Meta-Analysis of the Efficacy of Nicotine Replacement Therapy for Smoking Cessation: Differences Between Men and Women

Antonio Cepeda-Benito, Jose T. Reynoso, and Stephen Erath
Texas A&M University

Gender differences in the efficacy of nicotine replacement therapies (NRTs) were examined in a meta-analytical review of 90 effect sizes obtained from a sample of 21 double-blind, placebo-controlled randomized studies. Although NRT was more effective for men than placebo at 3-month, 6-month, and 12-month follow-ups, the benefits of NRT for women were clearly evident only at the 3- and 6-month follow-ups. Giving NRT in conjunction with high-intensity nonpharmacological support was more important for women than men. That is, NRT and low support were efficacious for women at only short-term follow-up, and men benefited from NRT at all the follow-ups regardless of the intensity of the adjunct support. The results suggest that long-term maintenance of NRT treatment gains decrease more rapidly for women than men.

In spite of the known health risks associated with cigarette smoking, nearly a quarter of the U.S. population continues to smoke (Centers for Disease Control and Prevention [CDC], 1998). Some data indicate that the reduction in smoking prevalence rates seen between 1965 and 1998 has halted and that smoking may be on the increase, particularly in adolescents and young adults (CDC, 1998; Rigotti, Lee, & Wechsler, 2000; Wechsler, Rigotti, Gledhill-Hoyt, & Lee, 1998). Each year, nearly half a million Americans succumb prematurely because of their dependence on tobacco, and it is projected that one third of all smokers will die from illnesses and diseases attributed to cigarette smoking (CDC, 1998; Fiore et al., 2000).

Women started smoking in greater numbers later than men, thus, the long-term health problems associated with cigarette use in women became clearly evident later in women than men (U.S. Department of Health and Human Services, 2001). Since 1980, 3 million women have died prematurely because of smoking, and on average these women died 14 years prematurely. In 2000, an estimated 27,000 more women died of lung cancer than of breast cancer—a fact not commonly reported.

There is little doubt that most smokers are interested in quitting cigarettes. For example, epidemiological data indicate that over 70% of the 50 million smokers in the United States have made at least one quit attempt, and nearly half (46%) attempt to quit each year (CDC, 1997). For women smokers, the interest in and attempts to quit smoking are similar to those of the general population of smokers. Data from the 1995 National Health Interview Survey (as cited in U.S. Department of Health and Human Services, 2001) indicated that approximately 75% of women daily smokers were interested in quitting, and of these nearly 47% attempted to quit during the previous year. Unfortunately, abstaining from cigarettes has proven difficult. For example, of the 17 million adult smokers who attempted to quit in 1991, only 7% were still abstinent 1 year later (CDC, 1993).

It is notable that most smokers are not offered effective (if any) assistance during smoking cessation attempts (Fiore et al., 2000). For example, in a study of national patterns of treatment, smoking status was identified in approximately 67% of clinic visits, but smoking cessation assistance was offered to only 21% of those smokers (Thorndike, Rigotti, Stafford, & Singer, 1998). Another population-based survey found that fewer than 15% of smokers who visited a physician were offered smoking cessation assistance, and only 3% were scheduled for follow-up appointments to monitor their tobacco use (Goldstein et al., 1997). This lack of assistance in quitting cigarette smoking is particularly problematic for women, as research indicates that physicians are less likely to ascertain women's smoking status and to advise women to quit smoking (Rogers, Johnson, Young, & Graney, 1997; Young & Ward, 1998), and women seem to have more difficulties in quitting cigarette smoking than men (Fiore et al., 2000).

Nicotine Replacement Therapy (NRT): Purpose and Efficacy

NRT was introduced over 20 years ago and is the most commonly used pharmacotherapy treatment for smoking cessation (Burton, Gitchell, & Shiffman, 2000). NRT was designed to replace blood nicotine and thus alleviate physiological withdrawal symptoms (e.g., depressed mood, irritability, anxiety, headaches, changes in appetite) and cigarette (i.e., nicotine) cravings experienced by most smokers after quitting cigarettes (Fiore, Jorenby, Baker, & Kenford, 1992; Henningfield, 1995; Hughes & Hatsukami, 1986). Treatment regimens typically range from 1–3

months for most NRT products (Okuyemi, Ahluwalia, & Harris, 2000). Moreover, NRT is safer than cigarette smoking because it does not contain carcinogens and the many other toxic chemicals found in cigarette smoke, and there is a low risk of addiction to and withdrawal from NRT (Benowitz, 1998; West et al., 2000).

The various forms of NRTs have proven effective for smoking cessation, particularly when coupled with psychoeducational counseling. Several meta-analyses of methodologically sound studies have demonstrated that, in comparison with placebo, NRT helps smokers quit cigarettes. Using 33 studies, Cepeda-Benito (1993) evaluated the effectiveness of nicotine chewing gum versus placebo and versus no-gum treatment controls. Cepeda-Benito differentiated between smoking cessation trials that prescribed the gum as an adjunct to an intensive smoking cessation program ($\geq$3 hr of client–provider contact) and treatments that prescribed the gum as an adjunct to a brief intervention (e.g., physician advice during routine medical visits). The results indicated that nicotine gum was superior to placebo and no-gum control at short-term follow-up ($\leq$8 weeks) within both intensive and brief intervention programs. However, at long-term follow-up ($\geq$9 months), NRT was effective only when given as an adjunct of intensive interventions.

Cepeda-Benito (1993) concluded that the positive effects of nicotine gum for smoking treatment were a function of an interaction between the gum's pharmacological properties and the effectiveness of intensive psychoeducational–behavioral treatment therapies. Cepeda-Benito suggested that nicotine gum's ability to temper nicotine withdrawal might allow the smoker to focus on and benefit from the psychological or nonpharmacological components of smoking cessation treatments. That is, in the absence of behaviorally effective treatments, the initial efficacy of NRT was lost over time.

