Review

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Pharmacogenomics

From genes to treatments: a systematic review of the pharmacogenetics in smoking cessation

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Smoking cessation treatment outcomes may be heavily influenced by genetic variations among smokers. Therefore, identifying specific variants that affect response to different pharmacotherapies is of major interest to the field. In the current study, we systematically review all studies published in or after the year 1990 which examined one or more gene–drug interactions for smoking cessation treatment. Out of 644 citations, 46 articles met the inclusion criteria for the systematic review. We summarize evidence on several genetic polymorphisms (*CHRNA5-A3-B4, CYP2A6, DBH, CHRNA4, COMT, DRD2, DRD4 and CYP2B6*) and their potential moderating pharamacotherarpy effects on patient cessation efficacy rates. These findings are promising and call for further research to demonstrate the effectiveness of genetic testing in personalizing treatment decision-making and improving outcome.

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Despite tremendous public health advances, smoking continues to be the leading preventable cause of death worldwide [1–4]. Multiple treatment options and rigorous clinical practice guidelines have been developed but cessation failure remains common [5,6]. The benefits smokers receive from individual therapies vary widely and can be partially predicted by biomarkers [7–10]. The high cost of cessation failure combined with the wide range of therapies with variable benefits lead to a need to identify treatments that are most likely to be effective for an individual smoker. Thus, efforts have been directed toward a precision medicine approach: using biomarkers to identify patients who may benefit from treatment. To date, the most investigated biomarkers for smoking cessation pharmacotherapy have been genetic or metabolic [11,12].

Heritability estimates indicate that genomic factors drive the population variability in both smoking quantity and smoking cessation [13]. Prior to the advent of genome-wide association studies (GWAS), multiple candidate gene studies evaluated the association between genetic variants and smoking behaviors [14–17]. The most robust genetic association with smoking found to date is between smoking behaviors and the nicotinic receptor subunit gene *CHRNA5*, first identified in a 2008 GWAS [18]. Further, GWAS meta-analyses have led to the discovery of multiple other genetic factors associated with smoking [19].

There is a growing body of studies evaluating genome-based responses to smoking cessation therapies [11,20]. Evidence has pointed to at least two genetic loci for nicotine dependence and smoking cessation. The *CHRNA5-A3-B4* gene cluster on chromosome 15 has been associated with cigarettes smoked per day (CPD); with lung cancer and chronic obstructive pulmonary disease and with smoking cessation [21–32]. The cytochrome P450 2A6 and the NMR 3-hydroxycotinine/cotinine have been associated with CPD, lung and other aerodigestive cancers and smoking cessation [23,30,31,33–47]. Other candidate genes and pathways have been explored for association with smoking cessation [25,48–60].

