Review

Study Characteristics Influence the Efficacy of Substance Abuse Treatments: A Meta-analysis of Medications for Smoking Cessation

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Abstract

Background: Understanding study characteristics' influence on treatment efficacy could improve interpretation of trials' outcomes. We examined study characteristics as predictors of outcomes in clinical trials of medications for tobacco use.

Methods: We obtained and analyzed data on 44 trials of nicotine gum, 37 trials of nicotine patch, 27 trials of varenicline, and 43 trials of bupropion from Cochrane reviews. We extracted and analyzed data for 15 study characteristics, odds ratios (ORs), and percent abstinent in control and medication conditions. We used general linear models to determine which study characteristics explained the variability among outcomes after controlling for medication characteristics.

Results: Study characteristics accounted for 12% of the variance in odds ratios among patch trials, 16% among gum trials, 16% among varenicline trials, and 34% among bupropion trials above and beyond medication characteristics. Patch and gum trials with industry funding had larger odds ratios than those without. Among patch trials, this appeared to be due to less abstinence in industry-funded trials' control conditions. Bupropion trials published earlier had larger odds ratios, which appeared to be due to less abstinence in control conditions. The reason for study characteristics' influence on varenicline trials was unclear.

Discussion: Study characteristics influenced the assessment of treatment efficacy above and beyond medication characteristics in smoking cessation trials. Our findings that study characteristics are associated with higher or lower efficacy does not suggest that the effect size under one versus another condition is the more valid outcome. Future studies are needed to determine which study characteristics reliably influence efficacy because this would help investigators and clinicians interpret trials.

Implications: Study characteristics influenced the estimates of treatment efficacy but individual characteristics' influence on efficacy appeared to differ among different medications for smoking cessation. We encourage researchers to report study characteristics to improve interpretation of findings and systematic reviews, and to account for nontreatment-related variables to better estimate the efficacy of treatments.

Introduction

Clinical researchers have long recognized that study characteristics can influence estimates of treatment efficacy, that is, the difference between active and control condition outcomes.^{1–3} However, which and how much study characteristics predict outcomes is unclear. Knowledge of which specific characteristics lead to increased or decreased effect sizes of treatments, and whether effects are due to changes in the active or control condition, should improve interpretation of findings from clinical trials and inform researchers of the potential impact of contextual influences and methodological decisions. In this meta-analysis, we test a large number of study characteristics as predictors of the estimate of efficacy of medications for tobacco use disorders.

Prior meta-analyses of medications for tobacco use disorders tested a limited number of study characteristics and examined different characteristics as predictors of estimates of treatment efficacy. Separate meta-analyses found that having industry funding¹ and shorter time to follow-up⁴ were associated with greater treatment efficacy. Another study found earlier publication date⁵ was associated with more abstinence in trials' control and active conditions. This decline in abstinence appeared to be associated with a shift from group to individual treatment formats⁵ or increasingly dependent participants.^{5,6} Others found that type of measurement of abstinence, for example, point prevalence versus prolonged abstinence, was not associated with treatment efficacy.^{7,8} Most meta-analyses examined only a few methodological variables and may have missed testing important characteristics or underestimated the total amount of variance accounted for by study characteristics.

Cochrane reviews identified nicotine replacement therapy (NRT),⁹ varenicline,¹⁰ and bupropion¹¹ as effective treatments for tobacco use disorder. These meta-analyses examined several study characteristics as moderators of outcomes and results varied among trials of different medications. Importantly, these analyses were limited to examining a single study characteristic at a time and, therefore, did not examine study characteristics' influence on treatment efficacy in the context of multivariable analyses. This variability in findings may be because most meta-analyses examined only a few variables and only one outcome. The present analysis improves on prior studies by examining (1) many (ie, 15) study characteristics and (2) three different outcomes (odds ratio [OR], and abstinence in active and control groups).