Fiore, Smith, Jorenby, and Baker (1994) examined the overall efficacy of the nicotine patch compared with placebo for treating tobacco dependence. Seventeen double-blind, placebo-controlled nicotine patch studies were included in their meta-analysis. The overall abstinence rates were significantly greater for the active patch compared with placebo at the end of treatment and at 6 months. The results also indicated that the active patch was superior to placebo regardless of patch type (16-hr vs. 24-hr), active treatment duration, weaning (dose reduction during treatment period), and counseling format or intensity. The authors concluded that the nicotine patch is an effective smoking cessation aid and that it has the potential to improve public health significantly. These findings confirmed those of an earlier meta-analysis ($N = 11$ studies), which found that smokers with the active patch were over 3 times more likely to be abstinent at short term (i.e., 3–10 weeks) and more than twice as likely to remain abstinent at long term (i.e., 24–52 weeks) than smokers treated with placebo patches (Po, 1993).

Silagy, Mant, Fowler, and Lodge (1994) conducted a meta-analysis on the efficacy of the four forms of NRT available at the time and included 53 trials: nicotine gum ($n = 42$), patch ($n = 9$), spray ($n = 1$), and inhaler ($n = 1$). Silagy et al. (1994) found that all forms of NRT were significantly more effective than placebo or no treatment. Smokers using an active form of NRT were over 1 1/2 times more likely to abstain from smoking throughout a 12-month period compared with smokers using placebo products. The patch, inhaler, and spray seemed to produce better results than the gum, but the differences were not statistically significant.

There was a trend for NRT to be more effective with highly dependent smokers, but neither intensity of additional support nor the setting in which NRT was offered appeared to add to its efficacy (Silagy et al., 1994). These findings were replicated in an update of this meta-analysis (Silagy, Lancaster, Stead, Mant, & Fowler, 2003), which included 110 trials and nearly 36,000 smokers.

A meta-analysis conducted for the *Treating Tobacco Use and Dependence: Clinical Practice Guideline* (Fiore et al., 2000) further confirmed that all forms of NRT are superior to placebo in increasing cessation rates. These authors also concluded that NRT has some treatment value over placebo among women and recommended its use, but they added that NRT might not be as effective for women as for men (Fiore et al., 2000). Their conclusion was tentative because, despite data from numerous clinical trials, they were unable to examine the differential efficacy of NRT (or any other treatment for that matter) with respect to gender. Thus, these authors called for further research to investigate comparative treatment outcomes for men and women (Fiore et al., 2000).

Do Men Benefit More Than Women From NRT?

Researchers have proposed that nicotine intake from cigarette smoking may be more reinforcing for men than women (Perkins, 1996, 2001; Perkins, Donny, & Caggiula, 1999). This hypothesis was based, in part, on the results of a few studies that reported that more men than women quit smoking after using NRT (Perkins, 1996). Perkins further noted that whereas men smoke mostly to experience the direct psychoactive effects of nicotine, women seek other types of reinforcement from smoking. That is, in comparison with men, women (a) are more craving reactive to smoking-related cues; (b) enjoy more the olfactory–taste and hand-to-mouth sensations associated with smoking; and (c) have greater expectations that smoking will enhance or facilitate social interactions, reduce negative mood, and prevent weight gain (e.g., Cepeda-Benito & Reig-Ferrer, 2000; Perkins, 1996, 2001; Perkins et al., 1999).

However, Perkins (1996) acknowledged that very few authors reported treatment outcome comparisons between men and women, and that the conclusion that NRT is more effective in men than women was made after reviewing a limited number of studies. That is, the conclusion that women do not benefit from NRT as much as men could have been a consequence of reporting bias, which occurs when authors do not report results that do not show statistical significance (Hedges, 1990). Moreover, the finding that NRT produces greater smoking cessation rates in men than women could simply reflect that, independent of the influence of nicotine's effects in maintaining smoking, women have poorer treatment outcomes across any, if not most, smoking cessation intervention (Fiore et al., 2000; Perkins, 2001). To establish that NRT is more effective in men than women, researchers need to compare the extent to which NRT enhances abstinence rates over placebo-controlled groups in men versus women rather than to compare abstinence rates in men versus women just in the NRT group.

Another important issue is that NRT was developed primarily to alleviate the symptoms of nicotine withdrawal, which peak within the first 2 weeks of abstinence. Accordingly, NRT is not typically recommended for use beyond 3 months. Thus, if treatment outcome effects are to be used to make inferences regarding the differential motivational value that nicotine's effects have in main-

taining cigarette smoking in men and women, NRT outcome effects should be evaluated at short term (i.e., ≤3 months). That is, treatment outcome differences between men and women at long-term follow-up could be influenced by factors other than the effectiveness of NRT to replace the nicotine effects of cigarette smoking.

Finally, researchers have found that withdrawal symptoms are at least as severe in women as in men, and that withdrawal from nicotine may play a larger role in smoking relapse in women than men (Gunn, 1986; Hatsukami, Skoog, Allen, & Bliss, 1995). For example, nicotine withdrawal symptoms include dysphoric or depressed mood and anxiety, and quitting cigarettes is associated with weight gain, all of which are more detrimental to smoking cessation outcomes in women than men (e.g., Hatsukami et al., 1995; Gritz, Nielsen, & Brooks, 1996; Gunn, 1986). Thus, given that NRT effectively reduces withdrawal symptoms in women, particularly at higher NRT doses (e.g., Allen, Hatsukami, Christianson, & Brown, 2000; Hatsukami et al., 1995), it seems counterintuitive to expect that women will not benefit from using NRT or that women will benefit less than men.