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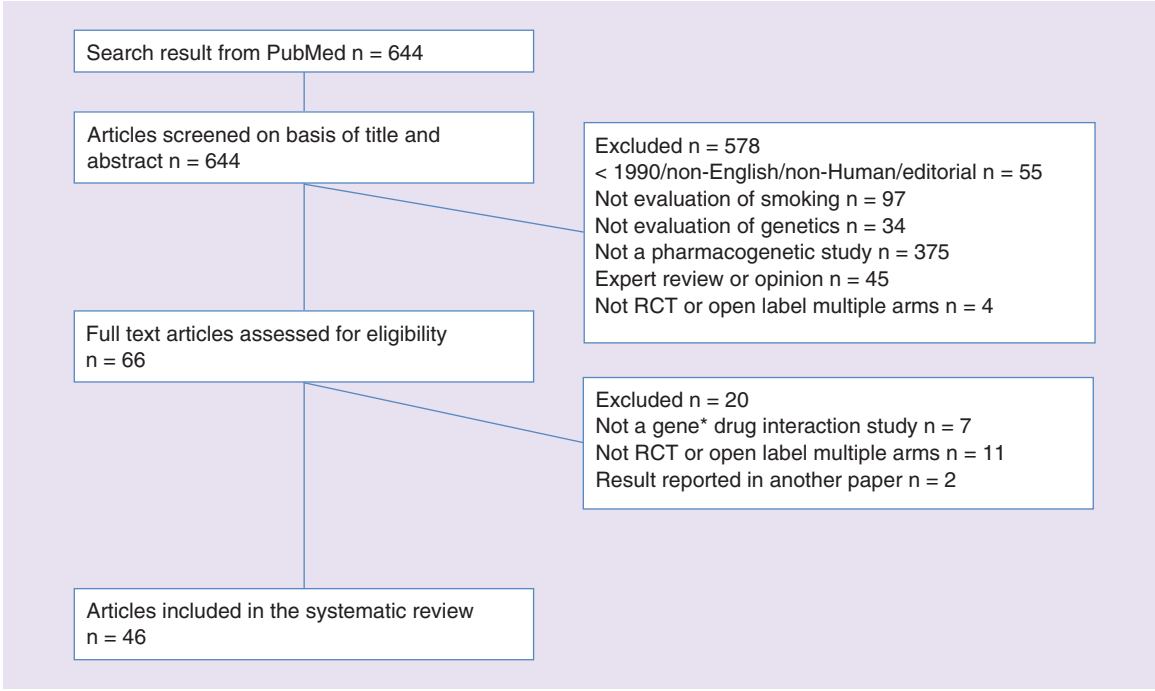

Figure 1. Flowchart of study inclusion.
RCT: Randomized controlled trial.

A recent Cochrane review of clinical trials that studied smoking cessation across genotypes identified associations between some polymorphisms in the *CHRNA3-A5-B4* region (rs1051730 and rs16969968) with short-term efficacy of nicotine replacement therapy (NRT), but not widespread differential treatment effects of pharmacotherapy [61]. Expanding upon this review, we conducted a systematic review of the literature that describes all studies of differential treatment effects of pharmacotherapy in smoking cessation.

Methods

We took a systematic approach to review pharmacogenetics studies of smoking cessation pharmacotherapy.

Search methods

On 22 May 2017 we searched PubMed for articles published after 1 January 1990 that were related to both smoking cessation and precision medicine. The full PubMed search text is given in the supplementary text, which identified 644 articles. Second, we reviewed the title and abstract of 644 articles and excluded 578 articles based on the following exclusion criteria (Figure 1): published before 1990, non-English, nonhuman, editorial, no smoking content, no genetic content, not a pharmacogenetic study, expert opinion or review, not a primary research report and not a clinical trial with multiple arms. For the remaining 66 articles, we reviewed the full text and excluded the additional 20 articles based on the same exclusion criteria. A total of 46 articles were included in the systematic review.

Inclusion criteria

The 46 articles were characterized based on the following study design criteria: trial design-randomized control trial (RCT) or open-label multiple treatment arms; comparison: placebo or other medication and outcome: efficacy, side effect or other outcomes. These characteristics for all included studies are outlined in Supplementary Table 1.

We then presented results in the following groups:

- RCT and open-label studies with comparative treatment arms for genes with identified GWAS hits (Table 1);
- RCT and open-label studies with comparative treatment arms for candidate genes based on a plausible biological rationale (Table 2).

Table 1. Genes based on genome-wide association study hits.

