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Symbiotic Relationship of Pharmacogenetics and Drugs of Abuse

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ABSTRACT

Pharmacogenetics/pharmacogenomics is the study of how genetic variation affects pharmacology, the use of drugs to treat disease. When drug responses are predicted in advance, it is easier to tailor medications to different diseases and individuals. Pharmacogenetics provides the tools required to identify genetic predictors of probable drug response, drug efficacy, and drug-induced adverse events—identifications that would ideally precede treatment decisions. Drug abuse and addiction genetic data have advanced the field of pharmacogenetics in general. Although major findings have emerged, pharmacotherapy remains hindered by issues such as adverse events, time lag to drug efficacy, and heterogeneity of the disorders being treated. The sequencing of the human genome and high-throughput technologies are enabling pharmacogenetics to have greater influence on treatment approaches. This review highlights key studies and identifies important genes in drug abuse pharmacogenetics that provide a basis for better diagnosis and treatment of drug abuse disorders.

KEYWORDS: Pharmacogenomics, addiction, treatment, psychiatric disease, SNP

INTRODUCTION

Pharmacogenetics/pharmacogenomics is the study of how genetic variation among individuals affects their capacity to metabolize drugs (pharmacokinetics) and the drugs' effects on the individuals (pharmacodynamics). Pharmacogenetics emerged several decades ago, but only recently have the tools been in place for the field to flourish, led in part by the availability of the human genome sequence and the improving genotyping technologies. Pharmacogenetics provides the foundation for scientists to identify biological predictors of drug response, drug efficacy, and drug-induced adverse events to enable clinicians to use the information to make the best treatment decisions. The understanding of genetic variation may hold the most promise in clinically evaluating and predicting a drug's effects, and successfully treating a patient.

Substance abuse is a unique psychiatric disorder given that genetic vulnerability can lead to disease only if the substance (licit or illicit) is readily available and used. In addition to the public health burden, addiction disorders cost society over $500 billion per year.[1] The gene-environment interaction of substance abuse and addiction may provide scientific building blocks to advance the field of pharmacogenetics. Understanding the genetics of the pharmacokinetics and pharmacodynamics of drugs, whether or not they are abused, can provide relevant crossover concepts for tailoring drug treatments. Drug use triggers the onset of the addictive process and maintains the neuroplastic changes after chronic use.[2] Thus, the genetics of substance abuse and addiction, by nature, is pharmacogenetic. The current impetus is to predict actual individual differences in risk of drug abuse vulnerability, drug response, and response to treatments for drug abuse based upon knowledge about specific genes. Genetic differences could contribute to acute drug responses (aversive vs nonaversive) and may also predict drug use and/or drug response.

Environmental interventions are likely to be most effective in reducing the number of people who start to use drugs, including alcohol and tobacco; however, these interventions may not be as effective in helping those already addicted. To unravel and point to biological targets highlighting genetic variants important for understanding addiction, drug treatment, and drug response, genetic and neurobiological studies are needed; they will help clarify the complex nature of addiction, which has a 40% to 60% genetic variance.[3-5] Although genetic studies are critical to advancing the field, some misconceptions are that genetic information will be used solely to identify those at high risk of addiction by screening people for susceptibility alleles,[6] or that susceptibility alleles will be "replaced" through gene therapy.[7] These approaches are not likely to be effective or efficient. Instead, studies to understand gene variants that confer vulnerability and predict treatment response are needed to provide a comprehensive approach to treating addiction effectively and to inform prevention strategies that will have a significant public health impact.

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This review highlights some of the research from the field of drug use, abuse, and addiction and the importance of pharmacogenetics/pharmacogenomics in working toward better treatments for these types of psychiatric disorders.

Pharmacogenetics of Metabolism, Drugs of Abuse, and Addiction Genetics

Pharmacogenetics of Drug Metabolism: Therapy Versus Toxicity

Drug treatment can result in effective therapy, can fail, and/or can create toxicities and other side effects. Administering the same dose of a given medication to individuals with different drug-metabolizing genotypes gives rise to differences in drug response phenotypes—namely, the drug's therapeutic and toxic effects.[8] Genetic variation in metabolism genes alters the activation of a drug, which can result in more potent metabolites, different metabolic patterns with varying half-lives, or inactive metabolites (eg, nicotine metabolized to inactive cotinine by CYP2A6). If certain drugs are not metabolized appropriately or are given at the wrong dose, they can cause liver damage, triggering certain enzymes normally found in the liver to be secreted into the bloodstream, signifying distress in liver function. Although plasma blood tests are used to assess high liver enzymes that indicate toxicity, this approach is crude since it does not indicate potential toxicities affecting other organs or take into account the reasons for the toxicity. Once liver toxicity is identified, the remedy often results in discontinued use of a needed medication, or a change in the medication to one that may be less effective.