We do not disagree with the idea that smoking behavior of women may be determined by factors other than nicotine to a greater extent than the smoking of men (see Cepeda-Benito, Reynoso, & Susabda, 2003; Perkins, 2001). We also concede that it is possible that nicotine's effects (physiological and/or subjective reactivity to nicotine from cigarette smoking) may play a larger role in motivating smoking in men than women; nonetheless, the above arguments should not necessarily lead to the conclusion that nicotine's psychoactive effects are irrelevant for women's smoking. For example, congruent with the notion that smoking fulfills more functions for women than men, Antonio Cepeda-Benito and Reig-Ferrer (2000) found that female smokers had greater expectancies that smoking would control body weight and would reduce nicotine cravings and negative affect. However, these authors also found that men and women had similar expectations with regards to the positively reinforcing effects of cigarette smoking. That is, these authors found that the expectancy that smoking would be mentally stimulating was not different between men and women.

Focus of the Investigation

The present study is a meta-analysis of double-blind, randomized, placebo-controlled studies investigating the efficacy of NRT in samples of smokers that include men and women. To reduce reporting bias confounds, we contacted the authors of studies that met inclusion criteria but did not examine gender effects. Women's and men's effect sizes were compared at short-, mid-, and long-term follow-up periods across high- and low-intensity smoking cessation programs. We also examined the extent to which reporting bias may have contributed to the current perception that women benefit less than men from NRT. That is, within each gender and at each follow-up period, we compared effects sizes between studies that reported and did not report treatment outcomes for men and women separately.

We propose that gender differential effects of NRT convey some important implications for smoking cessation and relapse-prevention treatment in men and women. For example, if nicotine's psychoactive effects play a greater role in motivating smoking in men than women, then the gains of NRT over placebo might

be greater in men than women at short-term follow-up. Nonetheless, regardless of the presence or absence of differential gender effects in NRT efficacy, NRT may still prove efficacious both in men and women at short-term follow-up. This pattern would suggest that although nicotine's effects pose a bigger obstacle to quitting for men than for women, deprivation from nicotine's effects should nonetheless impede smoking cessation efforts in both genders. Although we did not venture to hypothesize whether NRT would be more effective for men or women at short-term follow-up, we anticipated that NRT would be more effective than placebo treatment for both men and women.

Furthermore, we predicted that the abstinence-rate efficacy of NRT at short term would significantly decline at long-term follow-up. Moreover, if NRT given in conjunction with intense support contributes to long-term abstinence because NRT effects enhance the efficacy of the nonpharmacological components of the treatment (e.g., Cepeda-Benito, 1993), we anticipated that NRT efficacy at long-term follow-up would be greater when given in conjunction with intensive rather than brief treatment programs (cf. Silagy et al., 1994, 2003).

Method

Sample

Computer-based information searches were conducted combining the key words *smoking cessation, tobacco or nicotine or smoking, nicotine,* and *nicotine replacement therapy.* The following databases were used to find smoking cessation treatment outcome studies: Psychological Abstracts International, Dissertation Abstracts International, Social Science Citation Index, and MEDLINE. Studies were also sought through examination of the Cochrane Review and previous meta-analyses (Cepeda-Benito, 1993; Fiore, Smith, et al., 1994; Po, 1993; Silagy et al., 2003). The studies included in the sample had to (a) report treatment outcome results, (b) validate smoking status through biochemical tests or collateral reports, (c) assign subjects randomly to experimental and control groups, (d) use a double-blind, placebo-controlled design, and (f) include men and women in both the NRT and placebo groups.

We found 83 articles that met the inclusion criteria. Of these, 7 studies reported abstinence rates for men and women for both NRT and placebo-controlled groups separately. Thus, we made repeated requests to obtain abstinence rates for men and women separately from the corresponding authors and obtained unpublished data for only 14 of the remaining 76 studies. The most common reason given for not receiving the information was that the data were either difficult to retrieve or not in the format requested (broken down by gender). Two authors told us that rules and regulations from their institutions prohibited them from sharing the data, and one other author could not send the data in the format requested unless we paid for the additional statistical analyses ($1,300). Many requests were not answered (either because the request never reached the authors or because the requests were ignored). The studies included in the meta-analysis are identified with an asterisk in the References section.

Variables Coded From Each Study

The following information was coded from each report: (a) date of publication, (b) definition of abstinence (continuous or point-prevalence), and (c) whether quit rates were reported separately for men and women in the original published article or whether this information was obtained upon request from the author. Within each treatment group, the following characteristics were coded: (a) abstinence rates for women and men, (b) length and intensity of treatment (low vs. high), (c) type of group (NRT, placebo), and (d) type of NRT treatment (gum, patch, and spray–inhaler–

tablet). The definition for low- and high-intensity therapy was that used in the Cochrane Review: Nicotine Replacement Therapy for Smoking Cessation (Silagy et al., 2003). Low-intensity additional support–therapy was defined as part of the provision of routine care. High-intensity additional support–therapy was defined as any additional support–therapy (including assessment) that exceeded 30 min at the initial consultation, or if two or more additional assessment or reinforcement sessions were required.

Two independent judges coded the studies according to the previously specified criteria and calculated the effect sizes. Notwithstanding data entry errors, there was complete agreement between the judges.

