

Consideration of Sex in Clinical Trials of Transdermal Nicotine Patch: A Systematic Review

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Transdermal nicotine patch (TNP) is 1 of the most commonly used smoking cessation treatments; however, the efficacy of TNP by sex is not yet clear. The purpose of the current review was to synthesize how sex has been considered in published clinical trials of TNP for smoking cessation. The specific aims of the study were to examine the inclusion of sex in analyses of cessation outcomes, TNP-related variables (compliance, side effects), and quit-related variables (withdrawal, cravings); to review the consideration of sex-related variables (menstrual cycle phase, pregnancy); and to identify needs for future research. Potential articles published through December 31, 2013 were identified through a MEDLINE search of the terms “clinical trial,” “nicotine patch,” and “smoking cessation.” Forty-two studies used all 3 terms and met the inclusion criteria. Approximately half of the studies reported that they considered sex in smoking cessation outcomes, with 15 studies finding no difference by sex and 7 studies finding better outcomes for men versus women. Only 5 studies reported data on outcomes by sex in their publications. No studies reported analysis of TNP compliance or withdrawal by sex. In the 1 study that examined side effects by sex, more women than men reported discontinuing TNP because of skin irritation. No study examined the association of cessation outcomes with menstrual cycle phase. There is a need to include sex in research on TNP, as well as other pharmacological and behavioral smoking treatments, to clarify the picture of treatment efficacy for women compared with men.

Keywords: clinical trials, review, sex, smoking, transdermal nicotine patch

It is well-known that smoking exerts a negative impact on nearly every organ in the human body, leading to a wide range of negative health consequences and greater mortality (United States Department of Health and Human Services, 2010, 2014). Smoking causes approximately 480,000 deaths in the United States (U.S.) annually (United States Department of Health and Human Services, 2014),

whereas across the globe, tobacco accounts for 12% of deaths for adults over the age of 30 with approximately 6 million tobacco-users dying every year (World Health Organization, 2012). Although both male and female smokers experience smoking-related diseases and greater mortality than nonsmokers (United States Department of Health and Human Services, 2010, 2014), women are more likely than men to experience a number of serious health consequences of smoking (e.g., lung cancer, oral cancer, heart disease) (Ceribelli, Pino, & Cecere, 2007; Huxley & Woodward, 2011; Kiyohara & Ohno, 2010; Sarna & Bialous, 2004; United States Department of Health and Human Services, 2001). Further, women experience additional consequences of smoking such as dysmenorrhea and menstrual irregularity, altered ovarian cycle and hormone levels during menstrual cycle phases, infertility, ectopic pregnancy, and spontaneous abortion (Park & Middlekauff, 2009; United States Department of Health and Human Services, 2014; Whitcomb et al., 2010).

Women metabolize nicotine more quickly than men, most likely as a result of estrogen (Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006), and faster nicotine metabolism is associated with worse cessation outcomes (Schnoll, Patterson, Wileyto, Tyndale, Benowitz, & Lerman, 2009). Further, men demonstrate higher availability of the β^2 subunit nicotinic acetylcholine receptors after abstinence compared with women (Cosgrove et al., 2012), suggesting a potential biochemical mechanism for sex differences in nicotine response. Because women experience disproportionate

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consequences of smoking, it is important to ensure that women receive the most efficacious treatments to help them to quit smoking and reduce the impact of these harmful consequences. Because there are sex differences in nicotine metabolism, it is of particular importance to understand the response of women versus men to smoking treatments that rely on nicotine administration.

Transdermal nicotine patch (TNP), a Food and Drug Administration–approved treatment for nicotine dependence that is available over-the-counter or by prescription, is a form of nicotine replacement therapy (NRT) and one of the most commonly used treatments by smokers who are attempting to quit (Shiffman, Brockwell, Pillitteri, & Gitchell, 2008). Data suggest that 52.4% of adult smokers in the U.S. attempt to quit smoking for at least one day in a year (Centers for Disease Control and Prevention, 2011), and ~20% of smokers who attempt to quit use TNP (Shiffman et al., 2008). Based on 2011 data from the Centers for Disease Control and Prevention that show there are 43.8 million adult U.S. smokers (Centers for Disease Control and Prevention, 2012), it can be estimated that more than 3.5 million people in the U.S. alone use TNP each year. TNP is an effective treatment for smoking that improves quit rates relative to no treatment or placebo (Cahill, Stevens, & Lancaster, 2014; Fiore et al., 2008; Shiffman et al., 2008; Stead et al., 2012). The Clinical Practice Guidelines for Treating Tobacco Use and Dependence (2008 update; Fiore et al., 2008) reported that, across 32 treatment arms from 25 studies, smokers using TNP were approximately twice as likely to be abstinent from smoking after six months compared with smokers who received placebo (odds ratio [OR] = 1.9; 95% confidence interval [CI] = 1.7–2.3), whereas a recent Cochrane review (Stead et al., 2012) found that, across 43 clinical trials, smokers using TNP were 64% more likely than smokers in control or placebo groups to be abstinent from smoking at 6 months. Together these data show that TNP is a commonly used treatment that improves cessation outcomes for smokers.

