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A review of pharmacogenetic studies of substance-related disorders*

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Abstract

Background—Substance-related disorders (SRDs) are a major cause of morbidity and mortality worldwide. Family, twin, and adoption studies have demonstrated the substantial heritability of SRDs. To determine the impact of genetic variation on risk for SRD and the response to treatment, researchers have conducted a number of secondary data analyses and quasi-experimental studies that target one or more candidate gene variants.

Methods—This review examines studies in which candidate polymorphisms were examined as mediator variables to identify pharmacogenetic effects on subjective responses to drug administration or cues or outcomes of medication trials for SRDs. Efforts to use a meta-analytic approach to quantify these effects are premature because the number of available studies using similar methods and outcomes is limited, so the present review is qualitative.

Results—Findings from these studies provide preliminary evidence of clinically relevant pharmacogenetic effects. However, independent replication of these findings has been sparse.

Conclusions—Although this growing body of literature has produced conflicting results, improved statistical controls may help to clarify the findings. Additionally, the use of empirically derived sub-phenotypes (i.e., which serve to differentiate distinct groups of affected individuals) may also help to identify genetic mediators of pharmacologic response in relation to SRDs. The identification of genetic mediators can inform clinical care both by identifying risk factors for SRDs and predicting adverse events and therapeutic outcomes associated with specific pharmacotherapies.

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Contributions

Only the authors listed are responsible for the content and preparation of this manuscript. JDJ conducted the literature review and produced the first version of the manuscript. SDC participated in filling any gaps in the literature and helped finalize draft versions of review of the manuscript. All authors have approved this manuscript for publication.

Keywords

Genetics; Pharmacogenetics; Pharmacology; Medications Development; Clinical Trial; Drug Abuse

1. BACKGROUND

1.1. Drug Use and Addiction

Addiction is a chronic disease characterized by compulsive drug seeking and use [National Institute on Drug Abuse (NIDA), 2014]. Substance-related disorders (SRDs) cause and contribute to the deaths of millions of people each year by worsening comorbid psychiatric symptoms, such as depression, and medical conditions, such as cirrhosis of the liver, while also aiding in the spread of infectious diseases such as HIV, hepatitis B and hepatitis C. Substance-related disorders are also linked to crime and disability [United Nations Office on Drugs and Crime (UNODC), 2014].

Regular tobacco use contributes to many of the world's leading causes of death, including heart disease, stroke, and cancer (WHO, 2011). Cannabis is the world's most widely used illicit substance, with upwards of 177 million regular users worldwide (UNODC, 2014). Although the long-term effects of chronic cannabis use are debated, adverse effects on cognition and mental health have been demonstrated (Fergusson et al., 2008; Hall and Degenhardt, 2009). While not commonly considered to be "addictive," the world-wide use of the mild psychostimulant caffeine attests to its ability to serve as a reinforcer (Grigg, 2002).

More robust psychostimulants, such as cocaine and amphetamine-type drugs, are the second most widely used illegal drugs, with ~75 million estimated global users (UNODC, 2014). A number of serious medical complications are associated with cocaine use, including disturbances in heart rhythm, myocardial infarction, and neurological impairments (NIDA, 2009). Amphetamines may have a variety of neurotoxic, cardiotoxic and adverse neuropsychological effects as well (Scott et al., 2007; Shrem and Halkitis, 2008; Yu et al., 2003).

The abuse liability of naturally occurring opiates (e.g., morphine, codeine) and synthetic opioids (e.g., heroin, oxycodone, buprenorphine) is well known (Comer et al., 2008; Moratti et al., 2010; see also Meyer et al., 2014 and Trigo et al., 2010 for reviews). An estimated 9.2 million people worldwide are regular users of heroin (UNODC, 2014). The abuse of other opioids, including analgesics like oxycodone, is also widespread (Cicero, 2005; Darke et al., 1996; Gilson et al., 2004; Kintz et al., 2001; Substance Abuse and Mental Health Services Administration (SAMSHA), 2013). Opioids can significantly depress respiration, making overdose the most common cause of death among heroin users (Degenhardt et al., 2011; White and Irvine, 1999).

Although SRDs are a global public health concern, we have just begun to understand how genetics affect the initiation, course, and recovery from these disorders. A clearer understanding of the genetic contributions to these phenomena would inform the prevention,

identification, and treatment of SRDs. In the qualitative review that follows, we focus on genetic aspects of the more common drugs of abuse that contribute substantially to morbidity and mortality around the world.

1.2. Genetic Involvement in Substance-related Disorders

Twin and adoption studies provided the first strong evidence for a genetic contribution to the susceptibility to develop SRDs (See Goldman et al., 2005 for a review). These investigations revealed that the heritability, the proportion of observable differences in a trait between individuals that is due to additive genetic effects, of substance abuse is quite significant. Depending on the specific drug, it has been estimated that genetic factors contribute 40–80% of the vulnerability to addiction (Agrawal et al., 2012; Crabe et al., 2002; Kendler et al., 2000; Tsuang et al., 1996, 2001; Uhl et al., 1999).

Genetic studies have examined a variety of individual genes that could contribute to the development and maintenance of SRDs. Genetic linkage studies are family-based studies that aim to establish a link between a region of a specific chromosome and the expression of a behavior or trait of interest. Linkage analysis uses panels of markers to identify the chromosomal region that harbors a gene of interest. If a marker consistently segregates in families with the trait under investigation (in this case, drug abuse), it is likely that the gene of interest is located in the chromosomal region identified by that marker. Similarly, association analyses test for a correlation between disease status and genetic variation to identify candidate variants that either contribute to a specific disease, or are in linkage disequilibrium with a causative variant.

Genome-wide association (GWA) and whole exome/genome sequencing techniques have been extremely successful in identifying genetic contributors to a number of complex human traits and diseases (Hindorff et al., 2009). These “agnostic” studies (i.e., those without a prior hypothesis as to function or location) have identified multiple genes and polymorphisms for more targeted investigations into how they mediate vulnerability to abuse. Alternatively, candidate-gene association studies take a hypothesis-driven approach to identifying potential mediator genes. Positional candidate genes are identified through linkage analysis and fine mapping based upon their approximate chromosomal location. More commonly however, functional candidate genes are identified based on their known (or presumed), relevant biological function. Linkage, association, and candidate gene studies have identified a number of specific chromosomal regions, genes, and alleles for further investigation.

2. GOALS AND METHODOLOGY OF THE REVIEW

Scientists have begun to perform studies where the presence or absence of target gene variants is used as an independent variable in laboratory studies measuring the subjective effects produced by a drug or clinical trials measuring treatment outcomes. The present review focuses on this method, known as pharmacogenetics, of identifying how genetic variation contributes to the susceptibility and maintenance of SRD’s. In this review, preclinical, linkage and association studies are often cited to describe how a particular genetic variant could alter gene expression or neurobiological function. However, the

primary aim of this paper is to provide an overview of clinical pharmacogenetic studies investigating genetic mediators of the drug's subjective effects or pharmacotherapy treatment outcome.

Using PubMed and PsychINFO, we searched for English-language articles published between 1970 and 2013. We included various combinations of the following search terms: genetics, polymorphism, SNP, pharmacogenetics, caffeine, opioids, heroin, nicotine, cocaine, and amphetamine. Using this method, we identified over 500 publications. After removing duplicates, we reviewed the titles and/or abstracts to ensure relevance. Data from approximately 150 articles are included here. Due to the extensive literature concerning the pharmacogenetics of alcohol, this drug could not be included in the current review and remain within the length requirements of the journal. Over 90 relevant publications related to the pharmacogenetics of alcohol and treatment of alcohol use disorder were identified. As such, we felt this body of work necessitated a review of its own (see Jones et al., in press).

3. GENETIC AND DOPAMINERGIC INTERACTIONS

Although the various classes of commonly abused drugs act upon a multitude of neurobiological systems, prevailing theory implicates the effects of drugs on mesolimbic dopamine (DA) transmission as the basis for their rewarding and euphoric effects. All major drugs of abuse have been shown to enhance dopaminergic transmission in the "reward centers" of the brain, including the ventral tegmental area, nucleus accumbens, and prefrontal cortex (Di Chiara and Imperato, 1988; Sulzer, 2011; Tanda et al., 1997). As such, we begin this review with a focus on genetic and dopaminergic interactions. Because dopamine plays a key role in reward-related behavior, it has been the most extensively studied neurotransmitter systems. Variation in a number of genes involving dopaminergic signaling (synthesis, transmission, and metabolism) has been studied with respect to their contribution to SRDs.

The five dopamine receptor subtypes are typically divided into two groups, D1-like (D1 and D5) and D2-like (D2, D3 and D4; Girault et al., 2004). Collectively, the D2 dopaminergic pathway appears to be a key neural substrate for drug-related reward (see Di Chiara et al., 2004 for a review). Accordingly, several studies have focused on the connection between the D2 receptor gene (*DRD2*, which is on chromosome 11) and various drugs of abuse (Li et al., 2011). For example, many studies have shown an association between drug abuse and the presence of a polymorphism in the ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene adjacent to *DRD2* (see Li et al., 2011 for a review; Neville et al., 2004). This Taq1A polymorphism (rs1800497) is a C>T substitution located in a non-coding region of *ANKK1*. It was originally believed to map to *DRD2*, though it is 10 kb downstream of the gene. Rs1800497 has been associated with dependence on cocaine and amphetamines (Noble et al., 1993; Persico et al., 1996), nicotine (Noble et al., 1994; Comings et al., 1996; Spitz et al., 1998), cannabis (Nacak et al., 2012) and various drug combinations (Comings et al., 1994; O'Hara et al., 1993). However, the findings have not been consistent; other reports show no association of the Taq1A polymorphism with drug abuse (Heinz et al., 1996; Miginini et al., 2012).

The Taq1A polymorphism has been shown to be associated with altered dopamine transmission. Several studies have shown that the polymorphism is associated with an up to 30% reduction in D2 receptor density, decreased dopamine receptor sensitivity, and elevated dopamine transporter (DAT) density (Jonsson et al., 1999; Laine et al., 2001; Pohjalainen et al., 1998; Schellekens et al., 2012). Although less studied than the *ANKK1* single nucleotide polymorphism (SNP), a non-synonymous *DRD2* polymorphism (C957T polymorphism; rs6277) has been shown to be functional. In healthy subjects, the rs6277*C allele has been associated with lower striatal D2 binding than the T-allele (Hirvonen et al., 2004). In contrast, some *in vitro* studies have shown the C allele to be associated with greater stability of *DRD2* mRNA and protein (Duan et al., 2003). Two other functionally relevant *DRD2* intronic SNPs (rs1076560, rs2283265) have been demonstrated to influence gene splicing leading to increased expression of the short (D2S) vs. long (D2L) receptor isoform (Moyer et al., 2011; Zhang et al., 2007 B). These SNPs have also been reliably associated with cocaine, alcohol and heroin addiction (Clarke et al., 2014 B; Moyer et al., 2011).

Above are just a few examples of the functional influence of various polymorphisms affecting dopamine. Their potentially significant influence has led to several prospective pharmacogenetic studies. Because genetic mediators of dopamine function have been the most extensively investigated, this is where we begin this review. However, exciting pharmacogenetics research with other neurobiological systems (e.g., serotonergic and opioidergic) are introduced and discussed later.

4. PHARMACOGENETICS OF DRUG EFFECTS AND TREATMENT OUTCOME

4.1. Nicotine

To date, pharmacogenetic research on nicotine has focused mainly on the impact of genetic variation on the subjective response to the drug and on treatment outcome in smoking cessation trials. In a randomized, placebo-controlled laboratory study, 72 smokers were assigned to smoke normal and de-nicotinized cigarettes during positive and negative mood induction (Perkins et al., 2008a). In addition to rating the positive affective value of the cigarettes, participants were given the option of smoking the test cigarettes *ad libitum (ad lib)*. During negative mood states, Taq1A T-allele carriers [i.e., heterozygotes (A1/A2) or homozygotes (A2/A2)] reported greater “liking” of nicotine cigarettes and took more puffs than C-allele homozygotes. *DRD2* C957T*C allele homozygotes also smoked more nicotine cigarettes during negative mood states than during positive mood states. No such effect was seen among individuals with the other C957T genotypes. In another study by Perkins et al. (2008b), the subjective effects of intranasal nicotine (0, 5, or 10 μg/kg) were assessed among 101 non-smokers. Men who were 957T homozygotes reported greater dose-dependent subjective effects of nicotine, including “feel effect,” “anger,” and “reduced fatigue.” No significant associations were seen with the Taq1A polymorphism. Although both studies showed a possible mediating effect of the two polymorphisms on the subjective and reinforcing effects of nicotine, their results were contradictory.

