 12 months (24% vs. 17%). Another study that compared combination gum + patch to patch alone [93] demonstrated superior efficacy for combined treatment at six month follow-up (28% vs. 15%) but not at 1 year (18% vs. 13%). The other trial of gum + patch vs. patch alone was based on smokers with comorbid alcohol dependence. Treatment included a fairly intensive regimen (16–60-minute sessions) of psychosocial counseling for both alcohol and nicotine dependence. Outcomes were no different between groups at either three months (40% vs. 35%) or 6 months (20% vs. 12%), but did achieve statistical significance at 1 year (13% vs. 0%).

Four studies examined combined NRT using patch and prescription-based acute delivery products. The first [95] compared patch + spray to patch alone, in which combined NRT resulted in higher rates of sustained abstinence at both six months (31% vs. 16%) and at 1

year (27% vs. 11%), with marginally significant differences at the 6 year follow-up (16% vs. 9%). Another study tested combined patch + spray, but with comparisons to patch and spray individually [96]. Results were favorable for short term outcomes (end of treatment; six weeks): 27%, 21%, 14% in combined, patch alone, and spray alone groups, respectively. However, group differences in abstinence rates attenuated after six months: 9%, 8%, 7%, respectively. The third study [97] provided active nicotine inhaler for 26 weeks, which was combined with patch for either 6 or 12 weeks. Short term (three months or less) outcomes favored combined treatment, but six month and 1 year outcomes were not statistically different. Finally, an open label trial of inhaler + patch in a pulmonary clinic [98] demonstrated non-significant but numerically worse outcomes for combined treatment, both at six months of follow-up (sustained abstinence: 8.7%, 14.4%, and 5.9% for patch + inhaler, patch, inhaler groups, respectively) and at 1 year (3.5%, 8.7%, and 5.1%).

In sum, the studies we reviewed generally support a modest increase in efficacy of combination NRT as opposed to single formulation NRT, at least in the short term. Combination of patch + any acute delivery device were generally comparable (i.e., effects were not restricted to patch + one specific acute product). The effects for combination therapy were at least as strong, often stronger, in comparison to the literature on higher dose medication. This suggests that, in addition to amount of nicotine delivered, there is a specific benefit of combining products that deliver nicotine differently, allowing the smoker increased control for situational use of products. A second point of contrast from the above literature on high dose NRT is the inclusion criteria. As noted above, high dose studies are generally restricted to more dependent smokers, which likely deflates abstinence outcomes. Of the nine studies in Table IV, only 1 [94] was restricted to smokers of at least 15 cigarettes per day (CPD); the remainder were based on inclusion criteria of 10 CPD, and in 1 study [95], only 1 CPD. This also suggests that increasing dose of NRT, regardless of administration route, need not be restricted to highly dependent smokers alone.

3.3 Safety of Higher Dosing or Combined Treatment NRT

One concern of increased administration of nicotine, either through higher-dose delivery or through combination medication, is toxicity; i.e., side effects. In general, and across studies listed above in Tables III and IV, increased nicotine delivery resulted in few clinically significant adverse side effects. Most reported adverse events were mild, transient, and tolerated by study participants. In one study, in which outcomes favored lower dose NRT over higher dose [74], the authors attributed this difference to the higher rate of adverse events in the high dose patch group [99]. On the whole, however, and consistent with several prior commentaries [35, 37], the overwhelming evidence supports the conclusion that co-administration of nicotine is relatively safe. A second concern of increased nicotine administration is the potential for increased abuse liability. The currently approved NRT formulations have a low abuse liability [100] as all products deliver less nicotine, and at much slower rates, as compared to cigarette smoking [101]. Longer-term use of NRT products is uncommon [58], and long term problematic use (i.e., abuse) is even less common [102]. Thus, there is little evidence for concern that either high dose NRT or combination NRT will result in significant health harm.

