Sex differences in long-term smoking cessation rates due to nicotine patch

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Compared to men, women may be at greater risk for smoking-related diseases and have greater difficulty quitting smoking. Sex differences in medication response could guide treatment for smoking cessation to improve women's quit rates. We conducted a meta-analysis of the 14 placebo-controlled nicotine patch trials (N=6,250) for which long-term (6 months) clinical outcome results could be determined separately by sex. This analysis updated a meta-analysis of 11 of these trials that found no significant sex differences due to nicotine patch. The increase in quitting due to the nicotine vs. placebo patch was only about half as large in women as in men. Pooled absolute quit rates at 6 months for nicotine and placebo patch, respectively, were 20.1% and 10.8% in men, and 14.7% and 10.1% in women. The odds ratio for quitting due to nicotine vs. placebo patch was lower in women (OR = 1.61) than in men (OR = 2.20), with an interaction odds ratio of 1.40 (95% CI = 1.02–1.93, p = .04). This sex difference did not vary significantly by whether or not formal counseling was provided. Poorer outcomes in women vs. men treated with nicotine patch suggests that increasing the quit rates of women smokers may require supplementing patch treatment or use of other medications.

Introduction

Recent research has focused on genetic predictors of response to medications for smoking cessation (i.e., pharmacogenetics) (Munafo, Shields, Berrettini, Patterson, & Lerman, 2005), but relatively little attention has been paid to medication response as a function of perhaps the most prominent of genetic differences — a smoker's sex. Compared with men, women often have greater difficulty quitting smoking (Perkins, 2001; Piper et al., 2007; Scharf & Shiffman, 2004; Wetter et al., 1999; but see also Killen, Fortmann, Varady, & Kraemer, 2002). Women also may be at greater risk for some of the leading smoking-related illnesses (International Early Lung Cancer Action Program Investigators, 2006; Prescott, Hippe, Schnohr, Ole Hein, & Vestbo, 1998), although such differences are not always consistent and may depend on the specific endpoint examined (Pauk, Kubik, Zatloukal, & Krepela, 2005). For these reasons, targeting improvement in the quit rates of women smokers could have a greater impact on reducing the overall health toll due to smoking than the same improvement in quit rates among the broader population of smokers.

One step toward improving women’s quit rates is to identify sex differences in the efficacy of existing treatments. Those that work as well or better in women than men could be emphasized in clinical care of women smokers, whereas those working less well in women could be supplemented with additional treatment or avoided in favor of other treatments. Furthermore, differences in response to specific medications could provide directions for the identification of sex differences in factors promoting smoking persistence (Perkins, 2001). Across the many dozen clinical trials of various cessation medications, few report significant differences in quit rates between women and men. However, the lack of reported differences is due mostly to a failure of clinical trial authors to look for or present such differences, and not necessarily to their absence (Munafo, Bradburn, Bowes, & David, 2004a). Moreover, because the few trials that have reported results by sex were not sufficiently powered to detect sex differences in outcome, their typically

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nonsignificant findings contribute little to the evaluation of this question.

A common solution to this problem is to conduct a meta-analysis of results collapsed across relevant trials, to maximize statistical power. A few such analyses have been reported. One meta-analysis collapsed across trials of the various formulations (gum, patch, inhaler, and spray) of nicotine replacement therapy (NRT) and found poorer 1-year outcome in women vs. men due to nicotine vs. placebo (Cepeda-Benito, Reynoso, & Erath, 2004). Moreover, those authors found that NRT had no effect at 6-month follow-up in women given minimal counseling but was effective in women given high-intensity counseling, whereas NRT was effective in men regardless of counseling. Yet, formulation may matter, as at least one open-label trial found that women did poorer than men with gum, patch, and spray but better than men with inhaler (West et al., 2001).

The NRT formulation used most commonly is transdermal patch, with some 25% of all smokers having tried it (Bansal, Cummings, Hyland, & Giovino, 2004). A meta-analysis of sex differences in 6-month abstinence with the patch reported a nonsignificant odds ratio of 1.33 (95% CI = 0.91–1.95) for the interaction of patch condition by sex, with outcome due to nicotine vs. placebo (Munafo` et al., 2004a). However, the investigators acknowledged being unable to include two-thirds of the relevant studies in the analyses. They noted that only one of the 31 studies they identified reported outcome by sex, and authors of all but 10 of the remaining studies were either unable or unwilling to provide those data to the authors. When two additional relevant studies were brought to their attention, Munafo`, Bradburn, Bowes, and David (2004b) recalculated their findings and noted in a brief published reply that the interaction of sex by patch condition was marginally significant. Since then, at least one other analysis of sex differences in outcome due to nicotine patch has been published (Shiffman, Sweeney, & Dresler, 2005), and the resulting data may contribute to a more reliable conclusion regarding sex differences in nicotine patch efficacy.