Wang et al. (2008) examined the interaction of C957T genotype, mood, smoking behavior and nicotine withdrawal. They recruited 13 smokers to undergo two MRI scans separated by 1–3 weeks following either smoking as usual or after 12–14 hours of nicotine abstinence. During abstinence, *DRD2* 957T homozygotes exhibited less change in regional cerebral blood flow in brain areas previously associated with cigarette craving than C957 allele carriers. Gilbert et al. (2009) observed differences in electroencephalographic activity in Taq1A1 allele carriers during nicotine abstinence, and concluded that mood during nicotine withdrawal may be mediated by the Taq1A SNP.

Although variation in *DRD2* may mediate nicotine withdrawal, one prospective outcome trial in women ($N = 593$) found no association between smoking cessation and variation in a number of genes involved in dopamine synthesis, receptor activation, dopamine transporter reuptake activity and metabolism, including SNPs in *COMT* (rs4680), *DRD2* (rs1799732 and rs1800497), and *DRD3* (rs6280), and variable number of tandem repeat polymorphisms (VNTR) in *DRD4*, *SLC6A3*, and *TH* (Ton et al., 2009). The *COMT* Val158Met SNP (rs4680) is a well-studied G to A substitution that produces a valine (Val) to methionine (Met) exchange in the gene that encodes the enzyme catechol-*O*-methyltransferase, which degrades catecholamines (dopamine, epinephrine and norepinephrine). The Met allele is associated with a 40% reduction in enzyme activity (Diamond, 2007; Lotta et al., 1995; Mattay et al., 2003).

Other investigators used a similar methodology to investigate the effects of variation in *ANKK1* on pharmacological treatment outcome. Cinciripini and colleagues (2004) found that the Taq1A polymorphism mediated the response to the dopaminergic antidepressant venlafaxine in 134 participants in a smoking cessation trial. During the period following smoking cessation, smokers without the A1 allele (A2/A2) treated with venlafaxine showed a substantial reduction in negative affect. A1 allele carriers also quit significantly less often than A2 homozygotes. Interestingly, however, no genotype by treatment interaction was found on abstinence rates. Although, these data suggest that carriers of the Taq1 A1 allele may have more difficulty quitting smoking, the hypothesis was not confirmed in a subsequent clinical trial. In 116 smokers, Robinson and colleagues (2007) found that the Taq1 A1 allele was not associated with scores on the Wisconsin Smoking Withdrawal Scale (WSWS) or the Minnesota Withdrawal Symptom Checklist (MWSC), or with daily smoking abstinence rates during the 6-week post-quit observation period.

In contrast to results with the Taq1A SNP, Jonsson et al. (1999) found that the less studied Taq1B SNP (rs1079597) was associated with a lower D2 receptor density (Hauge et al., 1991). Robinson et al. (2007) found that smokers with the *ANKK1* Taq1 B1 allele reported significantly more daily nicotine withdrawal symptoms than those homozygous for the Taq1 B2 allele whose withdrawal symptoms decreased significantly over the same period. The study also showed that smokers carrying the Taq1 B1 allele were significantly less likely to be abstinent on a given day than those homozygous for the B2 allele.

Pharmacogenetic treatment trials of *ANKK1* have provided mixed results. A study of bupropion (a weak dopamine receptor antagonist) for smoking cessation in 577 heavy smokers showed that the medication was particularly effective among Taq1 A1

homozygotes (Breitling et al., 2010). Specifically, A1 homozygotes treated with bupropion had a 28% greater likelihood of smoking cessation, compared to a 12% greater likelihood of cessation among A2 allele carriers (i.e., A1/A2, or A2/A2 genotypes). In contrast, in a study of 30 smokers randomized to treatment with bupropion or placebo, the active medication reduced nicotine withdrawal symptoms (craving, irritability and anxiety) only among A2 homozygotes (David et al., 2003), a finding that was later replicated in a larger, two-site study (David et al., 2007a). In that study, 722 smokers were randomized to treatment with bupropion or placebo. In A2 homozygotes, those treated with bupropion were more than three times as likely as placebo-treated individuals to be abstinent at the end of treatment and at 6-month follow-up. There was no significant effect of bupropion on smoking cessation outcomes in Taq1 A1 carriers (A1/A1 or A1/A2). The Taq1A polymorphism was also shown to mediate smoking cessation outcomes using the medication rimonabant (an inverse agonist for the cannabinoid receptor CB1; Fong and Heymsfield, 2009). Wilcok and colleagues (2011) found that A2 homozygote smokers were significantly more successful in completely abstaining from smoking while on rimonabant (total $N = 76$).

Multiple studies have also evaluated the mediating effect of the Taq1A polymorphism on the effectiveness of nicotine replacement therapy (NRT). Yudkin et al. (2004) found that A1 allele carriers showed less therapeutic benefit from the nicotine patch than A2 allele homozygotes. Similarly, Johnstone et al. (2004) genotyped 755 heavy smokers for Taq1A alleles following completion of a randomized trial of the nicotine patch. They concluded that, at Week 1, heterozygous individuals for the *ANKK1* SNP (CT/TT *or* A1/A2) showed a better response to NRT than to placebo. However, the pharmacogenetic effect on abstinence did not persist at 12 weeks. There was significantly greater abstinence at 12 weeks among individuals with at least one A1 allele and an A allele of rs77905 in the dopamine beta hydroxylase gene (DβH). Dopamine beta hydroxylase is an enzyme that catalyzes the synthesis of norepinephrine from dopamine. Individuals with the DβH A allele tend to have lower dopamine levels, and smokers with the allele tend to smoke more cigarettes (McKinney et al., 2000; Zabetian et al., 2001; though see Shiels et al., 2008). Munafo et al. (2009) later failed to replicate these findings in a larger cohort. Similar prospective trials have also failed to find a significant mediating effect of the Taq1A genotype on the efficacy of NRT in smoking cessation (Berlin et al., 2005; De Ruyck et al., 2010; Stapleton et al., 2011).

Although Lerman et al. (2006) failed to find a relationship between the Taq1A SNP and response to pharmacotherapy for smoking cessation, using data pooled from two clinical trials they found a significant mediating effect of other *DRD2* polymorphisms. The first study was a double-blind, placebo-controlled trial of bupropion 300 mg/day ($N = 414$) and the second was an open-label trial that compared transdermal nicotine with nicotine nasal spray ($N = 368$). In addition to *ANKK1*, these investigators examined the mediating effect of an insertion/deletion polymorphism in the *DRD2* promoter region (−141C Ins/Del, rs1799732). The more common 141C Ins allele was previously shown to confer greater transcriptional efficiency than the 141C Del allele (Arinami et al., 1997). The possible influence of the aforementioned *DRD2* C957T SNP was also assessed. At the end of the 6-month treatment phase, 141C Ins allele homozygotes showed a more favorable response to

bupropion. In contrast, smokers carrying the 141C Del allele had significantly higher quit rates while on NRT, independent of NRT type. Individuals homozygous for the C957T T allele also demonstrated increased abstinence following NRT. Based on these data, the investigators concluded that bupropion may be a more effective pharmacologic treatment for smokers homozygous for the *DRD2* 14C1 Ins allele, while NRT may be more beneficial for those who carry the Del allele. Their data also suggest that T-allele homozygotes for the C957T variant may, in general, be better able to maintain abstinence. This is an interesting finding when considered in the context of the study by Wang et al. (2008), which found that individuals with this genotype may experience less nicotine withdrawal.

Lerman and colleagues replicated their findings with *DRD2*-141C Ins/Del in another 6-month NRT trial (N = 363; Dahl et al. 2006), in which they observed an interaction between *DRD2* 141C and variation in the gene encoding the neuronal calcium sensor-1 protein (*FREQ*), the protein product that regulates D2 receptor desensitization (Burgoyne et al. 2004; Kabbani et al., 2002). They found that 62% of the smokers with at least one copy of the *DRD2* 141C Del allele and two copies of the *FREQ* A allele (rs1054879) were abstinent from smoking, compared to 29–38% abstinence among other smokers.

Variants in the serotonin transporter gene (*SLC6A4*) have also been shown to influence the effectiveness of bupropion and nortriptyline on smoking cessation rates (Quaak et al., 2012). *SLC6A4* encodes the serotonin transporter, a membrane protein that takes serotonin back up into pre-synaptic neurons. In this study, 214 daily smokers were randomized and genotyped for the 5-HTTLPR variant (rs25531) that can result in a short (S) allele (14 repeats, associated with lower gene transcription) or a longer one (16 repeats, higher transcription, Nakamura et al., 2000). Primary outcome measures were prolonged abstinence from weeks 4–12, 4–26 and 4–52. The researchers concluded that bupropion and nortriptyline seem to be more effective in smoking cessation among *SLC6A4* high-activity variant carriers. See Table 1[1] for a list of nicotine pharmacogenetic treatment outcome trials.

4.2. Opioids

A number of studies have examined the effect of genetic variation on features of opioid dependence. One study investigated the mediating effect of the dopamine receptor gene (*DRD4*) 48-bp VNTR polymorphism (2, 4 and 7 repeat variants) on cueinduced craving in 420 heroin users (Shao et al., 2006). This polymorphism was selected based on its prior association with addictive disorders (Benjamin et al., 1996) and because of evidence that it is functional (Asghari et al., 1995; Van Tol et al., 1992). Following exposure to neutral and heroin-related cues, such as syringes, lighters, and tinfoil, participants completed a 5-item craving questionnaire. The study showed significantly greater cue-elicited heroin craving among individuals carrying the *DRD4* VNTR 7 (longer) allele than in non-carriers. A similar study showed significantly greater cue-elicited heroin craving among Taq1 A1 allele carriers (A1/A1 or A1/A2 genotypes) than in A2 homozygotes (Li et al., 2006). These variants were identified as potential genetic risk factors for cue-induced drug craving and subsequent relapse to substance use. Though other findings relating *DRD4* VNTR allele and

[1]The studies referenced in Tables 1–3 can be found grouped as a function of their target variant(s) in the online Supplementary Materials, which can be found by can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:…

cue reactivity have been contradictory (MacKillop et al., 2007; van den Wildenberg et al., 2007), Hutchison et al. (2002) found an association between this allele with greater cue-induced craving and arousal among smokers.

The effects of a number of opioid receptor gene polymorphisms have been implicated in subjective response to the first use of opioids. One such study assessed the association of several *OPRM1* variants with positive vs. negative subjective responses to initial heroin use (Zhang et al., 2007a). Heroin users (N = 336) were divided into two groups based on their retrospective recall concerning their first experience with heroin (i.e., positive vs. negative groups). Association analyses were performed between these two groups and nine *OPRM1* SNPs. An initially positive response upon first use of heroin was found to be associated with three *OPRM1* SNPs (rs696522, rs1381376, and rs3778151), although the functional significance of these SNPs has yet to be determined. These data highlight the need for more studies into the mediation of subjective response to drugs by genes and how this consequently affects susceptibility to abuse.

Additional research has shown an association between gene variants and treatment outcome among opioid users. Methadone and buprenorphine are two common and effective maintenance medications for opioid use disorder (Ball and Ross, 1991; Joseph et al., 2000; Mattick et al., 2008). Lawford and colleagues (2000) reported a four-fold increase in the frequency of the Taq1 A1 allele among a sample of 95 treatment-seeking opioid users who responded poorly to methadone treatment compared to those with successful treatment outcomes. However, the association of the Taq1 A1 allele with the treatment effectiveness of opioid substitution therapy was not confirmed by a later study (Barrat et al., 2006). No significant differences in A1 allele frequency were observed between methadone- and buprenorphine-treated patients with poor and successful treatment outcomes (N = 116). Interestingly, the researchers observed significantly less opioid withdrawal among carriers of the A1 allele who had a more successful treatment outcome on methadone. Crettol et al. (2008) also failed to find an association between the presence of the Taq1 A1 allele and response to methadone treatment in a sample of 238 methadone-maintained patients. They found that the Taq1 A1 allele was not associated with response to methadone treatment, as measured by use of heroin or cocaine, withdrawal symptoms, program attendance and required daily methadone dose. They also found a lack of an association with the common variants of the D1 dopamine (Ddel, −48A>G) and mu opioid Asn40Asp (A118G) receptor gene, though they did find an association with the other *DRD2* polymorphism C957T: patients with the C/C genotype were more frequently nonresponders to methadone treatment.

A later study failed to find an association between *OPRM1* alleles and methadone treatment response, but did report significant interactions with other genes implicated in the pharmacodynamics of methadone (Fonseca et al., 2010). In addition to *OPRM1*, researchers assessed the mediating effects of genes encoding the metabotropic glutamate receptors (*GRM6*, *GRM8*), the nuclear receptor (*NR4A2*), the photolyase enzyme cryptochrome 1 (*CRY1*), and the transcription factor myocardin (*MYOCD*), which have previously been associated with the risk of opioid abuse (Nielsen et al., 2008). A sample of 116 opioid-dependent patients were classified as methadone responders (n = 83) and nonresponders (n =

33) according to illicit opioid use detected with urinalysis. Participants carrying the *CRY1* AA genotype at (rs1861591) had a higher risk of being nonresponders. Participants carrying the *MYOCD* A allele (rs1714984) had an increased risk of being nonresponders but only if they were also carriers of the *GRM6* AG genotype (rs953741).