Most drugs are metabolized in the liver by the cytochrome P450 (CYP450) system, with metabolizing enzymes CYP3A4 and CYP2D6 responsible for the largest contribution. The CYP450 enzymes are expressed in most cells and are particularly abundant in the liver.[8] Although the roles of these enzymes are known (eg, metabolism of compounds), there is little understanding of how genetic variation in metabolizing enzymes, transporters, and receptor targets can be used in the clinical environment. One of the central aspects of pharmacogenetics involves understanding the genetic variations within the CYP450 system and how the variations affect drug metabolism and ultimately contribute to treatment response.

Extrahepatic organs such as the brain, kidney, and lung also express CYP450 enzymes that metabolize drugs. For psychiatric diseases and drugs that act centrally, in the central nervous system, the brain is an important organ to consider. It is a heterogeneous organ, so drug metabolism in different cell types may create microenvironments with differing drug and metabolic levels, which would not necessarily be predicted by plasma drug monitoring. This concept is important for toxicity, since hepatic cells can regenerate but neurons cannot. Thus, single nucleotide polymorphisms (SNPs) or other types of genetic variations in metabolism genes as well as other genes involved in drug receptor/transporter pathways may account for variations in responses to centrally acting drugs and may affect receptor adaptation, toxicities, altered drug effects, and cross-tolerance.[9] The following Web page has a list of SNPs in the metabolism genes: http://www.genome.utah.edu/genesnps/cgi-bin/query.cgi?FunctionClass=2. Further pharmacogenetic studies are needed to establish connections between CYP450 expression in the liver and in specific brain regions to determine the consequences on drug effects and brain function.

Smoking

Nicotine is a psychoactive substance responsible for establishing and maintaining tobacco dependence. There are more than 1.1 billion smokers worldwide, each dictating nicotine intake through markedly different behavioral patterns.[10] Smoking is a highly regulated behavior; those addicted are precise in maintaining steady-state brain levels of nicotine.[11] A recent prospective study examining the health consequences of smoking concludes that smoking as little as 1 to 4 cigarettes per day engenders significantly higher risk for all causes of mortality, most notably, heart disease and lung cancer.[12] Relative risks associated with increased cigarette consumption are unclear.[13-15] However, evidence indicates that smoking fewer cigarettes does not provide much, if any, protection.

When heavy smokers (at least 20 cigarettes per day) reduced their nicotine intake to 5 cigarettes per day, so that they more closely resembled "chippers" (smokers who average 1-5 cigarettes a day but do not become dependent), the heavy smokers compensated by increasing their nicotine intake 3-fold by lengthening their puff duration, but the chippers did not.[16] Pinpointing the genetic variance accounting for the level of self-regulation among smokers is an important step toward understanding the risks of becoming addicted, the consequences of being addicted, and the treatment options for those already addicted. In addition to prevention efforts, smoking cessation therapies with tailored drug treatments are important in fighting the health consequences of smoking. This paradigm may also be applied to other drugs of abuse as well as to treatment medications for other disorders. The National Institute on Drug Abuse (NIDA) has initiated an emphasis on this important avenue of smoking cessation research.

Drug prevention efforts will continue to be a public health need, with emphasis on targeting adolescents through school programs. However, even though some of these programs have shown reductions in cigarette use rates of up to 20%, less than 10% of the school districts are using the

programs.[17] Much of the success in decreasing the smoking prevalence since the 1950s has been realized through these types of preventive/educational programs (Figure 1). The steady decrease in prevalence from 1970 to 1990 appears to have reached a plateau and looks to have fluctuated little since 1990 (Figure 1 inset). This leveling off may indicate a significant preventive/educational role in decreasing the prevalence of smoking for a proportion of the population. The plateau may suggest that prevention may not be as effective in the actively smoking population, indicating that current smokers who cannot quit may represent a more genetically at-risk population. Understanding the genetics and pharmacogenetics of smoking may provide insight into the best treatments for those already addicted.