Gene	Chromosome	Medication	SNP	Number of positive studies (total n)	Number of negative studies
CHRNA5–A3–B4	15	NRT	rs588765	2 (3776)	2
			rs16969968	1 (328)	4
			rs16969968*rs680244	1 (1073)	0
			rs1051730	1 (2633)	3
			rs2036527	1 (1143)	0
			rs680244	0	1
			rs578776	0	5
			rs2229961, rs12914008, rs3813567, rs680244, rs8192475	0	1
		Bupropion	rs16969968*rs680244	1 (1073)	0
			rs16969968, rs578776	0	2
			rs588765, rs2036527, rs2229961, rs1051730, rs12914008, rs3813567, rs680244, rs8192475	0	1
		Varenicline	rs16969968	0	3
			rs578776	0	2
			rs588765, haplotype rs16969968 and rs588765	0	1
		Selegiline	rs3813567	1 (231)	0
			rs680244, rs16969968, rs578776, rs1051730, rs8192475, rs12914008	0	1
CYP2A6	19	NRT	Slow/Fast (genotype-based metric)	1 (709)	0
		Bupropion	Slow/Fast	0	1
CYP2A6-B6		NRT	rs4105144, rs6474412	0	1
		Varenicline	rs4105144, rs6474412	0	1
DBH	9	NRT	1368DBH A	1 (755)	0
			rs77905	0	1
		Bupropion	rs77905	0	1
CHRNA4	20	Varenicline	rs1044396	1 (483)	0k

Table includes only studies with efficacy outcome (abstinence or relapse).
Table includes genes that have GWAS hits and at least one positive gene x drug interaction study.
GWAS: Genome-wide association study; NRP: Nicotine replacement therapy.

To note, open-label studies with one treatment arm or studies not looking at gene × drug interaction were not included. For more details about the studies included, refer to Supplementary Table 1.

Results

Genes with identified genome-wide association studies hits

CHRNA5-A3-B4

Several variants in the *CHRNA5-A3-B4* gene cluster have been identified as moderators to the efficacy of NCT. A combined analysis of 8 randomized clinical trials comprising 2633 European-ancestry smokers showed that the minor alleles of rs1051730 and rs588765 were both associated with increased abstinence on NRT versus placebo at 6 months [21]. The variant rs1051730 is of particular importance because of its genome-wide significant association to smoking quantity [31]. However, rs1051730 was not found to be significantly associated with treatment outcomes in three other studies, albeit with small sample sizes [27,62,63]. Also, among 1143 African–Americans, individuals with the T-allele of rs588765 and A-allele of rs2036527 had higher and lower abstinence rates on nicotine gum versus placebo, respectively [32]. Of note, rs2036527 has been shown to be associated with genome-wide significance to CPD, in a genome-wide meta-analysis of 32,389 African-ancestry participants [24]. Another functional variant rs16969968, previously associated with smoking-related diseases such as cancer and COPD [64,65] has been shown in multiple studies to be associated with treatment response. A RCT of 1073 European–American smokers showed that individuals with high-risk haplotype, defined by rs16969968 and rs680244, had a threefold increased likelihood of responding to active treatment (NRT or bupropion) than individuals with low-risk haplotype [22]. Additional analyses performed on the NRT and placebo arms only (n = 328) revealed that individuals with the AA genotype of

Table 2. Candidate genes.

Gene	Chromosome	Medication	SNP	Number of positive studies (total n)	Number of negative studies
COMT	22	NRT	Val108/158Met (rs4680)	2 (991)	1
		Bupropion	rs165599	1 (511)	0
			rs165599*rs737865	1 (511)	0
			rs4680, rs737865	0	1
DRD2	11	NRT	Taq1A (rs1800497)	1 (755)	2
			Taq1B (rs1079597), 141C Ins/Del (rs1799732), Pro319Pro (rs6277), Exon 8	0	1
		Bupropion	Taq1A (rs1800497)	3 (1582)	3
			141C ins/del (rs1799732)	1 (414)	0
			C957T variant, Exon III VNTR	0	1
		Varenicline	Taq1A (rs1800497)	0	1
		Venlafaxine	Taq1A (rs1800497)	0	1
			Taq1B (rs1079597)	0	1
		Rimonabant	Taq1A (rs1800497)	1	0
DRD4	11	NRT	VNTR, C-521T	0	1
		Bupropion	Exon III VNTR	2 (1123)	1
CYP2B6	19	Bupropion	*CYP2B6*6* haplotype (rs2279343 + rs3745374)	1 (326)	1
			*CYP2B6*4* (rs2279343)	1 (478)	0
			*CYP2B6*5* (rs3211371), *CYP2B6*9* (rs3745274)	0	1