4. Tailored Treatment, Based on Individual Genotypes or Phenotypes

Recent research has focused on whether NRT efficacy can be enhanced through matching to specific smokers, whether by genotype, or to the outward expression of such genotypes; i.e., phenotype. The best test to determine the effect of tailoring NRT treatment to specific geno/phenotype would be based on a 2x2 factorial design in which separate geno/phenotypes (e.g., low vs. high dependent smokers) are crossed with varying levels of treatment (e.g., active vs. placebo NRT, or any other alternative of NRT delivery as discussed throughout

this review). To truly test the effect of tailoring, such a study would need to be *a priori* designed and powered to test for interaction effects between geno/phenotype and treatment (see Table V for hypothetical studies which do and do not show interaction effects). However, few studies fit this description. A more common approach is to conduct post-hoc analyses of the geno/phenotypic moderators of NRT efficacy. Here, it is the same interaction that is of interest, but the source study was not powered in advance on this analysis. Note that it is insufficient to demonstrate treatment efficacy within certain subgroups of smokers but not others, as is also common in the literature [103, 104]. For example, both studies in Table V show significant treatment effects in Subgroup 1 but not Subgroup 2, yet only in hypothetical study 1 is the interaction significant. Thus only study 1 allows for the interpretation that treatment is differentially effective by treatment. Such studies are rare.

4.1 Genotypic Moderators of NRT Efficacy

The most commonly tested genotypes include variants in nicotine metabolism (CYP2A6, CYP2B6), nicotine receptors (CHRNA4, CHRNB2), and dopamine receptors (DRD2, DRD4, among others), though others are beginning to be identified. At least 14 studies have examined genotypic moderators of NRT efficacy. Given this wide scope, and also the existence of two literature reviews on this topic [105, 106], we do not review each individual study further. Broadly speaking, the prior literature shows promising potential for tailored NRT treatment, as a function of specific metabolizing subtypes and/or variations in dopamine/nicotine/opioid pathways.

Since the publication of prior reviews, however, three relevant studies have emerged and warrant discussion. Each study had a unique genotypic focus. Munafo et al. [107] examined variants in one nicotinic acetylcholine receptor (CHRNA3) within two cessation trials, one of which randomized smokers to receive active vs. placebo patch, and the other provided patch to all smokers. There were no genotypic differences in cessation within the former. Within the latter, there was a small effect for increased cessation at short term (four weeks) but not long term (up to six months) follow-up among smokers without a T allele. This suggests a possible link between this variant and short term cessation, but also suggests that any such effect is not specific to NRT. Another study of an alternate dopaminergic receptor (galanin) included analysis of three sub-studies [108]: a placebo controlled bupropion trial, an open-label patch study, and a randomized trial of patch vs. spray. There was an overall genotype x treatment interaction, but only on the basis of response to bupropion treatment. There was no differential genotypic response to NRT treatment. Finally, in a study of CYP2B6 (another nicotine metabolizing enzyme, but with lower affinity than CYP2A6) [109], there was no differential response to NRT (patch, spray, placebo). The non-specific treatment effects within these studies, each with a unique genotypic focus, stand in contrast to the existing literature reviews above, and do not themselves offer promise for further investigation. While matching treatment to genotype on the whole seems promising, one tautological conclusion is that doing so will necessarily be genotype-dependent.

4.2 Phenotypic Moderators of NRT Efficacy

The most commonly tested phenotypes include subgroups of high/low dependent smokers, and fast/slow metabolizers of nicotine, as measured through nicotine clearance, i.e., the ratio of 3-hydroxycotinine to cotinine. The general rationale is that more dependent smokers, or those who metabolize nicotine more quickly, may benefit from higher doses and/or alternate delivery of NRT. As with genotype studies, most but not all of the relevant studies were not *a priori* designed to examine interactions between NRT and phenotypic subtypes of smokers. Given that prior reviews on the efficacy of NRT did not review the phenotype literature, we provide further detail of individual studies below.

4.2.1 Dependence Phenotypes—Two studies stratified smokers as being high vs. low in nicotine dependence and randomized smokers within each strata to varying levels of nicotine gum treatment. In the first [110], smokers in both dependence groups were randomized to 4mg, 2mg or placebo gum. Within the high dependence group, but not the low dependence group, there was a significant treatment effect across the three dosage groups for abstinence at both six month and one-year follow-up. However, at no time was there a significant gum x dependence interaction. A similar trial randomized high and low dependent smokers to 2mg gum vs. not [111]. There was a significant gum x dependence interaction early in treatment, but not at six or 12 months. Thus, one possibility is that matching treatment to level of dependence offers advantage during, but not beyond treatment.