Smoking Pharmacogenetics

Data from twin studies provide consistent and strong evidence for the heritability of smoking addiction (estimates range from 0.4 to 0.6).[18-20] Although the precise genetic variants responsible are not clearly delineated, research has focused on genes in the dopamine, serotonin, glutamatergic, and norepinephrine receptor pathways, and the *CYP450* metabolism pathways, such as *DRD2-4, DAT1, TPH1, GABAB2, 5 HTT/SERT, MAO-A, CYP2A6, CYP2D6, CHRNA4,* and *ANKK1* (Table 1).[21-31]

Approximately 70% to 80% of nicotine is metabolized to an inactive metabolite by *CYP2A6*. There are several genetic polymorphisms within *CYP2A6* that have been associated with nicotine metabolism and consumption. Since each individual receives 2 copies of every gene—maternal and paternal—each individual may have different combinations of forms of the gene, depending on the genetic variation that was inherited. Several studies have shown that polymorphisms in *CYP2A6* account for high enzyme activity.[41,42] Individuals receiving 2 copies of this allele are able to metabolize nicotine rapidly, while individuals receiving only 1 copy of the allele or no copies are intermediate or slow metabolizers, respectively.[41]

Effective smoking cessation pharmacologic intervention strategies are currently in use, such as nicotine replacement therapies (NRTs) and some nonnicotine agents (eg, antidepressant medications like bupropion).[74] Nevertheless, up to 80% of cessation attempts using these medications result in relapse within the year.[75]

NRTs such as nicotine gum, patches, inhalers, and nasal sprays can significantly increase smoking cessation rates compared with behavioral counseling[76] and are the standard treatment for smoking dependence. NRTs seem to be most effective for treating the withdrawal symptoms accompanying cessation but are not as effective in reducing the craving for cigarettes, which often renders the quit attempt unsuccessful.[77,78] However, some NRTs work well, in part because of the genotypic profile of the individual taking them. Lerman et al examined the mu-opioid receptor variant *OPRM1* A118G (discussed in further detail below) in either the transdermal nicotine patch or nicotine nasal spray in 320 smokers.[64] Smokers who were given the transdermal nicotine and who had the G allele were more likely to be abstinent by the end of the treatment period (odds ratio [OR] = 2.4; 95% confidence interval [CI] = 1.14-5.06).[64] Although the sample size was small, this finding gives credence to future studies attempting to identify gene variants for predicting successful treatment.

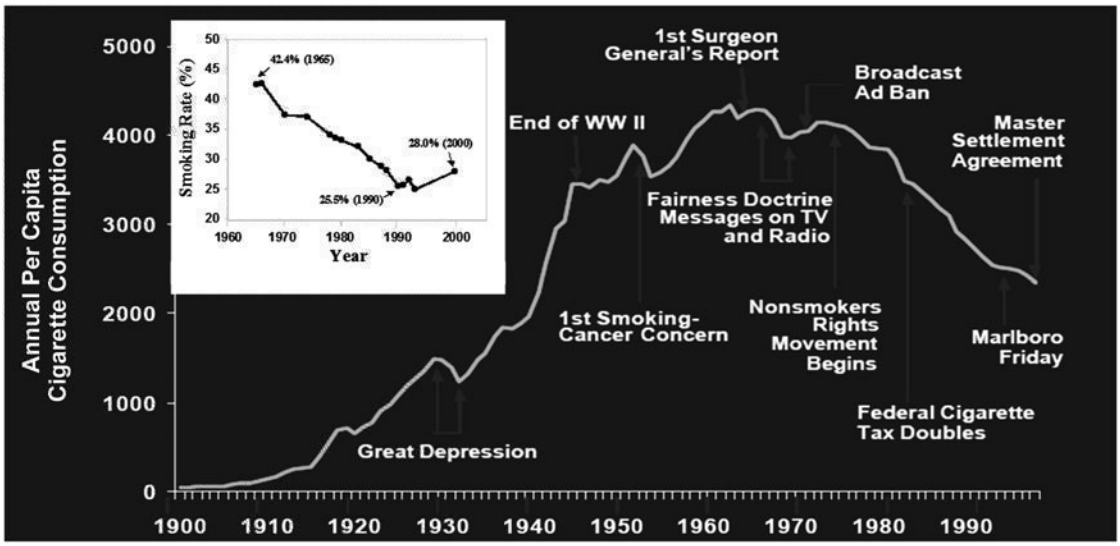

Figure 1. Historical Events Affecting Smoking in the United States, 1900-2000. Adapted from the US Department of Agriculture and the US Department of Health and Human Services (DHHS), *1986 Surgeon General's Report* and *Morbidity and Mortality Weekly Report* (www.cdc.gov/tobacco/news/achievements99.htm) 1999.