Computation and Analysis

The computation of the effect sizes was done with the aid of Biostat Comprehensive Meta-Analysis, a software program for the meta-analytic review of research literature (Borenstein & Rothstein, 1999). The effect size was the odds ratio (OR): the probability of quitting with the NRT treatment versus the probability of quitting with placebo treatment (e.g., Rosenthal, 1995). Values above 1.00 indicated that participants in the NRT group had a better chance of being abstinent at follow-up than participants in the placebo group. For each study, a maximum of six effect sizes were computed: short-term ($\leq$3 months), midterm (6 months), and long-term ($\geq$12 months) follow-ups for men and women separately. To test the null hypothesis of no added benefit of NRT over placebo, we transformed ORs to Z values by dividing the logOR by its standard error (SE logOR). Effect sizes were examined across four computational options (fixed and random for inverse variance, Mantel-Haenszel, and Peto) and the results were consistent across all estimates, suggesting that effect is resilient to computational options (Borenstein & Rothstein, 1999). The results reported herein are based on the fixed-effects model (Peto method; Yusuf, Peto, Lewis, Collins, & Sleight, 1985). This method was used by Silagy et al. (2003) and was chosen to facilitate comparisons across the two studies.

ORs were weighted by their sample size. Individual OR estimates were combined to obtain a pooled OR within each categorical classification. Categorical models are analogous to analyses of variance and were used to compare the effect sizes of men versus women (a) at each follow-up and (b) at each follow-up within intensive and brief interventions. At each follow-up and within each gender, we also compared effect sizes between studies reporting abstinence rates separately for men and women and studies for which these data were obtained upon request from the studies' corresponding authors. The calculation of effect sizes for each categorical model allows for calculating a between-classes effect. The between-classes effect is given by the $Q_{(B)}$ statistic, which has an approximate chi-square distribution with $p - 1$ degree of freedom for post hoc tests and 1 degree of freedom for a priori tests, in which p is the number of classes. In addition, effect sizes within each category were tested for homogeneity using the $Q_{(wi)}$ statistic, which in this case has an approximate chi-square distribution with $m - 1$ degree of freedom, in which m is the number of effect sizes in the class i.

Differences between each class cannot be interpreted as confidently if homogeneity within classes is not achieved. Thus, in cases of heterogeneity, outliers were identified and sequentially removed. This procedure may show that by removing one or a few aberrant effect sizes, homogeneity within a class can be achieved (see Hedges, 1990; Kite & Johnson, 1988). Inspection of the study's characteristics of the removed effect sizes may change the meta-analysis's categorization; this occurs if the outliers vary in a systematic way from the rest of the studies in their class. Conversely, it may be determined that the mean effect size obtained after the removal of extreme values is more representative of the population of studies of their class, or that outliers do not affect the overall pattern of results. That is, outliers would not constitute a new class.

Results

NRT Efficacy at Each Follow-Up

With the exception of women at long-term follow-up (OR = 1.24, 95% confidence interval [CI] = 0.99–1.56), NRT was nearly twice as effective as placebo (for all effect sizes combined across follow-ups and genders, OR = 1.90, 95% CI = 1.75–2.06; see Tables 1, 2, and 3). That is, the efficacy of NRT was statistically significant for both men and women at both short- and midterm follow-ups, and also for men at long-term follow-up. Gender comparisons at each follow-up period did not yield statistically significant results at short- and midterm follow-ups but confirmed that NRT was more efficacious for men than women at long-term follow-up, $Q_B(1) = 4.24$, $p < .04$ (see Table 3).

To examine the extent to which the efficacy of NRT deteriorated over time, we compared effect sizes at short-term versus midterm, short-term versus long-term, and midterm versus long-term follow-ups for men and women separately. The results suggest that women had greater difficulties maintaining short-term gains. That is, whereas effect sizes declined over time for both men and women, the decline was statistically significant only for women from short- to long-term follow-up, $Q_B(1) = 13.50$, $p < .01$, and from mid- to long-term follow-up, $Q_B(1) = 5.52$, $p < .02$ (see Table 4).

The ORs for women at the short-term follow-up were heterogeneous, $Q_W(15) = 26.34$, $p < .04$. Heterogeneity within this group was due to a single outlier. When this study was removed from the analysis homogeneity was achieved. However, because the patterns of results did not change with or without this study, this effect size was kept for completeness sake.

The finding that NRT was efficacious at short- and midterm follow-ups in both genders suggests that NRT increases smoking quitting rates in both men and women. However, the finding that the benefits of NRT dissipate significantly over time in women but not men, to the point that at long-term follow-up NRT does not statistically improve smoking cessation rates over placebo in women, is congruent with the hypothesis that women benefit less than men from NRT.

NRT Across High- and Low-Intensity Adjunct Support

At short-term follow-up, NRT was significantly better than placebo regardless of level of intensity of adjunct therapy for both men and women (combined OR = 2.19, 95% CI = 1.92–2.49). At midterm follow-up, NRT continued to be more effective than placebo for men within both the low-intensity (OR = 2.28, 95% CI = 1.45–3.60) and high-intensity (OR = 2.13, 95% CI = 1.74–2.60) categories. Conversely, in women the efficacy of NRT at midterm follow-up was apparent within the high-intensity (OR = 1.90, 95% CI = 1.58–2.30) but not the low-intensity category (OR = 1.03, 95% CI = 0.62–1.68). Long-term abstinence rates in the NRT groups were significantly higher than those found for the placebo groups for men only (high-intensity category OR = 1.71, 95% CI = 1.34–2.12; low-intensity category OR = 2.11, 95% CI = 1.06–4.18). Thus, the results supported the notion that the prescription of NRT without a comprehensive treatment program yields poorer results at long-term follow-up for women only. This was evident in women as early as the 6-month

Table 1
Odds Ratios and 95% CI for Women From All the Studies Used in the Meta-Analysis