Three studies of nicotine dependence and NRT were based on a similar design, in which high dependent smokers were randomized to treatment A vs. B, and low dependent smokers were randomized to treatment B vs. C. Thus, these studies do not allow for tests of phenotype x treatment interactions, yet they do offer indirect evidence on the effect of treatment matching. Two are gum studies [47, 112], in which outcomes were reported separately within each dependence group. For both trials, higher dose gum (4mg) was superior to lower dose (2mg) among high dependent smokers, and 2mg gum was superior to placebo among low dependent smokers. Finally, a third trial [78] tailored medication dosage according to whether a smoker had a high or low cotinine level at baseline. Smokers with high levels of cotinine were randomized to receive 25mg vs. 15mg patch, which yielded no differences in one year abstinence (9% vs. 11%). Smokers with low levels of cotinine were randomized to receive 15mg vs. placebo patch, which did show significant treatment effects at one year (28% vs. 9% abstinent).

4.2.2 Nicotine Metabolizing Phenotypes—Two recent studies examined the relationship between nicotine metabolism and NRT efficacy. The first [113] was an uncontrolled single arm study of nicotine patch, provided for eight weeks to 568 smokers. Pre-treatment ratio of nicotine metabolism (split into quartiles) was examined in relation to end of treatment abstinence. Smokers with the slowest metabolism (1^{st} quartile) had significantly higher 7-day point prevalence abstinence (42%) than did each of the remaining 3 quartiles (27–30%). A second study of nicotine metabolism, also assessed in quartiles, was based on 480 smokers randomized to receive either nicotine patch or spray [114]. There was a significant treatment x phenotype interaction, such that metabolism ratios predicted abstinence (higher abstinence among slower metabolizers) within the patch but not the spray group. The difference in six month abstinence rates between 1^{st} and 4^{th} quartile of metabolism ratio in the patch group was 28.8% (29.6% vs. 0.8%); among smokers in the spray group it was -1.0% (5.1% vs. 6.1%). Slower metabolism ratios were also associated with higher blood levels of nicotine during patch treatment, which suggested that high blood levels of nicotine result in increased likelihood of abstinence. Thus, the replicated relationship between nicotine metabolite ratio and response to nicotine patch suggests some form of personalized treatment for nicotine dependence involving a genetically-informed biomarker is on the horizon.

One recent study, briefly discussed above in Section 3.1, included combined analyses of both phenotypic and genotypic markers, all within a randomized trial of standard dose (21mg) vs. high dose (42mg) nicotine patch [77]. Smokers (N=479) were *a priori* categorized as high vs. low in nicotine dependence, and separately assigned a quit success score (high vs. low), on the basis of —groups of genomic markers. Six month abstinence rates showed a significant 3-way interaction between dose of patch, dependence phenotype, and genotype success group. Higher dose treatment offered a greater benefit than standard dose treatment, but only among high dependent smokers in the low-quit success genotype.

In contrast, high dose treatment actually impeded abstinence among less-dependent smokers with low-quit success genotypes. This interaction was fairly robust as well, with consistency across several points of follow-up and within subgroups of both European and African American smokers. Another recent trial was also based on a tailored approach, but with a unique twist. In this trial of 633 English smokers [115], all were provided with nicotine patch. Additional treatment (gum, lozenge, tablets, or spray) was tailored to each smoker, based on either genotype (OPRM1; opioid receptor) or phenotype (dependence). As an open label study, smokers in both groups were informed that their nicotine dose was based on either genotype or phenotype status. Rates of prolonged abstinence at six months were significantly higher among smokers whose NRT dose was genotypic vs. phenotypic based (14% vs. 8%), despite comparable dose and rates of NRT use in both groups.

In sum, the possibility of matching treatment to specific smokers offers promise for enhancing treatment response. Direct tests, adequately focused on treatment x geno/phenotype interactions, are needed. As research continues to uncover new genetic/phenotypic characteristics associated with smoking behavior, and as genetic testing becomes more accessible, this may be a way to enhance NRT efficacy further. Treatment matching need not be restricted to above-referenced moderators. For example, similar to a stepped care model [116], medication treatment could be tailored based on prior quitting history, providing more intensive treatment to smokers who have a significant history of failed quit attempts, to those who live with other smokers, or to those who have psychiatric comorbidities. However, this rationale also creates a higher burden of proof for pharmacogenomic approaches, in that they should improve cessation outcomes over and above what can be achieved by tailoring treatment to clinical characteristics already known to predict outcome but which are less costly to assess. Furthermore, healthcare providers who rely on pharmacogenomics-based treatment must guard against treatment minimization within individual smokers. Provision of less-intensive treatment to certain subgroups of smokers may result in the unintended inference that treatment is not necessary.