Although TNP improves cessation outcomes in general, there has been mixed evidence for the relative efficacy of TNP for women versus men. Munafò and colleagues (2004) conducted a meta-analysis of clinical trials of TNP published between 1989 and 2000. The authors were able to obtain data from 11 of 31 identified studies and determined that TNP improved cessation outcomes for both men and women with no greater efficacy for either sex. Four years later, Perkins and Scott (2008) published a meta-analysis of sex differences in TNP outcomes in 14 placebo-controlled clinical trials including the 11 clinical trials analyzed by the earlier meta-analysis plus 3 additional studies. This second meta-analysis reported a significant interaction effect with women experiencing lower efficacy of TNP than men (interaction OR = 1.40; 95% CI = 1.02, 1.94; $p < .05$). The authors of both meta-analyses called for the publication of more data on smoking outcomes by sex, as the majority of the data included in both sets of analyses had to be obtained by individual request from the authors because of the low availability of published cessation outcomes by sex.

There are a number of laboratory studies documenting sex differences in reactivity to nicotine. Women, compared with men, have reported a greater sensitivity to the negative subjective effects of nicotine administered intravenously or through nasal spray (e.g., “dizziness”; Myers, Taylor, Moolchan, & Heishman, 2008; Sofuoğlu & Mooney, 2009) and less sensitivity to the reinforcing effects of nicotine (e.g., “satisfying,” “want more”; Perkins et al., 2009).

Additionally, Perkins and colleagues (Perkins, 1999; Perkins, Jacobs, Sanders, & Caggiula, 2002) demonstrated that men are better able than women to discriminate between doses of nicotine administered by cigarettes and nasal spray. Further, women report greater craving relief from denicotinized tobacco cigarettes than men (Barrett, 2010), experience less of a change in subjective effects across doses of nicotine from cigarettes (Perkins et al., 2002), experience less reinforcement from nicotine in cigarettes in the absence of visual and olfactory stimuli (Perkins et al., 2001), and report greater reward and reinforcement related to verbal information about nicotine content in cigarettes (Perkins et al., 2006). These studies show that women are differentially sensitive to the effects of nicotine across a range of methods of administration including intravenous, nasal, and oral.

Laboratory studies have also demonstrated sex differences in side effects and withdrawal symptoms during the use of TNP. In one study, male ($n = 75$) and female ($n = 53$) smokers participated in four laboratory sessions during which they received one of four doses of TNP (0, 7, 21, 42 mg; Evans, Blank, Sams, Weaver, & Eissenberg, 2006). Female participants reported a greater increase in heart rate and self-reported dizziness, lightheadedness, and weakness with TNP compared with placebo patch. A second laboratory study of 124 adult smokers (men $n = 70$, women $n = 54$; Kleykamp, Jennings, Sams, Weaver, & Eissenberg, 2008) also found greater heart rate increases with 7 mg, 14 mg, and 21 mg TNP and higher ratings of nausea with the 7 mg TNP for women compared with men. These studies suggest that women are more sensitive than men to some potentially negative effects of nicotine delivered through TNP.

Although women demonstrate a greater reduction in withdrawal symptoms with oral nicotine (Xu et al., 2008), laboratory studies have reported mixed results with regard to sex differences in withdrawal relief with TNP. In two laboratory studies of TNP and withdrawal that reported greater sensitivity of women to the effects of TNP on heart rate (described above), there were no main effects of sex nor TNP dose by sex interactions related to withdrawal symptoms (Evans et al., 2006; Kleykamp et al., 2008). Also, whereas Kleykamp and colleagues (2008) reported no differences in withdrawal relief for men versus women using TNP, a recent study that compared relief of withdrawal symptoms for participants using low nicotine cigarettes with TNP compared with low nicotine cigarettes without TNP found that withdrawal relief was greater for men compared with women (Vogel et al., 2014). Further, in a study of 34 adults who received either TNP or placebo patch and participated in 5 overnight sessions that occurred during the week before and the week after stopping smoking and assessed both sleep and withdrawal (Wetter, Fiore, et al., 1999), TNP exacerbated the negative impact of withdrawal on sleep fragmentation for women but not men.