Table includes only studies with efficacy outcome (abstinence or relapse).
Table includes genes that have at least one SNP that has one or more replication studies and total n ≥500.
NRT: Nicotine replacement therapy; VNTR: Variable number of tandem repeat.

rs16969968 were more likely to be abstinent at the end of treatment to NRT compared with placebo [66]. Multiple studies however did not find a gene–drug interaction for this variant [32,63,67,68]. To note, the aforementioned results may have been affected by methodological limitations, unaccounted environmental moderators, small sample sizes and low statistical power. Importantly, the reported variants in *CHRNA5-A3-B4* cluster are highly correlated in haplotype structure among individuals of European ancestry. For example, the correlation between rs16969968 and rs1051730 is 1.0 in individuals of European ancestry. Therefore, different variants reported in these studies indicate a common genetic profile.

To note, no individual variants in the *CHRNA5-A3-B4* cluster were associated with either bupropion or varenicline (see Supplementary Table 1) [32,63,66–68]. The association of *CHRNA5-A3-B4* and response to transdermal selegiline was reported in one study, where the minor C allele of rs3814567 was associated with lower abstinence rates in selegiline-versus placebo-treated smokers [69].

CYP2A6

CYP450 2A6 enzyme represents the main metabolic enzyme for the conversion of nicotine to its inactive metabolite cotinine [70]. In a large GWAS of 83,317 smokers of European ancestry for the number of CPD, the SNP rs4105144 located in the *vw-B6* region was significantly associated with smoking quantity with an effect size of 0.39 ($p = 2.2 \times 10^{-12}$) [30]. This SNP, however, was not seen to moderate the effect of NRT or varenicline after 1 year of treatment in an open-label study of 525 Caucasian smokers, albeit showing significant association with tobacco dependence [68]. The interpretation of results is certainly limited by the absence of a placebo arm. In a placebo-controlled RCT of 709 European ancestry smokers, the effect of NRT, but not bupropion, differed with metabolism based on *CYP2A6* genotype [71]. compared with placebo, NRT was effective in fast, but not slow metabolizers, whereas bupropion proved effective regardless of *CYP2A6* genotype.

DBH

A GWAS found a significant association between *DBH* rs3025343 polymorphism and smoking cessation ($p = 3.6 \times 10^{-8}$) [31]. A placebo-controlled RCT of 755 smokers found that when considering only smokers with GA/AA of ^{1368}*DBH* and CT/TT of ^{32806}*DRD2*, subjects on the patch had an odds ratio (OR) of 3.59 of abstaining at

12 weeks compared with the subjects on placebo. This OR is reduced to 1.41 when running the same analysis on smokers with GG of ^{1368}*DBH* and CC of ^{32806}*DRD2* (P for difference in ORs = 0.04) [72]. Results for the same *DBH* SNP was not replicated in an open label study of 569 Caucasian smokers in Germany treated with either NRT or bupropion, at the physician's discretion [73].

CHRNA4

The *CHRNA4* gene garnered attention after being identified as a novel locus (rs2273500) for nicotine dependence in a GWAS meta-analysis of 17,074 Caucasian ever smokers [74]. *CHRNA4* gene expression may significantly affect smoking behavior as well as response to treatment. A cohort study of 483 smokers from mixed ethnicities who received treatment with either varenicline, bupropion and/or NRT, found that, on one hand, for subjects with CT/TT genotypes of *CHRNA4* rs1044396 polymorphism, success rate seems comparable between varenicline, varenicline plus bupropion (V+B) and bupropion plus NRT (B+NRT) (50.9, 50 and 42.2%, respectively). On the other hand, CC genotype puts subjects on varenicline at a particular disadvantage (success rate 29.5%) compared with the other two combination treatments (40% for V+B and 42.1% for B+NRT) [75].