Methodology

We examined randomized controlled trials that met inclusion criteria for the Cochrane reviews of NRT,⁹ varenicline,¹⁰ and bupropion.¹¹ We restricted analysis to trials in the Cochrane reviews because of Cochrane's rigorous assessment and documentation of trials' methodologies, its inclusion of data on multiple study characteristics, and its reputation. The Cochrane's reviews of NRT,⁹ varenicline,¹⁰ and bupropion¹¹ provide information on identification and selection of trials, including search strategies and PRISMA flowcharts of included and excluded trials. In all three reviews, randomized clinical trials of the medication versus control condition for adult cigarette smokers that assessed abstinence at at least 6 months were included.

We limited our analyses to NRT, varenicline, and bupropion because these are considered the most commonly used effective medications for tobacco use.¹² Among the NRT medications, we included trials of patch and gum but could not include trials of lozenge, inhaler, and intranasal or oral sprays due to insufficient data on

study characteristics.⁹ The analysis protocol was not registered. The Cochrane group excluded 107 NRT studies, 48 varenicline studies, and 80 bupropion studies primarily because they were short term (ie, <6 months), laboratory studies, or did not assess abstinence as an outcome. We extracted data for the 43 patch, 56 gum, 28 varenicline, and 44 bupropion trials included in the Cochrane reviews. Most included trials used a placebo-controlled condition. However, we also included the 17% of trials (one patch, 24 gum, three bupropion, and one varenicline) that used a no-medication control instead of placebo because these trials were included in the Cochrane reviews. We included trials' use of placebo as a study characteristic in our analyses to examine the influence of using placebo versus no treatment control conditions.

Data Extraction

Data used in this meta-analysis were obtained from the NRT,⁹ varenicline,¹⁰ and bupropion¹¹ Cochrane reviews. Variables tested in this meta-analysis were limited to those included in the Cochrane reviews. We included all study characteristics available in the Characteristics of Studies sections in the Cochrane reviews in our meta-analysis. In addition, we also coded (1) whether trials used placebo in control conditions and (2) the percent probability of being randomized to a treatment versus control condition as study characteristics for this meta-analysis. All three Cochrane reviews assessed the same categories of risk of bias: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding (performance and detection bias), (4) incomplete outcome data (attrition bias), and (5) other bias. We coded risk of bias as a study characteristic but did not include it in our analysis because Cochrane concluded the bias for most trials was unclear (see [Supplementary Document A](#)). Two research assistants independently entered data on 29 study characteristics, three dependent variables (odds ratio and percent abstinent in control and medication conditions), and six medication characteristics (outlined in [Table 1](#) and [Supplementary Document A](#)). We defined medication characteristics as methods of using medications (eg, dosage, treatment duration, and whether medication was used before quitting). We defined study characteristics as any nonpharmacological variable regarding trials' design, participants, or context (eg, time to last follow-up, participants' gender, and publication date). The rate of disagreement in coding across the variables was 1%.

Some study characteristics were rarely reported. To have an adequate sample, we did not examine characteristics that had more than 20% missing data. A total of 15 of the 29 study characteristics in the Cochrane reviews were retained. [Table 1](#) provides a description of included study characteristics, and [Supplementary Document A](#) provides a description of excluded characteristics.

Analyses

Our main questions were how much do study characteristics influence the estimate of efficacy (ie, odds ratio), which study characteristics explain that influence, and whether any influence on efficacy was due to changes in the active or control conditions. The overall strategy was to first control for medication characteristics in order to test the influence of study characteristics over and above the influence of pharmacological treatment. If we found that a study characteristic influenced the estimate of treatment efficacy, we examined the influence of that characteristic as a predictor of percent abstinent in trials' medication and control conditions. We tested the influence of study characteristics first when trials of different medications