TNP is the most commonly used pharmacotherapy for smoking cessation, yet sex differences in the efficacy of TNP are still not clear. Laboratory data have shown that women are more sensitive to some effects (e.g., physiological reactivity, dizziness) of nicotine administered through various routes including TNP, and indicate sex differences in TNP side effects and withdrawal relief. Sex differences that have been demonstrated when TNP is applied in laboratory settings may translate into differences also seen during TNP smoking cessation treatment including differences that impact quit outcomes. Consequently, it is important to examine

how outcomes, treatment-related variables (e.g., cravings, withdrawal), and TNP-related variables (e.g., compliance, side effects) differ by sex in treatment studies; however, the extent to which sex has been considered in the analyses of clinical trial data has not yet been systematically examined. The purpose of the current review is to examine whether and how sex has been considered in placebo-controlled clinical trials of TNP for smoking cessation. Published clinical trials of TNP were examined for the inclusion of sex in analyses of smoking cessation outcomes. To extend our knowledge of how sex has been considered in other aspects of research on TNP for smoking cessation, this review also assessed the consideration of sex in analyses of TNP-related (compliance, side effects) and quit-related (withdrawal, cravings) variables and the inclusion of sex-related (menstrual cycle phase, pregnancy) variables.

Method

A MEDLINE search was conducted in January 2014 using the terms “clinical trial,” “nicotine patch,” and “smoking cessation” to identify potential papers to be reviewed. Previous systematic and meta-analytic reviews of TNP for smoking cessation were examined for additional references (Munafò et al., 2004; Perkins & Scott, 2008; Stead et al., 2012). After removing duplicate articles and articles not published in English, the remaining articles were individually examined to determine whether they met inclusion criteria, namely that the study (a) was a clinical trial for smoking cessation, (b) involved administration of both TNP and placebo patch, (c) included both female and male participants (i.e., did not recruit a sample of only, or nearly only, men or women), and (d) reported smoking cessation outcomes for both male and female participants for at least one time point. Information collected from each study included location of the study (i.e., the country or countries in which the study was conducted), sample characteristics (e.g., sample size, sex composition), and smoking cessation outcomes (i.e., percentage of male and female participants abstinent from smoking). Data related to the inclusion of women in each study included whether there were sex-specific results and analyses reported for (a) smoking cessation outcomes, (b) compliance, (c) side effects, and (d) withdrawal symptoms. In addition, data were collected regarding whether menstrual cycle phase and pregnancy status was assessed for female participants.

Results

Study Characteristics

Forty-two placebo-controlled clinical trials of TNP for smoking cessation met eligibility criteria to be included in the current review (see Table 1). The majority of the clinical trials were conducted in the U.S. ($n = 25$) or the United Kingdom (U.K., $n = 8$). Sample sizes ranged from 62 to 3,575 ($M = 590$, $SD = 647$). Only two studies did not report the number of female participants in their sample. The majority of studies that did report sex composition included a relatively equal sex composition with an average of 54% percent of the sample reported to be female across studies. Among studies for which racial composition was reported

or could be calculated, primarily studies in the U.S., the majority of participants were white (72% to 99.6%). One study in the U.S. (Ahluwalia, McNagny, & Clark, 1998) studied TNP outcomes in a sample of African-American adults. Thirty-six studies recruited samples from the general communities or populations of adults, and six studies recruited specific subgroups of smokers. For studies that recruited subgroups of smokers, the subgroups of interest were adults with respiratory or cardiovascular disease (U.K., Campbell et al., 1996), adults who were referred by physicians to a specialty lung clinic (Denmark, Tønnesen & Mikkelsen, 2000), hospitalized adults (U.S., Lewis et al., 1998), adolescents (U.S., 13–19 years old, Hanson et al., 2003; 13–17 years old, Moolchan et al., 2005), and adults with a past diagnosis of alcohol dependence (U.S., Hughes et al., 2003).

Among the studies, one to three doses of TNP were examined in comparison with placebo with additional lower doses included as tapers at the end of the treatment period (see Table 1 for more details). The length of TNP treatment ranged from 4–26 weeks with a modal length of 12 weeks.

Smoking Cessation Outcomes

Out of the 42 articles reviewed, 22 (52.4%) reported examining treatment outcomes by sex.