Table 1. Selected Genes Associated With Addiction Genetics and Pharmacogenetics

Gene Symbol	Gene Name	Chromosomal Location	Drug Association	References
5HTT/SERT	5-hydroxy tryptamine transporter	17q11.1-q12	Nicotine, opioids	25,32
ANKK1	Ankyrin repeat and kinase domain containing 1	11q23.2	Nicotine	31
BCHE	Butyrylcholinesterase	3q26.1-q26.2	Cocaine	33
CGRP	Calcitonin/calcitonin-related polypeptide	11p15.2-p15.1	Opioids	34
CHRNA4	Nicotine acetylcholine receptor, alpha subunit	20q13.2-q13.3	Nicotine	35
CNR1	Cannabinoid receptor 1	6q14-q15	Nicotine, opioids	36,37
COMT	Catechol-o-methyltransferase	22q11-q21	Opioids, stimulants	38-40
CYP2A6	Cytochrome P450, family 2, subfamily A, polypeptide 6	19q13.2	Metabolism, nicotine	8,41,42
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6	22q13.1	Metabolism, nicotine, opioids	8
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4	7q21.1	Metabolism	8
DAT1	Dopamine transporter	5p15.3	Nicotine, opioids	24,27,43-47
DBH	Dopamine beta hydroxylase	9q34	Stimulants	32
DRD2	Dopamine receptor D2	11q23	Nicotine, opioids, stimulants	21,22,29,48-55
DRD3	Dopamine receptor D3	3q13.3	Nicotine, opioids, stimulants	55
DRD4	Dopamine receptor D4	11p15.5	Nicotine, opioids, stimulants	26,39,40,55,56
GABAB2	Gamma-aminobutyric acid (GABA) B receptor, subtype 2	9q22.1-q22.3	Nicotine	23
GABRG2	Gamma-aminobutyric acid (GABA) A receptor, gamma 2	5q31.1-q33.1	Methamphetamine	57
GSTP1	Glutathione-S-transferase P1	11q13	Stimulants	58,59
HOMER1	Homer homolog 1	5q14.2	Cocaine	60
HOMER2	Homer homolog 2	5q24.3	Cocaine	60
MAO-A	Monoamine oxidase-A	Xp11.3	Nicotine	30
MCR1	Melanocortin 1 receptor	16q24.3	Opioids	61,62
OPRD1	Opioid receptor, delta 1	1p36.1-p34.2	Opioids	63
OPRK1	Opioid receptor, kappa 1	8q11.2	Opioids	32
OPRM1	Opioid receptor, mu 1	6q24-q25	Nicotine, opioids	64-73
TPH1	Tryptophan hydroxylase 1	11p15.3-p14	Nicotine	28

Of other nonnicotine pharmacologic agents for smoking cessation, bupropion seems to be the most successful to date, offering further support for genetic profile–tailored agents, with some caveats. Swan et al indicate that women with at least one A1 allele of the *DRD2* gene reported early termination of the bupropion because of side effects (OR = 1.91, 95% CI = 1.01-3.60), but this result was not seen in men.[29] In 2 randomized clinical trials, Lerman et al examined *DRD2* variants in subjects given NRT or bupropion, respectively, for tobacco dependence. The bupropion trial showed that subjects homozygous for the ins C variant of the -141 C ins/del SNP responded better to bupropion compared with those carrying the del C allele (OR = 4.99; 95% CI = 1.42-17.62; P = 0.01).[48] The NRT trial, on the other hand, suggests that individuals carrying the ins C allele had fewer quit attempts than those with the del C (OR = 0.44; 95% CI = 0.25-0.79; P = .006). Thus, NRT may be most beneficial for those with the del C allele and bupropion best for those with the ins C allele.[48]

