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Sex Heterogeneity in Pharmacogenetic Smoking Cessation Clinical Trials

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Abstract

Approximately one-quarter of smokers who use treatments for nicotine dependence are able to achieve cessation. However, there is evidence that women do not respond as well to nicotine replacement therapy (NRT) and, perhaps, to bupropion, compared to men. In this contribution to the Special Issue of Drug and Alcohol Dependence concerning Women and Smoking, we begin with a brief overview of data supporting the role of sex in influencing response to NRT and bupropion. Next, we summarize the results of pharmacogenetic smoking cessation clinical trials which assessed sex as a moderator as well. A relatively small number of pharmacogenetic studies of nicotine dependence treatments have been conducted and 5 studies reported sex effects in these trials. Of these trials, sex moderated the association of genetic variation in drug pharmacokinetics or pharmacodynamics and treatment response. We conclude this paper with a summary and a brief discussion of the major caveats of this literature and priorities for future research.

Keywords

nicotine dependence; smoking cessation; sex; pharmacogenetic

1.0 Introduction

One of the major reasons for the significant decline in smoking rates over the past few decades has been the development of effective pharmacotherapies for nicotine dependence, including nicotine replacement therapy (NRT), bupropion, and varenicline (Schnoll & Lerman 2006). However, while the rate of tobacco use among men has declined by about 50% since 1960, the corresponding rate among women has decreased by only 38% (Giovino, 2002). In turn, sex differences in tobacco-related morbidity and mortality have been documented. For instance, the incidence of lung cancer-related deaths among women has increased by 600% over the past 50 years, whereas this rate has been decreasing among men since the 1980s (Patel et al. 2004). Further, tobacco use increases the risk for cervical cancer (Boyle et al., 2003) and may act synergistically to enhance the cancer risk associated with human papillomavirus infection

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(Beutner & Tyring, 1997). Consequently, addressing tobacco use among women, as hoped by this Special Issue of Drug and Alcohol Dependence, is an important public health concern.

While there are limited data on the comparative efficacy of varenicline across men and women, owing largely to its recent approval by the US Food and Drug Administration (FDA), empirical evidence suggests that women do not respond as well to NRT and perhaps not as well to bupropion, compared to men (Perkins & Scott, 2008; Killen et al., 2006). As discussed in more depth in a separate contribution to this Special Issue (Perkins, in press), nicotine dependence among women may be mediated less by physiological dependence and more by environmental factors, including smoking cues (also see Perkins and Scott, 2008). However, nicotine dependence and response to treatments, among both men and women, is also influenced by inherited differences in targets of pharmacotherapies and drug metabolism. Pharmacogenetic trials of nicotine dependence treatments evaluate the role of such genetic variability in determining treatment response, and several of these trials have also assessed the role of sex as a third factor (in addition to drug and genetic variation) in determining clinical outcome. A review of these clinical trials and the moderating effect of sex on genetic associations may provide useful information to broaden our understanding of sex heterogeneity in response to NRT and bupropion.

In this contribution to the Special Issue of Drug and Alcohol Dependence concerning Women and Smoking, we review evidence showing that women respond less favorably to NRT and bupropion (we omit varenicline given its recent FDA approval and limited pharmacogenetic assessment); review pharmacogenetic smoking cessation clinical trials which assessed sex effects; and discuss five pharmacogenetic smoking cessation clinical trials which identified sex as a moderator of treatment and genetic effects on treatment outcome. We conclude this paper with a summary and a brief discussion of the major caveats of this literature and the priorities for future research in this area.