Table 1. Description of Included Variables^a

Variable	Description	Missing, % (no.) of studies where data were unavailable
Dependent variables		
Mean odds ratio	2.6 (SD = 3.1)	None
Mean percent abstinent in control conditions	13 (SD = 8.4)	None
Mean percent abstinent in medication conditions	22 (SD = 11.4)	None
Medication characteristics covariates		
Medication class	25% NRT patch trials, 33% NRT gum trials, 26% bupropion trials, and 16% varenicline trials	None
Mean medication dosage ^b (mg)	20 (SD = 3.6) for NRT patch trials, 2 (SD = 0.5) for NRT gum trials, 300 (SD = 0) for bupropion trials, and 2 (SD = 0) for varenicline trials	12% (5), 27% (15), 11% (5), 4% (1)
Trials that used varied medication dosage	74% NRT patch trials, 14% NRT gum trials, 14% bupropion trials, and 64% varenicline trials	None
Trials where medication was optional	9% NRT gum trials only	None
Mean treatment duration (days)	71 (SD = 31) for NRT patch trials, 70 (SD = 26) for bupropion trials, and 96 (SD = 54) for varenicline trials; not retained for NRT gum trials because 73% missing	9% (4), 2% (1), 4% (1)
Trials that provided prequit medication	30% bupropion trials and 21% varenicline trials	None
Study characteristics		
Mean percent male participants	49 (SD = 19.8) across all trials	18% (30)
Trials that biochemically validated abstinence	87%	1% (1)
Mean percent probability of being randomized to treatment	54 (SD = 10) across all trials	None
Mean publication year (range 1979–2016)	1999 (SD = 9.3) across all trials	1% (2)
Mean sample size	187 (SD = 246) for control and 214 (SD = 307) for medication conditions across all trials	None
Trials that provided counseling ^c	8% none, 32% minimal, and 44% intensive	None
Country where trials occurred	21% other, 51% United States, and 27% Europe	None
Mean time to last follow-up (days)	301 (SD = 109) across all trials	1% (1)
Trials that recruited a restricted population ^d	28%	1% (1)
Government or nonprofit funded ^e	49% across all trials	13% (23)
Industry funded ^e	37% across all trials	13% (23)
Number of study sites	70% of trials had 1 site, 11% had 2–9 sites, and 19% had ≥10 sites	None
Outcome	71% of trials used prolonged abstinence and 25% of trials used point prevalence abstinence	5% (8)
Level of support provided to participants ^f (NRT)	NRT gum trials: 66% intensive, 17% none; NRT patch trials: 70% intensive, 23% none	4% (2), 7% (3)
Trials that included placebo	78%	5% (9)

NRT = nicotine replacement therapy, SD = standard deviation.

^aSee [Supplementary Document A](#) for a description of excluded study characteristics.

^bMean medication dosage was not retained in analyses for NRT gum, bupropion, and varenicline trials due to lack of variability.

^cWe categorized counseling composed of one session as minimal and more than one session as intensive.

^dTrials that studied participants with a unifying characteristic (eg, mental illness).

^e19% of studies had both industry and government or nonprofit funding.

^fCochrane defined trials that spent >30 min with participants (eg, conducting assessments) as intensive.

were combined in the same analysis and second when trials of nicotine patch, nicotine gum, varenicline, and bupropion were analyzed separately.

In order to test the three questions described in the previous paragraph, we used linear regressions with log-transformed odds ratios as the outcome as recommended by Fleiss.¹³ Some continuous predictors were transformed when the relationship with the outcome was found to be nonlinear. The results were not weighted by sample size because sample size was one of the study characteristics of interest and the main objective was to explain the variability in treatment efficacy rather than to estimate an overall effect size. We began by combining the data from all the medications to increase the power of the analysis. In the first step, the R^2 was calculated for the effect of the six medication characteristics. In the second step, to

reduce the effect of overfitting, which occurs when there is a large number of variables in relation to the sample size, the residuals from the first model were used instead of effect sizes when assessing the impact of the total set of study characteristics. The overfitting effect was further reduced by using backward selection to delete the least significant predictors one by one until only significant predictors were left. This reduced the probability of reporting an inflated R^2 . This resulted in a single final regression model with the medication characteristics and the final subset of significant study characteristics. Thus, unlike prior meta-analyses that conducted univariate assessments of each study characteristic, our multivariable meta-analysis identified the variables that account for most of the variance. Further, our analysis focused on how much of the overall study variation is due to study characteristics other than pharmacology.