Source of OR	NRT		Placebo	
	Code	Event/N	Event/N	OR (95% CI)
Women short-term follow-up				
Data reported in publication				
Tonnesen et al. (1993)	I/L	30/84	19/89	2.02 (1.04–3.91)
Killen et al. (1997) Tx only	P/L	17/49	11/54	2.05 (0.86–4.86)
Killen et al. (1997) Tx + video	P/L	15/50	12/47	1.25 (0.51–3.02)
Norregaard et al. (1993)	P/L	54/105	12/102	6.16 (3.44–11.03)
Sachs et al. (1993)	P/H	30/67	13/63	2.95 (1.42–6.11)
Data not reported in publication				
Hall et al. (1996)	G/H	18/50	21/55	0.91 (0.41–2.01)
Bolliger et al. (2000)	I/H	9/114	3/96	2.41 (0.75–7.75)
Abelin, Ehrsam, et al. (1989)	P/L	5/12	3/18	3.44 (0.68–17.46)
Abelin, Buehler, et al. (1989)	P/L	16/42	11/37	1.44 (0.57–3.64)
Fiore et al. (1994)				
Study 1	P/H	12/25	7/24	2.18 (0.70–6.79)
Study 2	P/H	13/39	8/37	1.78 (0.66–4.84)
Hughes et al. (1999)	P/H	66/406	12/117	1.6 (0.90–2.85)
Paoletti et al. (1996)	P/L	7/86	3/32	0.85 (0.20–3.64)
Richmond et al. (1997)	P/H	29/79	11/80	3.36 (1.64–6.86)
Yudkin et al. (1996)	P/H	80/449	50/480	1.85 (1.28–2.68)
Hjalmarson et al. (1994)	S/H	36/72	17/70	2.98 (1.51–5.87)
Total (16)		437/1,729	213/1,401	2.16 (1.80–2.59)
Women mid-term follow-up				
Data reported in publication				
Killen et al. (1997) Tx only	P/L	11/51	12/54	0.96 (0.38–2.42)
Killen et al. (1997) Tx + video	P/L	7/50	6/47	1.11 (0.35–3.55)
Sachs et al. (1993)	P/H	21/67	9/63	2.59 (1.15–5.85)
Data not reported in publication				
Hall et al. (1996)	G/H	16/50	14/55	1.37 (0.59–3.19)
Bolliger et al. (2000)	I/H	9/114	6/96	1.28 (0.45–3.66)
Abelin, Ehrsam, et al. (1989)	P/L	1/12	3/18	0.5 (0.06–4.12)
Abelin, Buehler, et al. (1989)	P/L	9/42	6/37	1.4 (0.46–4.28)
Fiore et al. (1994)				
Study 1	P/H	5/25	2/24	3.08 (0.69–13.78)
Study 2	P/H	6/39	3/37	1.99 (0.50–7.93)
Gourlay et al. (1995)	P/H	15/182	4/180	3.34 (1.33–8.41)
Hughes et al. (1999)	P/H	22/348	6/100	1.06 (0.42–2.64)
Paoletti et al. (1996)	P/L	21/86	8/32	0.97 (0.38–2.48)
Richmond et al. (1997)	P/H	24/79	December–80	2.39 (1.14–5.02)
TNSG (1991)	P/H	33/147	21/162	1.93 (1.07–3.46)
Yudkin et al. (1996)	P/H	56/449	39/480	1.6 (1.05–2.45)
Hjalmarson et al. (1994)	S/H	23/72	November–70	2.42 (1.12–5.22)
Shiffman et al. (2002)	L/H	106/517	59/513	1.95 (1.40–2.72)
Total (17)		386/2,330	221/2,048	1.76 (1.48–2.1)
Women long-term follow-up				
Data reported in publication				
Campbell et al. (1991)	G/H	10/52	8/41	0.98 (0.35–2.75)
Hjalmarson (1984)	G/H	21/57	12/59	2.23 (1.00–4.99)
Killen et al. (1990) ad lib & fixed	G/H	58/320	32/146	0.78 (0.48–1.29)
Data not reported in publication				
Hall et al. (1996)	G/H	12/50	14/55	0.93 (0.33–2.24)
Bolliger et al. (2000)	I/H	9/114	8/96	0.94 (0.35–2.55)
Abelin, Ehrsam, et al. (1989)	P/L	1/12	1/18	1.54 (0.09–27.40)
Abelin, Buehler, et al. (1989)	P/L	7/42	4/37	1.62 (0.46–5.76)
Hughes et al. (1999)	P/H	11/251	2/66	1.41 (0.36–5.52)
Paoletti et al. (1996)	P/L	19/86	6/32	1.22 (0.45–3.28)
Richmond et al. (1997)	P/H	18/79	9/80	2.25 (0.99–5.15)
Yudkin et al. (1996)	P/H	45/449	38/480	1.3 (0.83–2.03)
Hjalmarson et al. (1994)	S/H	17/72	10/70	1.82 (0.79–4.21)
Total (12)		228/1,584	144/1,180	1.24 (0.99–1.56)

Note. CI = confidence interval; OR = odds ratio; NRT = nicotine replacement therapy; Event = the number of abstinent smokers in each group; N = number of smokers in each group; I = inhaler; L = low-intensity adjunct therapy; Tx = treatment; P = patch; H = high-intensity adjunct therapy; G = gum; S = spray; TNSG = Transdermal Nicotine Study Group.

Table 2
Odds Ratios and 95% CI for Men From All the Studies Used in the Meta-Analysis

