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Addiction pharmacogenetics: A systematic review of the genetic variation of the dopaminergic system

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Abstract

Substance use disorders have significant personal, familial, and societal consequences. Despite the serious consequences of substance use, only a few therapies are effective in treating substance use disorders, thus highlighting a need for improved treatment practices. Substance use treatment response depends on multiple factors such as genetic, biological, and social. It is essential that each component is represented in treatment plans. The dopaminergic system plays a critical role in pharmacotherapy for the addictions and an understanding of the role of variation of genes involved in this system is essential for its success. This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines. A computerized literature search was conducted using *PubMed* and *Scopus* (all databases). Articles published up to April 2015 that examined the role of dopaminergic gene variation in the pharmacotherapy of alcohol, opioid, and cocaine substance use disorders were reviewed. Search terms were dopamine, gene, polymorphism, substance abuse, treatment, and response. Polymorphisms of the *DRD2*, *ANKK1*, *DAT1*, *DBH*, and *DRD4* genes have been found to moderate the effects of the pharmacotherapy of alcohol, opioid, and cocaine substance use disorders. The integration of genetic information with clinical data will inform health professionals of the most efficacious pharmacotherapy intervention for substance use disorders. More studies are needed to confirm and extend these findings.

Keywords

Abuse; addiction; alcohol; cocaine; dependence; dopamine; drug; gene; polymorphism; therapy

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Introduction

Current prevalence estimates of drug use highlight an urgent global health concern with few therapeutic options. Up to 324 million individuals worldwide aged 15-64 years have used an illicit drug (United Nations Office on Drugs and Crime, 2014). Within the United States alone, 24.6 million (9.4% of the population) Americans over age 12 were alcohol, tobacco, or illicit drug users in 2013 (SAMHSA, 2014). Use of addictive drugs directly impacts an individual's physical and socio-emotional health, including increased risk for comorbid drug use and addiction, emergency care, HIV infection, and family dysfunction (Baldwin *et al.*, 2012, Macgowan *et al.*, 1997, Meandzija *et al.*, 1994, Wolf *et al.*, 2004). Many mental health disorders and their symptoms also are associated with substance use: depression, suicidal ideation, suicide attempts, schizophrenia, bipolar disorder, borderline personality disorder, mood and anxiety disorders, conduct disorder, and antisocial personality disorder (Merikangas *et al.*, 1998, Mesholam-Gately *et al.*, 2014, Rasic *et al.*, 2013, Trull *et al.*, 2000, Wilens & Zulauf, 2014). In addition to the personal and familial impact, the fiscal consequences associated with addictive drug use have been estimated in the United States to be $122 billion per year in lost productivity and time (Horgan *et al.*, 2001). The serious personal, familial, and societal costs of substance use highlights the need to advance the understanding of the mechanisms underlying treatment response and, in turn, establish more precise pharmacotherapy practices to effectively treat drug addiction.

Drug addiction is characterized by the presence of psychological (e.g., craving, unsuccessful efforts to control use) and/or physical symptoms (e.g., a need for increased amounts of the drug to achieve intoxication or a desired effect) (American Psychiatric Association, 2013, World Health Organization, 1992). As an individual develops an addiction, drug use frequency increases and the amount of the drug needed in order to maintain the drug effects increases (tolerance). Drug cessation may lead to withdrawal symptoms (e.g., nausea, anxiety) and cravings (Kreek *et al.*, 2005b). The relief of withdrawal symptoms and cravings with subsequent drug use (relapse) perpetuates the substance abuse cycle. Thus, treatment plans that simultaneously reduce physiological and psychological symptoms related to withdrawal and craving are most effective.

Every patient responds to pharmacotherapy in an individualized manner. This response is, in part, moderated by genetic variation (Nielsen *et al.*, 2014a). Decision-making regarding initial psychiatric medication selection, which typically does not include a patients' genetic information, fails to reduce symptoms in 30-40% of individuals (Haile *et al.*, 2009). Incorporating genetic information into the decision-making process provides a targeted approach that may guide the selection of psychiatric medication (Gupta *et al.*, 2006, Malhotra *et al.*, 2004, Murphy *et al.*, 2003). With a genetically-guided approach, there may be an increase in compliance and positive therapeutic response and, at the same time, reduced risk for toxic side effects (Deleon *et al.*, 2006, Malhotra *et al.*, 2004, Murphy *et al.*, 2003, Rogers *et al.*, 2002). Due to its role in reward processing and substance use disorders, genetic analysis of the dopaminergic system may provide unique insights to the application of pharmacogenetics to improve treatment of substance abuse disorders. As such, herein we systematically review the current literature on variation of dopaminergic genes – i.e., *dopamine receptor D2* (*DRD2*), *ankyrin repeat and kinase domain containing 1* (*ANKK1*),

dopamine transporter 1 (*DAT1*, *SLC6A3*), *dopamine β-hydroxylase* (*DBH*), and *dopamine receptor D4* (*DRD4*) – and the pharmacotherapy of addiction to cocaine, alcohol, and opioids (see Table 1). This review complements our previous systematic evaluation of genetic variation of the opioidergic system in the pharmacotherapy of substance abuse (Bauer *et al.*, 2014).

The dopaminergic system

In recent years, an empirical link has emerged between neural reward processes, the dopaminergic system, and substance use disorders (for extensive review see Nutt *et al.*, 2015). Briefly, when there is anticipation of a reward (Schultz, 2002, Schultz, 2010) dopamine is released in the nucleus accumbens (NAc) from neurons originating in the ventral tegmental area (VTA) (Di Chiara & Imperato, 1988, Koob & Le Moal, 2001, Pfaus *et al.*, 1990, Small *et al.*, 2003, Wise, 1998). Dopamine is released after the use of drugs of abuse (Di Chiara & Imperato, 1988). Over time, continued drug lowers striatal dopamine receptor availability in cocaine, alcohol, and opioid dependent individuals (e.g., Martinez *et al.*, 2007, Volkow *et al.*, 2011, Volkow *et al.*, 1996, Wang *et al.*, 1997). In addition to substance use disorders being associated with lower striatal dopamine receptor availability, many are associated with blunted dopamine release (e.g., cocaine; Badiani *et al.*, 2011). The use of addictive drugs stimulates dopamine release thereby increasing dopamine levels above typical basal levels (Volkow *et al.*, 2011), eventually leading to craving and addiction. Notably, as highlighted by Nutt and colleagues, this is an oversimplification of the role of dopamine in substance use. Though the dopamine theory of addiction is generally accepted, Nutt and colleagues illustrate the importance of dissecting the relations between dopamine, reward, and specific drugs of abuse. Not all drugs evoke the same dopaminergic processes or effects, thus a broad theory of dopamine and addiction is incomplete (Nutt *et al.*, 2015).