To test the question of whether prediction of efficacy was associated with effects on control and/or medication conditions, we examined those study characteristics that predicted odds ratio as predictors of percent abstinent in each of the conditions (after arcsine transformation). Finally, we repeated all analyses separately among each medication class (ie, trials of NRT gum, NRT patch, varenicline, and bupropion). Given that our focus is on between-study variation rather than an overall estimate of efficacy, some typical aspects of meta-analyses, such as reporting tests of heterogeneity, were not pertinent for this meta-analysis. All analyses were run using SAS, version 9.4 (SAS Institute, Cary, NC), specifically Proc GLM and Proc GLMSELECT.

Results

The prevalence of reporting on study characteristics varied considerably among trials (Table 1). There were multiple significant correlations among study characteristics (see [Supplementary Document B](#)).

Medication Trials Combined

We excluded four trials of NRT patch, one of varenicline, and one of bupropion because we used treatment duration as a medication characteristic and data on treatment duration were unavailable in these trials. In addition, 12 trials of NRT gum, two trials of NRT patch, and six trials of bupropion were excluded because they did not report on the study characteristic retained in the model. Thus, we included a total of 44 trials of NRT gum, 37 trials of NRT patch, 27 trials of varenicline, and 37 trials of bupropion in this analysis.

After controlling for medication characteristics, study characteristics accounted for 3% of the variance. Having industry funding predicted greater odds ratios ($t = 2.15$, $p < .05$) and was the only significant study characteristic in the model. It was unclear whether this was due to the effect on abstinence in trials' control or medication conditions.

Six (4%) trials included multiple treatments and a single common control condition. Thus, each of these six trials contributed two effect sizes in our primary analysis when trials of different medications were combined. Findings were similar in a sensitivity analysis where we excluded these six trials.

NRT Trials

We excluded four trials of NRT patch because we used treatment duration as a medication characteristic and data on treatment duration were unavailable in these trials. In addition, we excluded 12 trials of NRT gum and two trials of NRT patch because they did not report on the study characteristic retained in the models. Thus, we

included a total of 44 trials of NRT gum and 37 trials of NRT patch when gum and patch trials were analyzed in separate models.

After controlling for medication characteristics, study characteristics accounted for 16% of the variance among gum trials and 12% among patch trials (Table 2). Study characteristics' effect on odds ratio appeared to be due to an influence on percent abstinent in control but not medication conditions for patch trials. Specifically, study characteristics accounted for 26% of the variance in patch trials' control conditions (Table 3). It was unclear whether the effect of study characteristics on gum trials' odds ratios was due to an influence on control or medication conditions. Having industry funding was again the only specific study characteristic that influenced estimates of treatment efficacy and it predicted greater odds ratios among both gum and patch trials (Table 2). The magnitude of this effect is illustrated in Figure 1. Industry funding's effect on odds ratios appeared to be due to less abstinence among industry-funded NRT patch trials' control conditions ($t = -3.5$, $p < .01$) but not medication conditions (Table 3). It was unclear whether industry funding's influence on NRT gum trials' odds ratios was due to an influence on control or medication conditions.

Varenicline Trials

We excluded one trial of varenicline because we used treatment duration as a medication characteristic and data on treatment duration were unavailable for this trial. Thus, we included 27 varenicline trials in this analysis. After controlling for medication characteristics, study characteristics accounted for 16% of the variance among varenicline trials (Table 2). This effect appeared to be due to study characteristics' influence on percent abstinent in control but not medication conditions. Specifically, study characteristics accounted for 17% of the variance among varenicline trials' control conditions (Table 3). Having industry funding was again the only specific study characteristic that influenced estimates of treatment efficacy. However, in contrast to NRT trials, industry funding in varenicline trials predicted smaller, not larger, odds ratios (Figure 1). In addition, industry funding predicted more, not less, abstinence in control ($t = 2.29$, $p < .05$) but not medication conditions (Table 3). This effect appeared to be driven by two influential trials that were small ($n = 21$ and 112) and had no abstinence in the control conditions, resulting in unusually large odds ratios ($OR = 10.73$ and 7.13). In a sensitivity analysis excluding these two trials, industry funding no longer predicted odds ratio or percent abstinent in varenicline trials' control conditions.