Fifteen studies found no association of sex with smoking cessation outcomes and seven studies found better TNP outcomes for men (see Table 1). One additional study reported outcomes of carbon monoxide (CO) levels by sex (Levin et al., 1994; see Table 1). Among the 21 studies that analyzed outcomes by sex, only 5 (24%) reported the percentages of abstinent participants by sex in the text of the publication. Even among these 5 studies, only one reported abstinence rates for all patch conditions separately. Glavaš and colleagues (2003) reported that, five years after TNP treatment, a greater number of men demonstrated CO-confirmed point-prevalence abstinence compared to women in both the active patch (21% vs. 16%) and placebo patch (21% vs. 11%) conditions (statistical significance or odds ratio were not reported). Notably, the abstinence rate was the same in both conditions for men whereas women did better with TNP compared with placebo patch. Two studies reported cessation rates by sex for combined study conditions, both finding higher rates of abstinence among men versus women (Stapleton et al., 1995: 20% vs. 14% for cotinine- and CO-confirmed continuous abstinence during the full 12 weeks of treatment, $p < .01$; Wetter, Kenford, et al., 1999: 45% vs. 29% CO-confirmed point-prevalence abstinence at end of treatment, $p < .001$; 25% vs. 12% CO-confirmed point-prevalence abstinence at 6-month follow-up, $p < .001$). Hays et al. (1999) presented results from participants who received active patch (one double-blind arm and one open-label arm) and found greater self-reported abstinence rates after six weeks of treatment for men versus women (double-blind arm: 26.3% vs. 14.5%; open-label arm: 27.7% vs. 18.8%; $p < .01$). Hays and colleagues (1999) also reported a significant sex difference for CO-confirmed abstinence at a 6-month follow-up for men versus women (double-blind arm: 15.4% vs. 7.9%; open-label arm: 18.1% vs. 11.3%; $p < .01$). One additional study (Tønnesen et al., 1999) reported a significant OR for CO-confirmed 12-month continuous abstinence for men versus women (OR = 1.50, 95% CI = 1.20–1.86, $p < .01$) but did not publish sex-specific cessation rates. Finally, Levin and colleagues