2.0 Sex and Response to NRT and Bupropion

2.1 NRT

The US FDA has approved 5 NRTs for treating nicotine dependence: transdermal patch, gum, nasal spray, inhaler, and lozenge. NRTs are designed to reduce abstinence-induced symptoms including feelings of withdrawal and craving. Although these NRTs have similar efficacy, generally doubling the odds of quitting relative to placebo, only 15% to 30% of NRT-treated smokers are able to maintain abstinence for at least 6 months (Stead et al., 2008). While two meta-analyses of sex effects in NRT trials found that NRTs have equal efficacy in both sexes (Killen et al., 2002; Munafo et al., 2004), these studies either included trials that provided only partial outcome data, omitted relevant trials, and may have included trials that possessed limited statistical power to examine sex differences in light of low absolute abstinence rates (Perkins, 2004). A third meta-analysis of NRT clinical trials reported that men and women showed similar quit rates at 3 and 6 months post-quit date, but women were significantly less likely to be abstinent at the 12-month follow-up, vs. men (Cepeda-Benita et al., 2004). A more recent meta-analysis of 14 transdermal nicotine patch clinical trials, the most commonly used NRT, also showed that women, vs. men, show significantly lower quit rates (Perkins & Scott, 2008). In particular, 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 versus placebo patch was lower in women (1.61), than in men (2.20), and the interaction odds ratio was significant (OR = 1.40, 95% CI [1.02, 1.93], $p = .04$).

There are several possible explanations for sex differences in NRT efficacy, including variability in withdrawal symptoms, adverse effects (Wetter et al., 1999), rates of compliance (Cooper et al., 2004), and sensitivity to non-nicotine factors, such as smoking cues (Perkins et

al., 1999) between men and women. Variability in phenotypic factors related to smoking behavior, such as rate of nicotine metabolism, may also underlie sex differences in response to NRT (Benowitz et al., 2006).

2.2 Bupropion

Bupropion, an antidepressant originally marketed as Wellbutrin, was approved by the US FDA for the treatment of nicotine dependence in 1997. The exact mechanism through which bupropion treats nicotine dependence is not fully known, but bupropion efficacy is likely mediated, in part, by the blockade of neurotransmitter uptake, particularly dopamine and norepinephrine uptake (Ascher et al., 1995) and/or nicotinic receptor antagonist effects (Slemmer et al., 2000). A second mechanism of bupropion efficacy may involve the drug's ability to prevent or diminish post-cessation negative mood symptoms and weight gain, which are frequently cited as causes of relapse among smokers (Lerman et al., 2002; Hurt et al., 1997). A meta-analysis that included 19 placebo-controlled trials with more than 4,000 subjects found that bupropion more than doubled the odds of cessation versus placebo for up to 12 months after the quit date (Hughes et al., 2004).

Overall, relative to NRT, the data concerning sex as a moderator of bupropion response for smoking cessation is more equivocal. On the one hand, a pooled analysis of 12 randomized clinical trials of bupropion for smoking cessation indicated that, while women showed significantly lower quit rates regardless of treatment arm (placebo vs. bupropion), their quit rates on bupropion were equivalent to those of men (Scharf & Shiffman, 2004). On the other hand, there are some data suggesting that women respond less favorably than men to bupropion. When bupropion was evaluated in a clinical trial that assessed the benefits of standard vs. extended treatment with bupropion, women showed significantly lower quit rates, compared to men, at week 11, week 25, and week 52 (Killen et al., 2006). Although this study does not provide conclusive answers regarding a sex effect for bupropion response, one important feature of this trial, relative to other bupropion clinical trials, was the a priori stratification of women and men to treatment arm. In this trial, women reported lower treatment compliance, and greater withdrawal, depression, and treatment side-effects, vs. men, suggesting potential mediators of the sex effect in this study. In another study that examined the number of days to lapse for men and women randomized to receive 10-weeks of either bupropion or placebo treatment, females reported significantly fewer days to lapse than male participants (Wileyto et al., 2005).

Thus, although bupropion may yield comparable initial quit rates for men and women, there is some, albeit limited, data suggesting that women may lapse more quickly and have lower rates of sustained abstinence following bupropion treatment in the long-term, compared to men. Assessment of the relationship between genetic variability in the target of bupropion or the metabolism of bupropion and treatment response, between men and women, may help to understand data suggesting a less favorable bupropion response among women.