Newer drugs are showing early promise for more successful smoking cessation, including rimonabant and varenicline.[79] Rimonabant is a selective cannabinoid receptor 1 (CB1) blocker. CB1 is expressed in brain and adipose tissue and is known to regulate food intake. Upon chronic stimulation with nicotine, the endocannabinoid system (and CB1) become dysregulated and imbalanced.[36,37] By blocking CB1, rimonabant stabilizes the endocannabinoid system. In clinical trials, patients receiving up to 20 mg of rimonabant were twice as likely to quit smoking and stay abstinent for

significantly longer (36.2%) than the placebo group (20.6%). Making the drug even more attractive is that on average, patients on rimonabant lost over a half-pound, while those on placebo gained 2.5 pounds.[80]

Varenicline is a partial nicotine agonist and selective nicotinic receptor modulator to the α4β2 nicotinic receptor. Genetic variants within the *CHRNA4* gene encoding the α4β2-containing nicotinic acetylcholine receptor seem to play a role in modulating the effects of nicotine and alcohol in mouse strains.[35] Varenicline appears to act on α4β2 receptors to remove feelings of reward from smoking and to prevent withdrawal symptoms.[79] Current NIDA-supported studies will further examine genetic variants known in metabolism and other targeted pathways of these medications. Although years away, a major goal is to determine a genetic profile that will result in high success rates for people given these medications.

Another treatment for smoking cessation is the nicotine vaccine. One vaccine, NicVAX, confers active immunity by inducing the formation of antibodies to nicotine.[81,82] The vaccine binds to nicotine prior to its crossing the blood-brain barrier and prevents it from entering the brain. In rats, NicVAX is effective in reducing nicotine's access to the brain more than it reduces nicotine's access to other tissues.[81] The vaccine had a good safety profile in a recent clinical trial. Healthy smokers receiving the vaccine did not smoke more cigarettes during the study period and did not experience cravings or withdrawal symptoms.[83] As the vaccine proves successful in some addicted smokers, pharmacogenetic studies may provide the evidence needed to prevent smoking addiction and expedite smoking cessation in vulnerable individuals.

NRTs and bupropion inhibit smoking for some smokers. However, many relapse, indicating that maintaining long-term abstinence is more difficult.[76,84] Although these 2 treatments are available, genetic information is not currently being used to pinpoint which treatment modality would be most effective. Emerging pharmacogenetic data, such as the *DRD2* -141C ins/del SNP and treatment response to NRT or bupropion, seem to support the notion that practitioners will eventually be able to individualize the choice of pharmacotherapies to be prescribed based on the genotypes of their patients who smoke. Perhaps this tailored treatment approach, along with the newer medications, will reduce the high rates of relapse.

Heroin and Other Opioid Substances

Heroin is an illicit opioid that is commonly abused. Genetic studies have revealed that heroin addiction disorder is highly heritable.[32,85-87] Several genes are associated with opioid addiction (*DRD2-4, CYP2D6, DAT1, 5HTT/SERT, GABRG2, OPRM1, OPRD1, OPRK1, CNR1*; see Table 1).[1,32] One recent study identified DRD2 as a strong susceptibility gene for heroin dependence in Chinese subjects (OR = 52.8; 95% CI = 7.2-382.5), but in a German sample this gene was associated with a low risk of heroin dependence.[49] These findings suggest that *DRD2* is a risk gene specific to heroin dependence in certain populations, as it has not been associated with disorders involving use of other substances, including alcohol and cocaine, in varying populations.[50-54,56] Also, the *DRD2* variant may be in linkage disequilibrium with another variant that is the actual functional variant. One possibility is the *ANKK1* gene, which is a serine/threonine kinase involved in signal transduction pathways.[31] Consequently, further clarification of the actual role in heroin addiction and potential roles in other drug and alcohol addictions is needed, including more dense SNP maps to reveal the underlying genetic architecture for *DRD2, ANKK1,* and other addiction candidate genes.