5. Use of NRT for Non-Cessation Purposes

5.1 Relapse Prevention

Recent research has begun to disentangle milestones of quitting: achieving initial abstinence, avoiding lapse, and preventing progression from lapse to relapse [117]. Two studies examined NRT effects on these milestones [118, 119] and found the largest effect to prevent progression from lapse to relapse. We searched for studies that directly tested whether NRT prevented relapse among smokers who achieved initial abstinence. Identification of relevant studies mirrored those from prior reviews [120, 121] and thus our description of these studies and their results is kept brief.

Two studies examined NRT individually and in combination with bupropion [122, 123]. Both trials provided open label medication for 2–3 months to facilitate initial cessation, after which smokers who were abstinent (4 weeks minimum) were randomized to receive continued treatment vs. not. In neither case did continued use of NRT promote abstinence; i.e. decrease rates of relapse (see Table VI; relative risk is for abstinence rates to maintain parallelism with previous tables). Two other studies provided nicotine gum to smokers who had achieved very early abstinence (1–2 days) on their own [124, 125]. In only one study arm, in which nicotine gum was paired with self-help materials [124], did NRT produce higher rates of short term abstinence rates.

Several observations can be drawn from Table VI. First, the limited number of trials is surprising, though it is worth mention that other relapse prevention studies exist but are not specific tests of NRT vs. not [126–129]. Second, it is unclear how long a smoker should be

abstinent before being enrolled in a relapse prevention study. There needs to exist a standard definition of abstinence before we consider prevention of lapse and relapse; brief success soon after an attempt is likely to be very different than sustained success over time. Third, we note the absence of patch studies to address relapse prevention. As discussed elsewhere in this review, acute products offer greater control over situation-specific cues that might compromise quitting success. On the other hand, ex-smokers may prefer stable, gradual delivery of nicotine (as via patch) over punctuated administration.

5.2 Withdrawal Relief During Temporary Abstinence

The ability of NRT to reduce craving and withdrawal is well established [68, 82, 83, 130–132], and reductions in craving and withdrawal mediate, at least partially, abstinence outcomes [70]. Given this evidence, some have argued that NRT should be expressly permitted (i.e., approved) for use during smoking restrictions when the smoker is temporarily abstinent [133]; i.e., within the confines of a smoking restricted environment. Smoking restrictions are becoming the norm worldwide [134], though historically have been more restrictive in western countries [135]. For example, all 27 EU Member States have some form of regulation that restricts exposure [136], and over 80% of the U.S. workforce is covered by smoke-free legislation [137]. International estimates suggest that over 8% of smokers who use NRT do so to cope with smoking restrictions [32]. Hospitalization represents another opportunity to engage smokers who are temporarily abstinent. However, direct (i.e., controlled) tests of NRT during periods of temporary abstinence (hospitalization or otherwise), and its impact on downstream quitting, are lacking.

The relevant question for this review is whether NRT use during temporary abstinence facilitates or undermines subsequent cessation. The latter is of concern if NRT is used, not to cut down or reduce smoking (see next section), but rather to circumvent smoking restrictions, which are known to promote quitting [138]. We are aware of no randomized studies that have provided NRT to manage periods of temporary abstinence. Such a trial would be important, and would ideally report on both short term effects (e.g., withdrawal relief, use of NRT beyond restrictions, smoking reduction) and long term cessation outcomes. However, several non-randomized studies exist. One study provided either patch and inhaler, each on alternating days, to hospital-bound smokers, but was not a controlled trial of NRT [139]. Nonetheless, provision of NRT decreased craving, led to few incidents of smoking outside the hospital, and increased interest in quitting upon discharge. A separate phone based survey of Massachusetts smokers [140] showed few smokers (7%) use NRT to cope with smoking restrictions, and doing so was prospectively associated with neither increased nor decreased rates of quit attempts or abstinence. However, a large cross-sectional survey among English smokers demonstrated that use of NRT during temporary abstinence was positively associated with past year quit attempts [141, 142]. Thus, the existing indirect evidence suggests that use of NRT during periods of temporary abstinence could, at worst have no effect, or at best promote cessation. There is strong need for controlled trials to directly test downstream effects of NRT during periods of temporary abstinence.