3.0 Pharmacogenetic Studies of Treatments for Nicotine Dependence

Two meta-analyses concluded that 60–67% of the variability in smoking persistence (i.e., transitioning from initiation to dependence) is attributable to genetic factors (Sullivan & Kendler, 1999; Li et al., 2003). More recent studies report that 55–69% of the variance in smoking persistence is attributable to genetic factors (Hamilton et al., 2006; Hardie et al., 2006). Likewise, 51–58% of the variability in the ability to quit smoking is due to genetic factors (Xian et al., 2003; 2005; Hardie et al., 2006; Broms et al., 2006). An adoption study reported that adoptees who had quit smoking were more than 3 times as likely to have a biological sibling that had also quit smoking (Osler et al., 2001); if the adoptee was an ex-smoker, there was no greater risk that the adoptee's half-siblings were also former smokers.

The genetic influence on nicotine dependence is also reviewed in separate contributions to this Special Issue (see Bierut, in press; Uhl, in press)

Such data have sparked great interest in pharmacogenetic studies of treatments for nicotine dependence; these studies are designed to assess whether response to nicotine dependence medications is affected by genetic variants that influence nicotine metabolism (pharmacokinetics) or the targets (pharmacodynamics) of the medication (see Schnoll et al., 2007; Lerman et al., 2007). A summary of pharmacogenetic smoking cessation trials is presented in Table 1. All trials assessed genetic associations with response to NRT or bupropion, except one, which evaluated the serotonin-norepinephrine reuptake inhibitor (SNRI), venlafaxine. A review of these trials indicated that: 7 studies did not report sex as a moderator of gene $\times$ treatment effects, 19 studies reported that sex did not moderate the gene $\times$ treatment effect, and 5 studies reported a significant sex effect. The 5 studies that reported a sex effect assessed enzymes that metabolize drugs (CYP2B6), genes that influence dopamine concentrations (DRD2, COMT), and genes that affect endogenous opioids (OPRM1).

4.0 Sex Effects in Pharmacogenetic Studies of Nicotine Dependence Treatments

4.1 NRTs

A series of pharmacogenetic studies of response to transdermal nicotine have been published by a research team in the United Kingdom (Johnstone et al., 2004; Yudkin et al., 2004; Munafò et al., 2007). The original clinical trial compared transdermal nicotine patch to placebo patch and collected DNA from 755 of 1500 smokers subsequent to completion of the study. Based on previous evidence that nicotine's rewarding effects are mediated, in part, by dopaminergic mechanisms (e.g., blockade of dopamine reuptake; Pontieri et al., 1999; Balfour, 2002), pharmacogenetic analyses focused on genes in the dopamine reward pathway. A long-term follow-up of this trial that included outcome data out to 8 years, identified an association of the dopamine D2 receptor (DRD2) Taq1 A1 variant, originally thought to be in the DRD2 gene, but later determined to be in a neighboring gene, ANKK1 (Neville et al., 2004), with abstinence at all follow-up assessments (1-, 12-, and 24-weeks, and 1- and 8-years; Yudkin et al., 2004). The Taq1 A A1 polymorphism in DRD2 is related to a reduced number of dopamine binding sites (Thomson et al., 1997). However, the genotype effect on treatment outcome was observed only among women. In particular, at each time-point, women with at least one A1 allele of DRD2 had greater benefit from active patch, compared to women homozygous for the A2 allele. The gene $\times$ treatment effect for men approached significance at 24 weeks, 52 weeks, and 8 years, but the nature of the interaction was in the opposite direction as that found for women. The small number of men providing data, relative to women, in this trial may have contributed to the lack of statistical significance for men. These findings suggest that the efficacy of transdermal nicotine may be influenced by different genetic and biological factors in males and females such as dopamine receptor binding differences across the sexes (Munro et al., 2006).