One factor associated with differences in the relations between drugs and dopamine, is that the specific mechanisms of action for each class of abused drugs differs. Alcohol and opioids primarily act on mesolimbic dopaminergic pathways, while cocaine blocks the action of three of the major neurotransmitter system transporters, dopamine, serotonin, and norepinephrine (Han & Gu, 2006). Albeit by different mechanisms, alcohol, opioids, and cocaine increase the release and synaptic availability of dopamine. Alcohol has been shown to promote the release of endogenous opioids (Imperato & Di Chiara, 1986, Koob, 1992, Weiss *et al.*, 1993). Current opinion is that alcohol may increases dopamine levels via μ-opioid receptors in the mesolimbic system (Heilig *et al.*, 2011). The binding of the endogenous opioid peptide β-endorphin disinhibits the GABAergic interneurons in the VTA stimulating the release of dopamine and increasing extracellular mesolimbic dopamine levels in the NAc (Bourdy & Barrot, 2012). Opioids, however, bind directly to the μ-opioid receptors on the GABAergic interneurons, depolarizing their membrane and inhibiting the release of GABA. This inhibition of GABA subsequently stimulates the release of dopamine in the NAc (Johnson & North, 1992). Cocaine increases the availability of dopamine in the synapse by binding to the dopamine transporter and inhibiting reuptake of dopamine from the synapses. These drug-specific dopaminergic responses underscore the utility of reviewing the connection between genetic variants of dopaminergic genes and their role in substance use disorders and pharmacotherapeutic response.

Dopaminergic genes relevant to addiction

Dopamine receptor D2 (DRD2)/ankyrin repeat and kinase domain containing (ANKK1) genes

DRD2 and *ANKK1* are situated approximately 10,000 nucleotides apart on chromosome 11q22-23. *DRD2* and *ANKK1* polymorphisms have been found to be associated with alcohol, heroin, cocaine, and opioid substance use disorders and substance dependence (Blum *et al.*, 1991, Lawford *et al.*, 2000, Moyer *et al.*, 2011, Noble, 1994). *DRD2* transcripts may be alternatively spliced to code for two different protein isoforms: the long (D2L) and short (D2S, lacking exon 6) forms of the receptor protein. The single-nucleotide polymorphism (SNP) rs2283265 (in intron 5), which is a G to T transversion in an intron of the *DRD2* gene, increases the ratio of D2L to D2S protein isoforms (Moyer *et al.*, 2011). The T allele of rs2283265 is found more commonly in cocaine-addicted individuals (Meyers *et al.*, 2013, Zhang *et al.*, 2007). Another *DRD2* variant, rs6277, is a synonymous (does not alter the amino acid coding) C to T transition in *DRD2*. Individuals with the T allele have greater D2 receptor availability, altered mRNA folding, and reduced mRNA stability (Duan *et al.*, 2003, Hirvonen *et al.*, 2009), and is carried more often in those with opioid substance dependence relative to healthy controls (Doehring *et al.*, 2009b).

The *ANKK1* gene encodes the ankyrin repeat and kinase domain containing 1 protein receptor also known as receptor interacting protein 5 (RIP5). The *ANKK1* polymorphisms are one of the most examined genetic variants in connection with substance use and other psychiatric disorders (Blum *et al.*, 1990, Comings *et al.*, 1991), particularly alcoholism. *ANKK1/DRD2 Taq*IA, also known as rs1800497, is a functional SNP located in the final exon of *ANKK1* that codes for a non-synonymous glutamic acid to lysine (C to T) amino acid change in the C-terminus of the *ANKK1* protein. The *Taq*IA1 allele has been found to be associated with a reduced dopamine receptor D2 density (Jonsson *et al.*, 1999) and an increased rate of substance dependence to cocaine, opioids, and alcohol (Volkow *et al.*, 1990, Volkow *et al.*, 1996, Wang *et al.*, 1997).

The *ANKK1* variant rs7118900 also may contribute to drug-related dopaminergic system changes in D2 levels. This variant codes for an alanine to threonine (Ala239Thr) substitution that creates a predicted phosphorylation site and is found to be in strong linkage disequilibrium with *ANKK1/DRD2 Taq*IA (Garrido *et al.*, 2011). Cells transfected with the *ANKK1* rs7118900 Thr239 variant constructs had higher expression levels than did cells containing the Ala239 variant constructs. When treated with the dopamine agonist apomorphine, the Thr239 constructs decreased expression while the Ala239 constructs increased expression. This differential response of the *ANKK1* alleles highlights a potential functional link to the dopaminergic system.

Dopamine transporter (DAT1, SLC6A3) gene

The *DAT1* gene codes for the dopamine transporter (DAT), a member of the sodium and chloride-dependent family of neurotransmitter transporters (Vandenbergh *et al.*, 1992b). DAT mediates the reuptake of dopamine from synapses into the presynaptic nerve terminals (Amara & Kuhar, 1993, Giros & Caron, 1993, Iversen, 1971). The *DAT1* gene contains a

variable number tandem repeat (VNTR) located in the 3'-untranslated region (Sano *et al.*, 1993, Vandenbergh *et al.*, 1992a) that may contain 3-11 copies of the repeat. This VNTR has been shown to alter *DAT1* gene expression, with the 9 allele showing a higher level expression compared to the 10 allele (Miller & Madras, 2001). Variation of this VNTR is associated with multiple disorders/diseases related to dopamine including alcoholism (Franke *et al.*, 1999, Muramatsu & Higuchi, 1995, Sander *et al.*, 1997), attention-deficit/hyperactivity disorder (Cook Jr *et al.*, 1995), Parkinson's disease (Le Couteur *et al.*, 1997, Mercier *et al.*, 1999), and schizophrenia (Blum *et al.*, 1997, Inada *et al.*, 1996, Maier *et al.*, 1996).