Candidate genes based on pharmacogenetic association studies

COMT

Genes acting on the dopamine pathway are of obvious importance to the nicotine addiction pharmacogenetic studies. Namely, the gene coding for the enzyme COMT, which degrades dopamine released in the extraneuronal space. The Val108/158Met polymorphism or rs4680 of the *COMT* gene has been examined in multiple studies in relation to NRT but results have been inconclusive. An RCT of 741 smokers of European ancestry found greater benefit of active treatment compared with placebo on the likelihood of abstinence in the Met/Met genotype group, in comparison to the Met/Val + Val/Val group [76]. In contrast, a more recent study of 250 Asian smokers resulted in greater abstinence rates on NRT versus placebo in the group with Val/Val genotype versus the group with Met allele [77]. This may highlight the pharmacogenetic variability between different ethnicities, although the divergence in study results might simply be attributed to low power. A third RCT found no gene–drug association for this variant among 233 Caucasians smokers [62].

No gene–drug interaction was found either for rs4680 and bupropion in an analysis of two RCTs [78]. However, in a placebo-controlled RCT of 511 smokers from different ethnic backgrounds, Caucasians with at least one A allele of rs165599 had 19% abstinence on placebo and 33% on bupropion, while those with a GG genotype displayed 38% abstinence on placebo versus 22% on bupropion. In contrast, although trending towards the same results, no significant association was found among AA smokers, probably due to their small sample size [79].

DRD2

DRD2 gene is one of the most studied genes before the era of GWAS research in the pharmacogenetics of nicotine dependence, especially Taq1A, or rs1800497. This variant has been shown to alter DRD2 availability in postmortem striatal samples [80]. Among 755 smokers participating in a placebo-controlled RCT, those who possessed at least 1 T-allele had a significantly better response to NRT than placebo (OR = 2.8), while the observed OR for the response smokers with CC genotype on the patch compared with placebo was 1.41 (P for difference in ORs = 0.04) [72]. These results were not replicated however in two independent studies, an RCT and an open-label effectiveness trial [62,73].

Taq1A showed more remarkable results when studied in association with outcomes to bupropion treatment. Three independent studies, with a combined sample size of 1582 Caucasians, demonstrated consistently that smokers with *Taq1A* CC genotype had significantly higher rates of abstinence when treated with bupropion as opposed to placebo, while showing no difference when possessing one or two T alleles [73,81,82]. One open-label trial did not show however a gene–drug interaction with either bupropion or varenicline, perhaps owing to methodological limitations (open label, lack of placebo, mixed ethnicities) [83]. Furthermore, rs1799732, an ins/del variant of the *DRD2* gene, was associated with differential response to bupropion compared with placebo in that, on bupropion, individuals with CC genotype responded better than those with at least one N allele, whereas on placebo, smoker with at least one N allele were more likely to be abstinent [84]. This result still requires replication.

DRD4

Pharmacogenetic studies have mostly focused on a variable number of tandem repeats (VNTR) polymorphism located in exon III of the *DRD4* gene. A study of two pooled RCTs resulted in a significant gene–drug interaction for exon III VNTR in *DRD4* and bupropion on smoking lapse rates [78]. In a more recent trial, participants with at least one L allele of this same variant had higher odds of abstinence on bupropion compared with placebo while no differential effect was seen in SS participants [85]. This result was not replicated however in a subsequent study of 416 smokers of European ancestry [86]. No association was found between exon III VNTR and NRT in a separate placebo-controlled RCT of 720 Caucasians smokers [52].