The enzyme catechol-o-methyl-transferase (COMT) is expressed in brain where it metabolizes and inactivates dopamine. There is a common polymorphism (val108/158met) in the COMT gene which results in conversion of a val high-activity allele to a met low-activity allele, resulting in a three- to four-fold reduction in COMT activity and increased dopamine (Lachman et al., 1996). COMT is also involved in estrogen metabolism (Shield et al., 2004), supporting the possibility that COMT associations with smoking behavior may vary by sex. Collilla et al. (2005) examined quit rates from transdermal nicotine and nicotine nasal spray among men and women and across COMT genotypes. Among women, but not in men, this polymorphism was associated with smoking cessation, independent of the type of NRT. Among women, the odds

of abstinence increased significantly with each met allele (lower COMT activity, higher dopamine concentrations). The met allele might facilitate smoking cessation for women by attenuating changes in dopamine levels following nicotine exposure, thereby reducing positive reinforcement from smoking lapses. Effects of the COMT enzyme on estrogen metabolism may also contribute to sex differences in associations of COMT with smoking cessation; however, this requires further investigation. Notably, in this study, women with the COMT Met/Met allele were more likely to be former vs. current smokers in a case-control study, thereby confirming an association between the COMT alleles and smoking behavior among women across two independent samples.

Lastly, the role of a functional polymorphism in the mu-opioid receptor (OPRM1) gene was examined in the UK placebo-controlled smoking cessation clinical trial of transdermal nicotine (Munafo et al., 2007). Nicotine increases levels of endogenous opioids that bind to mu opioid receptors on GABA interneurons in the ventral tegmental area (VTA), which has downstream effects on dopamine (Nestler, 2005). The OPRM1 gene has a common functional Asn40Asp (A118G) missense SNP; the G (Asp40) allele of OPRM1 yields lower mRNA and lower protein levels, suggesting that this allele is a partial loss of function allele (Zhang et al., 2005). In addition, sex influences mu-opioid binding (Zubieta et al., 1999), possibly through the mediation of estrogen regulation (Mills et al., 2004), and the OPRM1 gene has been found to be related to the relative reinforcing value of nicotine (i.e., how rewarding the drug is perceived to be) in women, but not in men (Ray et al., 2006). The pharmacogenetic clinical trial (Munafo et al., 2007) identified a gene X sex interaction that was significant or marginally significant at all time-points (up to 8-years). In particular, men homozygous for the AA allele of OPRM1 were more likely to be abstinent than those in the GA/GG group, whereas the reverse was true for female subjects. In addition, there was a marginal 3-way interaction at week 26, which indicated that women with the G allele in the placebo condition showed a higher likelihood for abstinence; there was no interaction effect for men between treatment condition (placebo vs. active patch) and OPRM1 genotype. These results are consistent with data showing that the G allele reduces the rewarding effects of nicotine in women only (Ray et al., 2006), possibly because of increased mu-opioid receptor binding activity among women, compared to men (Zubieta et al., 1999).

4.2 Bupropion

A placebo-controlled pharmacogenetic clinical trial examined the role of functional variation in the cytochrome p450 CYP2B6 gene, which has been implicated in bupropion kinetics (i.e., absorption, metabolism, and excretion of the drug; Kirchheiner et al., 2003) as well as in brain metabolism of nicotine (Miksys et al., 2003). Participants in this trial (Lerman et al., 2002) provided blood samples and received bupropion (300 mg/day for 10 weeks) or placebo, plus behavioral counseling. Smokers with a reduced function variant of CYP2B6 (1459C>T; slower metabolizers) reported greater increases in cravings for cigarettes following the target quit date and had significantly higher relapse rates, compared to those with normal function CYP2B6 alleles (i.e., normal metabolizers). These effects were modified by a significant sex X genotype X treatment interaction, such that bupropion attenuated the effects of genotype among female smokers. For men, CYP2B6 polymorphism did not affect quit rates across treatment arms; but, for women, bupropion increased quit rates for women who possess a reduced activity variant in CYP2B6. Women with a reduced activity variant of CYP2B6 on placebo had a 19% quit rate but, with bupropion, the quit rate increased to 54%. There was no gene X treatment effect for treatment-related side effects, suggesting that bupropion pharmacokinetics may not be responsible for this effect. However, women reported greater negative mood from withdrawal, compared to men, and bupropion's effects on mood may underlie beneficial effects for women who have a reduced function variant of CYP2B6.