Source of OR	NRT		Placebo	
	Code	Event/N	Event/N	OR (95% CI)
Men short-term follow-up				
Data reported in publication				
Tonnesen et al. (1993)	I/L	23/61	6/52	3.89 (1.68–9.05)
Killen et al. (1997) Tx only	P/L	24/52	8/48	3.82 (1.66–8.83)
Killen et al. (1997) Tx + video	P/L	18/56	11/54	1.82 (0.78–4.24)
Norregaard et al. (1993)	P/L	23/40	12/42	3.22 (1.35–7.68)
Sachs et al. (1993)	P/H	21/46	15/44	1.61 (0.70–3.73)
Data not reported in publication				
Hall et al. (1996)	G/H	16/48	18/48	0.84 (0.36–1.92)
Bolliger et al. (2000)	I/H	4/86	1/104	4.19 (0.71–24.84)
Abelin, Ehrsam, et al. (1989)	P/L	17/44	8/38	2.27 (0.89–5.79)
Abelin, Buehler, et al. (1989)	P/L	20/58	11/62	2.38 (1.05–5.37)
Fiore, et al. (1994)				
Study 1	P/H	14/19	10/19	2.41 (0.66–8.86)
Study 2	P/H	8/18	3/18	3.57 (0.88–14.46)
Hughes et al. (1999)	P/H	80/373	13/143	2.3 (1.4–3.8)
Paoletti et al. (1996)	P/L	27/151	28-Feb	2.2 (0.74–6.54)
Richmond et al. (1997)	P/H	26/73	Sep-73	3.56 (1.67–7.59)
Yudkin et al. (1996)	P/H	83/393	50/364	1.66 (1.14–2.42)
Hjalmarson et al. (1994)	S/H	30/53	16/53	2.9 (1.35–6.23)
Total (16)		434/1,571	193/1,190	2.21 (1.83–2.67)
Men mid-term follow-up				
Data reported in publication				
Killen et al. (1997) Tx only	P/L	15/52	7/48	2.28 (0.89–5.84)
Killen et al. (1997) Tx + video	P/L	11/56	7/54	1.62 (0.59–4.43)
Sachs et al. (1993)	P/H	17/46	4/44	4.67 (1.77–12.33)
Data not reported in publication				
Hall et al. (1996)	G/H	14/48	17/48	0.75 (0.32–1.77)
Bolliger et al. (2000)	I/H	2/86	5/104	0.50 (0.11–2.26)
Abelin, Ehrsam, et al. (1989)	P/L	9/44	1/38	5.18 (1.39–19.35)
Abelin, Buehler, et al. (1989)	P/L	13/58	6/62	2.58 (0.97–6.85)
Fiore et al. (1994)				
Study 1	P/H	9/19	7/19	1.52 (0.43–5.43)
Study 2	P/H	4/18	1/18	3.88 (0.60–24.97)
Gourlay et al. (1995)	P/H	5/133	4/134	1.27 (0.34–4.78)
Hughes et al. (1999)	P/H	39/311	5/120	2.49 (1.24–4.98)
Paoletti et al. (1996)	P/L	38/151	4/28	1.83 (0.71–4.72)
Richmond et al. (1997)	P/H	18/73	9/73	2.25 (0.98–5.18)
TNSG (1991)	P/H	32/102	10/91	3.29 (1.66–6.52)
Yudkin et al. (1996)	P/H	52/393	33/364	1.52 (0.97–2.38)
Hjalmarson et al. (1994)	S/H	21/53	8/53	3.4 (1.45–7.95)
Shiffman et al. (2002)	L/H	111/392	53/396	2.47 (1.75–3.49)
Total (17)		410/2,035	181/1,694	2.16 (1.79–2.59)
Men long-term follow-up				
Data reported in publication				
Campbell et al. (1991)	G/H	11/55	13/64	0.98 (0.40–2.4)
Hjalmarson (1984)	G/H	10/49	4/41	2.23 (0.71–6.96)
Killen et al. (1990) ad lib & fixed	G/H	70/280	24/163	1.85 (1.15–2.96)
Data not reported in publication				
Hall et al. (1996)	G/H	12/48	14/48	0.81 (0.33–1.99)
Bolliger et al. (2000)	I/H	7/86	4/104	2.19 (0.65–7.41)
Abelin, Ehrsam, et al. (1989)	P/L	6/44	1/38	4.02 (0.86–18.84)
Abelin, Buehler, et al. (1989)	P/L	7/58	5/62	1.55 (0.47–5.1)
Hughes et al. (1999)	P/H	21/228	4/94	1.99 (0.81–4.88)
Paoletti et al. (1996)	P/L	33/151	3/28	1.99 (0.73–5.43)
Richmond et al. (1997)	P/H	14/73	6/73	2.51 (0.98–6.43)
Yudkin et al. (1996)	P/H	46/393	27/364	1.63 (1.01–2.65)
Hjalmarson et al. (1994)	S/H	17/53	8/53	2.54 (1.04–6.21)
Total (12)		254/1,518	113/1,132	1.75 (1.39–2.21)

Note. CI = confidence interval; OR = odds ratio; NRT = nicotine replacement therapy; Event = the number of abstinent smokers in each group; N = number of smokers in each group; I = inhaler; L = low-intensity adjunct therapy; Tx = treatment; P = patch; H = high-intensity adjunct therapy; G = gum; S = spray; TNSG = Transdermal Nicotine Study Group.

Table 3
Odds Ratios of Smoking Cessation Outcomes for Women and Men for All NRT Methods at Short-Term (3-Month), Midterm (6-Month), and Long-Term (12-Month) Follow-Ups

Comparison	No. of effect sizes	No. of participants	OR	95% confidence interval Lower limit	95% confidence interval Upper limit	Test of null (two tailed) z value	Test of null (two tailed) p ≤	Q_B (df)	p	Q_W (df)	p
				Short-term							
Women	16	3,482	2.16	1.80	2.60	8.32	.0001			26.05 (15)	.0374
Men	16	2,975	2.21	1.83	2.67	8.22	.0001			15.33 (15)	.4274
Combined	32	6,457	2.19	1.92	2.49	11.67	.0001	0.37 (1)	.8687	41.42 (30)	.0806
				Midterm							
Women	17	4,376	1.76	1.46	2.10	6.28	.0001			12.47 (16)	.7109
Men	17	3,739	2.15	1.79	2.59	8.19	.0001			21.10 (16)	.1746
Combined	34	8,115	1.94	1.70	2.20	10.21	.0001	2.44 (1)	.1184	33.57 (32)	.3910
				Long-term							
Women	12	2,922	1.24	0.99	1.56	1.86	.0622			9.35 (11)	.5891
Men	12	2,681	1.75	1.39	2.21	4.73	.0001			7.40 (11)	.7652
Combined	24	5,603	1.47	1.25	1.73	4.65	.0001	4.23 (1)	.0395	16.76 (22)	.7763
Total	90	20,175	1.90	1.75	2.06	15.78	.0001	20.51 (5)	.0010	91.73 (84)	.2642

Note. NRT = nicotine replacement therapy; OR = odds ratio.

follow-up but did not occur for men even at the 12-month follow-up (see Table 5).