Subsequent research has shown pharmacogenetic interactions between methadone pharmacokinetics and dosing requirements in a sample of 312 opioid-dependent patients (Hung et al., 2011). This study examined SNPs (G516T, A785G) in *CYP2B6*, which encodes the liver enzyme that is partially responsible for methadone metabolism and the activity of which is known to alter methadone plasma levels (Crettol et al., 2006). Also assessed were a common SNP (C3435T) of the highly polymorphic *ABCB1* gene (rs1045642) that has been associated with disease severity and treatment response (Coller et al., 2006; Levran et al., 2008a) and the A118G SNP in of the gene encoding the mu opioid receptor (*OPRM1*). Investigators also assessed several polymorphisms associated with D2 expression or function: *DRD2* C957T, *DRD2* C939T, *DRD2* A214G, *ANKK1* C2137T (Crettol et al., 2008; Doehring et al., 2009; Lawford et al., 2000). Carriers of the variant *ABCB1* 3435C>T and *CYP2B6* 516G>T alleles were significantly more likely to require higher methadone doses than non-carriers. In contrast, carriers of the *DRD2* -214A>G and 939C>T alleles required a significantly lower methadone dosage than non-carriers (Hung et al., 2011, see also Levran et al., 2013 and Barratt et al., 2012). A recent meta-analysis of the literature concerning a number of *ABCB1* and *CYP2B6* failed to find an overall effect of allelic variation and treatment response to methadone (Dennis et al., 2014). Their analysis did find that the CYP2B6*6 haplotype did significantly influence methadone metabolism. Specifically, methadone metabolism was significantly slower in *6 homozygous carriers.

Although variation in *OPRM1* has been more extensively studied than the genes encoding other opioid receptors, variation in the delta opioid receptor gene (*OPRD1*) has been associated with the risk of opioid abuse and dependence (Mayer et al., 1997; Zhang et al 2008). Accordingly, researchers have attempted to assess whether *OPRD1* variants may also mediate the response to opioid substitution therapy. In one such trial, patients (N = 643) were randomized to receive buprenorphine/naloxone or methadone maintenance treatment over the course of 24 weeks (Crist et al., 2013 a). The researchers' primary measure of treatment effectiveness was illicit opioid use, measured by weekly urinalysis. Six *OPRD1* SNPs were genotyped as predictor variables. Among African-American participants (N = 77), an intronic *OPRD1* SNP (rs678849) predicted treatment outcome for both pharmacotherapies. Methadone patients with the C/C genotype were less likely to have opioid-positive urine tests than T-allele carriers (C/T and T/T genotypes). The opposite outcome was observed with respect to buprenorphine/naloxone treatment. Patients with the C/C genotype were more likely to have positive opioid drug screens than T-allele carriers. Though it is unclear what effect this SNP has on *OPRD1* transcription or delta receptor function, its association with both methadone and buprenorphine/naloxone treatment outcome suggests that it either directly affects or is in linkage disequilibrium with a functional variant that mediates the effects of these medications. Interestingly, this group of investigators found similar associations between *OPRD1* SNPs and cocaine abuse that were

specific to African-Americans, highlighting the possible influence of population genetics in this type of research (Crist et al., 2013 b).

In a more recent study, investigators found that two other intronic *OPRD1* SNPs (rs581111 and rs529520) predicted buprenorphine treatment outcomes. However, this interaction was found only in females. Women with the AA or AG genotypes at rs581111 had significantly worse outcomes compared to women with the GG genotype, while women with rs529520 AA genotype had a significantly worse outcome compared to women with the CC genotype (Clarke et al., 2014 A). These studies highlight the potential of pharmacogenetic studies to provide important information for the selection of treatment when different options are available. Table 2 lists opioid use disorder pharmacogenetic treatment outcome trials, and the nature of their findings.

4.3. Cocaine

Cocaine dependence has a strong genetic component, with an estimated heritability of 72%, but unlike the other substances discussed here, lacks an FDA-approved pharmacotherapy (Goldman et al., 2005). Researchers have tested over 60 medications, and though some have shown promise, none so convincingly as to have received FDA approval (Grabowski et al. 2004; Vocci and Ling 2005). Pharmacogenetics may help to identify subsets of users who respond to a particular pharmacotherapy, which could then be developed and marketed to a patient population with a specific genetic profile.

The acetaldehyde dehydrogenase-inhibiting drug disulfiram (Antabuse, Antabus), has been used to treat alcoholism since the 1940's (Hald et al., 1948). Disulfiram has also shown some potential in treating cocaine abuse, and research has begun to examine whether genetic variation mediates treatment response (Carroll et al., 1998; 2004). Some researchers have proposed that by inhibiting dopamine β-hydrolylase (*DβH*), disulfiram alters cocaine signaling and/or availability (Bourdelat-Parks et al., 2005; Schank et al., 2006; Vaccari et al., 1996). Consequently, genetic variants affecting the *DβH* gene were among the first to be examined as genetic mediators of the efficacy of disulfiram in treating cocaine dependence.

A functional *DβH* gene polymorphism that alters transcription and decreases DβH plasma levels was studied with respect to its interaction with disulfiram (Bhaduri et al., 2008; Zabetian et al., 2001). The C-1021T polymorphism (rs1611115) accounts for up to 52% of the variation in DβH enzyme levels, with individuals homozygous for the T allele having the lowest levels (Khonke et al., 2002; Deinum et al., 2004). In their assessment of the influence of this polymorphism, Kosten and colleagues (2013) randomized 72 cocaine- and opioid-dependent patients to receive disulfiram (250 mg/day) or placebo for 10 weeks. Overall, disulfiram treatment significantly reduced the number of cocaine-positive urines but the effect was only seen among subjects with the *DβH* gene variant that is associated with normal DβH levels.

Spellicy et al. (2013) also found that the aforementioned *ANKK1* (rs1800497) and *DRD2* (rs2283265) polymorphisms interacted with disulfiram treatment response. Patients homozygous (T/T) or heterozygous (C/T) for the minor alleles of both SNPs had a significantly lower number of cocaine-positive urines when maintained on disulfiram (250

mg/day), while their homozygous counterparts showed a marginal (rs2283265*CC) or no (rs1800497*CC) treatment effect (N = 68).

Other analyses of genetic mediators of disulfiram treatment have focused on a SNP in the gene that encodes 5, 10-methylene tetrahydrofolate reductase (*MTHFR*). *In vitro* studies have shown that the minor T allele of the C677T SNP (rs1801133) results in an enzyme with reduced activity and increased thermolability (Frosst et al., 1995). Because this enzyme affects a number of developmental and biochemical pathways, Spellicy and colleagues (2013) hypothesized that the polymorphism would be associated with the response to disulfiram treatment in cocaine users. The primary treatment outcome measure was the number of cocaine-positive urines. The percentage of cocaine-positive urines dropped from 73% to 52% for the combined C/T and T/T group pre- to post-disulfiram treatment. Subjects with the C/C genotype had a smaller reduction in cocaine-positive urines (from 81% to 69%) while on disulfiram, a small but significant treatment effect when compared to placebo.

Investigations into the interaction between disulfiram and a functional variant of the gene that encodes the α-1 adrenergic receptor (*ADRA1A*) are based on disulfiram's effect on norepinephrine production (Shorter et al., 2013). This polymorphism (rs1048101) in exon 2 results in a substitution of arginine for a cytosine within the C-terminus of the protein (Cys347Arg). Data suggest that this single amino acid change alters the activity of the receptor and may impact cognition (Lei et al., 2005). Using the clinical trial methodology described above (disulfiram 250 mg/day, 69 cocaine and opioid co-dependent participants; Shorter et al., 2013), the investigators found a significant interaction between genotype and treatment, where the patients who were carriers of the minor T allele had a significantly lower percentage of cocaine-positive urines, while those homozygous for the major C allele showed no treatment effect.

Genetic mediation of treatment response has also been found for a novel immunotherapy that produces selective anti-cocaine antibodies (cocaine vaccine (TA-CD); Carrera et al., 1995). Nielsen et al. (2013) genotyped 66 of 114 cocaine- and opioid-dependent patients enrolled in a 16-week trial of the vaccine for a variant of the kappa subtype of opioid receptor, *OPRK1* gene (rs6473797), an A to G transition, with the G allele previously shown to be a risk allele for opioid dependence (Levran et al., 2008b). Participants homozygous for the major (A) allele had a significantly better vaccine treatment response (i.e., decrease in cocaine-positive urines) than carriers of the G allele. A similar investigation by this group (Kosten et al., 2013) identified the *C-1021T DβH* SNP as a mediator of cocaine vaccine response (See Table 3 for pharmacogenetic medication trials for cocaine abuse trials).

Cocaine-induced paranoia is another interesting area of pharmacogenetic research. Association studies have failed to consistently demonstrate heritability and genetic influence in the occurrence of this drug effect (Gelernter et al., 2005; Kalayasiri et al., 2006). However, candidate gene studies have found evidence of allelic association with cocaine-induced paranoia. Variants that have been implicated as possible mediators include: *SLC6A3* 3' VNTR (Gelernter et al., 1994), *COMT* variants: rs737866, rs4680, rs174696, rs4680,

rs933271, rs993883, rs740603 (Ittiwut et al., 2011), DβH rs1611115 (Kalayasiri et al., 2007), *CNR1* rs806368 (Zuo et al., 2009) and *MANEA* rs9387522 (Farrer et al., 2009).

4.4. Amphetamines and Caffeine

Pharmacogenetic research on methamphetamine and caffeine is very limited. However, there is research to suggest that *OPRM1* variation mediates subjective response to amphetamine. One hundred and sixty-two Caucasian participants completed three sessions receiving either placebo or d-amphetamine (10 and 20 mg). Several *OPRM1* SNPs (rs510769, rs2281617, rs1799971, rs510769, rs1918760, rs2281617 and rs1998220) were associated with significantly higher subjective ratings of "Euphoria," "Energy" and "Stimulation" after 10 mg amphetamine. These data imply that genetic variability in the μ-opioid receptor gene influences the subjective effects of amphetamine, though the investigators were later unable to replicate these findings (Duglos et al., 2011).

With respect to methamphetamine, another area under investigation is possible genetic involvement in the occurrence of methamphetamine-induced psychosis. The majority of this research has focused on D2 receptor gene variants. A number of publications have identified *DRD2* alleles as possible risk genotypes for methamphetamine psychosis (Harano et al., 2004; Ujike et al., 2009) with the body of literature expanding each year (Chanasong et al., 2013; Kishi et al., 2011; Kobayashi et al., 2004; Matsuzawa et al., 2007; Ujike et al., 2003).

Similarly, the aversive effects of caffeine consumption may have a genetic link. Caffeine produces mild psychostimulant and anxiogenic effects by antagonizing adenosine receptors and increasing dopaminergic transmission (Daly and Fredholm, 1998). Childs et al. (2008) examined functional polymorphisms in the genes for adenosine and dopamine receptors as possible mediators of caffeine-induced anxiety. They examined associations between self-reported anxiety following caffeine administration and variation in the genes for the A_{2A} receptor (*ADORA2A*) and D2 (*DRD2*) receptor. Healthy male and female individuals (N = 102), who consumed less than 300 mg caffeine per week, ingested capsules containing caffeine 0, 50, 150, or 450 mg under double-blind conditions, in four separate experimental sessions. Subjective anxiety was measured before and multiple times after ingestion of the capsules. They found a significant association between caffeine-induced anxiety and *ADORA2A* alleles: rs5751876, rs2298383, rs4822492, and *DRD2* allele: rs1110976. This study provides evidence of mediation of aversive drug effects by genetic variation and suggests a mechanism by which these alleles may influence caffeine intake.

5. CONCLUSIONS

One cautionary tale concerning the reproducibility of pharmacogenetic research comes from one of the most prolific groups in this field, the Department of Human Genetics at the University of Chicago. Investigators there assessed acute response to d-amphetamine in 398 individuals with no history of drug abuse. Interim pharmacogenetic analyses using 99–162 participants from this data set found associations between a number of gene variants and amphetamine response: *ADORA2A* (Hohoff et al., 2005), *BDNF* (Flanagin et al., 2006), *CSNK1E* (Veenstra-VanderWeele et al., 2006), *COMT* (Hamidovic et al., 2010a), *DRD2* (Hamidovic et al., 2009), *FAAH* (Dlugos et al., 2010), *OPRM1* (Dlugos et al., 2011),

SLC6A3 (Hamidovic et al., 2010b; Lott et al., 2005), *SLC6A4* (Lott et al., 2006), and *SLC6A2* (Dlugos et al., 2007). The promising data from these publications were cited throughout the psychiatric genetics literature. However, these researchers recently conducted a study with an additional 200 participants, in which they were unable to replicate the aforementioned findings (Hart et al., 2013).