The *OPRM1* susceptibility gene is the primary site of action of the most commonly used opiates, including heroin, morphine, and most drugs used to treat opiate dependence, such as methadone, LAAM (levo-alpha-acetylmethadol), and buprenorphine. A polymorphism in *OPRM1* changes the more common allele at position 118 from an A to a G (A118G) and results in a functionally relevant coding change in the protein from an asparagine residue at amino acid position 40 to an aspartate residue. The literature is inconsistent regarding associations of the A118G polymorphism with addictions, possibly because of differences in minor allele frequencies among different populations,[32,65,66] the need for larger sample sizes to detect associations of small effect, or linkage disequilibrium associations with another allele. It has been suggested that the mu-opioid receptors encoded by the aspartate variant bind beta-endorphin and activate receptors more potently,[67] causing a gain of function, but this mechanism has not been replicated.[68-70] Zhang et al instead have shown by allele-specific expression in *OPRM1* mRNA that the G-allele is 1.5- to 2.5-fold less abundant than the A-allele, translating to ~10-fold lower protein levels.[70] These results suggest a loss of function rather than a gain of function. Either way, the functional data presented provide strong evidence supporting the importance of A118G for abuse and addiction susceptibility.[70]

Opioid Receptor Gene Variants in Opioid Pharmacogenetics

The A118G variant may be pharmacogenetically relevant as well. In a recent randomized, placebo-controlled clinical trial, Oslin et al[71] examined the A118G polymorphism among patients treated for alcohol dependence with either naltrexone or placebo. Naltrexone is an opioid receptor antagonist that was originally used to treat dependence on opioid drugs but has been beneficial for treating alcohol

dependence. In survival analysis for time to relapse, naltrexone-treated subjects carrying a 118G allele showed significantly longer time to relapse (OR = 3.52; 95% CI = 1.03-11.96, P = .04).[71] These data, although preliminary, suggest that genotyping may be useful for identifying patients who may benefit from naltrexone more than they would from other treatment options. Since naltrexone's effects are mediated by the mu-opioid receptor, investigating the outcomes of subjects treated with other medications acting through this receptor will be valuable, as the A118G variant may be a key predictor of response to other μ-opioid receptor-mediated drugs.

Opioid Receptors and Pain

There is a large array of individual variability in sensitivity and perception of pain.[34,88] Morphine is the most commonly prescribed opioid, although only 10% to 30% of chronic pain patients do not respond or have intolerable side effects,[89] especially those with renal disease who have an accumulation of active metabolite that is normally cleared by the kidney. Opioid treatment has been a conundrum for many treatment providers trying to strike a balance between pain management on the one hand, and abuse and addiction liability on the other. Dose escalation based upon patient feedback has resulted in discrepancies in pain management that have often resulted in under- or overmedication. A small (10%) portion of morphine is metabolized to morphine-6-glucuronide (M6G), an opioid agonist that contributes to morphine's clinical effects.[90] In a study examining the effects of morphine and MG6 by measuring pupil diameters, heterozygous and homozygous individuals with the A118G variant had reduced M6G potency in constricting pupils, but this effect was not seen in variant carriers who were administered morphine.[72] This finding indicates that A118G carriers are at lower risk for renal side effects of morphine therapy,[72] especially in individuals with impaired renal function.

Heritability of pain perception has been reported to be in the range of 10% to 46%.[73,91] Other genes, such as *OPRD1*,[63] *COMT*,[38] *CGRP*,[34] and *MCR1*,[61,62] were shown to be associated with certain types of pain responses. *COMT* polymorphisms are associated with altering downstream responses of the mu-opioid neurotransmitter system, likely through changes in receptor concentration, binding affinity for beta-endorphin, or allele-specific expression, each of which can modulate pain perception.[92]

Work by Fillingim et al[73] supports the role of the dopamine system and the opioid receptor pathway in pain perception. Healthy subjects with at least 1 rare allele (118G) exhibited lower sensitivity to pressure pain compared with subjects homozygous for the common allele (A118). Ross et al found no association with the A118G variant in cancer patients with chronic pain who were unable to tolerate morphine after dose escalation and switched to other opioid analgesics.[89] An association was found with beta-arrestin, a protein involved with desensitizing the mu-opioid receptor and internalized receptor trafficking.[89] These data suggest that other genes such as those involved with receptor signaling, receptor density, and receptor trafficking, in addition to those involved in the complex process of pain perception, require further study.

Pharmacogenetics has the potential to affect pain management by providing information on genetic variants that are associated with clinical effects and possibly by elucidating biological correlates of prescription opioid addiction risk. Research in this area is ongoing, and more studies are needed.