5.3 Cessation Induction & NRT Sampling

A central tenet of cessation treatment studies is that smokers desire to quit, and participate in such trials in an effort to do so. While most smokers do express interest in quitting, most lack immediate plans to do so. For example, almost 70% of smokers want to quit, but in 2010 only 52% made a quit attempt [5]. In fact, over the last decade, the incidence of quit attempts has held steady at about 40% [143]. National data also suggest that fewer than 10% of smokers desire to quit in the next month [144]. Thus, pharmacotherapies, as currently

indicated, reach a fairly limited proportion of smokers, leading many to consider expansion of NRT use to smokers who lack firm or immediate intentions to quit.

The most common approach in which NRT is given to smokers who do not want to quit in the next month (hereafter called unmotivated smokers) is through smoking reduction, not to be confused with studies of abrupt vs. gradual cessation for smokers who do want quit soon [145, 146]. Studies of smoking reduction typically recruit smokers not ready to quit within the next month and randomize them to either NRT-assisted reduction vs. placebo-assisted reduction [147–151], or to NRT-assisted reduction vs. other treatment [15, 152–155]. The former tests whether NRT can help smokers reduce, and the latter tests reduction itself. Both types of studies report reduction and cessation outcomes. A number of literature reviews [17, 156–160] and meta-analyses [161, 162] have examined this issue in great detail, and have concluded that NRT-assisted reduction often promotes eventual quitting among smokers not ready to quit Given this literature base, and given the number of associated trials, further discussion of smoking reduction studies is beyond the scope of this review.

A more recent advance has been to examine provision of NRT to unmotivated smokers in the absence of any structured intervention. The rationale is that giving NRT to smokers who are not yet ready to quit will familiarize them with cessation medication, enhance motivation and confidence, and promote quit attempts and cessation. In a cross-sectional survey of smokers who were asked what would motivate them to quit, the offer of free NRT was cited as the most common catalyst [16]. Other studies have shown brief exposure to NRT (i.e., NRT sampling) can shift attitudes towards and subjective experiences with NRT [84, 163]. In one uncontrolled study, smokers across the motivational spectrum were provided with six weeks of nicotine patch, without any further intervention [164]. Among contemplators at baseline (i.e., smokers wanting to quit, but not in next 30 days), 31% were abstinent at six month follow-up, as compared to 35% of those in preparation (i.e., smokers wanting to quit in next 30 days). This indirectly suggests that provision of NRT to unmotivated smokers yields outcomes that are not all dissimilar to outcomes of motivated smokers.

Our group recently completed a randomized trial of NRT sampling vs. not among smokers unmotivated to quit [14]. Smokers (N=849) were recruited nationally through online channels, and were randomized to receive samples of nicotine lozenges or not. To facilitate the sampling experience, participants in both groups were asked to engage in a series of practice quit attempts,‘ meant to ease the smoker towards quitting. Sampling NRT led to increases in motivation and confidence, as well as increases in favorable opinions, and decreases in unfavorable opinions of NRT. More importantly, NRT sampling led to a higher rate of quit attempts, and marginally higher rates of abstinence. If replicated, these results suggest that provision of NRT to smokers not immediately ready to stop serves as a catalyst towards cessation.

6. Emergent NRT Delivery Systems

Currently approved formulations of NRT deliver nicotine slowly compared to cigarettes, which may explain their modest efficacy for smoking cessation. A number of novel delivery systems that increase the speed or magnitude of nicotine delivery have been introduced in recent years, all with the general purpose to better manage craving. These include a nicotine —cannon [165], nicotine inhalator [166], nicotine pouch [167], and rapid delivery gum [168], all of which have been shown via human lab studies to control withdrawal and/or offer user satisfaction, often to greater extent than existing NRTs. One new system that has reached the point of clinical trial testing is an oral nicotine spray. Two cross-over studies suggest this new device is at least as effective in controlling craving as current products [169, 170]. In one placebo controlled trial [171], abstinence outcomes significantly favored

oral spray both at short term (16% vs. 7%) and one year (14% vs. 6%) follow-up. Within another trial based on head to head comparisons [172], there were roughly comparable rates of abstinence at six months for oral spray (16%), gum (20%) and inhaler (8%). One year outcomes slightly favored the oral spray (12% vs. 8% vs. 4%).