In another trial, Swan et al. (2005) evaluated the role of the DRD2 Taq1A polymorphism in an open-label, randomized effectiveness trial comparing 150mg and 300 mg doses of bupropion. The effect of bupropion on nicotine dependence is mediated, in part, by the medication's inhibition of dopamine reuptake, suggesting the potential role of the Taq1A A1 polymorphism in DRD2, which is related to a reduced number of dopamine binding sites (Thomson et al., 1997). Further, DRD2 receptor affinity may be lower in women than in men (Pohjalainen et al., 1998), suggesting the possibility for sex moderation of the gene X treatment interaction effect. In this trial, smokers were randomized to either 150mg or 300mg bupropion and either basic or intensive behavioral counseling. Compared to women homozygous for the A2 allele of DRD2, women with at least one A1 allele were less likely to quit smoking; there was no effect of genotype on cessation among men. Further, women with at least one DRD2 A1 allele were less able to tolerate the adverse side effects of bupropion and were less adherent to drug treatment, than women with both A2 alleles. These data suggest that sex differences in the metabolism of bupropion may underlie adverse reactions, low adherence, and lower quit rates in bupropion smoking cessation clinical trials. Possible mechanisms for these relationships include variation in the estrous cycle phase, which can affect dopamine transmission, and lower DRD2 receptor affinity among women, vs. men (Swan et al., 2005).

5.0 Summary and Major Caveats and Directions for Future Research

Unfortunately, the same significant reductions in tobacco use among men over the past several decades have not been achieved among women. As a consequence, women are experiencing higher rates of tobacco-related morbidity and mortality, including lung cancer, compared to men. This contribution to the Special Issue of Women and Smoking for Drug and Alcohol Dependence endeavored to review sex differences in pharmacogenetic smoking cessation clinical trials to enhance our understanding of issues related to the treatment of nicotine dependence.

Studies indicate that women, compared to men, respond less favorably to NRT and may respond less favorably to bupropion, although this should not be interpreted to mean that women should not utilize these pharmacotherapies to quit smoking. Pharmacogenetic clinical trials of smoking cessation treatments evaluate the role of genetic variation in drug pharmacokinetics or pharmacodynamics in determining treatment outcome and several of these trials have found that sex moderates the effect of genotypes on treatment outcome. However, there are several important limitations to this field that should be considered.

Overall, a relatively small number of pharmacogenetic studies of nicotine dependence treatments have been conducted and, in our review of these studies, only 5 found that sex was related to the association of genetic variation in drug pharmacokinetics or pharmacodynamics and treatment response. To summarize the results of these trials: 1) one study reported that genetic variation in CYP2B6 influences response to bupropion for women, such that women who possess a reduced activity variant in CYP2B6 may respond more favorably to bupropion; 2) two studies reported that genetic variation in DRD2 (Taq1A) may interact with sex to predict treatment outcomes, such that women with alleles that alter dopamine binding (DRD2 Taq1 A1) respond less favorably to bupropion and more favorably to NRT; 3) one study, involving 2 independent samples, reported that sex interacts with COMT val108/158met alleles to affect smoking behavior, such that women with COMT alleles that lower dopamine metabolism (met) may respond more favorably to NRT; and 4) one study reported that sex interacts with OPRM1 Asn40Asp alleles to affect response to NRT, such that female carriers of the G at this locus respond more favorably to NRT and counseling.

It should be emphasized that these findings, and any potential implications of these results, should not be used to guide treatment recommendations or personalize pharmacotherapy for

nicotine dependence based on sex and genotype. These findings should be considered hypotheses generating not confirmatory, since many genetic findings have not been replicated, many of the analyses are post-hoc, and these clinical trials are underpowered to detect complex interaction effects. Indeed, pharmacogenetic studies of nicotine dependence treatments were not statistically powered to examine sex $\times$ gene $\times$ treatment interactions. Further, most of the pharmacogenetic smoking cessation clinical trials have been conducted in smokers of European ancestry to minimize bias from population stratification, even though there are important racial and ethnic influences on smoking risk and tobacco-related morbidity and mortality as discussed by Wallace (in press) in this Special Issue. As such, this literature, as a whole, has limited external validity. A third important limitation to consider is that most of this literature is based on just a few clinical trials, so findings may be attributable to inflated type I error. Lastly, with two exceptions, these trials have focused only on genetic and sex moderation of NRT and bupropion response.