In sum, the only peer-reviewed meta-analysis on sex differences in the clinical efficacy of the most widely used cessation medication, nicotine patch (Munafo` et al., 2004a), concludes there are no significant sex differences, but an analysis that includes more of the relevant patch studies would provide a more complete evaluation and greater statistical power, and may arrive at a different conclusion. In the current analysis, we sought to obtain results for additional relevant nicotine patch trials and add them to the results reported by Munafò et al. (2004a) to provide a more reliable comparison of sex differences in long-term smoking cessation rates due to nicotine patch. We also examined whether these results varied as a function of formal cessation counseling.

Method

Data sources

We sought data from all prospective, placebo-controlled clinical trials with transdermal nicotine that included both men and women and reported biochemically verified abstinence rates at 6-month follow-up. We identified 14 such studies, comprising a total of 6,250 patients in the comparisons of nicotine vs. placebo patch outcome. The first 11 studies were those reported by Munafò et al. (2004a), who describe the full details of their search strategy. Three additional relevant reports were known to the present authors (Davis et al., 1994; Wetter et al., 1999) or were published after the Munafò et al. (2004a) paper (Shiffman et al., 2005). Two of these studies provided outcome results by sex (Davis et al., 1994; Shiffman et al., 2005). Wetter et al. (1999), who combined outcome results from three similar patch studies, provided the quit rates by sex upon a request from the first author. A subsequent search on the ISI Web of Science (http://portal.isiknowledge.com/portal.cgi) with the key words “nicotine replacement AND gender” generated 73 citations going back to 1996 but did not identify any additional relevant clinical outcome studies with nicotine patch.

Data extraction

Our primary outcome of interest was the interaction between sex and treatment (nicotine vs. placebo patch) on 6-month abstinence. To quantify the magnitude of this effect, we used the ratio of the odds ratio for the effect of nicotine patch on 6-month abstinence in men to the analogous odds ratio for women. We refer to this ratio of odds ratios as the interaction odds ratio. We calculated these interaction odds ratios and their 95% confidence intervals for the 11 studies described by Munafò et al. (2004a) from data provided by the first author of that meta-analysis. The publications by Shiffman et al. (2005) and Davis et al. (1994) provided raw 6-month abstinence rates on NRT and placebo patch for men and women separately, and we obtained sex-specific abstinence rates for Wetter et al. (1999) via personal communication with the first author. We used these data to calculate the interaction odds ratios and their 95% confidence intervals.
We also calculated the odds ratios and their 95% confidence intervals for the effect of nicotine vs. placebo patch on 6-month abstinence separately for men and women across the 11 studies used in Munafò et al. (2004a) and for each of the additional three studies (Davis et al., 1994; Shiffman et al., 2005; Wetter et al., 1999). A study was viewed as providing formal cessation counseling if the counseling was described as structured (i.e., formal behavioral cessation counseling and not simply usual care), interactive, and lasting more than 15 min in total prior to the quit attempt. Otherwise, it was viewed as not providing formal counseling.

**Data analyses**

To obtain a pooled estimate of the difference in treatment efficacy between men and women across the 14 studies, we first transformed the interaction odds ratios to the natural logarithm scale and calculated the asymptotic standard errors of each of the log odds ratios. We calculated the pooled log odds ratio and its standard error using either the DerSimonian-Laird (1986) random-effects model or a fixed-effects model, according to the observed presence or absence, respectively, of heterogeneity between studies. Heterogeneity was assessed using Cochran’s Q test. A rank correlation test for funnel plot asymmetry (Begg & Mazumdar, 1994) was used to assess the possibility of publication bias among the sources of data. We used the same procedure to calculate separate pooled estimates of the interaction odds ratios for the studies that did and did not provide formal counseling. We then used a z-test to compare the pooled log odds ratio for the studies with formal counseling to that for the studies without formal counseling.

Finally, we used the same procedure to determine the separate estimates of 6-month efficacy for nicotine vs. placebo patch in men and women. To establish the clinical significance of the sex difference in nicotine patch efficacy, we calculated the number needed to treat (NNT) for men and women using the sex-specific pooled odds ratios and the control event rate (CER). The NNT here represents the minimum number of smokers required to be treated with nicotine patch to expect one additional smoker abstinent at 6 months, relative to placebo (Cook & Sackett, 1995). We also present total raw abstinence rates for men and women separately on nicotine and placebo across the 14 studies.

We considered tests for heterogeneity and publication bias to be significant at $p=.10$ and all other tests to be significant at $p=.05$ (two-tailed). We used version 2.4.1 of the R statistical software package with the rmeta library for all analyses (R Development Core Team, 2006).