One concern of any nicotine delivery product is the potential for long term abuse liability. In an effort to decrease withdrawal and craving through more efficient delivery systems, manufacturers may seek to increase either/both the magnitude and speed of nicotine administration. This increases potential for maintaining nicotine dependence and perhaps even inducing dependence in non-smokers. If and when new products come to market, continued surveillance will be necessary to protect against such unwanted effects, though history of existing products shows that few smokers will become dependent on nicotine replacement products [102, 173]. Even so, long term use of nicotine replacement systems offers significantly reduced health risks than does a chronic history of cigarette smoking.

7. Summary & Conclusions

Studies reviewed herein, conducted within and outside the US, share the common rationale to challenge current formulations or indications of NRT delivery. Summaries within each topic area are presented above. Across all topics discussed, we now attempt to identify those strategies that:

- **A.** have strong support and are ready for clinical application now: combination NRT, and (though not reviewed here, see above) NRT-assisted smoking reduction
- **B.** have conflicting data but deserve further testing: pre-quit NRT
- **C.** have potential utility but need further study: tailoring treatment to genotype or phenotype, use of NRT for non-cessation purposes such as temporary abstinence, sampling during practice quit attempts and relapse prevention, or
- **D.** do not offer promise and do not warrant further investigation: non-tailored higher dose NRT and extended duration NRT

Summary of findings and categorization of strategies will raise some debate, which we encourage. Some topic areas that showed generally poor (e.g., extended duration NRT) or inconsistent results (e.g., relapse prevention) were based on a limited number of studies (e.g., extended duration NRT) and thus it may be premature to abandon further study. Outcomes from pre-quit NRT studies were quite variable, a likely function of the broad range of methodology. Across all the treatment approaches we reviewed, the effect sizes are rather modest. However, we caution against an overly pessimistic interpretation of these effects for two reasons. First, comparisons in almost all studies reviewed were of active vs. active treatment, creating a challenge to show superior efficacy over and above an already proven treatment. This should not be construed as offering limited population impact, however, since even small increments in successful quitting, when widely used, could significantly increase rates of cessation. Second, the vast majority of treatment variations summarized above offered increased short term, if not long term efficacy. This is not unlike any other treatment, whether pharmacologic or behavioral. This underscores what the public health community has known for a long time- that treatment of tobacco dependence as a chronic medical condition often requires intensive, recurrent intervention.

What is clear from this review is that in order to further decrease smoking prevalence, new and creative strategies to deliver and enhance the use of evidence-based treatments for smoking cessation are needed. Strategies may be based on, but need not be limited to, those described in this review. One obvious path forward is to combine some of the strategies described herein; e.g., providing combination treatment tailored to specific smokers, or

allowing smokers to sample products during periods of trial abstinence. Only through innovative clinical strategies will we move beyond what appears to be a glass ceiling in NRT efficacy.

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Table I

Pre-Quit NRT: Summary Results from Randomized Clinical Trials of at Least Six Months

Study [citation #]	Pre-Quit Duration (weeks)	Pre-Quit Group	Pre-Quit Control Group	Post-Quit Treatment (duration)	Total N	Relative Risk (6 Months)
Bullen 2010 [48]	2	Gum and/or Patch	--	Gum and/or patch (8 wks.)	1100	1.1
Schuurmans 2004 [49]	2	Patch	Placebo Patch	Patch (12 wks.)	200	1.8
Rose 2006 [50]	2	Patch[1]	Placebo Patch[1]	Patch[2] (6 wks.) + Mecamylamine (4 wks.)	96	1.7
Rose 2009 [51]	2	Patch + Usual Brand Cigarettes	Placebo Patch + Usual Brand	Patch (9 wks.)	200	1.5
Rose 2009 [51]	2	Patch + LTN Cigarettes	Cigarettes Placebo Patch + LTN Cigarettes	Patch (9 wks.)	200	3.1
Rezaishiraz 2007 [52]	2	Patch + Denic Cigarettes	Switch to Light Cigs	Patch (8 wks.)	98	1.3
Rose 1998 [53]	4	Patch + Mecamylamine	Mecamylamine	Patch + Mecamylamine (6 wks.)	40	2.7
Rose 1998 [53]	4	Patch	--	Patch + Mecamylamine (6 wks.)	40	1.3
Etter 2009 [54]	4	Gum	--	Gum (8 wks.)	314	1.1[3]