The authors acknowledged that their failure to replicate indicated that the previous findings may have been false positives. The paper also cites insufficient correction for multiple testing (within each study and across the various studies) and publication bias as contributors to their erroneous findings. The influence of these factors requires that appropriate caution be used in pharmacogenetics research, which may warrant novel statistical or methodological approaches to control for their influence (Bosker et al., 2011; Munafó et al, 2007).

Though we have reviewed several studies showing a pharmacogenetic effect, the literature is often inconsistent about whether a particular gene alteration is related to the treatment outcome under observation. In addition to statistical sources of discrepant findings, other methodological differences in these studies may contribute to inconsistencies in the literature. Therefore, as the field of pharmacogenetics continues to develop, it would greatly benefit from standardization in measures such as the dosage of the pharmacological treatment being studied and how relapse is defined.

It has also been suggested that the source of this problem lies in the fact that our classification system for SRDs lacks etiological (causative) justification. Following this argument, the new DSM-V classification system, which combines substance abuse and dependence into an overarching disorder (Substance Use Disorder), does little to improve upon this issue. Some argue that the classification of patients with SRDs based upon endophenotypes related to disease pathogenesis may identify more distinct groups of affected individuals, which would be more suitable for experimental genetic approaches (see Ball et al., 1995; Basu et al., 2004; Chan et al., 2011; Kranzler et al., 2008 and Moss et al., 2007). For example, two possible endophenotypes of heroin users may be differentiated based their motivation to use the drug. The ability of heroin to activate the opioid and dopaminergic systems and produce pleasurable effects is undoubtedly an important contributor to its abuse liability. However, multiple studies have suggested that some individuals abuse opioids to self-medicate anxiety, depression, mania and psychosis (Fatseas et al., 2009). As such, the etiology of heroin abuse in some patient populations (initially at least) may be attributed to the positive subjective effects of the drug; these individuals may be genetically distinct from those whose abuse can be attributed to the negative reinforcing properties of the drug. As such, studies that examine pharmacogenetics of heroin abuse treatment response may yield different results, depending on the endophenotype of the sample that was tested. In addition to controlling for sample heterogeneity, employing larger samples sizes could improve replicability, leading to more clinically meaningful findings. In this respect, the field of substance abuse could learn from genetic studies investigating response to antidepressants (which utilize large sample sizes, control for population stratification, and employ sound statistical methodology) as a model for future studies (see Hunter et al., 2013 for an example).

The data presented in this review indicate that genetic variation as minimal as a single nucleotide change may alter drug effects, craving, withdrawal and abstinence. Because DA may constitute a pathway to addiction common to all drugs, the majority of this research has focused on genetic alteration in the dopaminergic pathway. However, the gene targets of this type of research are expanding each year. When combined with polygenetic approaches examining the combined effects of multiple variants, we continue to gain a more comprehensive view of the multitude of genetic factors involved in drug abuse. Despite the obstacles in this novel area of research, once refined, pharmacogenetics may allow for the identification of a subset of treatment-seeking patients most likely to respond to a particular medication and those who may be at an increased risk of more severe complications related to drug abuse. The development and course of drug addiction is a highly individualized experience. Genetics may allow us to determine why there is such variability in susceptibility, response, and prognosis. In the future, understanding the influence of genetic factors may change standard clinical practices and improve the lives of those suffering from drug abuse worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

Agrawal A, Verweij KJ, Gillespie NA, Heath AC, Lessov-Schlaggar CN, Martin NG, Nelson EC, Slutske WS, Whitfield JB, Lynskey MT. The genetics of addiction a translational perspective. Transl. Psychiatry. 2012; 2:e140. [PubMed: 22806211]

Al-Eitan LN, Jaradat SA, Su SY, Tay GK, Hulse GK. Mu opioid receptor (OPRM1) as a predictor of treatment outcome in opiate-dependent individuals of Arab descent. Pharmgenomics Pers. Med. 2012; 5:99–111. [PubMed: 23226066]

Arinami T, Gao M, Hamaguchi H, Toru M. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Hum. Mol. Genet. 1997; 6:577–582. [PubMed: 9097961]

Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J. Neurochem. 1995; 65:1157–1165. [PubMed: 7643093]

Ball, JC.; Ross, A. The Effectiveness Of Methadone Maintenance Treatment. New York: Springer-Verlag; 1991.

Ball SA, Carroll KM, Babor TF, Rounsaville BJ. Subtypes of cocaine abusers: support for a type A-type B distinction. J. Consult. Clin. Psychol. 1995; 63:115–124. [PubMed: 7896976]

Barratt DT, Coller JK, Hallinan R, Byrne A, White JM, Foster DJ, Somogyi AA. ABCB1 haplotype and OPRM1 118A > G genotype interaction in methadone maintenance treatment pharmacogenetics. Pharmgenomics Pers. Med. 2012; 5:53–62. [PubMed: 23226062]

Basu D, Ball SA, Feinn R, Gelernter J, Kranzler HR. Typologies of drug dependence: comparative validity of a multivariate and four univariate models. Drug Alcohol Depend. 2004; 73:289–300. [PubMed: 15036551]

Barratt DT, Coller JK, Somogyi AA. Association between the DRD2 A1 allele and response to methadone and buprenorphine maintenance treatments. Am. J. Med. Genet. B. Neuropsychiatr. Genet. 2006; 141B:323–331. [PubMed: 16583408]

Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. Nat. Genet. 1996; 12:81–84. [PubMed: 8528258]

Berlin I, Covey LS, Jiang H, Hamer D. Lack of effect of D2 dopamine receptor TaqI A polymorphism on smoking cessation. Nicotine Tob. Res. 2005; 7:725–728. [PubMed: 16191743]

Berrettini WH, Wileyto EP, Epstein L, Restine S, Hawk L, Shields P, Niaura R, Lerman C. Catechol-O-methyltransferase (COMT) gene variants predict response to bupropion therapy for tobacco dependence. Biol. Psychiatry. 2007; 61:111–118. [PubMed: 16876132]

Bhaduri N, Mukhopadhyay K. Correlation of plasma dopamine beta-hydroxylase activity with polymorphisms in DβH gene: a study on eastern Indian population. Cell. Mol. Neurobiol. 2008; 28:343–350. [PubMed: 18172755]

Bourdelat-Parks BN, Anderson GM, Donaldson ZR, Weiss JM, Bonsall RW, Emery MS, Liles LC, Weinshenker D. Effects of dopamine beta-hydroxylase genotype and disulfiram inhibition on catecholamine homeostasis in mice. Psychopharmacol. (Berl.). 2005; 183:72–80.

Bosker FJ, Hartman CA, Nolte IM, Prins BP, Terpstra P, Posthuma D, van Veen T, Willemsen G, DeRijk RH, de Geus EJ, Hoogendijk WJ, Sullivan PF, et al. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Mol. Psychiatry. 2011; 16:516–532. [PubMed: 20351714]

Breitling LP, Twardella D, Hoffmann MM, Witt SH, Treutlein J, Brenner H. Prospective association of dopamine-related polymorphisms with smoking cessation in general care. Pharmacogenomics. 2010; 11:527–536. [PubMed: 20350135]

Burgoyne RD, O'Callaghan DW, Hasdemir B, Haynes LP, Tepikin AV. Neuronal Ca2+-sensor proteins: multitalented regulators of neuronal function. Trends Neurosc. 2004; 27:203–209.

Carrera MR, Ashley JA, Parsons LH, Wirsching P, Koob GF, Janda KD. Suppression of psychoactive effects of cocaine by active immunization. Nature. 1995; 378:727–730. [PubMed: 7501020]

Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, et al. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. Arch. Gen. Psychiatry. 2004; 61:264–272. [PubMed: 14993114]

Carroll KM, Nich C, Ball SA, McCance E, Rounsavile BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. Addiction. 1998; 93:713–727. [PubMed: 9692270]

Chanasong R, Thanoi S, Watiktinkorn P, Reynolds GP, Nudmamud-Thanoi S. Genetic variation of GRIN1 confers vulnerability to methamphetamine-dependent psychosis in a Thai population. Neurosci. Lett. 2013; 551:58–61. [PubMed: 23880023]

Chan G, Gelernter J, Oslin D, Farrer L, Kranzler HR. Empirically derived subtypes of opioid use and related behaviors. Addiction. 2011; 106:1146–1154. [PubMed: 21306596]

Chen LS, Bloom AJ, Baker TB, Smith SS, Piper ME, Martinez M, Saccone N, Hatsukami D, Goate A, Bierut L. Pharmacotherapy effects on smoking cessation vary with nicotine metabolism gene (CYP2A6). Addiction. 2014; 109:128–137. [PubMed: 24033696]

Childs E, Hohoff C, Deckert J, Xu K, Badner J, de Wit H. Association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. Neuropsychopharmacol. 2008; 33:2791–2800.

Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of oxycontin and other opioid analgesics in the United States: 2002–2004. J. Pain. 2005; 6:662–672. [PubMed: 16202959]

Cinciripini PM, Wetter DW, Tomlinson GE, Tsoh JY, De Moor CA, Cinciripini LG. The effects of the DRD2 polymorphism on smoking cessation and negative affect: evidence for a pharmacogenetic effect on mood. Nicotine Tob. Res. 2004; 6:229–239. [PubMed: 15203796]

Clarke TK, Crist RC, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W, Hillhouse MP, Bruce RD, Woody G, Berrettini WH. Genetic variation in OPRD1 and the response to treatment for opioid dependence with buprenorphine in European-American females. Pharmacogenomics J. 2014 a; 14:303–308. [PubMed: 24126707]

Clarke TK, Weiss AR, Ferarro TN, Kampman KM, Dackis CA, Pettinati HM, O'brien CP, Oslin DW, Lohoff FW, Berrettini WH. The dopamine receptor D2 (DRD2) SNP rs1076560 is associated with opioid addiction. Ann. Hum. Genet. 2014 b; 78:33–39. [PubMed: 24359476]

Colilla S, Lerman C, Shields PG, Jepson C, Rukstalis M, Berlin J, DeMichele A, Bunin G, Strom BL, Rebbeck TR. Association of catechol-O-methyltransferase with smoking cessation in two independent studies of women. Pharmacogenet. Genomics. 2005; 15:393–398. [PubMed: 15900212]

Coller JK, Barratt DT, Dahlen K, Loennechen MH, Somogyi AA. ABCB1 genetic variability and methadone dosage requirements in opioid-dependent individuals. Clin. Pharmacol. Ther. 2006; 80:682–690. [PubMed: 17178268]

Comer SD, Sullivan MA, Whittington RA, Vosburg SK, Kowalczyk WJ. Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. Neuropsychopharmacol. 2008; 33:1179–1191.

Comings DE, Muhleman D, Ahn C, Gysin R, Flanagan SD. The dopamine D2 receptor gene: a genetic risk factor in substance abuse. Drug Alcohol Depend. 1994; 34:175–180. [PubMed: 8033754]

Comings DE, Ferry L, Bradshaw-Robinson S, Burchette R, Chiu C, Muhleman D. The dopamine D2 receptor (*DRD2*) gene: a genetic risk factor in smoking. Pharmacogenetics. 1996; 6:73–79. [PubMed: 8845863]

Conti DV, Lee W, Li D, Liu J, Van Den Berg D, Thomas PD, Bergen AW, Swan GE, Tyndale RF, Benowitz NL, Lerman C. Nicotinic acetylcholine receptor beta2 subunit gene implicated in a systems-based candidate gene study of smoking cessation. Hum. Mol. Genet. 2008; 17:2834–2848. [PubMed: 18593715]

Crabbe JC. Genetic contributions to addiction. Ann. Rev. Psychol. 2002; 53:435–462. [PubMed: 11752492]

Crettol S, Besson J, Croquette-Krokar M, Hämmig R, Gothuey I, Monnat M, Déglon JJ, Preisig M, Eap CB. Association of dopamine and opioid receptor genetic polymorphisms with response to methadone maintenance treatment. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2008; 32:1722–1727. [PubMed: 18687376]

Crettol S, Deglon JJ, Besson J, Croquette-Krokar M, Hammig R, Gothuey I. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. Clin. Pharmacol. Ther. 2006; 80:668–681. [PubMed: 17178267]

Crist RC, Clarke TK, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W, Hillhouse MP, Bruce RD, Woody G, Berrettini WH. An intronic variant in OPRD1 predicts treatment outcome for opioid dependence in African-Americans. Neuropsychopharmacol. 2013a; 38:2003–2010.