Table 1
Placebo-Controlled Clinical Trials for Transdermal Nicotine Patch

Reference	Location	Sample size	Sub-group ^a	% Female	% White	Nicotine patch dose or doses (per day) ^b	No. of weeks of patch treatment	Analyzed outcomes by sex	Sex analyses outcomes ^c	Note ^d
Abelin et al., 1989	Switzerland	199	—	40	—	30, 20, 10 cm ²	12	No	—	
Buchkremer et al., 1989	Germany	131	—	—	—	15 cm ²	7	No	—	
Daughton et al., 1991	U.S.	158	—	—	—	15 cm ²	4	No	—	
Tønnesen et al., 1991	Denmark	289	—	72	—	30 (20, 10) cm ²	16	No	—	
Transdermal Nicotine Study Group, 1991	U.S.	935	—	60	—	21, 14, 7 mg	6-10	Yes	n.s.	See Imperial Cancer Research Fund General Practice Research Group, 1994
Imperial Cancer Research Fund General Practice Research Group, 1993	U.K.	1686	—	55	—	30 (20, 10) cm ²	12	No	—	See Stapleton et al., 1995
Russell et al., 1993	U.K.	600	—	61.5	—	25, 15 (10, 5) mg	18	Yes	n.s.	
Sachs et al., 1993	U.S.	220	—	59	—	30 (20, 10) cm ²	18	Yes	n.s.	
Westman et al., 1993	U.S.	159	—	57	92	25 (12.5) mg	6	No	—	
Fiore et al., 1994	U.S.	87 (Study 1) 112 (Study 2)	—	56 (1) 68 (2)	—	22 mg (1) 22 (11) mg (2)	8 (1) 6 (2)	No	—	See Wetter et al., 1999
Hurt et al., 1994	U.S.	240	—	54	99.6	22 mg	8	Yes	n.s.	
Kenford et al., 1994	U.S.	87 (Study 1) 112 (Study 2)	—	56 (1) 68 (2)	—	22 mg (1) 22 (11) mg (2)	8 (1) 6 (2)	No	—	See Wetter et al., 1999
Imperial Cancer Research Fund General Practice Research Group, 1994	U.K.	1686	—	55	—	30 (20, 10) cm ²	12	No	—	
Levin et al., 1994	U.S.	62	—	66	—	22 mg	8	Yes	M > F	
Richmond et al., 1994	Australia	315	—	52	—	21 (14, 7) mg	10	Yes	n.s.	
Kornitzer et al., 1995	Belgium	374	—	39	—	15 (10, 5) mg	24	No	—	
Stapleton et al., 1995	U.K.	1200	—	57	—	25, 15 (10, 5) mg	18	Yes	M > F	
Campbell et al., 1996	U.K.	234	1	54	—	40, 30, 20, 10 cm ²	12	Yes	n.s.	
Jorenby et al., 1996	U.S.	211	—	54	98	21 mg	4	No	—	
Paoletti et al., 1996	Italy	297	—	40	—	25, 15 (10, 5) mg	18	No	—	
Killen et al., 1997	U.S.	424	—	50	82	21 (14, 7) mg	16	Yes	n.s.	
Sønderskov et al., 1997	Denmark	522	—	63	—	21, 14 (7) mg	12	Yes	n.s.	
Ahluwalia et al., 1998	U.S.	410	—	65	0 ^e	21, 14, 7 mg	10	No	—	
Daughton et al., 1998	U.S.	724	—	59	—	21 (14, 7) mg	10	Yes	n.s.	
Davidson et al., 1998	U.S.	802	—	54	89	22 mg	6	No	—	
Lewis et al., 1998	U.S.	185	2	46	—	22 (11) mg	6	Yes	n.s.	
West & Willis, 1998	U.K.	308	—	61	—	15 mg	4	No	—	
Daughton et al., 1999	U.S.	369	—	60	—	21, 14, 7 mg	12	Yes	n.s.	
Hays et al., 1999	U.S.	958	—	50	83	22 mg	6	Yes	M > F	
Hughes et al., 1999	U.S., Australia	1039	—	50	—	42, 35, 21 mg	16	Yes	n.s.	
Tønnesen et al., 1999	17 countries ^f	3575	—	48	—	25, 15 (10) mg	26	Yes	M > F	
Wetter, Kenford, et al., 1999	U.S.	632	—	61	—	22 mg (1) 22 (11) mg (2)	8 (1) 6 (2)	Yes	M > F	See Fiore et al., 1994
Tønnesen & Mikkelsen, 2000	Denmark	446	1	54	—	15 mg	12	Yes	M > F	
Shiffman et al., 2002	U.S.	567	—	52	87	21 (14, 7) mg	10	No	—	
Glavas et al., 2003	Croatia	112	—	66	—	30, 20, 10 cm ²	3	Yes	M > F	
Hanson et al., 2003	U.S.	100	3	57	87	21 (14, 7) mg	10	Yes	n.s.	

Table 1 (continued)

Reference	Location	Sample size	Sub-group ^a	% Female	% White	Nicotine patch dose or doses (per day) ^b	No. of weeks of patch treatment	Analyzed outcomes by sex	Sex analyses outcomes ^c	Note ^d
Hughes et al., 2003	U.S.	115	4	32	93	21, 14, 7 mg	12	No	—	
Smith et al., 2003	U.S.	893	—	52	—	21 (14, 7) mg	8	Yes	n.s.	
Schuurmans et al., 2004	South Africa	200	—	44	87	15 (10, 5) mg	12	No	—	
Moolchan et al., 2005	U.S.	120	3	70	72	21, 14 mg	12	No	—	
Shiffman et al., 2005	U.K., U.S.	502	—	62	95	21 mg	12	Yes	n.s.	Secondary analysis of Transdermal Nicotine Study Group, 1991
Piper et al., 2009	U.S.	1,504	—	58	84	21 (14, 7) mg	8	No	—	

Note. — indicates not applicable, not reported, or unable to calculate from data available.

^a Subgroup: 1 = Adults with a Medical Illness, 2 = Hospitalized Patients, 3 = Adolescents, 4 = Adults with an Alcohol Use Disorder. ^b Includes both primary treatment doses and doses used for taper periods in the metric listed in the article. Doses given as a taper are listed in parentheses. ^c Sex Analyses: n.s., no significant differences in abstinence outcomes by sex; M > F, higher abstinence outcomes for men compared with women; — outcomes by sex were not reported. ^d Other references that used some or all of the data from the study. ^e African-American adults. ^f Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Spain, Sweden, Switzerland, The Netherlands, U.K., U.S. ^g Results for CO levels at Week 2.

(1994) reported that whereas men receiving TNP showed significantly greater decreases in CO levels than men receiving placebo patch over the first week after starting the patch, there was no similar significant difference by patch condition for women.