Dopamine β-hydroxylase (DBH) gene

Dopamine β-hydroxylase (DβH) is an enzyme located primarily within the synaptic vesicles that store the catecholamine neurotransmitters dopamine and norepinephrine where it metabolizes dopamine into norepinephrine [reviewed in (Kaufman & Friedman, 1965, Weinshilboum, 1978)]. Although the majority of DβH is membrane bound in the vesicle, some DβH is free and is concurrently released with the catecholamines during synaptic transmission from neurons and into the blood from neurosecretory cells of the adrenal medulla (Stewart & Klinman, 1988). DβH levels in serum and cerebral spinal fluid are heritable (Oxenstierna *et al.*, 1986), having been found to be highly correlated between siblings, but not between unrelated subjects (Weinshilboum *et al.*, 1973).

Numerous polymorphisms of the *DBH* gene have been shown to be associated with DβH levels, but one variant appears to best predict DβH levels: the C-1021T rs1611115 variant, also known as C-970T (Bhaduri & Mukhopadhyay, 2008, Zabetian *et al.*, 2001, Zabetian *et al.*, 2003). In a study that examined 11 SNPs across *DBH*, the C-1021T variant was determined to be the best predictor of DβH plasma levels, accounting for 35-52% of the variation (Zabetian *et al.*, 2003). The rs1611115 variant has been associated with alcohol dependence in females (Preuss *et al.*, 2013) and with heroin self-administration (Xie *et al.*, 2013).

Dopamine receptor D4 (DRD4) gene

DRD4 is a relevant dopaminergic gene related to pharmacotherapy and substance use (Hutchison *et al.*, 2002). *DRD4* has a VNTR in exon 3 with three common alleles of two, four, and seven repeats (Van Tol *et al.*, 1992). Subjects who were carriers of the seven or longer repeats had a greater "urge to drink" and lower "subjective high" following alcohol consumption compared to peers without this allele (Hutchison *et al.*, 2002). The *DRD4* seven tandem repeat allele codes for a dopaminergic receptor D4 that attenuates intracellular forskolin-stimulated cyclic AMP (cAMP) response to dopamine to a greater extent than that produced by the receptor encoded by the two or four tandem repeat alleles (Asghari *et al.*, 1995). Thus, this VNTR appears to contribute to an individual's subjective sensitivity to drugs (e.g., increased urges).

Material and Methods

Literature Review

This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines (http://www.prisma-statement.org/). Peer-reviewed and published scientific papers were identified through a computerized literature search using *PubMed* and *Scopus* (all databases). Articles published up to April 2015 were reviewed. The following search terms were used: “dopamine,” “gene,” “polymorphism,” “substance abuse,” “treatment,” and “response.” Inclusion criteria were that articles have been: 1) published in English, 2) utilized human clinical population(s) with addictive disorders (e.g., substance use), 3) examined genetic polymorphisms, and 4) measured treatment response. Exclusion criteria were: 1) animal models, 2) human clinical population(s) with mood disorders, and 3) non-substance use clinical trials of psychotropic medication. Article search and selection was completed by two non-blinded reviewers (MP, DN). Articles that did not meet inclusion criteria and/or met exclusion criteria were removed (see Figure 1).

Results

Dopaminergic genetics and the pharmacotherapy of drug addiction

Bromocriptine—Bromocriptine is an ergot alkaloid and dopamine receptor D2 agonist. It is commonly used to treat Parkinsonian syndrome, hyperprolactinaemia, growth hormone, and prolactin-related disorders (e.g., infertility, hypogonadism), and also has been efficacious in the treatment of alcoholism (Balldin *et al.*, 1993, Balldin *et al.*, 1992). Administration of bromocriptine inhibits the release of prolactin from the pituitary gland (Jarvik *et al.*, 2000). Since alcoholics have reduced *DRD2* receptor sensitivity even several years after discontinuing alcohol use (Balldin *et al.*, 1993, Balldin *et al.*, 1992), bromocriptine may decrease the symptoms of alcohol withdrawal by activating the DRD2 receptor. Symptom improvements following bromocriptine appear to be moderated by the presence of the *Taq*IA1 variant. Specifically, alcohol-addicted subjects who were *Taq*IA1 carriers showed the greatest reduction in self-reported alcohol cravings and anxiety following a 6-week randomized double-blind clinical trial of bromocriptine (Lawford *et al.*, 1995). Individuals received bromocriptine (2.5 mg, three times daily) or placebo. Notably, the overwhelming majority of subjects (94%) were male and findings should not be generalized to female populations. The attrition was also highest in the placebo-treated A1 group emphasizing the positive effects of bromocriptine in treating alcohol withdrawal.

Cocaine vaccine—A specific cocaine vaccine composed of succinyl norcocaine conjugated to cholera toxin (Martell*et al.*, 2005) was delivered through a series of vaccinations in an effort to aid in the recovery from cocaine addiction. Vaccination of patients provided therapeutic levels of anti-cocaine antibodies in approximately 40% of patients (Haney *et al.*, 2010). It was hypothesized that if a cocaine-abstinent patient who has received this vaccine relapses and uses cocaine, the anti-cocaine antibodies will sequester cocaine in the blood reducing the ability of cocaine to enter the brain. In one study, individuals who received a higher total dose (2000 *μg*) versus a lower total dose (400 *μg*) of

the vaccine had higher mean antibody titer response and greater reduction of cocaine use (Martell *et al.*, 2005).