Amphetamines, Cocaine, and Other Stimulants

Abuse of amphetamine, especially methamphetamine, is a growing trend in the United States, with persistent abuse often causing a paranoid psychotic state.[93,94] Methamphetamine increases levels of dopamine in the brain and elicits euphoria, contributing to its addictive properties.[95] Heritability estimates for psychostimulants are around 66%.[86,96,97] Many of the genetic studies have concentrated on the contribution of variants within the dopamine system genes (*DAT1*, *DRD2*, and *DBH*; see Table 1) and *GABA* genes[57] to determine the association with abuse and treatment of cocaine and methamphetamine, but further studies focusing on other abused stimulants are needed. Glutamatergic transmission seems to be important for cocaine's effects of tolerance and withdrawal. The genes *HOMER1* and *HOMER2* have recently been identified as mediators of glutamate transmission and may be good targets for future genetic and pharmacogenetic study.[60]

Chen et al[55] examined the *DRD2*, *DRD3*, and *DRD4* gene variants in 851 methamphetamine subjects with and without psychosis (416 methamphetamine abusers and 435 controls). Results showed that the 7-repeat (exon III) *DRD4* polymorphism occurred more frequently in the methamphetamine abusers than in the controls (2% vs 0.6%; respectively, OR = 3.4; 95% CI = 1.2-9.4).[55] No other differences were noted. In a follow-up study, Li et al[39] examined the *DRD4* gene variants in combination with the Val158Met *COMT* gene variant. There was a modest interaction among the high-activity allele of *COMT* and *DRD4* genotypes (OR = 1.45; 95% CI = 1.1-1.8) among the methamphetamine abusers.[39] Another study showed significant main effects of these 2 genes but no interaction[40] suggesting that further studies are needed. If the interaction is upheld, it suggests that the lower-activity allele of *COMT* may be protective against methamphetamine abuse and that *DRD4* alleles may also contribute to the protective effects.[39]

The *DAT1* gene is associated with the effects of amphetamine and cocaine. Several studies support the notion that genetic variations in *DAT1* may contribute to the individual variability in response to these drugs. Gelernter et al demonstrated that the 9 allele of the *DAT1* gene was present in more subjects with cocaine-induced paranoia than without cocaine-induced paranoia ($P = .047$).[43] The 9-repeat allele results in reduced expression of *DAT1*,[44] but it is not yet clear how or whether the reduced expression explains the effect of cocaine-induced paranoia. The 9-repeat allele of *DAT1* contributes to reduced responsiveness to acute amphetamine administration,[45] suggesting that with amphetamine, the 9-repeat allele seems to protect individuals from dependence.[45] Indirectly supporting this finding is the finding that individuals with the 9-repeat allele showed a significantly reduced responsiveness to methylphenidate, an amphetamine-like compound used to treat attention deficit hyperactivity disorder.[46] If this finding is replicated, the 9-repeat allele may be an effective pharmacogenetic marker to predict who will not respond well to methylphenidate.

Mice with mutated *dat1* have shown reduced binding to cocaine and methylphenidate but not amphetamine or methamphetamine, indicating that the binding sites for cocaine and methylphenidate may overlap but are distinct from those for amphetamine and methamphetamine.[47] Clinical trials examining drugs that target *DAT1* have been somewhat disappointing, but some data suggest that genotyping for *DAT1* may help clinicians select appropriate treatments for psychostimulant addictions.

In a Japanese population study, the *GSTP1* I105V gene variant was associated with methamphetamine abusers with psychosis compared with controls (OR = 1.84; 95% CI = 1.13-2.97), but it was not associated with spontaneous relapse.[58] This variant results in a 30% decrease in enzyme activity,[59] which may contribute to reduced metabolism of methamphetamine and higher abuse risk.

Butyrylcholinesterase (BChE), an enzyme involved in cocaine hydrolysis, has genetic variants in the *BCHE* gene that affect the rate of cocaine detoxication.[33] The variant D70G in *BCHE* had a 10-fold lower binding affinity for cocaine, and individuals with this variant may not be able to metabolize cocaine as fast, resulting in severely toxic or fatal outcomes.[33] A pharmacogenetic approach would be to screen for this genetic variant in cocaine overdose victims so that treatment action for those with the G variant could be to provide them with exogenous BChE to attenuate the cocaine toxicity.