Crist RC, Clarke TK, Ang A. Case-control association analysis of polymorphisms in the delta-opioid receptor, OPRD1, with cocaine and opioid addicted populations. Drug. Alcohol Depend. 2013b; 127:122–128. [PubMed: 22795689]

Dahl JP, Jepson C, Levenson R, Wileyto EP, Patterson F, Berrettini WH, Lerman C. Interaction between variation in the D2 dopamine receptor (DRD2) and the neuronal calcium sensor-1 (FREQ) genes in predicting response to nicotine replacement therapy for tobacco dependence. Pharmacogenomics J. 2006; 6:194–199. [PubMed: 16402081]

Daly JW, Fredholm BB. Caffeine: an atypical drug of dependence. Drug Alcohol Depend. 1998; 51:199–206. [PubMed: 9716941]

David SP, Munafò MR, Murphy MF, Proctor M, Walton RT, Johnstone EC. Genetic variation in the dopamine D4 receptor (DRD4) gene and smoking cessation: follow-up of a randomised clinical trial of transdermal nicotine patch. Pharmacogenomics J. 2008; 8:122–128. [PubMed: 17387332]

David SP, Niaura R, Papandonatos GD, Shadel WG, Burkholder GJ, Britt DM, Day A, Stumpff J, Hutchison K, Murphy M, Johnstone E, Griffiths SE, Walton RT. Does the DRD2-Taq1 A polymorphism influence treatment response to bupropion hydrochloride for reduction of the nicotine withdrawal syndrome. Nicotine Tob. Res. 2003; 5:935–942. [PubMed: 14668077]

David SP, Strong DR, Munafò MR, Brown RA, Lloyd-Richardson EE, Wileyto PE, Evins EA, Shields PG, Lerman C, Niaura R. Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1 A polymorphism: analysis of pooled data from two clinical trials. Nicotine Tob. Res. 2007a; 9:1251–1257. [PubMed: 18058343]

David SP, Brown RA, Papandonatos GD, Kahler CW, Lloyd-Richardson EE, Munafo MR, Shields PG, Lerman C, Strong D, McCaffery J, Niaura R. Pharmacogenetic clinical trial of sustained-release bupropion for smoking cessation. Nicotine Tob. Res. 2007b; 9:821–833. [PubMed: 17654295]

David SP, Munafo MR, Murphy MF, Walton RT, Johnstone EC. The serotonin transporter 5-HTTLPR polymorphism and treatment response to nicotine patch: follow-up of a randomized controlled trial. Nicotine Tob. Res. 2007c; 9:225–231. [PubMed: 17365753]

Darke SG, Rossn J, Hall W. Overdose among heroin users in Sydney, Australia: I. Prevalence and correlates of non-fatal overdose. Addiction. 1996; 91:405–411. [PubMed: 8867202]

Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, McLaren J. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011; 106:32–51. [PubMed: 21054613]

De Ruyck K, Nackaerts K, Beels L, Werbrouck J, De Volder A, Meysman M, Salhi B, Van Meerbeeck J, Thierens H. Genetic variation in three candidate genes and nicotine dependence, withdrawal and smoking cessation in hospitalized patients. Pharmacogenomics. 2010; 11:1053–1063. [PubMed: 20712524]

Deinum J, Steenbergen-Spanjers GC, Jansen M, Boomsma F, Lenders JW, van Ittersum FJ, Huck N, van den Heuvel LP, Wevers RA. DβH gene variants that cause low plasma dopamine beta hydroxylase with or without a severe orthostatic syndrome. J. Med. Genet. 2004; 41:e38. [PubMed: 15060114]

Dennis BB, Bawor M, Thabane L, Sohani Z, Samaan Z. Impact of ABCB1 and CYP2B6 genetic polymorphisms on methadone metabolism, dose and treatment response in patients with opioid addiction: a systematic review and meta-analysis. PLoS One. 2014

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. 1988; 85:5274–5278. [PubMed: 2899326]

Di Chiara G, Bassareo V, Fenu S, De Luca M, Spina L, Cadoni C, Acquas E, Carboni E, Valentini V, Lecca D. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacol. 2004; 47:227–241.

Diamond A. Consequences of variations in genes that affect dopamine in prefrontal cortex. Cereb. Cortex. 2007; 17:i161–i170. [PubMed: 17725999]

Doehring A, Hentig N, Graff J, Salamat S, Schmidt M, Geisslinger G. Genetic variants altering dopamine D2 receptor expression or function modulate the risk of opiate addiction and the dosage requirements of methadone substitution. Pharmacogenet. Genomics. 2009; 19:407–414. [PubMed: 19373123]

Duan J, Wainwright MS, Comeron JM, Saitou N, Sanders AR, Gelernter J, Gejman PV. Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. Hum. Mol. Genet. 2003; 12:205–216. [PubMed: 12554675]

Dlugos A, Freitag C, Hohoff C, McDonald J, Cook E, Deckert J, de Wit H. Norepinephrine transporter gene variation modulates acute response to D-amphetamine. Biol. Psychiatry. 2007; 61:1296–1305. [PubMed: 17239355]

Dlugos AM, Hamidovic A, Hodgkinson CA, Goldman D, Palmer AA, de Wit H. More aroused, less fatigued: fatty acid amide hydrolase gene polymorphisms influence acute response to amphetamine. Neuropsychopharmacol. 2010; 35:613–622.

Dlugos AM, Hamidovic A, Hodgkinson C, Shen PH, Goldman D, Palmer AA, de Wit H. OPRM1 gene variants modulate amphetamine-induced euphoria in humans. Genes Brain Behav. 2011; 10:199–209. [PubMed: 21029375]

Farrer LA, Kranzler HR, Yu Y, Weiss RD, Brady KT, Anton R, Cubells JF, Gelernter J. Association of variants in MANEA with cocaine-related behaviors. Arch. Gen. Psychiatry. 2009; 66:267–274. [PubMed: 19255376]

Fatseas M, Lavie E, Denis C, Auriacombe M. Self-perceived motivation for benzodiazepine use and behavior related to benzodiazepine use among opiate-dependent patients. J. Subst. Abuse Treat. 2009; 37:407–411. [PubMed: 19339146]

Fergusson DM, Boden JM. Cannabis use and later life outcomes. Addiction. 2008; 103:969–976. [PubMed: 18482420]

Flanagin B, Cook E Jr, de Wit H. An association study of the brain-derived neurotrophic factor Val66Met polymorphism and amphetamine response. Am. J. Med. Genet. 2006; 141:576–583. [PubMed: 16823800]

Fong TM, Heymsfield SB. Cannabinoid-1 receptor inverse agonists: current understanding of mechanism of action and unanswered questions. Int. J. Obes. (Lond.). 2009; 33:947–955. [PubMed: 19597516]

Fonseca F, Gratacòs M, Escaramís G, De Cid R, Martín-Santos R, Fernández-Espejo E, Estivill X, Torrens M. Response to methadone maintenance treatment is associated with the MYOCD and GRM6 genes. Mol. Diagn. Ther. 2010; 14:171–178. [PubMed: 20560679]

Frosst P, Blom H, Milos R, Govette P, Sheppard C, Matthews R, Boers GJH, den Heijer M, Kluijtmans LAJ, van den Heuve LP, Rozen R. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat. Genet. 1995; 10:111–113. [PubMed: 7647779]

Grabowski JA, Shearer J, Merrill J, Negus SS. Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. Addict. Behav. 2004; 29:1439–1464. [PubMed: 15345275]

Gelernter J, Panhuysen C, Weiss R, Brady K, Hesselbrock V, Rounsaville B, Poling J, Wilcox M, Farrer L, Kranzler HR. Genomewide linkage scan for cocaine dependence and related traits: significant linkages for a cocaine-related trait and cocaine-induced paranoia. Am. J. Med. Genet. B. Neuropsychiatr. Genet. 2005; 136B:45–52. [PubMed: 15909294]

Gelernter J, Kranzler HR, Satel SL, Rao PA. Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. Neuropsychopharmacol. 1994; 11:195–200.

Gilbert DG, Zuo Y, Rabinovich NE, Riise H, Needham R, Huggenvik JI. Neurotransmission-related genetic polymorphisms, negative affectivity traits, and gender predict tobacco abstinence symptoms across 44 days with and without nicotine patch. J. Abnorm. Psychol. 2009; 118:322–334. [PubMed: 19413407]

Gilson AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. J. Pain Symptom Manage. 2004; 28:176–188. [PubMed: 15276196]

Girault JA, Greengard P. The neurobiology of dopamine signaling. Arch. Neurol. 2004; 61:641–644. [PubMed: 15148138]

Goldman G, Oroszi F, Ducci F. The genetics of addictions: uncovering the genes. Nat. Rev. Genet. 2005; 6:521–532. [PubMed: 15995696]

Grigg D. The worlds of tea and coffee: patterns of consumption. Geojournal. 2002; 57:283.

Hald J, Jacobsen E, Larsen V. The sensitizing effect of tetraethylthiuramdisulphide (antabuse) to ethylalcohol. Acta. Pharmacol. Toxicol. (Copenh). 1948; 4:285–296.

Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet. 2009; 374:1383–1391. [PubMed: 19837255]

Hamidovic A, Dlugos A, Palmer AA, de Wit H. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. Psychiatr. Genet. 2010a; 20:85. [PubMed: 20414144]

Hamidovic A, Dlugos A, Palmer AA, de Wit H. Polymorphisms in dopamine transporter (SLC6A3) are associated with stimulant effects of d-amphetamine: an exploratory pharmacogenetic study using healthy volunteers. Behav. Genet. 2010b; 40:255–261. [PubMed: 20091113]

Hamidovic A, Dlugos A, Skol A, Palmer AA, de Wit H. Evaluation of genetic variability in the dopamine receptor D2 in relation to behavioral inhibition and impulsivity/sensation seeking: an exploratory study with d-amphetamine in healthy participants. Exp. Clin. Psychopharmacol. 2009; 17:374–383. [PubMed: 19968402]

Harano M, Uchimura N, Abe H, Ishibashi M, Iida N, Yanagimoto K, Tanaka T, Maeda H, Sora I, Iyo M, Komiyama T, Yamada M, Sekine Y, Inada T, Ozaki N, Ujike H. A polymorphism of DRD2 gene and brain atrophy in methamphetamine psychosis. Ann. N.Y. Acad. Sci. 2004; 1025:307–315. [PubMed: 15542731]

Hart AB, de Wit H, Palmer AA. Candidate gene studies of a promising intermediate phenotype: failure to replicate. Neuropsychopharmacol. 2013; 38:802–816.

Hauge XY, Grandy DK, Eubanks JH, Evans GA, Civelli O, Litt M. Detection and characterization of additional DNA polymorphisms in the dopamine D2 receptor gene. Genomics. 1991; 10:527–530. [PubMed: 1679742]

Heinz A, Sander T, Harms H, Finckh U, Kuhn S, Dufeu P, Dettling M, Gräf K, Rolfs A, Rommelspacher H, Schmidy LG. Lack of allelic association of dopamine D1 and D2 (TaqIA) receptor gene polymorphisms with reduced dopaminergic sensitivity to alcoholism. Alcohol. Clin. Exp. Res. 2006; 20:1109–1113. [PubMed: 8892535]

Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS, Manolio TA. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc. Natl. Acad. Sci. 2009; 106:9362–9367. [PubMed: 19474294]

Hirvonen M, Laakso A, Nagren K, Rinne JO, Pohjalainen T, Hietala J. C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. Mol. Psychiatry. 2004; 9:1060–1061. [PubMed: 15278099]

Hohoff C, Mcdonald JM, Baune BT, Cook EH, Deckert J, de Wit H. Interindividual variation in anxiety response to amphetamine: possible role for adenosine A 2Areceptor gene variants. Am. J. Med. Genet. 2005; 139B:42–44. [PubMed: 16118787]

Hung CC, Chiou MH, Huang BH, Hsieh YW, Hsieh TJ, Huang CL, Lane HY. Impact of genetic polymorphisms in ABCB1, CYP2B6, OPRM1, ANKK1 and DRD2 genes on methadone therapy in Han Chinese patients. Pharmacogenomics. 2011; 12:1525–1533. [PubMed: 21902500]

Hunter AM, Leuchter AF, Power RA, Muthén B, McGrath PJ, Lewis CM, Cook IA, Garriock HA, McGuffin P, Uher R, Hamilton SP. A genome-wide association study of a sustained pattern of antidepressant response. J. Psychiatr. Res. 2013; 47:1157–1165. [PubMed: 23726668]

Hutchison KE, Allen DL, Filbey FM, Jepson C, Lerman C, Benowitz NL, Stitzel J, Bryan A, McGeary J, Haughey HM. CHRNA4 and tobacco dependence: from gene regulation to treatment outcome. Arch. Gen. Psychiatry. 2007; 64:1078–1086. [PubMed: 17768273]

Hutchison KE, Lachance H, Niaura R, Bryan A, Smolen A. The DRD4 VNTR polymorphism influences reactivity to smoking cues. J. Abnorm. Psychol. 2002; 111:134–143. [PubMed: 11866166]

Ittiwut R, Listman JB, Ittiwut C, Cubells JF, Weiss RD, Brady K, Oslin D, Farrer LA, Kranzler HR, Gelernter J. Association between polymorphisms in catechol-O-methyltransferase (COMT) and cocaine-induced paranoia in European-American and African-American populations. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2011; 156:651–660. [PubMed: 21656904]

Johnstone EC, Elliot KM, David SP, Murphy MF, Walton RT, Munafo MR. Association of COMT Val108/158Met genotype with smoking cessation in a nicotine replacement therapy randomized trial. Cancer Epidemiol. Biomarkers Prev. 2007; 16:1065–1069. [PubMed: 17548664]

Johnstone EC, Yudkin PL, Hey K, Roberts SJ, Welch SJ, Murphy MF. Genetic variation in dopaminergic pathways and short-term effectiveness of the nicotine patch. Pharmacogenetics. 2004; 14:83–90. [PubMed: 15077009]

Jones JD, Comer SD, Kranzler HR. The pharmacogenetics of alcohol use disorder. Alcohol. Clin. Exp. Res. 2014 (In Press).