[1]Both pre-quit patch and placebo groups were randomized into subgroups of usual brand smoking vs. low tar/nicotine vs. denicotinized cigarette use; 6-month abstinence outcomes not reported separately for these sub-groups

[2]Post-quit treatment randomized into subgroups of 0 vs. 21mg vs. 42mg patch; abstinence outcomes not reported separately for these sub-groups

[3]Outcomes reported at one year

Table II

Extended Treatment NRT: Summary Results from Randomized Clinical Trials of at Least Six Months

Study [citation #]	NRT	Extended Treatment (weeks)	Control Treatment (weeks)	Total N	Relative Risk	
					Six Months	Longest Follow-Up
Schnoll 2010 [64]	Patch	24 wks.	8 wks.	568	1.6	1.0 (1year)
Tonnesen 1999 [65]	Patch	26 wks.[1] 26 wks.[2]	12 wks.[1] 12 wks.[2]	1430[1] 1431[2]	0.9[1] 1.2[2]	1.0[1] 1.2[2](1 year)
Hall [66] 2009	Gum	52 wks.[3] 52 wks.[4]	12 wks.[3] 12 wks.[4]	199[3] 203[4]	1.1[3] 1.0[4]	1.1[3] 0.8[4](2 years)
Joseph 2011 [67]	Patch, Gum, and/or Lozenge[5]	52 wks.	8 wks.	443	0.9	1.3 (18 months)

[1]Treatment based on 25mg patch; parent study included placebo group (not included here)

[2]Treatment based on 15mg patch; parent study included placebo group (not included here)

[3]Comparison during extended treatment period: gum vs. no gum

[4]Comparison during extended treatment period: gum + counseling vs. counseling

[5]Including combination NRT; outcomes not reported by single vs. combination NRT

Table III

High Dose NRT: Summary Results from Randomized Clinical Trials of at Least Six Months

Study [citation #]	High Dose NRT	Control[1]	Total N[2]	Minimum Smoking Level (cpd) of Sample[3]	Relative Risk	
					Six Months[4]	Longest Follow-Up
Dale 1995 [72]	44mg patch	11mg patch, 22mg patch	53	10	1.3 (44 vs. 11) 1.4 (44 vs. 22)	21.6 (44 vs. 11) 1.9 (44 vs. 22) (1 year)
Jorenby 1995 [73]	44mg patch	22mg patch	504	15	0.9	6 months (see left)
Kalman 2006 [74]	42mg patch	21 mg patch	130	20	0.5	0.5 (9 months)
Hughes 1999 [75]	42mg patch 35mg patch	21mg patch	see below[5]	30	1.3 (42 vs. 21) 1.0 (35 vs. .21) 1.3 (42 vs. 35)	1.5 (42 vs. 21) 0.7(35 vs. 21) 2.1 (42 vs. 35) (1 year)
Tonnesen 1999 [65]	25mg patch[6] 25mg patch[7]	15 mg patch[6] 15mg patch[7]	1431[6] 1430[7]	15	1.4[6] 1.1[7]	1.4[6] 1.1[7](1 year)
Killen 1999 [76]	25mg patch	15mg patch	408	26	1.1	1.0 (1 year)

[1] Other (usually placebo) comparison groups may have been included; only standard course NRT comparison group(s) included here [2] total sample size across groups of comparison (study may have included other groups, with larger N)

[3] Based on eligibility criterion

[4] most common follow-up point across all studies listed

[5] Study was based on N=1039, with inclusion of 4th group (placebo control). Sample size per group, across 3 groups included above, was unstated

[6] Treatment provided for 12 weeks

[7] Treatment provided for 26 weeks

Table IV

Combined NRT: Summary Results from Randomized Clinical Trials of at Least Six Months