The *DBH* variant rs1611115 (−1021C>T) was tested to determine if it would moderate this response (Kosten *et al.*, 2013a). Subjects were randomized to a double-blind placebo-controlled 16-week trial. Subjects received five vaccinations over the first 12 weeks. It was found that subjects with the low DβH level genotypes (T allele carriers) had a greater reduction in cocaine use (77% to 51% cocaine-positive urines) compared to those with the normal DβH level (CC) genotype (83% to 72% cocaine-positive urines) (Kosten *et al.*, 2013a). Since the low expressing DβH rs1611115 variant has been found to be associated with increased cocaine-induced paranoia (Cubells *et al.*, 2000), it is possible that this increased paranoia persuades individuals to reduce cocaine use following cocaine vaccine immunization. Similar to the study of bromocriptine, however, the majority of subjects in this study were male and are not necessarily representative of female response. Kosten and colleagues did control for population structure by including it in analyses as a covariate. Only two other studies (Kosten *et al.*, 2013b, Spellicy *et al.*, 2013) controlled for population structure in their analyses.

Disulfiram—Disulfiram (Antabuse, Antabus) has been used for treatment of alcoholism since the early 1950s (Chick, 1999). Following ingestion, disulfiram is oxidized to diethyldithiocarbamate, which is a copper chelator. In the treatment of alcoholism, disulfiram attenuates the conversion of acetaldehyde to acetate through the inhibition of aldehyde dehydrogenases (ALDH). This causes accumulation of acetaldehyde, triggering negative symptoms after the consumption of alcohol (e.g., nausea, vertigo, flushing). Due to the chelating properties of the disulfiram metabolite, copper-containing enzymes also are inhibited, including DβH, the enzyme that converts dopamine to norepinephrine. Treatment with disulfiram reduces DβH activity, increases the levels of dopamine, and decreases the norepinephrine to dopamine ratio in noradrenergic neurons (Bourdélat-Parks *et al.*, 2005, Goldstein & Nakajima, 1967, Karamanakos *et al.*, 2001, Musacchio *et al.*, 1966).

Disulfiram has not only been demonstrated to reduce alcohol consumption, but also to decrease cocaine use (Carroll *et al.*, 2004, Carroll *et al.*, 1998, Petrakis *et al.*, 2000). There are two potential mechanisms of action regarding cocaine and disulfiram: 1) inhibition of DβH and/or 2) inhibition of enzymes that systematically inactivate cocaine, plasma and microsomal carboxylesterases and plasma cholinesterase (Mccance-Katz *et al.*, 1998). One potential site of action of disulfiram, DβH, was examined in individuals codependent on cocaine and opioids (Kosten *et al.*, 2013b). After these subjects were stabilized on methadone for two weeks, they were randomized to receive either disulfiram (250 mg/day) or placebo. The disulfiram-treated subjects showed reduced cocaine use (measured via urine cocaine metabolites), but had no significant reduction in opioid use. When the disulfiram treatment group was separated based on the presence/absence of the *DBH* rs1611115 T allele, the CC genotype group with normal DβH expression reduced their cocaine use while those patients carrying a low-expressing DβH T allele did not. It was hypothesized that subjects with low DβH levels may have an upregulation of dopamine receptors and, as such, cocaine use was not decreased in response to disulfiram treatment in the subjects with low DβH expression.

Another potential site of action is the *ANKK1* rs1800497 variant (*Taq*IA). Genetic analysis determined that the subjects that were *ANKK1* rs1800497 T allele (*Taq*IA1) carriers showed fewer cocaine-positive urines during the disulfiram pharmacotherapy, whereas CC homozygous individuals (those carrying two copies of the C allele) showed no treatment response (Spellicy *et al.*, 2013). Across both disulfiram studies, the majority of subjects were again male but both studies controlled for population structure to account for variance due to differences by ancestry group.

Olanzapine—Olanzapine binds to several neurotransmitter receptors including dopaminergic, adrenergic, and serotonergic (Bymaster *et al.*, 1997). It is a second-generation dopamine D_2 receptor and serontonergic 5-HT_2 receptor antagonist that is typically used as psychopharmacologic treatment of schizophrenia and mania-related bipolar disorder, and has been tested in the past decade for use in treating alcohol substance dependence.

Olanzapine treatment appears to diminish the cravings related to alcohol, but only in individuals with certain dopaminergic genetic profiles. Specifically, one study examined the effects of olanzapine (5 mg) relative to a control medication (cyproheptadine, 4 mg) after subjects ingested three drinks of alcohol (Hutchison *et al.*, 2003). The amount of alcohol was determined by taking height, weight, and gender into consideration in order to achieve peak blood alcohol levels of 0.06 g/dL. For males, each drink contained 0.15g/kg doses of ethyl alcohol and 0.11g/kg for females. Cyproheptadine was used as a control since it antagonizes 5-HT_2 receptors in humans, but does not block dopamine receptors (Kapur *et al.*, 1997). Subjects self-reported their cravings, stimulation, and sedation following consumption and those who were carriers of a seven or longer repeat of *DRD4* VNTR had decreased craving following alcohol consumption. Conversely, individuals without this allele who received olanzapine did not experience reduced cravings following alcohol consumption. At baseline (i.e., before any exposure to alcohol including alcohol cues) and prior to alcohol use (i.e., after baseline and exposure to alcohol cues), olanzapine did reduce cravings in subjects with either genotype. Subjects were predominantly male and younger (undergraduate students, mean age approximately 22 years old) compared to subjects in the other reviewed studies (mean age around mid-30s to 40s). Both gender and developmental effects may limit the generalizability of the findings.

Tiapride—Tiapride is a substituted benzamide related to sulpiride and is a selective dopamine receptor D_2 and D_3 antagonist (Costall & Naylor, 1977). It is different from other neuroleptics as it is not sedative and does not cause Parkinsonism (Jenner & Marsden, 1979). Treatment using tiapride has demonstrated reductions in psychological stress, decreased drinking, and improved reintegration into society (Peters & Faulds, 1994). Its anxiolytic effects also are used to treat symptoms of alcohol withdrawal syndrome. Similar to findings regarding dopamine receptor agonist bromocriptine, tiapride may be efficacious in treating alcohol withdrawal symptoms due to the reduced dopamine D_2 receptor sensitivity that alcoholics demonstrate (Balldin *et al.*, 1993, Balldin *et al.*, 1992).