Reporting Bias

Although effect sizes were for the most part homogeneous within each follow-up for men and women, we examined the extent to which reporting bias could have influenced the pattern of results within each gender. We thus compared the ORs at each follow-up period between those studies that reported outcome comparisons between men and women and those studies for which these data were received upon request. The analyses conducted with each of these two data subsets (see Tables 6 and 7) and those including the entire data set (Table 3) yielded slightly different

Table 4
Odds Ratio Comparisons at Short-Term Versus Midterm, Long-Term Versus Short-Term, and Midterm Versus Long-Term Follow-Ups for Men and Women

Comparison	Q_B (df)	p	Q_W (df)	p
	Short-term vs. Midterm			
Women	2.55 (1)	.1099	38.52 (31)	.1657
Men	0.04 (1)	.8485	36.44 (31)	.2303
	Short-term vs. Long-term			
Women	13.5 (1)	.0002	35.80 (26)	.0953
Men	2.26 (1)	.1328	24.69 (26)	.5367
	Midterm vs. Long-term			
Women	5.52 (1)	.0188	21.83 (27)	.7461
Men	1.86 (1)	.1724	28.51 (27)	.3850

results, suggesting the presence of some reporting bias in the literature. The ORs of studies that reported abstinence rates for men and women separately showed that whereas men benefited from NRT at all follow-up periods, women benefited only from NRT at short-term follow-up. In contrast, the ORs of studies that provided the data upon request were statistically significant for men and women at all follow-up periods. These patterns of results suggest that investigators are more likely to report abstinence rates separately for men and women when the efficacy of NRT differs between the genders.

Discussion

The present study is to our knowledge the first systematic quantitative review of the smoking cessation outcome literature to examine the differential efficacy of NRT for smoking cessation between men and women. The findings of the present study provide clear empirical evidence about whether or not NRT is similarly useful for smoking cessation in men and women. The results indicate that NRT was superior to placebo and similarly effective for men and women at short- and midterm follow-ups. That is, NRT increased probability of remaining abstinent through midterm follow-up to the same extent in men and women. This suggests that physiological dependence in nicotine is likely an important factor in the maintenance of cigarette smoking, or the failure to quit cigarettes, in both men and women.

In agreement with previous findings (e.g., Cepeda-Benito, 1993), the efficacy of NRT declined as the length of the follow-up period increased, but this decline was statistically significant only in women from short-term (3-month) to long-term (12-month) and even from midterm (6-month) to long-term follow-ups. That is, after cigarettes are abandoned, the short-term gains achieved with the help of NRT are more likely to be maintained in men than in

Table 5
*Odds Ratios of Smoking Cessation Outcomes for Women (W) and Men (M) for NRT Methods
With Low Versus High-Adjunct Therapy at Short-Term, Midterm, and Long-Term Follow-Ups*

| Comparison | No. of effect sizes | OR | 95% confidence interval | | Test of null (two tail) | | Q_W (df) | p |
			Lower limit	Upper limit	z value	$p \leq$		
				Short-term				
W High	9	2.02	1.62	2.52	6.22	.0001	9.16 (8)	.3288
W Low	7	2.49	1.81	3.42	5.62	.0001	15.76 (6)	.0151
M High	9	2.00	1.59	2.51	5.88	.0001	10.26 (8)	.2475
M Low	7	2.74	1.96	3.82	5.93	.0001	2.73 (6)	.8419
				Midterm				
W High	12	1.90	1.58	2.30	6.69	.0001	6.48 (11)	.8396
W Low	5	1.03	0.63	1.69	0.11	.9160	0.79 (4)	.9395
M High	12	2.13	1.74	2.60	7.38	.0001	18.83 (11)	.0643
M Low	5	2.29	1.45	3.60	3.57	.0004	2.19 (4)	.6995
				Long-term				
W High	9	1.23	0.97	1.57	1.70	.0899	9.16 (8)	.3290
W Low	3	1.37	0.65	2.91	0.82	.4130	0.13 (2)	.9387
M High	9	1.71	1.34	2.19	4.26	.0001	6.16 (8)	.6269
M Low	3	2.11	1.06	4.19	2.13	.0333	0.94 (2)	.6257

Note. NRT = nicotine replacement therapy; OR = odds ratios.

women. Thus, at long-term follow-up, the efficacy of NRT was greater in men than women, and NRT was statistically superior to placebo in men but not in women. This pattern of results is congruent with the hypothesis that NRT benefits men more than women.

We found that NRT given with low-adjunct support was efficacious across all follow-up periods for men only. At midterm follow-up, NRT was efficacious for women if the treatment was given only in conjunction with an intensive treatment approach. At long-term follow-up, men benefited and women did not benefit from NRT regardless of whether or not they received the treatment in conjunction with high or low levels of support. These results show that prescribing NRT in conjunction with high-intensity nonpharmacological support was more important for women than men. Noting that the minimum criteria for the high-intensity adjunct treatment was rather low (30 min of additional support or two or more additional assessments), these findings suggest that women may benefit from NRT at long-term follow-up if they receive the treatment in conjunction with a truly comprehensive psychological intervention that addresses the many variables that influence smoking behavior in women (see Perkins, 2001).