Study [citation #]	Combination NRT	Control[1]	Total N[2]	Treatment Duration	Relative Risk	
					Six Months[3]	Longest Follow-Up
Piper [89] 2009	Patch + Lozenge	Patch, Lozenge	789	8 weeks (patch); 12 weeks (lozenge)	1.2 (vs. patch) 1.2 (vs. lozenge)	6 months (see left)
Smith [90] 2009	Patch + Lozenge	Patch, Lozenge	822	8 weeks (patch); 12 weeks (lozenge)	1.5 (vs. patch) 1.4 (vs. lozenge)	6 months (see left)
Puska 1995 [92]	Gum + patch	Gum + placebo patch	300	18 weeks (patch); 12 months (gum)	1.3	1.4 (52 weeks)
Kornitzer 1995 [93]	Patch + gum	Patch + placebo gum	299	24 weeks	1.8	1.4 (52 weeks)
Cooney 2009 [94]	Patch + gum	Patch + placebo gum	96	12 weeks (patch); 24 weeks (gum)	1.7	see below[4]
Blondal 1999 [95]	Patch + spray	Patch + placebo spray	239	5 months (patch); 1yr (spray)	2.0	1.9 (6 yrs.)
Croghan 2003 [96]	Patch + spray	Patch, Spray	1384	6 weeks	1.2 (vs. patch); 1.3 (vs. spray)	6 months (see left)
Bohadana 2000 [97]	Inhaler + Patch	Inhaler + placebo patch	400	26 weeks (inhaler); 6 weeks (patch)	1.1	1.4 (52 weeks)
Tonnesen 2000 [98]	Inhaler + Patch	Inhaler, Patch	Patch	Up to 9 months	0.6 (vs. patch); 1.5 (vs. inhaler)	0.4 (vs. patch); 0.7 (vs. inhaler) (12 months)

[1] Other comparison groups may have been included; only monotherapy NRT group(s) included here

[2] Total sample size across groups of comparison (study may have included other groups, with larger N)

[3] Most common follow-up across all studies listed

[4] Abstinence rates were 13% (combination) vs. 0% (patch alone). Unable to calculate relative risk based on 0% abstinence rate in control condition

Table V

Hypothetical Studies of Smoker Subgroups; e.g.., Geno/Phenotypes (% denotes abstinence rates)

Hypothetical Study 1				
	Treatment A	**Treatment B**	**RR (95% CI)**	**p for interaction[1]**
Subgroup 1	10%	40%	0.25 (.13 - .47)	.0004
Subgroup 2	40%	42%	0.95 (.68–1.33)	
Hypothetical Study 2				
Subgroup 1	25%	40%	0.63 (.41 - .95)	.7
Subgroup 2	30%	42%	0.74 (0.49–1.04)	

[1] Subgroup x treatment interaction

Table VI

NRT for Relapse Prevention: Summary Results from Randomized Clinical Trials of at Least Six Months

Study [citation #]	Initial Abstinence Period	Prevention Medication Prevention Medication	Prevention Medication	Total N	Duration Relapse Prevention Treatment	Relative Risk	
						Six Months	One Year
Medication Assisted Initial Cessation							
Covey 2007 [122]	4 weeks[1]	Gum + Bupropion	Placebo Gum+ Bupropion	146	16 weeks	0.8	0.9
Covey 2007 [122]	4 weeks[1]	Gum	Placebo Gum	143	16 weeks	1.3	1.4
Croghan 2007 [123]	7 days[2]	Inhaler + Bupropion	Placebo Inhaler + Bupropion	96	9 months	1.2	1.1
Croghan 2007 [123]	7 days[2]	Inhaler	Placebo Inhaler	94	9 months	1.0	1.1
Croghan 2007 [123]	7 days[3]	Inhaler	Placebo Inhaler	74	9 months	1.6	1.5
Unaided Initial Cessation							
Killen [125] 1990	48hrs	Gum[4]	No Gum[5]	1218	3 months	1.2	1.2
Fortmann 1995 [124]	24hrs	Gum + Self Help Materials	Self Help Materials	521	unstated	1.6	1.3
Fortmann 1995 [124]	24hrs	Gum	No gum	523	unstated	1.3	1.3

[1] Initial cessation facilitated by 8 weeks open label treatment of gum + bupropion + counseling

[2] Initial cessation facilitated by 3 months open label treatment of inhaler + bupropion

[3] Initial cessation facilitated by 3 months open label treatment of inhaler

[4] Collapsed groups of instructional (n=301) and ad libitum gum (n=299) groups

[5] Collapsed groups of placebo (n=309) and no gum (n=309) groups