**Results**

**Results for men and women separately**

The studies used in our analysis and our results are summarized in Table 1. The overall 6-month abstinence rates across the 14 studies were 20.1% for men on nicotine (334/1,665), 10.8% for men on placebo (130/1,204), 14.7% for women on nicotine (272/1,850), and 10.1% for women on placebo (154/1,531). Thus the nicotine patch was about half as effective in women as in men in terms of the increase in quitting beyond placebo patch use (4.6% vs. 9.3% for women and men, respectively). We obtained the following estimates of the odds ratios for efficacy of nicotine patch: for men, $OR=2.20$ (95% CI=1.75–2.76, $p<.001$), and for women, $OR=1.61$ (95% CI=1.29–2.00, $p<.001$). We used the fixed-effects model to calculate these pooled odds ratios because there was no evidence of heterogeneity in either case ($Q=14.45$, $df=13$, $p=.34$ for women; $Q=11.21$, $df=13$, $p=.59$ for men). Based on these odds ratios and CERs of 10%, we calculated NNTs of 10 for men and 19, nearly twice as many, for women. Thus, for every 10 men or every 19 women treated with nicotine patch, we would expect one additional success (6-month abstinence) relative to placebo patch.

**Interaction of nicotine by sex**

We found no evidence of heterogeneity in interaction odds ratios among the 14 studies together ($Q=7.48$, $df=13$, $p=.88$), as well as no heterogeneity among the seven studies with formal counseling ($Q=2.48$, $df=6$, $p=.87$) or among the seven studies without counseling ($Q=4.47$, $df=6$, $p=.61$). Accordingly, we again used fixed-effects models, which yielded a pooled estimate of the interaction odds ratio of 1.40 (95% CI=1.02–1.94, $p=04$) for the 14 studies together, indicating significantly worse outcome with nicotine vs. placebo patch in women compared with men. A forest plot summarizing the interaction odds ratio results for all 14 studies is shown in Figure 1.

**Moderating influence of counseling**

Pooled estimates of the interaction odds ratio as a function of counseling were 1.57 (95% CI=1.01–2.43, $p=.04$) for the seven studies with formal counseling, indicating a significant sex difference in patch efficacy, and 1.24 (95% CI=0.78–1.97, $p=.37$) for the seven studies without formal counseling, indicating no significant sex difference in patch efficacy (see Table 1). However, the difference between the pooled log odds ratios for the studies with and without counseling was not statistically significant ($z=0.73$, $p=.47$). Finally, the rank
Table 1. Summary of studies included in meta-analysis and pooled results.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Description</th>
<th>Men</th>
<th>Women</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>%Abst Nic</td>
<td>%Abst Plac</td>
</tr>
<tr>
<td>Abelin</td>
<td>1989</td>
<td>Primary care patients; usual care</td>
<td>118</td>
<td>19.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Ehrsam</td>
<td>1991</td>
<td>Primary care patients; usual care?</td>
<td>82</td>
<td>13.6%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Killen</td>
<td>1997</td>
<td>Community sample; self-help</td>
<td>100</td>
<td>28.8%</td>
<td>14.6%</td>
</tr>
<tr>
<td>Paoletti</td>
<td>1996</td>
<td>Community sample; brief info on smoking and health</td>
<td>179</td>
<td>25.2%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Sachs</td>
<td>1993</td>
<td>Community sample, usual care</td>
<td>90</td>
<td>37.0%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Tonnesen</td>
<td>1991</td>
<td>Community sample, self-help brochure</td>
<td>82</td>
<td>17.5%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Yudkin</td>
<td>1993</td>
<td>Primary care patients; self-help brochure or booklet, brief advice at follow-ups</td>
<td>757</td>
<td>13.2%</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1408</td>
<td>18.6%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Davis</td>
<td>1994</td>
<td>Community sample, individual counseling</td>
<td>111</td>
<td>42.1%</td>
<td>18.5%</td>
</tr>
<tr>
<td>Hughes</td>
<td>1999</td>
<td>Multi-site community sample; group counseling; regular and high NRT doses</td>
<td>516</td>
<td>10.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Jorenby</td>
<td>1999</td>
<td>Multi-site community sample; individual counseling</td>
<td>184</td>
<td>27.1%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Lewis</td>
<td>1998</td>
<td>Inpatients; individual counseling via phone</td>
<td>65</td>
<td>14.3%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Richmond</td>
<td>1994</td>
<td>Community sample; intensive group counseling</td>
<td>146</td>
<td>23.3%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Shiffman</td>
<td>2005</td>
<td>Multi-site community sample; group counseling</td>
<td>193</td>
<td>31.4%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Wetter</td>
<td>1999</td>
<td>Multi-site community sample; group or individual counseling</td>
<td>246</td>
<td>31.7%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Pooled (counseling):</td>
<td></td>
<td></td>
<td>1461</td>
<td>21.3%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Pooled (overall):</td>
<td></td>
<td></td>
<td>2869</td>
<td>20.1%</td>
<td>10.8%</td>
</tr>
</tbody>
</table>
correlation tests showed no evidence of publication bias in our selection among all studies ($z = 0.71$, $p = 0.48$), the studies with counseling ($z = 1.35$, $p = 0.18$), or the studies without counseling ($z = -1.05$, $p = 0.29$).