Table 6
*Odds Ratios of Smoking Cessation Outcomes for Women and Men for All NRT Methods for
Studies That Reported Outcome by Gender at Short-Term, Midterm, and Long-Term Follow-Ups*

| Comparison | No. of effect sizes | OR | 95% confidence interval | | Test of null | | Q_W (df) | p |
			Lower limit	Upper limit	z value	$p \leq$		
				Women				
Short-term	5	2.86	2.08	3.94	6.43	.0001	11.67 (4)	.0199
Midterm	3	1.54	0.90	2.64	1.56	.1186	2.88 (2)	.2366
Long-term	3	1.04	0.70	1.53	0.18	.8551	4.74 (2)	.0936
				Men				
Short-term	5	2.68	1.84	3.92	5.11	.0001	3.83 (4)	.4293
Midterm	3	2.60	1.48	4.56	3.34	.0008	2.31 (2)	.3146
Long-term	3	1.67	1.13	2.47	2.57	.0101	1.78 (2)	.4103

Note. NRT = nicotine replacement therapy; OR = odds ratio.

Table 7

Odds Ratios of Smoking Cessation Outcomes for Women and Men for All NRT Methods for Studies That Provided Data on Request at Short-Term, Midterm, and Long-Term Follow-Ups

Comparison	No. of effect sizes	OR	95% confidence interval		Test of null		Q_W (df)	p
			Lower limit	Upper limit	z value	$p \leq$		
Women								
Short-term	11	1.39	1.52	2.36	5.68	.0001	10.07 (10)	.4343
Midterm	14	1.79	1.48	2.15	6.11	.0001	9.32 (13)	.7485
Long-term	9	1.37	1.03	1.82	2.17	.0298	3.34 (8)	.9112
Men								
Short-term	11	2.07	1.67	2.58	6.53	.0001	10.17 (10)	.4260
Midterm	14	2.11	1.73	2.56	7.51	.0001	18.30 (13)	.1463
Long-term	9	1.80	1.35	2.40	3.98	.0001	5.54 (8)	.6988

Note. NRT = nicotine replacement therapy; OR = odds ratios.

The results are thus congruent with the recommendation to use NRT in conjunction with comprehensive smoking cessation programs rather than as the sole or main component of treatment. Conversely, women's fast return to smoking in the low-intensity NRT group could also lead to a recommendation to prolong the prescription of NRT. These two recommendations are not incompatible because at some point NRT needs to be discontinued, and at that point smokers still need and benefit from learned skills and increased motivation to prevent smoking relapse. For example, women could benefit from help designed to prevent relapse due to the expectancy that smoking prevents weight gain, facilitates social interactions, regulates mood, or causes some other smoking expectancy.

The implications of the results are obviously limited by the extent to which the present sample may not be representative of the entire population of placebo-controlled randomized studies. The analyses suggested that the superior efficacy of NRT in men instead of women was more pronounced in those studies that reported abstinence rates for men and women separately than in those studies for which these data were requested and obtained. Thus, if the effect sizes we requested but did not obtain were more similar to those studies for which the data were requested and obtained than to those studies for which the data were published, it would be safe to assume that the added statistical power would render NRT efficacious in women at long-term follow-up (particularly within the high-intensity category). Nonetheless, greater statistical power would also mean that at long-term follow-up ORs would continue to be greater in men than women and that this difference would be statistically significant.

It is also noticeable that none of the comparisons between the reported and requested data within each gender at each of the three follow-up periods was statistically significant. That is, the efficacy of NRT for women in the studies that did not break their outcome results by gender was not greater than the NRT efficacy for women in the studies that reported the outcome data separated for men and women. Likewise, NRT was equally efficacious for men in studies that did and did not report abstinence rates separately for men and women. Moreover, the patterns of the effect sizes between both classes of studies were rather similar, with NRT being clearly efficacious for both genders at short-term follow-up, and with men showing greater gains from NRT than women at long-term follow-up regardless of adjunct treatment. Moreover, given that most effects sizes were calculated with data sent to us upon request rather than with data obtained from the original journal articles, it is safe to say that the present meta-analysis provides a fairly good picture of the efficacy of NRT in men and women.

The results suggest that further meta-analyses testing gender differences in the efficacy of other medications for the treatment of nicotine addiction, and perhaps other drug dependencies, might be warranted. For example, smoking cessation trials have found evidence that both supports and rejects the hypothesis that bupropion is differentially effective for men and women. Lerman et al. (2001) reported that at short-term follow-up smoking cessation rates for bupropion (48%) and placebo (43%) were similar for men but significantly different for women (39% for bupropion but 20% for placebo). These results suggest that bupropion has greater relative efficacy in women compared with men. Conversely, Gonzalez et al. (2002) reported that bupropion was equally effective for men and women. The point-prevalence cessation rates at Week 7 were 62% for men and 56% for women. Continuous cessation rates at Week 52 were 38% for men and 36% for women in the active group compared with 37% and 30% for men and women in the placebo conditions, respectively. A meta-analysis would certainly clarify whether men and women respond differently to bupropion. However, bupropion trials seldom examine gender differences in treatment outcome. On the basis of our experience, the greatest challenge to conduct the meta-analysis will be to obtain the data from the investigators.

When the meta-analysis was conceived our intention was to take into account important variables such as smoking rates, other measures of level of nicotine dependence (e.g., Fagerstrom's score), severity of withdrawal, and weight changes following smoking cessation. Including these data would have allowed us a more fine-grain analysis of the factors that may contribute to differences in NRT efficacy between men and women. Unfortunately, these variables are seldom reported separately for men and

women in outcome studies, and when we asked authors for the data the response rates were abysmal. Thus, future smoking cessation treatment outcome research should report both abstinence rates and analyses of the factors that contribute to success separately for men and women.

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