Among studies that did not find a significant sex difference in outcomes, one study (Sønderskov, Olsen, Sobroe, Meillier, & Overvad, 1997), which examined outcomes for two doses of TNP (14 mg/day, 21 mg/day), reported outcomes after four weeks of treatment with either active or placebo patch for men versus women (14 mg patch: 66.7% vs. 51.2%, placebo: 63.4% vs. 46.3%; 21 mg patch: 49.2% vs. 43.1%, placebo: 46.6% vs. 32.9%). A second study (Shiffman, Sweeney, & Dresler, 2005) reported a nonsignificant main effect of sex (Hazard Ratio [HR] = 1.07, 95% CI = 0.97–1.19, $p = .17$) and a nonsignificant sex by treatment condition interaction (HR = 1.06, 95% CI = 0.96–1.18, $p = .24$) for continuous smoking abstinence at six months.

TNP-Related, Quit-Related, and Sex-Related Variables

In the current review, 19 studies stated that they assessed TNP compliance, but no study reported data on compliance for men versus women. Although 33 of 42 studies reported side effect data associated with TNP use, only one study reported examining side effects by sex (Levin et al., 1994). Levin and colleagues (1994) stated that although the same percentage of male and female participants reported skin reactions to TNP (percentages not reported), more women than men acknowledged dropping out of the study during the eight-week treatment period because of this side effect, although this difference was not statistically significant (43% vs. 10%, $p = .07$). With regard to quit-related variables, 24 studies reported assessing withdrawal symptoms and/or cravings to smoke. No study reported sex-specific outcomes or analyses related to withdrawal or cravings.

Finally, with regard to sex-related variables, no study included in the current review reported that they assessed for menstrual cycle phase or oral contraceptive use at baseline or during the trial. The majority of studies in the current review (37 of 42, 88%) specifically noted that they excluded women who were pregnant or lactating or reported giving a pregnancy test at the screening appointment to determine eligibility.

Discussion

TNP is one of the most commonly used treatments for smoking and significantly improves outcomes in the general adult population of smokers attempting to quit. Further, because of its established nature as a first line treatment for smoking, TNP is now included in research studies as a control or standard treatment against which to test alternative or additional treatments (e.g., (Bullen et al., 2013; Okuyemi et al., 2013; Smith et al., 2013)). Consequently, there are both clinical and research-related reasons why it is important to understand patch efficacy for men vs. women. This systematic review of published clinical trials of TNP identified the need for sex-specific data on not just cessation outcomes, but other important treatment- and cessation- related variables that are important to treatment outcomes and may differ for women vs. men. Each variable is discussed in more detail below.

Cessation Outcomes

The majority of smokers are unable to successfully quit smoking and maintain abstinence over time (Fiore et al., 2008), suggesting a continued need to determine how to improve long-term abstinence rates for smokers. Two previous meta-analyses of TNP outcomes for women versus men found conflicting results (Munafò et al., 2004; Perkins & Scott, 2008), with the more recent analyses suggesting enhanced outcomes for men versus women. In the current review, analysis of cessation outcomes by sex was only reported for half of published studies, and only 12% of published studies (5 of 42) reported outcome data for men versus women. Only one study was identified that was published after the last meta-analysis, perhaps because TNP is being used as a comparison variable in new trials with all participants receiving active patch, as described above. Consequently, the most recent statistical summary of the data is the meta-analysis by Perkins and Scott (2008), which reported significantly worse outcomes for women using TNP compared with men, analyzing 14 studies from an available 34 studies at the time of publication. Both meta-analyses and this current review noted that most studies do not publish numerical outcomes or statistics by sex, eliminating many studies from inclusion in formal analyses. There is a need for data on outcomes by sex to be included in future publications of TNP clinical trials so that future analyses can include the greatest amount of possible data. These important data will allow researchers to clarify whether women have different outcomes than men using TNP and under what conditions differences do and do not appear (e.g., dose of TNP, length of TNP treatment) to maximize outcomes for both sexes.

Compliance

Better smoking outcomes are associated with greater TNP compliance (Cooper et al., 2004; Fish et al., 2009; Lam, Abdullah, Chan, & Hedley, 2005), although a number of studies report overall low levels of compliance with TNP directions (Fish et al., 2009; Lam et al., 2005; Stein, Anderson, & Niaura, 2006; Wiggers et al., 2006). No study in this review reported compliance to TNP by sex. The few non-placebo-controlled clinical trial studies that have examined sex and TNP adherence have reported mixed findings. One study that administered TNP and one of three behavioral interventions to 619 adult smokers in primary care settings noted greater TNP adherence in men compared with women (Cooper et al., 2004), whereas a second study of 101 adults from the community receiving TNP and one of three psychosocial interventions found no interaction of sex and patch adherence (Alterman, Gariti, Cook, & Cnaan, 1999). Additional placebo-controlled studies would clarify whether TNP compliance differs by sex and how compliance is associated with treatment outcomes for men and women.

