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Review

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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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 and Boden, 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 et al., 2005; Darke et al., 1996; Gilson et al., 2004; Kintz, 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; Crabbe, 2002; Kendler et al., 2000; Tsuang et al., 1996, 2001; Uhl, 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 SRDs. 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