Jönsson EG, Nöthen MM, Grünhage F, Farde L, Nakashima Y, Propping P, Sedvall GC. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol. Psychiatry. 1999; 3:290–296. [PubMed: 10395223]

Joseph H, Stancliff S, Langrod J. methadone maintenance treatment (mmt): a review of historical and clinical issues. Mount Sinai Med. J. 2000; 5–6:347–364.

Kabbani N, Negyessy L, Lin R, Goldman-Rakic P, Levenson R. Interaction with neuronal calcium sensor NCS-1 mediates desensitization of the D2 dopamine receptor. J. Neurosci. 2002; 22:8476–8486. [PubMed: 12351722]

Kalayasiri R, Kranzler HR, Weiss R, Brady K, Gueorguieva R, Panhuysen C, Yang BZ, Farrer L, Gelernter J, Malison RT. Risk factors for cocaine-induced paranoia in cocaine-dependent sibling pairs. Drug Alcohol Depend. 2006; 84:77–84. [PubMed: 16413147]

Kalayasiri R, Sughondhabirom A, Gueorguieva R, Coric V, Lynch WJ, Lappalainen J, Gelernter J, Cubells JF, Malison RT. Dopamine beta-hydroxylase gene (DbetaH)-1021C-T influences self-reported paranoia during cocaine self-administration. Biol. Psychiatry. 2007; 61:1310–1313. [PubMed: 17157269]

Kendler KS, Karkowski LM, Neale MC, Prescott CA. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. Arch. Gen. Psychiatry. 2000; 57:261–269. [PubMed: 10711912]

Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci. Int. 2001; 121:65–69. [PubMed: 11516889]

Kishi T, Fukuo Y, Okochi T, Kitajima T, Kawashima K, Naitoh H, Ujike H, Inada T, Yamada M, Uchimura N, Sora I, Iyo M, Ozaki N, Iwata N. Serotonin 6 receptor gene is associated with methamphetamine-induced psychosis in a Japanese population. Drug Alcohol Depend. 2011; 113:1–7. [PubMed: 20705401]

Kobayashi H, Ide S, Hasegawa J, Ujike H, Sekine Y, Ozaki N, Inada T, Harano M, Komiyama T, Yamada M, Iyo M, Shen HW, Ikeda K, Sora I. Study of association between alpha-synuclein gene polymorphism and methamphetamine psychosis/dependence. Ann. N. Y. Acad. Sci. 2004; 1025:325–334. [PubMed: 15542733]

Köhnke MD, Zabetian CP, Anderson GM, Kolb W, Gaertner I, Buchkremer G, Vonthein R, Schick S, Lutz U, Köhnke AM, Cubells JF. A genotype-controlled analysis of plasma dopamine beta-hydroxylase in healthy and alcoholic subjects: evidence for alcohol-related differences in noradrenergic function. Biol. Psychiatry. 2002; 52:1151–1158. [PubMed: 12488060]

Kosten TR, Wu G, Huang W, Harding MJ, Hamon SC, Lappalainen J, Nielsen DA. Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine β-hydroxylase. Biol. Psychiatry. 2013; 73:219–224. [PubMed: 22906516]

Kranzler HR, Wilcox M, Weiss RD, Brady K, Hesselbrock V, Rounsaville B, Farrer L, Gelernter J. The validity of cocaine dependence subtypes. Addict. Behav. 2008; 33:41–53. [PubMed: 17582692]

Laine TP, Ahonen A, Räsänen P, Pohjalainen T, Tiihonen J, Hietala J. The A1 allele of the D2 dopamine receptor gene is associated with high dopamine transporter density in detoxified alcoholics. Alcohol Alcohol. 2001; 36:262–265. [PubMed: 11373265]

Lawford BR, Young RM, Noble EP, Sargent J, Rowell J, Shadforth S, Zhang X, Ritchie T. The D(2) dopamine receptor A(1) allele and opioid dependence: association with heroin use and response to methadone treatment. Am. J. Med. Genet. 2000; 96:592–598. [PubMed: 11054765]

Lee AM, Jepson C, Hoffmann E, Epstein L, Hawk LW, Lerman C, Tyndale RF. CYP2B6 genotype alters abstinence rates in a bupropion smoking cessation trial. Biol. Psychiatry. 2007a; 62:635–641. [PubMed: 17223085]

Lee AM, Jepson C, Shields PG, Benowitz N, Lerman C, Tyndale RF. CYP2B6 genotype does not alter nicotine metabolism, plasma levels, or abstinence with nicotine replacement therapy. Cancer Epidemiol. Biomarkers Prev. 2007b; 16:1312–1314. [PubMed: 17548706]

Lei B, Morris DP, Smith MP, Svetkey LP, Newman MF, Rotter JI, Buchanan TA, Beckstrom-Sternberg SM, Green ED, Schwinn DA. Novel human alpha-1a-adrenocepter single nucleotide polymorphisms alter receptor pharmacology and biological function. Naunyn Schmiedebergs Arch. Pharmacol. 2005; 371:229–239. [PubMed: 15900517]

Lerman C, Jepson C, Wileyto EP, Epstein LH, Rukstalis M, Patterson F. Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of two randomized clinical trials. Neuropsychopharmacol. 2006; 6:47–64.

Lerman C, Shields PG, Wileyto EP, Audrain J, Pinto A, Hawk L, Krishnan S, Niaura R, Epstein L. Pharmacogenetic investigation of smoking cessation treatment. Pharmacogenetics. 2002; 12:627–634. [PubMed: 12439223]

Lerman C, Shields PG, Wileyto EP, Audrain J, Pinto A, Hawk L Jr, Pinto A, Kucharski S, Krishnan S, Niaura R, Epstein LH. Effects of dopamine transporter and receptor polymorphisms on smoking cessation in a bupropion clinical trial. Health Psychol. 2003; 22:541–548. [PubMed: 14570538]

Lerman C, Wileyto EP, Patterson F, Rukstalis M, Audrain-McGovern J, Restine S, Shields PG, Kaufmann V, Redden D, Benowitz N, Berrettini WH. The functional mu opioid receptor (OPRM1) Asn40Asp variant predicts short-term response to nicotine replacement therapy in a clinical trial. Pharmacogenomics J. 2004; 4:184–192. [PubMed: 15007373]

Levran O, O'Hara K, Peles E, Li D, Barral S, Ray B. ABCB1 (MDR1) genetic variants are associated with methadone doses required for effective treatment of heroin dependence. Hum. Mol. Genet. 2008a; 17:2219–2227. [PubMed: 18424454]

Levran O, Londono D, O'Hara K, Nielsen DA, Peles E, Rotrosen J, Casadonte P, Linzy S, Randesi M, Ott J, Adelson M, Kreek MJ. Genetic susceptibility to heroin addiction: a candidate gene association study. Genes Brain Behav. 2008b; 7:720–729. [PubMed: 18518925]

Levran O, Peles E, Randesi M, Shu X, Ott J, Shen PH, Adelson M, Kreek MJ. Association of genetic variation in pharmacodynamic factors with methadone dose required for effective treatment of opioid addiction. Pharmacogenomics. 2013; 14:755–768. [PubMed: 23651024]

Li Y, Shao C, Zhang D, Zhao M, Lin L, Yan P, Xie Y, Jiang K, Jin L. The effect of dopamine D2, D5 receptor and transporter (SLC6A3) polymorphisms on the cue-elicited heroin craving in Chinese. Am. J. Med. Genet. B. Neuropsychiatr. Genet. 2006; 141:269–273. [PubMed: 16526040]

Li CY, Zhou WZ, Zhang PW, Johnson C, Wei L, Uhl GR. Meta-analysis and genome-wide interpretation of genetic susceptibility to drug addiction. BMC Genomics. 2011; 12:508. [PubMed: 21999673]

Lott D, Kim S, Cook E Jr, de Wit H. Dopamine transporter gene associated with diminished subjective response to amphetamine. Neuropsychopharmacol. 2005; 30:602–609.

Lott D, Kim S, Cook E Jr, de Wit H. Serotonin transporter genotype and acute subjective response to amphetamine. Am. J. Addict. 2006; 15:327–335. [PubMed: 16966188]

Lotta T, Vidgren J, Tilgmann C, Ulmanen I, Melen K, Julkunen I, Taskinen J. Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. Biochem. 1995; 34:4202–4210. [PubMed: 7703232]

Mackillop J, Menges DP, McGeary JE, Lisman SA. Effects of craving and DRD4 VNTR genotype on the relative value of alcohol: an initial human laboratory study. Behav. Brain Funct. 2007; 3:11. [PubMed: 17309802]

Matsuzawa D, Hashimoto K, Miyatake R, Shirayama Y, Shimizu E, Maeda K, Suzuki Y, Mashimo Y, Sekine Y, Inada T, Ozaki N, Iwata N, Harano M, Komiyama T, Yamada M, Sora I, Ujike H, Hata A, Sawa A, Iyo M. Identification of functional polymorphisms in the promoter region of the human PICK1 gene and their association with methamphetamine psychosis. Am. J. Psychiatry. 2007; 164:1105–1114. [PubMed: 17606663]

Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst. Rev. 2008; 16:CD002207. [PubMed: 18425880]

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. Catechol *O*-methyltransferase *val158-met* genotype and individual variation in the brain response to amphetamine. Proc. Natl. Acad. Sci. U.S.A. 2003; 100:6186–6191. [PubMed: 12716966]

Mayer P, Rochlitz H, Rauch E, Rommelspacher H, Hasse HE, Schmidt S, Hollt V. Association between a delta opioid receptor gene polymorphism and heroin dependence in man. Neuroreport. 1997; 8:2547–2550. [PubMed: 9261824]

McKinney EF, Walton RT, Yudkin P, Fuller A, Haldar NA, Mant D. Association between polymorphisms in dopamine metabolic enzymes and tobacco consumption in smokers. Pharmacogenetics. 2000; 10:483–491. [PubMed: 10975602]

Meyer R, Patel AM, Rattana SK, Quock TP, Mody SH. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. Popul. Health Manag. EPub Ahead of Print. 2014

Mignini F, Napolioni V, Codazzo C, Carpi FM, Vitali M, Romeo M, Ceccanti M. DRD2/ANKK1 TaqIA and SLC6A3 VNTR polymorphisms in alcohol dependence: association and gene-gene interaction study in a population of Central Italy. Neurosci. Lett. 2012; 522:103–107. [PubMed: 22698582]

Moratti E, Kashanpour H, Lombardelli T, Maisto M. Intravenous misuse of buprenorphine: characteristics and extent among patients undergoing drug maintenance therapy. Clin. Drug Investig. 2010; 30:3–11.

Moss HB, Chen CM, Yi HY. Subtypes of alcohol dependence in a nationally representative sample. Drug Alcohol Depend. 2007; 91:149–158. [PubMed: 17597309]

Moyer RA, Wang D, Papp AC, Smith RM, Duque L, Mash DC, Sadee W. Intronic polymorphisms affecting alternative splicing of human dopamine D2 receptor are associated with cocaine abuse. Neuropsychopharmacol. 2011; 36:753–762.

Munafò MR, Elliot KM, Murphy MF, Walton RT, Johnstone EC. Association of the mu-opioid receptor gene with smoking cessation. Pharmacogenomics J. 2007; 7:353–361. [PubMed: 17224915]

Munafò MR, Johnstone EC, Aveyard P, Marteau T. Lack of association of OPRM1 genotype and smoking cessation. Nicotine Tob. Res. 2013; 15:739–744. [PubMed: 22990223]

Munafo MR, Johnstone EC, Wileyto EP, Shields PG, Elliot KM, Lerman C. Lack of association of 5-HTTLPR genotype with smoking cessation in a nicotine replacement therapy randomized trial. Cancer Epidemiol. Biomarkers Prev. 2006; 15:398–400. [PubMed: 16492936]

Munafò MR, Timpson NJ, David SP, Ebrahim S, Lawlor DA. Association of the DRD2 gene Taq1 A polymorphism and smoking behaviour: a meta-analysis and new data. Nicotine Tob. Res. 2009; 11:64–76. [PubMed: 19246443]

Nakamura M, Ueno S, Sano A, Tanabe H. The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. Mol. Psychiatry. 2000; 5:32–38. [PubMed: 10673766]

Nacak M, Isir AB, Balci SO, Pehlivan S, Benlier N, Aynacioglu S. Analysis of dopamine D2 receptor (DRD2) gene polymorphisms in cannabinoid addicts. J. Forensic Sci. 2012; 57:1621–1624. [PubMed: 22536882]

Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum. Mutat. 2004; 23:540–545. [PubMed: 15146457]

National Institute on Drug Abuse (NIDA). [Last Accessed, Nov. 14th 2013] Research Report Series: Cocaine Abuse and Addiction. 2009. http://www.drugabuse.gov/sites/default/files/rrcocaine.pdf.