CYP2B6

CYP450 2B6 gene, *CYP2B6,* encodes the isoenzyme that metabolizes bupropion to hydroxybupropion [87], therefore playing an important role in bupropion treatment outcome. In an open-label study of 478 smokers receiving bupropion or varenicline (+/- NRT, treated as a covariate), *CYP2B6*4* rs2279343 was observed to moderate the effect of bupropion, but not varenicline, on abstinence; wild-type AA genotype had higher success rate (48.0 %) compared with patients carrying AG or GG genotypes (35.5 %) on bupropion therapy (p = 0.05). Success rates in the varenicline sample remained virtually the same, regardless of genotype (43.4 and 43.2%, respectively) [83]. In another placebo-controlled RCT, 326 Caucasian smokers were randomized to bupropion or placebo and haplotyped for *CYP2B6*6* (which comprises rs2279343 and rs3745374). A genotype by treatment interaction was found after 10 weeks of treatment, the bupropion resulted in a higher abstinence rate than placebo in the *CYP2B6*6* group (*CYP2B6*1/*6* or *CYP2B6*6/*6* genotype), while no difference was observed between bupropion and placebo for *CYP2B6*1* group (*CYP2B6*1/*1*) [88]. The favorable effect of bupropion on smoking cessation in the *CYP2B6*6* group may result from the association of the latter on decreased bupropion metabolism in the liver [89], leading to increased bupropion plasma levels.

Discussion

With this systematic review, we identify the potential of genetic markers, identified by the GWAS discoveries, in predicting the efficacy of smoking cessation pharmacotherapy, based on the review of 46 studies. Multiple pharmacodynamics (e.g., *CHRNA5, DBH, CHRNA4*) and pharmacokinetic (e.g., *CYP2A6*) markers may predict efficacy of NRT, although both positive and negative studies exist. These discrepant results may be influenced by the sample ascertainment, study power, concurrent nonpharmacological therapy and other potential confounders. One of the most studied gene clusters is *CHRNA5-A3-B4*, which has been heavily linked to smoking characteristics including nicotine dependence [29], smoking quantity [90] and biomarkers of smoking [91,92].

Other GWAS-identified genes that were also shown to be associated with treatment efficacy included *CYP2A6*, a highly polymorphic gene that has been associated with multiple smoking phenotypes [36,45], *DBH* that catalyzes the conversion of dopamine to norepinephrine, hence playing an important role in the addictive properties of smoking and *CHRNA4* which encodes one of the subunits that form the nicotinic acetylcholine receptors, the activation of which leads to downstream dopamine release. We also reviewed 30 pharmacogenetic studies for a treatment by genotype effect of candidate genes, not yet identified by GWAS and show inconsistent results; however, multiple candidate genes (e.g., *COMT, DRD2, DRD4* and *CYP2B6*) may predict efficacy of bupropion.

In addition, we find that study design is crucial in the linkage of evidence and clinical applications. Randomization is key in determining whether the difference is based on the medication or other selecting factors and 30% of the studies categorized under pharmacogenetics do not have a randomization design. Having a placebo-controlled arm is another key in determining whether the medication efficacy (defined as medication vs placebo) varies by genetic markers. Many studies (60%) have no placebo control or use a different medication as control.

This systematic review also highlights the highly variable level of replication and nonreplication across these gene–drug pairs examined in the RCTs. For example, for *CHRNA5*, there are 4 reports from 11 studies showing positive pharmacogenetics associations and seven reports from 14 studies showing negative associations. Replication and sample size are both important in determining the strength of the evidence. In addition, few pharmacogenetics studies (10%) examined individuals of non-European ancestry. This clearly indicates a research gap because the effect and distribution of genetic markers may differ across diverse populations. For example, the frequency distribution of risk haplotypes in *CHRNA5-A3-B4* varied significantly across individuals of European, African and Asian ancestry [93]. Therefore, the validity and utility of these pharmacogenetics findings may vary across populations.