Bupropion Trials

We excluded one trial of bupropion because we used treatment duration as a medication characteristic and data on treatment duration

Table 2. Study Characteristics as Predictors of Odds Ratio

	NRT patch ($n = 37$)	NRT gum ($n = 44$)	Varenicline ^a ($n = 27$)	Bupropion ($n = 43$)
Medication characteristics ^b	$R^2 = .06$	$R^2 = .01$	$R^2 = .10$	$R^2 = .14$
Study characteristics	$R^2 = .12$	$R^2 = .16$	$R^2 = .16$	$R^2 = .34$
Industry funded	$t = 2.16^*$	$t = 2.88^{**}$	$t = -2.23^*$	—
Publication year	—	—	—	$t = -4.63^{**}$

NRT = nicotine replacement therapy.

^aWhen two extreme trials were removed, the $R^2 = .06$ and industry funding no longer predicted odds ratios.

^bSee [Supplementary Document C](#) for full findings for medication characteristics.

* $p < .05$, ** $p < .01$.

Table 3. Study Characteristics as Predictors of Abstinence in Control and Medication Conditions

	NRT patch (<i>n</i> = 37)	NRT gum (<i>n</i> = 44)	Varenicline (<i>n</i> = 27)	Bupropion (<i>n</i> = 43)
<i>Control conditions</i>				
Medication characteristics ^a	$R^2 = .01$	$R^2 = 0$	$R^2 = .03$	$R^2 = .14$
Study characteristics	$R^2 = .26$	$R^2 = .01$	$R^2 = .17$	$R^2 = .15$
Industry funded	$t = -3.50^{**}$	$t = -.55$	$t = 2.29^*$	—
Publication year	—	—	—	$t = 2.72^{**}$
<i>Medication conditions</i>				
Medication characteristics ^a	$R^2 = .02$	$R^2 = .08$	$R^2 = .06$	$R^2 = .03$
Study characteristics	$R^2 = .05$	$R^2 = .01$	$R^2 = .01$	$R^2 = 0$
Industry funded	$t = -1.39$	$t = 0.68$	$t = 0.39$	—
Publication year	—	—	—	$t = -0.11$

NRT = nicotine replacement therapy.

^aSee [Supplementary Document C](#) for full findings for medication characteristics.

* $p < .05$, ** $p < .01$.

Figure 1. Impact of significant study characteristics on odds ratio. ^aWhen two extreme trials were removed, industry funding no longer predicted odds ratios among varenicline trials. CI = confidence interval, NRT = nicotine replacement therapy.

were unavailable for this trial. Thus, we included 43 bupropion trials in this analysis. After controlling for medication characteristics, study characteristics accounted for 34% of the variance among bupropion trials (Table 2). This effect appeared to be due to study characteristics' influence on percent abstinent in the control but not medication conditions. Specifically, study characteristics accounted for 15% of the variance among bupropion trials' control conditions (Table 3). Publication date was the only significant study characteristic in the model. Bupropion trials published earlier had greater odds ratios than more recent trials (Figure 1). This effect appeared to be due to less abstinence among earlier published bupropion trials' control conditions ($t = -2.72$, $p < .01$) but not medication conditions (Table 3).