National Institute on Drug Abuse (NIDA). [Last Accessed, Dec. 15th 2014] The Science of Drug Use and Addiction: The Basics. 2014. http://www.drugabuse.gov/sites/default/files/mediaguide_web_3_0.pdf.

Nielsen DA, Hamon SC, Kosten TR. The κ-opioid receptor gene as a predictor of response in a cocaine vaccine clinical trial. Psychiatr. Genet. 2013; 23:225–232. [PubMed: 23995774]

Nielsen DA, Ji F, Yuferov V, Ho A, Chen A, Levran O, Ott J, Kreek MJ. Genotype patterns that contribute to increased risk for or protection from developing heroin addiction. Mol. Psychiatry. 2008; 13:417–428. [PubMed: 18195715]

Noble EP, Blum K, Khalsa ME, Ritchie T, Montgomery A, Wood RC, Fitch RJ, Ozkaragoz T, Sheridan PJ, Anglin MD. Allelic association of the D2 dopamine receptor gene with cocaine dependence. Drug Alcohol Depend. 1993; 33:271–285. [PubMed: 8261891]

Noble EP, St. Jeor ST, Ritchie T, Syndulko K, St. Jeor SC, Fitch RJ, Brunner RL, Sparkes RS. D2 dopamine receptor gene and cigarette smoking: a reward gene? Med. Hypotheses. 1994; 42:257–260. [PubMed: 8072432]

O'Gara C, Stapleton J, Sutherland G, Guindalini C, Neale B, Breen G, Ball D. Dopamine transporter polymorphisms are associated with short-term response to smoking cessation treatment. Pharmacogenet. Genomics. 2007; 17:61–67. [PubMed: 17264803]

O'Hara BF, Smith SS, Bird G, Persico AM, Suarez BK, Cutting GR, Uhl GR. Dopamine D2 receptor RFLPs, haplotypes and their association with substance use in black and Caucasian research volunteers. Hum. Hered. 1993; 43:209–218. [PubMed: 8102114]

Patterson F, Schnoll RA, Wileyto EP, Pinto A, Epstein LH, Shields PG, Hawk LW, Tyndale RF, Benowitz N, Lerman C. Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. Clin. Pharmacol. Ther. 2008; 84:320–325. [PubMed: 18388868]

Perkins KA, Lerman C, Coddington S, Jetton C, Karelitz JL, Wilson A, Jennings JR, Ferrell R, Bergen AW, Benowitz NL. Gene and gene by sex associations with initial sensitivity to nicotine in nonsmokers. Behav. Pharmacol. 2008b; 19:630–640. [PubMed: 18690117]

Perkins KA, Lerman C, Grottenthaler A, Ciccocioppo MM, Milanak M, Conklin CA, Bergen AW, Benowitz NL. Dopamine and opioid gene variants are associated with increased smoking reward and reinforcement owing to negative mood. Behav. Pharmacol. 2008a; 19:641–649. [PubMed: 18690118]

Perkins KA, Lerman C, Mercincavage M, Fonte CA, Briski JL. Nicotinic acetylcholine receptor beta2 subunit (CHRNB2) gene and short-term ability to quit smoking in response to nicotine patch. Cancer Epidemiol. Biomarkers Prev. 2009; 18:2608–2612. [PubMed: 19755656]

Pohjalainen T, Rinne JO, Nagren K, Lehikoinen P, Anttila K, Syvalahti EK. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol. Psychiatry. 1998; 3:256–260. [PubMed: 9672901]

Quaak M, van Schayck CP, Postma DS, Wagena EJ, van Schooten FJ. Genetic variants in the serotonin transporter influence the efficacy of bupropion and nortriptyline in smoking cessation. Addiction. 2012; 107:178–187. [PubMed: 21658141]

Ray LA, Bujarski S, Chin PF, Miotto K. Pharmacogenetics of naltrexone in asian americans: a randomized placebo-controlled laboratory study. Neuropsychopharmacol. 2012; 37:445–455.

Ray R, Jepson C, Wileyto EP, Dahl JP, Patterson F, Rukstalis M, Pinto A, Berrettini W, Lerman C. Genetic variation in mu-opioid-receptor-interacting proteins and smoking cessation in a nicotine replacement therapy trial. Nicotine Tob. Res. 2007; 9:1237–1241. [PubMed: 17978999]

Robinson JD, Lam CY, Minnix JA, Wetter DW, Tomlinson GE, Minna JD, Chen TT, Cinciripini PM. The DRD2 TaqI-B polymorphism and its relationship to smoking abstinence and withdrawal symptoms. Pharmacogenomics J. 2007; 7:266–274. [PubMed: 17189962]

Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: 2013.

Schank JR, Ventura R, Puglisi-Allegra S, Alcaro A, Cole CD, Liles LC, Seeman P, Weinshenker D. Dopamine beta-hydroxylase knockout mice have alterations in dopamine signaling and are hypersensitive to cocaine. Neuropsychopharmacol. 2006; 31:2221–2230.

Schellekens AF, Franke B, Ellenbroek B, Cools A, de Jong CA, Buitelaar JK, Verkes RJ. Reduced dopamine receptor sensitivity as an intermediate phenotype in alcohol dependence and the role of the COMT Val158Met and DRD2 Taq1A genotypes. Arch. Gen. Psychiatry. 2012; 69:339–348. [PubMed: 22474103]

Schnoll RA, Patterson F, Wileyto EP, Tyndale RF, Benowitz N, Lerman C. Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: a validation study. Pharmacol. Biochem. Behav. 2009; 92:6–11. [PubMed: 19000709]

Scott JC, Woods SP, Matt GE, Meyer RA, Heaton RK, Atkinson JH, Grant I. Neurocognitive effects of methamphetamine: a critical review and meta-analysis. Neuropsychol. Rev. 2007; 17:275–297. [PubMed: 17694436]

Shao C, Li Y, Jiang K, Zhang D, Xu Y, Lin L, Wang Q, Zhao M, Jin L. Dopamine D4 receptor polymorphism modulates cue-elicited heroin craving in Chinese. Psychopharmacol. (Berl.). 2006; 186:185–190.

Shiels MS, Huang HY, Hoffman SC, Shugart YY, Bolton JH, Platz EA, Helzlsouer KJ, Alberg AJ. A community-based study of cigarette smoking behavior in relation to variation in three genes involved in dopamine metabolism: catechol-O-methyltransferase (COMT), dopamine beta-hydroxylase (DβH) and monoamine oxidase-A (MAO-A). Prev. Med. 2008; 47:116–122. [PubMed: 18486967]

Shorter D, Nielsen DA, Huang W, Harding MJ, Hamon SC, Kosten TR. Pharmacogenetic randomized trial for cocaine abuse: disulfiram and α1A-adrenoceptor gene variation. Eur. Neuropsychopharmacol. 2013; 23:1401–1407. [PubMed: 23849431]

Shrem MT, Halkitis PN. Methamphetamine abuse in the United States: contextual, psychological and sociological considerations. J. Health. Psychol. 2008; 13:669–679. [PubMed: 18519440]

Spellicy CJ, Kosten TR, Hamon SC, Harding MJ, Nielsen DA. ANKK1 and DRD2 pharmacogenetics of disulfiram treatment for cocaine abuse. Pharmacogenet. Genomics. 2013; 23:333–340. [PubMed: 23635803]

Spitz MR, Shi H, Yang F, Hudmon KS, Jiang H, Chamberlain RM, Amos CI, Wan Y, Cinciripini P, Hong WK, Wu X. Case-control study of the D2 dopamine receptor gene and smoking status in lung cancer patients. J. Natl. Cancer. Inst. 1998; 90:358–363. [PubMed: 9498485]

Stapleton JA, Sutherland G, O'Gara C, Spirling LI, Ball D. Association between DRD2/ANKK1 Taq1A genotypes, depression and smoking cessation with nicotine replacement therapy. Pharmacogenet. Genomics. 2011; 21:447–453. [PubMed: 21540761]

Sulzer D. How addictive drugs disrupt presynaptic dopamine neurotransmission. Neuron. 2011; 69:628–649. [PubMed: 21338876]

Swan GE, Jack LM, Valdes AM, Ring HZ, Ton CC, Curry SJ, McAfee T. Joint effect of dopaminergic genes on likelihood of smoking following treatment with bupropion SR. Health Psychol. 2007; 26:361–368. [PubMed: 17500623]

Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science. 1997; 276:2048–2050. [PubMed: 9197269]

Ton TG, Rossing MA, Bowen DJ, Srinouanprachan S, Wicklund K, Farin FM. Genetic polymorphisms in dopamine-related genes and smoking cessation in women: a prospective cohort study. Behav. Brain Funct. 2007; 3:22. [PubMed: 17466074]

Trigo JM, Martin-García E, Berrendero F, Robledo P, Maldonado R. The endogenous opioid system: a common substrate in drug addiction. Drug Alcohol Depend. 2010; 108:183–194. [PubMed: 19945803]

Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard Twin Study of Substance Abuse: what we have learned. Harv. Rev. Psychiatry. 2001; 9:267–279. [PubMed: 11600486]

Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, Meyer JM, Toomery R, Faraone SV, Eaves L. Genetic influences on DSM-III–R drug abuse and dependence: a study of 3,372 twin pairs. Am. J. Med. Genet. 1996; 67:473–477. [PubMed: 8886164]

United Nations Office on Drugs and Crime. World Drug Report. United Nations publication, Sales No. E.12.XI.1. 2014

Uhl GR. Molecular genetics of substance abuse vulnerability: a current approach. Neuropsychopharmacol. 1999; 20:3–9.

Ujike H, Harano M, Inada T, Yamada M, Komiyama T, Sekine Y, Sora I, Iyo M, Katsu T, Nomura A, Nakata K, Ozaki N. Nine-or fewer repeat alleles in VNTR polymorphism of the dopamine transporter gene is a strong risk factor for prolonged methamphetamine psychosis. Pharmacogenomics J. 2003; 3:242–247. [PubMed: 12931138]

Ujike H, Katsu T, Okahisa Y, Takaki M, Kodama M, Inada T, Uchimura N, Yamada M, Iwata N, Sora I, Iyo M, Ozaki N, Kuroda S. Genetic variants of D2 but not D3 or D4 dopamine receptor gene are associated with rapid onset and poor prognosis of methamphetamine psychosis. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2009; 33:625–629. [PubMed: 19275926]

Vaccari A, Saba PL, Ruiu S, Collu M, Devoto P. Disulfiram and diethyldithiocarbamate intoxication affects the storage and release of striatal dopamine. Toxicol. Appl. Pharmacol. 1996; 139:102–108. [PubMed: 8685891]

Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O, Kennedy J, Seeman P, Niznik HB, Jovanovic V. Multiple dopamine D4 receptor variants in the human population. Nature. 1992; 358:149–152. [PubMed: 1319557]

van den Wildenberg E, Janssen RG, Hutchison KE, van Breukelen GJ, Wiers RW. Polymorphisms of the dopamine D4 receptor gene (DRD4 VNTR) and cannabinoid CB1 receptor gene (CNR1) are not strongly related to cue-reactivity after alcohol exposure. Addict. Biol. 2007; 12:210–220. [PubMed: 17508995]

Veenstra-VanderWeele J, Qaadir A, Palmer AA, Cook EH, de Wit H. Association between the Casein Kinase 1 Epsilon gene region and subjective response to D-amphetamine. Neuropsychopharmacol. 2006; 31:1056–1063.

Vocci FJ, Ling WW. Medications development: successes and challenges. Pharmacol. Ther. 2005; 108:94–108. [PubMed: 16083966]

Wang Z, Ray R, Faith M, Tang K, Wileyto EP, Detre JA, Lerman C. Nicotine abstinence-induced cerebral blood flow changes by genotype. Neurosci. Lett. 2008; 438:275–280. [PubMed: 18499348]

White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction. 1999; 94:961–972. [PubMed: 10707430]

Wilcox CS, Noble EP, Oskooilar N. ANKK1/DRD2 locus variants are associated with rimonabant efficacy in aiding smoking cessation: pilot data. J. Investig. Med. 2011; 59:1280–1283.