Side Effects

Only one study in the current review examined the experience of TNP side effects by sex.

Although male and female participants in this study equally reported skin irritation, the most common side effect associated with TNP (Hays & Ebbert, 2010; Mills, Wu, Lockhart, Wilson,

& Ebbert, 2010), more women than men reported discontinuing TNP because of skin irritation (Levin et al., 1994). Laboratory study data suggest that women are more sensitive to some effects of TNP (Evans et al., 2006; Kleykamp et al., 2008). More research is needed to clarify whether women also experience greater sensitivity to the effects of TNP versus placebo during long-term use of TNP to quit smoking and whether the association of side effects to duration of use of TNP and smoking cessation outcomes are different for women versus men.

Withdrawal Symptoms and Cravings

Women experience both greater and more variable withdrawal symptoms than men when they abstain from smoking (Jorenby et al., 1995; Leventhal et al., 2007; Pang & Leventhal, 2013; Piasecki, Fiore, & Baker, 1998; Piasecki, Jorenby, Smith, Fiore, & Baker, 2003; Wetter, Fiore, et al., 1999; Xu et al., 2008). Although some laboratory research has provided evidence of sex differences in the experience of withdrawal with use of TNP (e.g., Vogel et al., 2014; Wetter, Fiore, et al., 1999), no clinical trial of TNP in this review reported examining withdrawal symptoms for women versus men. Laboratory and non-placebo-controlled clinical trials have reported mixed findings regarding the relationship of sex to TNP-related withdrawal relief (Evans et al., 2006; Kleykamp et al., 2008; Vogel et al., 2014; Wetter, Fiore, et al., 1999). A clinical trial that examined patterns of withdrawal with 44 mg/day TNP compared with 22 mg/day TNP (Jorenby et al., 1995), reporting no sex differences in cessation outcomes with the two doses, found that women demonstrated a greater representation in the patterns of withdrawal that were more variable over time as opposed to the pattern that showed a consistent and steady decline (Jorenby et al., 1995). Another study (Piasecki et al., 2003), which examined data from a large clinical trial of TNP and bupropion for smoking cessation, found greater withdrawal variability in women compared to men in the full analyzed sample ($p < .05$) and no significant difference by sex when restricting the sample to participants who lapsed to smoking ($p = .081$). Together, the data suggest that women experience a greater amount of some withdrawal symptoms and greater variability in withdrawal than men and that, because of mixed findings from the few studies that have investigated sex differences in TNP and withdrawal, more data are needed to clarify whether TNP relieves withdrawal symptoms in women to the same degree as men. Additionally, future studies can examine whether TNP differentially improves specific symptoms of withdrawal for men versus women.

Menstrual Cycle Phase

No study in the current review reported assessing for menstrual cycle phase in their female participants. Women experience differences in withdrawal symptoms and cravings during different phases of the menstrual cycle with a number of studies reporting greater withdrawal and cravings during the late luteal or premenstrual phase (Allen, Allen, & Pomerleau, 2009; Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006) and increased premenstrual symptoms and withdrawal during the

premenstrual phase have been associated with smoking relapse (Allen et al., 2009). Studies have found mixed results regarding the ability to achieve abstinence by phase cycle. Some studies have found greater relapse rates for women who attempt to quit during the follicular phase (Allen, Allen, Lunos, & Hatsukami, 2009; Allen, Bade, Center, Finstad, & Hatsukami, 2008), whereas other studies report greater relapse for women who attempt to quit during the luteal phase (Carpenter, Saladin, Leinbach, Larowe, & Upadhyaya, 2008; Franklin et al., 2008). Few studies have examined differences in smoking behavior by menstrual cycle for women who are using TNP. Franklin and colleagues (2008) examined smoking outcomes for 102 participants (65 men, 16 women who began treatment during the follicular phase, 21 women who began treatment during the luteal phase), all of whom received TNP and behavioral counseling. A greater number of women who began the study during the luteal phase were smoking at 3 days (52%) and 9 weeks (71%) after the start of treatment compared with women who began the study during the follicular phase (Day 3, 19%; Week 9, 31%). The authors reported that, as a comparison, smoking rates for men were 25% at Day 3 and 68% at Week 9. Allen and colleagues (2000) examined differences in withdrawal symptoms, cravings to smoke, and premenstrual symptoms in 30 adult women, abstinent from smoking for 5 days, who received either active or placebo TNP. Women who received active TNP reported lower cravings, premenstrual pain, and premenstrual water retention than women who received the placebo patch, especially during the late luteal phase of the cycle. Future research can provide a better understanding how menstrual cycle phase affects success at quitting smoking using TNP for women at different phases of their cycle and for women compared to men. No study was found to report assessing for oral contraceptive use in female participants. Oral contraceptives, specifically those with estrogen, are associated with quicker metabolism of nicotine (Benowitz et al., 2006) which itself is associated with worse quit outcomes (Schnoll et al., 2009), suggesting that studies of the association of oral contraception to TNP outcomes are also warranted.