Discussion

Our analysis of cessation rates due to nicotine vs. placebo patch across 14 studies indicated that women gain significantly less long-term benefit than men from using the patch. This sex difference in nicotine patch efficacy may be clinically significant as well as statistically significant, as the increase in percent quit with nicotine vs. placebo patch was about half as great in women as in men. Similarly, there was an almost twofold increase in the estimated number needed to treat for women relative to men to get one additional long-term abstinent ex-smoker. Contrary to some research (Perkins, 2001; Piper et al., 2007; Scharf & Shiffman, 2004; Wetter et al., 1999), we did not find a lower overall quit rate in women vs. men among those receiving placebo patch (Table 1); only the quit rates in response to nicotine patch differentiated men and women.

More than half of all the relevant long-term controlled trials of nicotine vs. placebo patch in men and women could not be included in this meta-analysis because those trials have not reported outcome results separated by sex, as discussed in detail elsewhere (Munafo et al., 2004a). A subsequent analysis based on more of these trials could yield a different result. Yet the current analysis included more of the relevant patch studies and a larger combined sample than any prior analysis of sex differences in nicotine patch outcome, thereby representing the most complete examination of this question to date. Moreover, subsequent meta-analyses with data from a larger number of relevant trials would have greater statistical power and so could find an even greater sex difference in efficacy of the nicotine patch.

Reasons why women may respond less well than men to nicotine patch are not known, but smoking behavior in women compared with men appears to be reinforced less by nicotine and more by non-nicotine factors (e.g., smoking cues) (Perkins, in press; Perkins et al., 1996; Perkins, Jacobs, Sanders, & Caggiula, 2002). A treatment that focuses exclusively on addressing the influence of nicotine likely would not be as efficacious among smokers who are less sensitive to nicotine’s reinforcing effects. Men and women also may differ in withdrawal or craving relief from NRT. Consistent with this notion, nicotine replacement via gum may be less effective in relieving withdrawal among women vs. men (Hatsukami, McBride, Pirie, Hellerstedt, & Lando, 1991). Thus whether the sex difference in efficacy observed for the patch is also significant for the other formulations of NRT is not clear but warrants explicit examination (Cepeda-Benito et al., 2004; West et al., 2001).

Unlike Cepeda-Benito et al. (2004), we did not find a significant influence of formal counseling on the sex difference in the efficacy of nicotine vs. placebo patch. If anything, the sex difference appeared somewhat stronger in those studies with formal counseling, compared with those without. Cepeda-Benito et al. (2004) collapsed results across several NRT formulations, and the influence of counseling on the sex difference in NRT response may be stronger for some formulations than others, such as patch.

By contrast, we know of no comparable sex difference in the efficacy of non-nicotine smoking cessation medications, suggesting that this difference is specific to nicotine replacement. In a meta-analysis of 12 placebo-controlled bupropion trials (Scharf & Shiffman, 2004), the medication was as effective in women as in men (odds ratios for abstinence were 2.47 and 2.53, respectively, at the end of treatment), although cessation rates were poorer overall in women vs. men, regardless of treatment ($OR = 0.77$). Several medications not approved by the U.S. Food and Drug Administration (FDA) for smoking cessation, such as mecamylamine, clonidine, and naltrexone, may be equally or more efficacious in women than in men (Perkins, 2001), whereas varenicline, approved by the FDA in 2006, appears to be equally efficacious in women and men (Gonzales et al., 2006).

Figure 1. Forest plot of interaction odds ratios of quitting with nicotine versus placebo patch in men versus women.
Nicotine patch still warrants consideration for smoking cessation in women due to its considerable advantages over other alternatives, including its safety, accessibility (e.g., it is available over the counter), low cost, and ease of use. Moreover, this meta-analysis is based on large samples of women smokers, and individual women smokers may respond very well to nicotine patch. Nevertheless, we found in the present analysis that long-term cessation rates with nicotine patch were significantly poorer in women than in men, indicating that women using nicotine patch treatment may be more likely than men to need additional help to quit or should consider using another medication. Research aimed at understanding this sex difference in nicotine patch efficacy may reveal important differences in the factors that maintain dependence between men and women, and provide directions for improving cessation interventions aimed at women smokers (Perkins, in press).

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References