Study Characteristics That Did Not Predict Trials' Outcomes

The following study characteristics did not predict odds ratios in the final multivariable models when trials of different medications were combined or tested separately: percent male participants; whether studies biochemically verified abstinence; participants'

probability of being randomized to a treatment condition; sample size; whether studies provided intensive, minimal, or no counseling; country in which the trial occurred; time to the last follow-up for data collection; whether the study recruited a restricted population (eg, participants with mental illness); whether the study received any government funding; number of study sites; whether the study used prolonged or point prevalence abstinence as the primary outcome; the level of support provided to participants; and whether the trial included placebo in its control condition.

Abstinence Rate in Control Conditions as Predictors of Odds Ratios

Prior studies suggest that greater control group outcomes are associated with smaller effect sizes^{14,15}; thus, we also examined this possibility. In the current analysis, a greater percent abstinent in control conditions predicted smaller odds ratios when trials of the different medications were combined ($t = -6.07$, $p < .001$), among NRT patch trials ($t = -3.37$, $p < .01$), varenicline trials ($t = -8.15$, $p < .001$), and bupropion trials ($t = -4.47$, $p < .001$) but not NRT gum trials. Specifically, a 10% increase in abstinence among control conditions

was associated with an absolute decrease of 0.69 units (ie, a relative decrease of 31%) in odds ratio when medication trials were combined, 0.63 units (ie, 37%) decrease in odds ratio among NRT patch trials, 0.53 units (ie, 47%) decrease in odds ratio among varenicline trials, and 0.59 units (ie, 41%) decrease in odds ratio among bupropion trials.

Discussion

Summary of Results

Our findings indicate that study characteristics have a small but significant influence on the estimate of efficacy (ie, odds ratio) of tobacco treatment medications when trials of different medications were combined. When medications were tested separately, study characteristics accounted for a relatively larger proportion of the variance than when medication trials were combined. This may be because a relatively large proportion of the between-study variability when trials of four tobacco medications were combined was explained by the medication characteristics leaving a smaller proportion of the variance to be explained by the study characteristics. If this is correct, the results for the individual medications may be more valid estimates.

Among both gum and patch trials, industry funding was associated with greater odds ratios. This appeared to be due to less abstinence in control conditions among patch (but not gum) trials. This did not occur within the bupropion trials and industry funding's influence on varenicline trials was unclear. Among bupropion (but not gum, patch, or varenicline) trials, having an earlier publication date was associated with greater odds ratios and this appeared to be due to earlier trials having less abstinence in control conditions. In a separate analysis, more abstinence in control conditions was associated with smaller odds ratios among patch, varenicline, and bupropion (but not gum) trials.

Comparison to Other Studies' Results

Our finding that industry funding is associated with greater NRT efficacy is consistent with a prior review of NRT trials¹ as well as meta-analyses of medications for other health problems.^{16,17} The prior review interpreted this effect as an indication of a selection bias to publish trials with positive but not negative results.¹ The possibility of a publication bias is supported by a funnel plot in the NRT Cochrane review.⁹ Another explanation is that industry-funded patch trials recruited participants less likely to quit without medication (ie, more dependent or heavier smokers). In fact, both our meta-analysis and a prior meta-analysis¹⁸ found industry funding was associated with decreased abstinence among control conditions. We were unable to directly test the effect of dependence because of a lack of trials reporting on nicotine dependence (see [Supplementary Document A](#)).

We initially found opposite results among varenicline trials; that is, industry funding was associated with lower, not higher odds ratios but this effect was entirely due to two influential trials. Thus, it is unclear whether industry funding influences varenicline trials.

Our finding that bupropion trials published earlier had larger odds ratios than those published later is consistent with findings from our prior meta-analysis of alcohol treatments¹⁹ and a number of prior meta-analyses on medications for other mental and health problems.^{2,15,20-23} This effect could be because early trials recruited participants most likely to respond to the medication whereas later trials test more heterogeneous samples or participants more resistant

to current treatments. A prior study examined NRT for smoking cessation and found that abstinence among both medication and placebo groups decreased over time.⁵ In contrast, we found abstinence in bupropion trials' control conditions increased over time but did not change in medication conditions, resulting in an overall decline in treatment efficacy. One explanation for this pattern^{24,25} is that, over time, medications (ie, bupropion) gain public recognition as effective which could increase participants' treatment expectations and placebo response. Consequently, later trials could have more abstinence in control conditions and smaller odds ratios. Unfortunately we were unable to directly test this hypothesis. Further, publication date's influence on treatment efficacy was not replicated among trials of other medications. It is unclear why publication date was significant for bupropion but not patch, gum, or varenicline trials.