Pregnancy

TNP is classified as a Class D agent for pregnancy by the Food and Drug Administration, meaning that the drug contains risks for a human fetus, but the use of the drug by pregnant women may provide benefits that outweigh the risks (Food and Drug Administration, 2008), and smokers who are pregnant are encouraged to quit without using TNP (Fiore et al., 2008). As would be expected in clinical trials in the general population, no study in the current review included women who were pregnant. A small number of clinical trials have evaluated the safety and efficacy of TNP use to quit smoking during pregnancy. Two meta-analyses examined the use of NRT (Coleman, Chamberlain, Cooper, & Leonardi-Bee, 2011) or pharmacotherapy (Myung et al., 2012) during pregnancy. Coleman and colleagues (2011) examined 5 cessation trials ($n = 695$), 4 of which included TNP, and found no significant differences in smoking cessation rates with NRT versus placebo. Myung and colleagues (2012) reviewed seven trials ($n = 1386$), the five trials in the previous meta-analysis plus two studies that did not

include a placebo-control, and found improved smoking cessation outcomes for pregnant smokers who received active pharmacotherapy; however, this difference became nonsignificant when only placebo-controlled trials were analyzed. Two placebo-controlled clinical trials of TNP published after these two meta-analyses similarly found no significant differences in smoking rates for pregnant women who received active TNP compared with women who received placebo patch (Berlin, Grangé, Jacob, & Tanguy, 2014; Coleman et al., 2012). It should be noted that abstinence rates were low across both conditions in these studies (Berlin et al., 2014: TNP 5.5%; placebo patch 5.1%; Coleman et al., 2012: TNP, 9.4%, placebo patch 7.6%). Although some clinical trials of TNP versus placebo patch have reported no differences in safety or birth outcomes (e.g., preterm birth, perinatal mortality, miscarriage, spontaneous abortion; e.g., Berlin et al., 2014; Coleman et al., 2011; Coleman et al., 2012), the findings of other studies raise significant safety concerns for the use of TNP with pregnant women (Pollak et al., 2007) and nicotine itself is a teratogen associated with a range of harmful impacts on fetal development and birth outcomes (e.g., Dempsey & Benowitz, 2001; Pauly & Slotkin, 2008).

Similar to research cited earlier, women who are pregnant report low adherence to TNP instructions, and greater use of TNP is associated with a greater likelihood of successful smoking cessation (Fish et al., 2009).

Conclusions

TNP is a globally used treatment for smoking cessation and the most commonly used quit smoking pharmacotherapy in the U.S. This systematic review identified that more data by sex are needed for a wide range of treatment-related variables. There is a need to analyze cessation outcomes for TNP by sex and to include outcome data by sex in publications to continue to clarify the picture of the efficacy of TNP for women compared with men. In addition to the need for more smoking cessation data for men versus women, there are virtually no data from placebo-controlled clinical trials on differences in compliance and side effects, withdrawal and cravings, and menstrual cycle phase. Although this article focused on TNP, significant sex differences in response to treatments and cessation outcomes have been reported for other forms of nicotine replacement, as well as other medication and behavioral smoking interventions (e.g., Hatsukami, Skoog, Allen, & Bliss, 1995; Killen, Fortmann, Newman, & Varady, 1990; Scharf & Shiffman, 2004; Wetter, Kenford, et al., 1999), so it is important to examine sex differences in treatment response and outcomes for all smoking cessation treatments. This position is supported by recent legislation (Section 907 of the Food and Drug Administration Safety and Innovation Act -Pub.L. 112-144; Federal Register, 2012) requiring the Food and Drug Administration to develop an action plan to improve the completeness and quality of analyses of data on demographic subgroups (including sex) in summaries of product safety and effectiveness data. Ultimately, knowledge about sex-specific differences in aspects of TNP and other smoking interventions will help to tailor treatments with the goal of reaching the best cessation outcomes for all smokers, men and women.

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