Tiapride may be most effective in individuals who have the A/G or G/G genotype of rs71653615 of *DRD2*. During a combined 9-day detoxification therapy and abstinence-focused psychotherapy, alcohol dependent individuals with the A/G or G/G genotype

required lower doses of tiapride to treat alcohol withdrawal symptoms (Lucht *et al.*, 2001). These individuals with the A/G or G/G genotype also self-reported lower anxiety and depression at admission and two weeks later (Lucht *et al.*, 2001). The overwhelming majority of subjects were male (93%), however. Further, the interpretation of the findings cannot be completely attributed to tiapride since abstinence-focused psychotherapy was administered concurrently with tiapride.

Levodopa/Carbidopa—Levodopa (administered with carbidopa; L-dopa) increases dopamine availability, which is hypothesized to stabilize neural reward circuits (Koob, 2008). After repeated use of cocaine, dopamine stores are depleted (Volkow *et al.*, 2011). Although direct administration of dopamine is not possible, administration of L-dopa in combination with carbidopa (a peripheral decarboxylase inhibitor) can increase levels of synaptic dopamine in the brain, and lower caudate and putamen [^{11}C]raclopride binding potentials (Pavese *et al.*, 2006, Tedroff *et al.*, 1996).

In a recent 12-week randomized double-blind parallel group study, cocaine-dependent individuals were given L-dopa/carbidopa (400/100mg, twice daily) or placed in a placebo group (Liu *et al.*, 2014). Subjects who were given L-dopa/carbidopa were genotyped for *DBH* rs1611115. T allele carrier subjects with low DβH expression had decreased cocaine-positive urines relative to placebo-treated subjects carrying a T allele. This DβH-moderated response to L-dopa/carbidopa was not observed in subjects with normal levels of DβH (CC genotype). The majority of subjects in this study were also male (ranged from 66-95% male in each genotype group).

Naltrexone—Naltrexone is a non-specific opioid antagonist that has been demonstrated to reduce alcohol drinking in animal models and humans (Carmen *et al.*, 2004, Volpicelli *et al.*, 1986), and has been approved by the U.S. Food and Drug Administration for the treatment of alcohol dependence since 1994. One of the most consistent findings regarding naltrexone has been the reduction in relapse of heavy drinking (Carmen *et al.*, 2004). Additionally, decreases in heavy drinking days, overall drinking, and craving have been found (Garbutt, 2010).

Although naltrexone has been shown to be efficacious in the treatment of alcohol abuse (Anton*et al.*, 2004, Anton *et al.*, 2008), not all alcohol-dependent individuals benefit. It has been shown that A118G rs1788821 variant alters response to naltrexone treatment for alcoholism (Anton *et al.*, 2008, Oslin *et al.*, 2003). In particular, carriers of the less common *OPRM1* 118G allele responded better to naltrexone treatment. Studies have demonstrated that the 118G allele codes for a receptor that is expressed at lower levels (Kroslak *et al.*, 2007, Wand *et al.*, 2002, Zhang *et al.*, 2005), but binds β-endorphins with a higher affinity (Bond *et al.*, 1998). In a study of non-treatment-seeking individuals with alcohol dependence, subjects were randomized to naltrexone or placebo for seven days and the number of drinks consumed were measured (Anton *et al.*, 2012). Subjects who were *DAT1* 9 repeat VNTR carriers and were homozygous for the *OPRM1* 118A allele had reduced drink consumption under natural conditions in response to naltrexone treatment. Those subjects who were *DAT1* 10/10 repeat homozygotes and *OPRM1* 118A homozygotes did not reduce drinking in response to naltrexone.

Methadone—Methadone is a long-acting synthetic μ-opioid receptor agonist metabolized in the liver by CYP3A4, CYP2D6, and CYP1A2 (Kreek *et al.*, 2005a) and is used to treat opioid-dependent individuals (Dole *et al.*, 1966, Faggiano *et al.*, 2003, Mattick *et al.*, 2009). Treatment with methadone or methadone maintenance therapy has been successful in reducing illicit opioid use, criminal behavior, and HIV risk (Marsch, 1998), as well as decreasing mortality rates due to opioid overdose (Cornish *et al.*, 2010, Degenhardt *et al.*, 2009, Gibson *et al.*, 2008, Kimber *et al.*, 2010). As a result, methadone maintenance therapy is the most common opioid maintenance therapy in the United States and Canada (Kurdyak *et al.*, 2012).

Studies demonstrate that the effective methadone maintenance dosage may vary by the presence of *DRD2* −214A>G alleles. In an analysis of heroin dependent subjects stabilized on low (<55 mg/day), medium (55-99 mg/day), or high (100-150 mg/day) methadone maintenance dose those A allele carriers were two times more likely to require a lower methadone dose than those were who were GG homozygotes (Hung *et al.*, 2011). In addition, patients who were carriers of the CCACT, CTACT, or TCAAC haplotypes of *ANKK1* 2137C>T, *DRD2* 32+14266C>T, −214A>G, 811-83C>A, or the 939C>T allele required lower methadone doses than did noncarriers of these haplotypes. When combined in proportional odds regression analysis and controlling for liver function, height, weight, and HIV infection, *DRD2*, *ANKK1*, *ABCB1*, *CYP2B6*, and *OPRM1* variants together best predicted ideal methadone dosage suggesting that methadone dose is not related only to a single gene but is polygenetic. Importantly, this was the only study to examine the potential polygenetic effect of pharmacotherapy for drug addiction. Additionally, this study was conducted with a large sample size (N = 321) that was more than three times the sample size of other studies reviewed. Similar to the other reviewed studies, the majority of subjects were male (76-81% male).

Discussion

The dopaminergic system plays a prominent role in the development and treatment of substance abuse. Since there is a clear role of dopamine, the pharmacogenetics literature examining the treatment implications and differential outcomes related to the dopaminergic system is burgeoning. The present systematic review reveals the promise, as well as complexity, of using an individual's genetic profile to guide pharmacotherapy selection.