Consequently, to further enhance our understanding of the role of genes and sex in determining response to pharmacotherapies for nicotine dependence, future research is needed to replicate the findings reported thus far in the literature. Such studies should be designed at the outset to address these research questions and to ensure adequate statistical power to test for complex interaction effects. Meta-analytic techniques may be applied to overcome issues related to the relatively small sample sizes of the initial trials and to achieve adequate statistical power without conducting new, large clinical trials. Further, novel methodological approaches, including genome-wide association studies, can help identify influential sources of genetic variation to subsequently evaluate in clinical trials (see Bierut, in press; Uhl, in press). Future studies should also be sure to evaluate these research questions in ethnically/racially diverse samples and, importantly, research is needed to assess the role of other neurobiological pathways (e.g., nicotine receptors) and evaluate gene and sex effects following treatment with varenicline.

This contribution to the Special Issue on Women and Smoking for Drug and Alcohol Dependence is intended to highlight the moderating role of sex in pharmacogenetic smoking cessation clinical trials. While pharmacogenetic smoking cessation clinical trials that assessed sex effects may offer useful knowledge for understanding variability in NRT and bupropion response among women, this area of research remains in its preliminary stages. At this point, decisions concerning treatment selection for women should not be made based on genetic variation. NRT and bupropion (and varenicline) remain effective and recommended treatment options for both women and men. Future pharmacogenetic smoking cessation clinical trials designed with consideration of the methodological and conceptual issues raised above may eventually lead to personalized treatments for nicotine dependence. It is hoped that this review helps to support continued studies in this area, which hold promise for enhancing the efficacy of treatments for nicotine dependence and reducing tobacco rates and tobacco-related morbidity and mortality among women.

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Table 1

Summary of Sex Effects in Pharmacogenetic Studies of Nicotine Dependence Trials

Gene	Treatment	Sex Interaction	Reference
CYP2A6	NRT	Not Reported	Malaiyandi et al. (2006)
CYP2A6 (3-HC/COT)	NRT	Not Reported	Lerman et al. (2006b)
CYP2B6	Bupropion	Yes	Lerman et al. (2002)
	Bupropion	No	Lee et al. (2007)
DRD2 (Taq1A)	NRT	Yes	Yudkin et al. (2004)
	NRT	No	Johnstone et al. (2004)
	Bupropion	Yes	Swan et al. (2005)
	Bupropion	No	David et al. (2007a)
	Bupropion	No	David et al. (2007b)
	Venlafaxine	Not Reported	Cinciripini et al. (2004)
	Venlafaxine	Not Reported	Robinson et al. (2007)
DRD2 (-141 Ins/Del)	NRT	No	Lerman et al. (2006a)
	NRT	No	Dahl et al. (2006)
	Bupropion	No	Lerman et al. (2006a)
DRD2 (C957T)	NRT	No	Lerman et al. (2006a)
	Bupropion	No	Lerman et al. (2006a)
DRD4	NRT	Not Reported	David et al. (2008)
DBH	NRT	No	Johnstone et al. (2004)
COMT	NRT	Yes	Colilla et al. (2005)
	NRT	No	Johnstone et al. (2007)
	NRT	No	Munafo et al. (2008)
	Bupropion	Not reported	Berrettini et al. (2007)
SLC6A3	Bupropion	No	Lerman et al. (2003)
	Bupropion	No	Swan et al. (2007)
	NRT/Bupropion	No	O'Gara et al. (2007)
OPRM1	NRT	No	Lerman et al. (2004)
	NRT	Not Reported	Ray et al. (2007)
	NRT	Yes	Munafo et al. (2007)
5-HTTLPR	NRT	No	David et al. (2007c)
	NRT	No	Munafo et al. (2006)
CHRNA4	NRT	No	Hutchison et al. (2007)

Note. NRT = Nicotine Replacement Therapy.