Yu Q, Larson DF, Watson RR. Heart disease, methamphetamine and AIDS. Life Sci. 2003; 73:129–140. [PubMed: 12738029]

Yudkin P, Munafò M, Hey K, Roberts S, Welch S, Johnstone E, Murphy M, Griffiths S, Walton R. Effectiveness of nicotine patches in relation to genotype in women versus men: randomised controlled trial. BMJ. 2004; 328:989–990. [PubMed: 15033882]

Zabetian CP, Anderson GM, Buxbaum SG, Elston RC, Ichinose H, Nagatsu T. A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity: evidence for a major functional polymorphism at the DβH locus. Am. J. Hum. Genet. 2001; 68:515–522. [PubMed: 11170900]

Zhang D, Shao C, Shao M, Yan P, Wang Y, Liu Y, Liu W, Lin T, Xie Y, Zhao Y, Lu D, Li Y, Jin L. Effect of mu-opioid receptor gene polymorphisms on heroin-induced subjective responses in a Chinese population. Biol. Psychiatry. 2007 A; 61:1244–1251. [PubMed: 17157823]

Zhang Y, Bertolino A, Fazio L, Blasi G, Rampino A, Romano R, Lee ML, Xiao T, Papp A, Wang D, Sadee W. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. Proc. Natl. Acad. Sci. U.S.A. 2007 B; 104:20552–20557. [PubMed: 18077373]

Zhang H, Kranzler HR, Yang BZ, Luo X, Gelernter J. The OPRD1 and OPRK1 loci in alcohol or drug dependence: OPRD1 variation modulates substance dependence risk. Mol. Psychiatry. 2008; 13:531–543. [PubMed: 17622222]

Zuo L, Kranzler HR, Luo X, Yang BZ, Weiss R, Brady K, Poling J, Farrer L, Gelernter J. Interaction between two independent CNR1 variants increases risk for cocaine dependence in European Americans: a replication study in family-based sample and population-based sample. Neuropsychopharmacol. 2009; 34:1504–1513.

Highlights

- We reviewed pharmacogenetic studies on drug subjective effects and medication trials
- These studies provide evidence of clinically relevant pharmacogenetic effects
- This body of literature has produced conflicting results that require resolution
- More rigorous procedural and statistical controls may reduce false positives
- Understanding genetic modulation may advance individualized Tx of drug use disorders

Table 1

Pharmacogenetic Medication Trials for Nicotine Abuse

Gene	Polymorphism	Treatment Medication	Sample Size	Population	Treatment × Genotype Finding* ↑ More effective ↓ Less effective ↔ No interaction	Citation
ANKK1	rs1800497	Bupropion	577	German	↑ CC genotype	Breitling et al., 2010
	rs1800497	Transdermal Nicotine	755	Primarily Caucasian (98%)	↑ CT/TT genotypes	Johnstone et al. (2004)
	rs1800497	Transdermal Nicotine	752	European	↑ CT/TT genotypes (women only)	Yudkin et al. (2004)
	rs1800497	Bupropion	722	Caucasian /European Ancestry	↑A2/A2 (CC) genotype	David et al. (2007b)
	rs1800497	Transdermal Nicotine	908	European or Unknown Ancestry	↓ CT/TT genotypes	Munafo et al. (2009)
	rs1800497	Transdermal Nicotine	419	Primarily Caucasian/European	↔	Stapleton et al. (2011)
	rs1800497	Rimonabant	76	European Decent	↑A2/A2 (CC) genotype	Wilcox et al. (2011)
ARRB2	rs1045280 rs2036657	NRT (transdermal, nasal spray)	374	European Ancestry	↔	Ray et al. (2007)
CHRNA4	rs2236196	NRT (all formulations)	316	European Ancestry	↔	Hutchison et al. (2007)
CHRNB2	rs2072661	Bupropion	412	European	↔	Conti et al. (2008)
	rs2072661	Transdermal Nicotine	156	European	↑ GG genotype	Perkins et al. (2009)
COMT	Val158Met: rs4680	NRT (transdermal nicotine, nicotine spray)	290	Females of European and African ancestry	↑ Met/Met	Colilla et al. (2005)
	rs4680	Transdermal Nicotine	749	European	↑ Met/Met	Johnstone et al. (2007)
	rs737865 rs165599	Bupropion	511	Caucasian- and African-American	↑ A/G allele of rs165599 ↑ GG at both SNPs (AA participants only)	Berrettini et al. (2007)
CYP2A6		Bupropion	414	European	↑ Fast metabolizers	Patterson et al. (2008)
		Transdermal Nicotine	568	European	↓ Fast metabolizers	Schnoll et al. (2009)
	CYP2A6 *CHRNA5*: rs1696998, rs680244	Bupropion NRT (lozenge, transdermal) Bupropion + NRT	709	Caucasian -American	↑ Fast metabolizers (NRT) ↑ *CYP2A6*: Fast metabolizers + *CHRNA5*: GG/TT,GA/CT, AA/CC (NRT)	Chen et al. (2014)
CYP2B6	C1459T: rs3211371	Bupropion	426	Caucasian-European	↑Female CT/TT	Lerman et al. (2002)
	CYP2B6: rs3211371	Bupropion	291	European	↑ *CYP2B6* CT/TT variant + A*NKK1* A2/A2	David et al. (2007b)

Gene	Polymorphism	Treatment Medication	Sample Size	Population	Treatment × Genotype Finding* ↑ More effective ↓ Less effective ↔ No interaction	Citation
	ANKK1: rs1800497 SLC6A3 3' VNTR: rs27072					
	*6	Bupropion	326	European Ancestry	↑ *CYP2B6*6* carriers	Lee et al. (2007a)
	*1, *4, *6	NRT (transdermal, nasal spray)	369	European Ancestry	↔	Lee et al. (2007b)
DβH	*DβH*: rs77905 *ANKK1*: rs1800497	Transdermal Nicotine	755	Primarily Caucasian (98%)	↑ Taq1A CT/TT + *DβH* GA/AA genotypes	Johnstone et al. (2004)
	rs77905	Bupropion	577	German (98%)	↔	Breitling et al. (2010)
DRD2	−141C Ins/Del: rs1799732	NRT (transdermal, nasal spray)	368	European	↑ Smokers with at least one copy of the *Del C* allele	Lerman et al. (2006)
	rs1799732 *FREQ*: rs1054879	NRT (transdermal, nasal spray)	363	European	↑ Smokers with at least one copy of *−141 Del* allele and two copies of *FREQ*	Dahl et al. (2006)
	rs1799732	Bupropion	414	European	↑ Smokers homozygous for the Ins C allele	Lerman et al. (2006)
	C957T: rs6277	NRT (transdermal, nasal spray)	368	European	↑ C allele	Lerman et al. (2006)
	rs6277	Bupropion	414	European	↔	Lerman et al. (2006)
	Exon 8 A/G: rs6276	Transdermal Nicotine	755		↔	Johnstone et al. (2004)
DRD4	VNTR	Transdermal Nicotine	720	European Ancestry	↔	David et al. (2008)
	C-521T: rs1800955	Transdermal Nicotine	720	European	↔	David et al. (2008)
HINT1	rs3852209 rs2278060	NRT (transdermal, nasal spray)	374	European Ancestry	↑ rs3852209 TT genotype	Ray et al. (2007)
OPRM1	*Asn40Asp (A118G)*: rs1799971	NRT (transdermal, nasal spray)	320	European	↑ G carriers w/transdermal nicotine (no interaction with nasal nicotine)	Lerman et al. (2004)
	rs1799971	Transdermal Nicotine	710	European Ancestry	↑ AA carriers	Munafo et al. (2007)
	rs1799971	NRT (transdermal, nasal spray)	374	European	↑ G carriers	Ray et al. (2007)
	rs1799971	Transdermal Nicotine	598	European Ancestry	↔	Munafo et al. (2013)
SLC6A3 ANKK1	3′ UTR VNTR Taq1A: rs1800497	Bupropion	418	European	↔	Lerman et al. (2003)
	3′ UTR VNTR Taq1A: rs1800497	Bupropion	416	European	↓ *ANKK1* A1 and *SLC6A3-9*	Swan et al. (2007)
SLC6A3	3′ UTR VNTR	NRT (all formulations) Bupropion	583	European	↔	O'Gara et al. (2007)
	3′ UTR VNTR	Bupropion	291	European	↔	David et al. (2007b)

Gene	Polymorphism	Treatment Medication	Sample Size	Population	Treatment × Genotype Finding* ↑ More effective ↓ Less effective ↔ No interaction	Citation
SLC6A4	5-HTTLPR	Nicotine Replacement Therapy (NRT): (transdermal patch, nasal spray)	397	European	↔	Munafo et al. (2006)
	5-HTTLPR	Transdermal patch	741	European	↔	David et al. (2007c)
	5-HTTLPR	Bupropion Nortriptyline	214	Caucasian	↑ carriers L-variant (rs25531) Bupropion ↑ carriers of 3 combined high-activity variants Bupropion & Nortriptyline	Quaak et al. (2012)

* Relationship between genotype and pharmacotherapy effectiveness outcome

Table 2

Pharmacogenetic Medication Trials for Opioid Abuse

Gene	Polymorphism	Treatment Medication	Drug of Abuse	Sample Size	Population	Treatment × Genotype Finding* ↑ More effective ↓ Less effective ↔ No interaction	Citation
ANKK1	rs1800497	Methadone	Heroin	95	Caucasian	↓ T allele	Lawford et al. (2000)
	rs1800497	Buprenorphine	Heroin	25	Primarily Caucasian (88%)	↔	Barrat et al. (2006)
	rs1800497	Methadone	Heroin	46	Primarily Caucasian (89%)	↔	Barrat et al. (2006)
	rs1800497	Methadone	Heroin	238	Caucasian	↔	Crettol et al. (2008)
CYP3A4	*1B	Methadone	Opioids	245	Caucasian-European	↔	Crettol et al. (2006)
CYP2B6	*4, *5, *6, *9	Methadone	Opioids	245	Caucasian-European	↔	Crettol et al. (2006)
DRD1	rs4532	Methadone	Heroin	238	Caucasian	↔	Crettol et al. (2008)
DRD2	rs6277	Methadone	Heroin	238	Caucasian	↑ CC genotype	Crettol et al. (2008)
Multiple Variants	*MYOCD*: rs1714984, *GRM8*: rs1034576, *CRY1*: rs1861591, *GRM6*: rs953741, *OPRM1*: rs1074287, *NR4A2*: rs1405735, intergenic variants: rs965972, rs1867898	Methadone	Opioids	169	Caucasian	↓*CRY1* AA ↓ MYOCD A allele + *GRM6* AG	Fonseca et al. (2010)
OPRD1	rs2234918	Methadone	Heroin	238	Caucasian	↔	Crettol et al. (2008)
	rs678849 rs1042114 rs10753331 rs59520 rs581111 rs2234918	Buprenorphine	Opioids	566 Caucasian 77 African-American	Caucasian- and African-American	↓ African-American rs678849 CC genotype	Crist et al. (2013 A)
	rs678849 rs1042114 rs10753331 rs59520 rs581111 rs2234918	Methadone	Opioids	566 Caucasian 77 African-American	Caucasian- and African-American	↑ African-American rs678849 CC genotype	Crist et al. (2013 A)

Gene	Polymorphism	Treatment Medication	Drug of Abuse	Sample Size	Population	Treatment × Genotype Finding* ↑More effective ↓Less effective ↔ No interaction	Citation
	rs678849 rs1042114 rs10753331 rs59520 rs581111 rs2234918	Buprenorphine Methadone	Opioids	582	European-American	↓ Female rs581111 AA/AG genotype ↓ Female rs529520 AA genotype	Clarke et al. (2014 A)
OPRM1	rs1799971	Methadone	Heroin	238	Caucasian	↔	Crettol et al. (2008)
	G-172T: rs6912029 G-1510A: rs12205732	Oral Naltrexone	Opioids	138	Arab	↓ 172GG and 1510GG	Al-Eitan et al. (2012)

Table 3

Pharmacogenetic Medication Trials for Cocaine Abuse

Gene	Polymorphism	Treatment Medication	Sample Size	Population	Treatment × Genotype Finding* ↑ More effective ↓ Less effective ↔ No interaction	Citation
ADRA1A	rs1048101	Disulfiram	69	Caucasian (>50%); others unidentified	↑ carriers of at least one T allele	Shorter et al. (2013)
	rs1611115	Cocaine Vaccine	71	Primarily Caucasian (79% and greater)	↑ CT/TT genotype	Kosten et al. (2013)
	rs1611115	Disulfiram	74	Primarily Caucasian (67% and greater)	↑ CC/TT genotype	Kosten et al. (2013)
ANKK1	rs1800497	Disulfiram	68	Caucasian-, African- and Latino -American	↑ CT/TT genotypes	Spellicy et al. (2013)
DRD2	rs2283265	Disulfiram	68	Caucasian, African-American, & Latino	↑ GT or TT genotypes	Spellicy et al. (2013)
MTHFR	rs1801133	Disulfiram	67	Between 43% and 90% Caucasian, others unidentified	↑ CT or TT genotypes	Spellicy et al. (2013)
OPRK1	rs6473797	Cocaine Vaccine	114	Primarily Caucasian (80% and greater)	↑ AA allele carriers	Nielsen et al., (2013)