It appears that many dopaminergic, as well as serotonergic and opioidergic genes, are involved in the specific individual responses to pharmacotherapy (Bauer *et al.*, 2014, Nielsen *et al.*, 2014a). This is highlighted by the results described above for methadone maintenance therapy that *DRD2*, *ANKK1*, *ABCB1*, *CYP2B6*, and *OPRM1* together are related to the ideal methadone maintenance dosage. As such, pharmacotherapy for substance use may be polygeneic with multiple genes playing a role in an individual's response to pharmacotherapy or oligogenic with a few genes playing a significant role in an individual's response to pharmacotherapy. Although dopaminergic genes play a significant role in the response to pharmacotherapy, investigations of broader systems such as serotonergic and opioidergic genes may define a more comprehensive genetic profile that better predicts individualized response to pharmacotherapies.

When genes interact, they may have variants that mask certain effects that would be expressed (epistasis). Variants only may be expressed (or masked) in specific combinations in certain individuals, thus changing the effectiveness of pharmacotherapy in these patients. To statistically quantify these effects, relevant genes for substance use disorders including serotonergic (e.g., *SLC6A4, TPH2*; for review see Nielsen *et al.*, 2014b), opioidergic (e.g., *OPRM1, OPRD1, OPRK1*; for review see Bauer *et al.*, 2014, Nielsen *et al.*, 2014b), dopaminergic (e.g., *DRD4, ANKK1, DRD2, DBH*), and other relevant genes (e.g., *brain-derived neurotrophic factor*) could be examined via multivariate statistical methods (e.g., structural equation modeling, hierarchical linear regression). The identification of gene patterns and other multivariate approaches would quantitatively identify the genes comprising the polygeneic or oligogenic profiles related to pharmacotherapy outcomes.

Due to the emerging field of pharmacogenetics, the current studies reviewed have limitations, including small sample sizes, low statistical power, are comprised of predominately male subjects, and have short length of treatment. Outcome variables also differed. Some studies utilized primarily subjective variables of drug use (e.g., self-reported cravings, stimulation, sedation), whereas other studies used only objective measures (e.g., cocaine positive urines). Due to publication bias (i.e., only studies with significant results are typically published), studies that failed to produce significant findings were not included. It is also important to fully disclose all analyses conducted and account for increased Type I error rates.

Future studies will need to improve upon these limitations by recruiting larger cohorts as practical by utilizing robust recruitment strategies. This is important when examining polymorphisms with low allele frequencies or small effect sizes. Effect sizes for the current studies reviewed ranged from small (eta squared = .012; Spellicy *et al.*, 2013) to large (eta squared = .6268; Hung *et al.*, 2011). To inform future research design, we conducted power analyses with using G*Power software (Faul *et al.*, 2009) for a 2 group × 4 measurement ANOVA using small (η^2 = .01), medium (η^2 = .06), and large (η^2 = .14) effect sizes (Cohen, 1988). Table 3 shows the corresponding sample sizes required in order to obtain a power of .80. For example, a cohort of 778 participants would be needed to obtain a power of .80 for a 2 × 4 ANOVA with a small effect size (η^2 = .01). Power analyses, such as the ones conducted in Table 3, should be conducted during study design.

Since many polymorphisms vary by ethnicity, it is also essential to control for population structure in future studies. The use of objective outcome variables (e.g., cocaine positive urines) will be necessary due to the responder bias present when self-reporting drug use. Additionally, an emerging area of investigation may find new dopaminergic genetic targets for substance abuse. For example, the dopamine D3 receptor recently was highlighted as a target for medications treating substance use disorders, particularly cocaine abuse (similar to analyses described in Kosten *et al.*, 2013a, Kosten *et al.*, 2013b, Spellicy *et al.*, 2013). *COMT*, which metabolizes dopamine, has not been investigated in relation to cocaine, alcohol, or opioid addiction although it has been investigated in the pharmacological treatment of tobacco addiction (Keck *et al.*, 2015). In combination with continued evidence from hypothesis- and theory-driven SNP studies, genome-wide association studies may identify important new genes from which hypotheses can be developed and tested. Further,

pathway analyses may provide new computational approaches to identifying groups of genetic targets. For example, pathway analyses have already proved valuable in the identification of rare genetic variants that are associated with risk for bipolar disorder (e.g., Berrettini *et al.*, 2007). New genetic targets and analyses for identification may be examined in future studies of the pharmacogenetics of cocaine, alcohol, and opioid addiction.

The studies reviewed herein illuminate the capability of genetics to inform a more precise, targeted approach to the pharmacotherapy of alcohol, cocaine, and opioid addiction. The heterogeneity regarding treatment response is, at least partially, moderated by the dopaminergic system and quantification of this intricate relationship is critical for establishing practices that ensure optimal treatment outcomes. Ultimately, it is hoped that genetic insights of pharmacotherapy interventions and outcomes will provide medical professionals with a patient-specific tool that ensures the best opportunity for successful remission.