CONCLUSIONS

Pharmacogenetics may not yet be able to conclusively predict adverse events or ensure the most effective treatment, but it is contributing to the much-needed development of tailored care. In the future, an important part of the process of assigning an effective medication at an appropriate dose will be incorporating pharmacogenetic data that provide an understanding of how an individual's profile of genetic variation will best predict treatment response and outcome. For example, taking the medication less frequently, taking dosages adjusted for the rates of metabolism inferred from a genetic profile, or changing the medication to one better tailored to a patient's genetic makeup may prevent the onset of liver toxicities or other untoward side effects.

Addiction is a chronic brain disease[98] that is driven by 2 critical elements, genes and environment; neither can be ignored. Genetic studies have been invaluable in identifying addiction vulnerability loci and genetic variants that are important for understanding the neurobiology of the disease, pointing to potential drug targets, and identifying alleles that may be useful for tailored treatment interventions. Social and environmental elements such as family, peer, community, and social attitudes and beliefs are also important psychobehavioral domains that contribute to the complexity of addiction. Treatment and prevention interventions for substance abuse disorders and other complex diseases will have maximum benefit when multifaceted approaches, which incorporate genetic, pharmacologic, and environmental influences, are taken into account.[99] Management of drug abuse and addiction must be individualized according to the drugs involved and the specific problems of the individual patient. Effective treatment options for psychiatric diseases, which often include a high incidence of comorbidity or co-occurring disease, are still not well understood.[100,101] Many chronic disorders, such as addictions, diabetes, heart disease, and asthma, require behavioral intervention and/or long-term medication, but identifying the best treatment may involve trying several medications to determine which is most effective and has the fewest side effects. Some pharmacogenetics research suggests that pharmacogenetics may be a powerful tool for informing treatment options for those needing long-term pharmacotherapy.

This review highlighted many genetic targets for addiction vulnerability and treatment. However, the review is neither exhaustive nor complete. The genes reviewed in the article, listed in Table 1, are related to common pathways of addiction, such as dopamine, serotonin, glutamate, and metabolism. Many of the genes reviewed have overlapping roles for each class of drug discussed. Some of the genes may be associated with addiction in general, while some may be drug-specific.[102,103] When pharmacogenetic strategies to individualize the treatment of drug abuse and addiction are being designed, all of these genes, gene systems, and cell-type-specific expression of the genes must be considered.

The next step is to incorporate into the clinical setting those data that are reliably consistent. To this end, the US Food

and Drug Administration is facilitating the use of pharmacogenetic data in drug development[104] and has issued several guidelines for industry as well as voluntary genomic data submissions from clinical trials (http://www.fda.gov/cder/genomics/regulatory.htm). Furthermore, analogous to the National Institutes of Health (NIH) Roadmap initiative, the neuroscience institutes within NIH have implemented the Blueprint Initiative (http://neuroscienceblueprint.nih.gov). One initiative is the NIH Blueprint Microarray Consortium, consisting of 4 microarray centers to serve the expression profiling and SNP genotyping needs of grantees within the neuroscience institutes. This resource will provide the most updated tools and allow investigations of many pharmacogenomic questions.

Other consortiums are in place and are making progress in incorporating pharmacogenetics into many areas of biological research. The Pharmacogenetics Research Network and Knowledge Base (http://www.pharmgkb.org), for example, is a relatively new initiative working toward correlating drug response phenotypes with genetic variation in various areas (eg, nicotine addiction and treatment, metabolism, transport, cancer and cancer treatment, asthma, cardiovascular disease). The idea is to create a valuable knowledge base populated with reliable information that links phenotypes to genotypes, and to promote interactive science to elevate the field of pharmacogenetics with knowledge, tools, and resources. For a more thorough mining of pharmacogenetic data in drug abuse, one can go to http://pharmdemo.stanford.edu/pharmdb/main.spy and search by drug name (eg, "heroin" or "cocaine").[105]

The NIDA Genetics Consortium (http://zork.wustl.edu/nida) is a group of investigators collecting samples (currently over 20 000) and comprehensive diagnostic information from individuals with smoking, cocaine, opioid, and polysubstance abuse and addictions. These resources are used to increase the understanding of addiction vulnerability and addiction treatment response, and most are available to the broad scientific community for further study.

Genetic data to date have pointed to pharmacodynamic genes involved in drug abuse and addiction, which have in turn elucidated genetic variants that may be helpful in identifying appropriate treatment medications for different individuals. These combined investments should begin to elucidate the importance of human genome variation on clinical treatment of addiction.

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