This review needs to be interpreted with several limitations in mind. First, findings that are not published or indexed in PubMed before 5/22/2017 are not included. However, PubMed is the primary database that indexes the medical literature including pharmacogenetics findings. Second, our focus is on pharmacogenetics (does the genetic marker predict a superior or inferior efficacy of medication compared with placebo or a different medication?), therefore we focused on papers with study design to answer the pharmacogenetic question (RCT with placebo control, RCT with comparative arms and open-label trial with comparative arms). This paper does not cover the other related questions (e.g., Does the genetic marker predict medication efficacy among individuals taking the same specific medication? Does the genetic marker predict smoking cessation among individuals taking the placebo or no medication?). Other reviews on genetics of smoking cessation [94,95] and a Cochrane review of different pharmacogenetics studies are available to provide insights into these related questions [61].

Conclusion

In conclusion, pharmacogenetics of smoking cessation is a rapidly growing field and likely to benefit from these scientific efforts: Larger GWAS of smoking behaviors [19,74] are likely to reveal exponentially increasing number of promising genetic markers for translational investigation; we need more clinical trials with genetic markers in diverse populations beyond European ancestry; meta-analyses of existing studies with careful adjudication are necessary because of the limited sample size in treatment trials and the need to compare and combine different pharmacotherapy arms. Replication and sufficient study power are only possible with large collaborative efforts and necessary for clinical translation and anticipate future use of polygenic predictors in predicting cessation success, smoking-related health outcomes, efficacy and side effects of pharmacotherapy. Smoking cessation pharmacotherapy such as NRT, bupropion and varenicline are moderately effective, yet have side effects. Identifying genes predicting efficacy and side effects may lead to improved treatment algorithms that further the precision treatment to help smokers quit successfully.

Executive summary

Methods

- We conducted a systematic review of pharmacogenetics in smoking cessation.
- We searched the PubMed, identified 644 articles and included a total of 46 articles based on predefined criteria.

Genes with genome-wide association studies hits

- *CHRNA5-A3-B4* gene cluster is the most extensively studied in smoking cessation pharmacogenetics. The following single nucleotide polymorphisms (rs1051730, rs588765, rs2036527 and rs16969968) have all shown significant interaction with nicotine replacement therapy (NRT) outcomes. However, several studies have not been able to replicate the results for rs16969968.
- *CYP2A6* genotype variation moderates the outcome to NRT but not bupropion.
- GA/AA of ^{1368}*DBH* and CT/TT of ^{32806}*DRD2* moderate the comparative effect of NRT to placebo.
- *CHRNA4* rs1044396 polymorphism moderates the effect of varenicline when compared with combined varenicline and bupropion or NRT and bupropion.

Candidate genes

- In *COMT,* rs4680 moderates the effect of NRT whereas rs165599 moderates the effect of bupropion.
- Moderating effects of *DRD2* Taq1A and *DRD4* exon III VNTR on bupropion treatment outcome have been replicated in several studies.
- *CYP2B6*4* and *CYP2B6*6* were both shown to be associated with bupropion treatment outcomes when compared with varenicline and placebo respectively.

Conclusion

- Multiple pharmacodynamics marker (e.g., *CHRNA5, DBH and CHRNA4*) and pharmacokinetic marker (e.g., *CYP2A6*) may predict efficacy of NRT.
- Multiple candidate genes (e.g., *COMT, DRD2, DRD4 and CYP2B6*) may predict efficacy of bupropion.
- Discrepant results may be influenced by the sample ascertainment, study power, concurrent nonpharmacological therapy and other potential confounders.
- Study design is crucial, particularly the use of randomization and a placebo-controlled arm.
- Meta-analyses of existing studies with careful adjudication are necessary to generate pharmacogenetic evidence before clinical translation.

Future perspective

With increasing use of genetic markers in medicine, we anticipate future use of polygenic predictors for patients in predicting cessation success, smoking-related health outcomes and for providers in choice of cessation pharmacotherapy for maximized efficacy and minimized side effects.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at:

https://www.futuremedicine.com/doi/suppl/10.2217pgs-2018-0023

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