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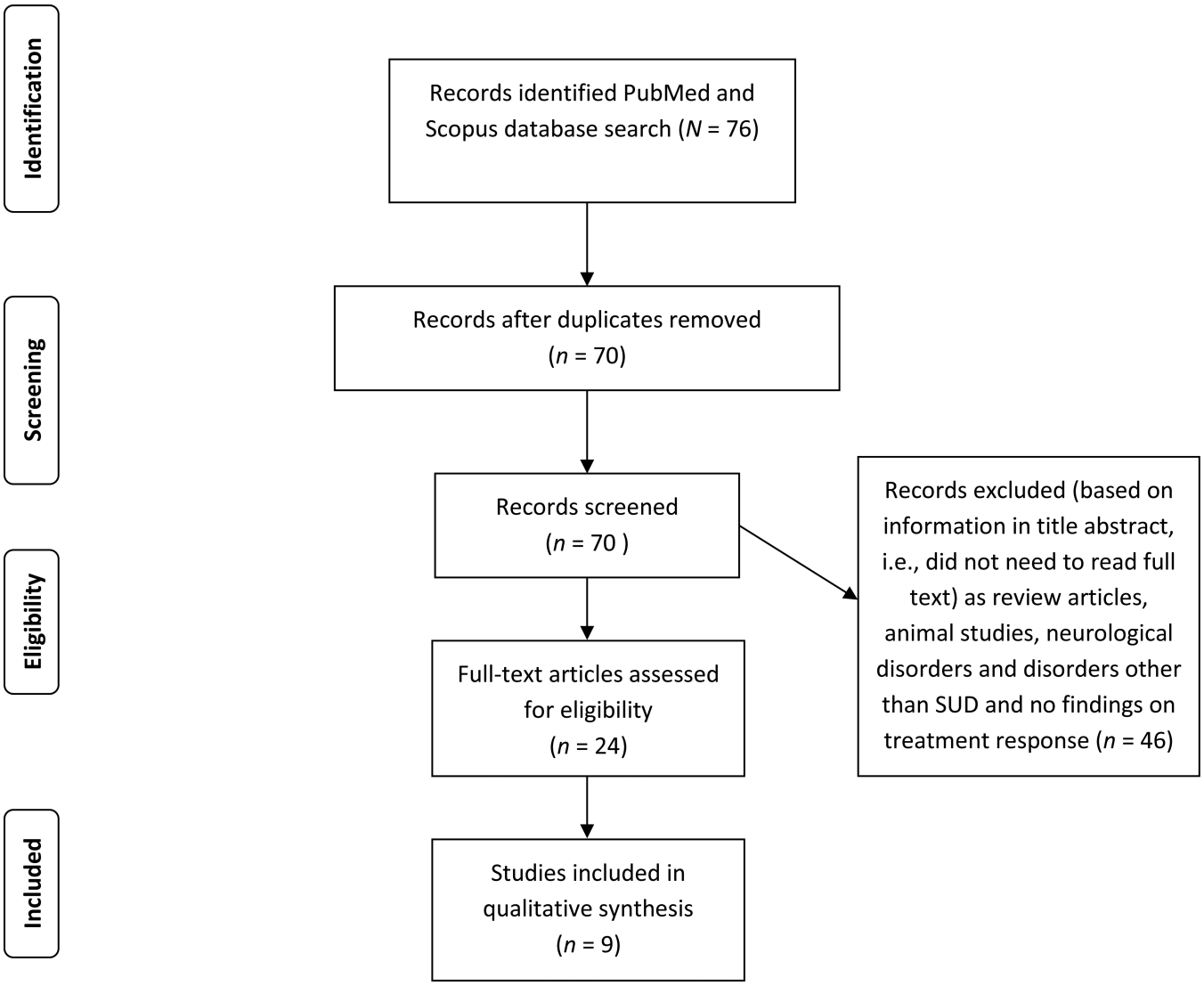

Figure 1.

PRISMA Flowchart showing the filtering process used to select the nine studies included in the systematic review of studies investigating the relationship among dopaminergic gene polymorphisms and treatment response to pharmacotherapies for drug addiction.

Table 1

Dopaminergic gene variants involved in pharmacotherapy for the addictions

Gene	Product	Variant	Addiction	Pharmacotherapy
DRD2	Dopamine receptor D2	rs6275, rs6277, rs1799978	Cocaine, alcohol, opioids (Ament *et al.*, 2015)	Bromocriptine, disulfiram, methadone (Doehring *et al.*, 2009a, Volkow *et al.*, 1990, Volkow *et al.*, 1996, Wang *et al.*, 1997)
ANKK1	Ankyrin repeat and kinase domain-containing 1	rs1800497 (*Taq*IA1)	Cocaine, alcohol, opioids (Hung *et al.*, 2011, Lawford *et al.*, 1995, Spellicy *et al.*, 2013)	Disulfiram, naltrexone, methadone (Doehring *et al.*, 2009a, Volkow *et al.*, 1990, Volkow *et al.*, 1996, Wang *et al.*, 1997)
DAT1, SLC6A3	Dopamine transporter 1	exon 9 VNTR	Alcohol (Anton *et al.*, 2012, Hung *et al.*, 2011, Spellicy *et al.*, 2013)	Naltrexone (Franke *et al.*, 1999, Muramatsu & Higuchi, 1995, Sander *et al.*, 1997)
DBH	Dopamine β-hydroxylase	rs1611115 (C-1021T)	Alcohol, opioid (Anton *et al.*, 2012)	Disulfiram, cocaine vaccine (Preuss *et al.*, 2013, Xie *et al.*, 2013)
DRD4	Dopamine receptor D4	exon 3 VNTR	Alcohol (Kosten *et al.*, 2013a)	Olanzapine (Hutchison *et al.*, 2002)

VNTR = variable number tandem repeat.

Table 2

Description of the nine studies examining the relationship between dopaminergic genes and treatment response to pharmacotherapies of drug addiction.