Implications

Our finding that study characteristics influence estimates of the magnitude of effect of smoking cessation treatment indicates these are important to consider when reporting and interpreting randomized controlled trials' findings. Specifically, we encourage researchers to report the study characteristics listed in [Table 1](#), in [Supplementary Document A](#), and in guidelines for clinical trials²⁶ and, when possible, report whether these study characteristics influenced outcomes. When interpreting randomized controlled trials, clinicians should be aware that odds ratios from industry-funded NRT trials and older bupropion trials are typically larger and that less abstinence in control conditions is associated with larger odds ratios among NRT patch, bupropion, and varenicline trials. However, the fact that a study characteristic (eg, presence vs. absence of industry funding) is associated with higher or lower efficacy does not suggest that the effect size under one versus the other condition is the more valid outcome. Thus, while our findings identify study characteristics that account for heterogeneity among trials' results, future research is needed to understand implications for validity.

Limitations and Strengths

One limitation is that we only included trials published in the Cochrane reviews on NRT,⁹ bupropion,¹¹ and varenicline.¹⁰ The Cochrane inclusion criteria were more stringent and thus included different trials than other meta-analyses.^{1,5} The Cochrane reviews only included trials conducted prior to 2012 for NRT, 2016 for varenicline, and 2013 for bupropion. In addition, the Cochrane reviews required a 6-month follow-up, eliminating many studies. We only tested study characteristics described in the Cochrane reviews and thus did not test other face-valid study characteristics that might have influenced efficacy (eg, participants' nicotine dependence or self-efficacy to quit). Further, some of the study characteristics tested in this meta-analysis (eg, publication date) cannot be altered by researchers but are useful to improve interpretation of trials' findings or future meta-analysis. Another limitation is that we had a relatively small number of trials for a large number of predictors. Multiple characteristics were correlated (see [Supplementary Document B](#)) and some may have been nonsignificant due to multicollinearity. Thus, our decision to retain only statistically significant variables to reduce the problem of overfit could have resulted in an underestimate in R^2 . Another limitation is that the results for the individual characteristics as predictors were not consistent across medications or analyses. On the other hand, our findings that study characteristics as a whole significantly increased or decreased estimates of the efficacy of medications were quite consistent across methods and medications.

A strength of our analysis is that the Cochrane reviews from which we drew our data both for independent and dependent variables are well respected for methodological rigor and were fairly consistent across reviews. Also, we tested many more study characteristics than prior reviews and examined three outcomes simultaneously (treatment efficacy and absolute outcomes in control and medication conditions). Other strengths include independent coding of data with almost no disagreements, sensitivity testing (testing with trials of different medications combined and separately), and presentation both of statistical reliability and magnitude of results.

Conclusion

Study characteristics significantly influence estimates of treatment efficacy above and beyond medication characteristics in trials of medications for smoking cessation. Determining whether studies show similar outcomes across these variables (eg, with government vs. industry funding) can help clinicians and administrators assess the reliability and validity of study results. We encourage researchers to report on study characteristics to improve readers' interpretation of findings and allow future systematic reviews to account for the influence of nontreatment-related variables.

Supplementary Material

Supplementary data are available at *Nicotine & Tobacco Research* online.

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Declaration of Interests

EMK and SN have nothing to disclose. JRH has received consulting and speaking fees from several companies that develop or market pharmacological and behavioral treatments for smoking cessation or harm reduction and from several nonprofit organizations that promote tobacco control. He also consults for Swedish Match and Philip Morris International on their harm reduction products.

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