Paper	Sample Characteristics *N* $M_{age} \pm SD$ in years	Gender	Addiction	Design	Outcomes	Results & Effect Size (η^2)
Bromocriptine						
Lawford et al., 1995	*N* = 83 43.7±1.3	94% male	Alcohol	6-week, randomized, double-blind clinical trial; bromocriptine (2.5 mg three times daily) or placebo administered to A1/A1, A1/A2, A2/A2 genotypes	•Self-report craving •Self-report anxiety •Self-report depression •Attrition	•Bromocriptine-treated A1/A1 group less craving and anxiety than any other group •Attrition highest in placebo-treated A1 group • η^2 = data not available
Cocaine vaccine						
Kosten et al., 2013a	*N* = 114 Vaccine CT/TT: 34±9 CC: 35±10 Placebo CT/TT: 35±10 CC: 39±9	Vaccine CT/TT: 50% male CC: 72% male Placebo CT/TT: 60% male CC: 74% male	Cocaine Opioids	16-week, randomized, double-blind placebo-controlled trial; examined subjects with five vaccinations over first 12 weeks	•Cocaine-positive urines	•Vaccine group with low DβH level dropped use from 77% to 51% •Vaccine group with normal DβH level dropped from 83% to 72% • η^2 = .0763-.3855
Disulfiram						
Kosten et al., 2013b	*N* = 74 Disulfiram CT/TT: 37±10 CC: 38±11 Placebo CT/TT: 37±10 CC: 43±10	Disulfiram CT/TT: 53% male CC: 70% male Placebo CT/TT: 63% male CC: 71% male	Cocaine Opioids	Subjects randomized into either disulfiram (250mg/d) or placebo groups for 10 weeks	•Cocaine-positive urines	•Normal DβH level dropped from 84% to 56% on disulfiram •Low DβH level showed no disulfiram effect • η^2 = .1478-.1939
Spellicy et al., 2013	*N* = 68 *ANNK1*/Disulfiram CT/TT: 39.7±9.5 CC: 37.8±11 *ANNK1*/Placebo CT/TT: 42.7±10.6 CC: 36.7±10.5 *DRD2*/Disulfiram GT/TT: 38.9±9.1 GG: 38.2±10.7 *DRD2*/Placebo GT/TT: 42.7±12 GG: 37.7±9.9 *ANKK1/DRD2*/ Disulfiram CC/GG: 38.5±10.9 Others: 39.7±9.5 *ANKK1/DRD2*/Placebo CC/GG: 36.6±10.5	*ANNK1*/Disulfiram CT/TT: 61.5% male CC: 61.1% male *ANNK1*/Placebo CT/TT: 65.0% male CC: 70.6% male *DRD2*/Disulfiram GT/TT: 44.4% male GG: 69.5% male *DRD2*/Placebo GT/TT: 71.4% male GG: 68.2% male *ANKK1/DRD2*/ Disulfiram CC/GG: 58.8% male Others: 68.4% male *ANKK1/DRD2*/Placebo CC/GG: 70.6% male Others: 61.5% male	Cocaine Opioids	Subjects randomized into either disulfiram (250mg/d) or placebo groups, subjects also provided manual-based cognitive behavioral therapy	•Cocaine-positive urines	•CT or TT *ANKK1* genotypes drop from 80 to 52% positive urines, no placebo effect, on disulfiram •GT/TT *DRD2* genotype showed decrease positive urine on disulfiram, 67 to 48% •Carriers of at least one minor allele of *DRD2* or *ANKK1* responded better to disulfiram than those only carrying major alleles • η^2 = .2204-.2692

Paper	Sample Characteristics *N* M_{age}±*SD* in years	Gender	Addiction	Design	Outcomes	Results & Effect Size (η^2)
	Others: 42.4±10.8					
Olanzapine						
Hutchison et al., 2003	*N* = 67 Olanzapine DRD4 S: 22.9±2.5 DRD4 L: 24.2±2.9 Cyproheptadine DRD4 S: 22.4±3.2 DRD4 L: 21.1±1.6	Olanzapine DRD4 S: 78% male DRD4 L: 50% male Cyproheptadine DRD4 S: 52% male DRD4 L: 66% male	Alcohol	Subjects randomly assigned into either olanzapine (5 mg) or control medication (cyproheptadine, 4 mg) prior to ingesting three drinks of alcohol in one experimental session	•Self-report cravings •Self-report stimulation •Self-report sedation	•Olanzapine reduced craving for alcohol at baseline for DRD4 S and DRD4 L •Reduced cravings after exposure to alcohol cues and drink for only DRD4 L subjects • η^2 = .0665-.1403
Tiapride						
Lucht et al., 2001	*N* = 110 42.5±9.3	93% male	Alcohol	9-day detoxification therapy and abstinence-focused psychotherapy	•Self-report anxiety •Self-report depression •Tiapride dosage	•*DRD2* E8 A/A genotype had increased dose of tiapride, as well as increased anxiety and depression at admission and 2 weeks later • η^2 = .0336-.0405
Levodopa/Carbidopa						
Liu et al., 2014	*N* = 71 Levodopa CT/TT: 42.33±8.10 CC: 45.23±7.81 Placebo CT/TT: 41.77±6.89 CC: 49.95±41.77	Levodopa CT/TT: 66% male CC: 84% male Placebo CT/TT: 76% male CC: 95% male	Cocaine	12-week, randomized, double-blind parallel-group; levodopa/ carbidopa (400/100 mg, Sinemet CR, twice daily) or placebo groups	•Cocaine positive urines	• Low DβH level genotypes (CT/TT) odds of having positive urines significantly decreased over levodopa treatment relative with placebo subjects with CT/TT genotypes • Normal DβH level (CC) subjects showed no differences to levodopa • η^2 = .1153
Naltrexone						
Anton et al., 2012	*N* = 83 Naltrexone Asn40: 31±7 Asp40: 29±10 Placebo Asn40: 23±10 Asp40: 28±10	Naltrexone Asn40: 68% male Asp40: 63% male Placebo Asn40: 67% male Asp40: 63% male	Alcohol	Subjects randomized to naltrexone or placebo for 7 days	•# drinks consumed	•Subjects given naltrexone with a least one *DAT1* 9 VNTR and that were *OPRM1* Asn40 homozygotes showed reduced alcoholic drinks consumed in natural setting • η^2 = .0357
Methadone						
Hung et al., 2011	*N* = 321 36.5±18.7	Methadone dose Low: 78% male Medium: 81% male High: 76% male	Opioids	Subjects received low (<55 mg/day), medium (55-99mg/day), and high dosages (100-150 mg/day) to obtain methadone maintenance dose	•Dosage of methadone required for maintenance	•A allele carriers had twofold increase chance of requiring lower methadone dose than those who were GG homozygotes • CCACT, CTACT, or TCAAC haplotypes of *ANKK1* 2137C>T, *DRD2* 32+14266C>T, −214A>G, 811-83C>A, or the 939C>T allele required lower methadone doses

Paper	Sample Characteristics *N* $M_{age} \pm SD$ in years	Gender	Addiction	Design	Outcomes	Results & Effect Size (η^2)
						•*ABCB1, CYP2B6, OPRM1, ANKK1, DRD2* *ABCB1* correlated with methadone dose • η^2 = .0663-.6268

Table 3

Power analysis for small (η^2 = .01), medium (η^2 = .06), and large (η^2 = .14) effect sizes to determine adequate sample size for a 2-group, 4-measurement ANOVA with alpha = .05.

Effect size (η^2)	Power (1-β)	Total *N*-size
.01	.80	778
.06	.80	126
.14	.80	52
.01	.90	1,044
.06	.90	168
.14	.90	68
.01	.95	1,290
.06	.95	206
.14	.95	82