Available online at www.sciencedirect.com

SCIENCE DIRECT®

Addictive Behaviors 31 (2006) 923–928

ADDICTIVE BEHAVIORS

Editorial

Novel approaches to phenotyping drug abuse

1. Introduction

A major challenge for drug abuse[1] research is to identify phenotypes that are maximally informative for etiology, genetics, treatment and prevention. At present, typical phenotypes include any use of a drug, drug seeking, regular or heavy use, inappropriate use of a drug (i.e., drug misuse), and the categories of drug abuse and drug dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders - IV (DSM-IV). It has become increasingly clear, however, that none of these is completely satisfactory for many areas of drug abuse research, and that alternative phenotypes for drug abuse might be more fruitful. In order to stimulate research on this topic, the theme of this year's special issue of Addictive Behaviors and the Addictions 2006 Conference is "Novel Approaches to Phenotyping Drug Abuse." This conference reflects a collaborative effort between Elsevier, Addictive Behaviors, and the National Institute on Drug Abuse (NIDA; National Institutes of Health). The papers published in this special issue and presented at the conference emphasize innovative research that better describes, discriminates, and predicts the complex nature and course of drug abuse so as to offer more precise phenotypic indicators for testing the hypothesized underlying genetic and environmental risks for drug abuse.

1.1. Rationale and Background to the Special Issue and Conference Theme

Available evidence indicates that drug abuse is a complex disorder arising from interplay between underlying genetic susceptibility and environmental risk. Like many other relatively common human diseases, drug abuse is believed to arise from multiple genes exerting small effects, gene-by-gene interactions, gene-by-environment interactions, and a host of environmental factors and risk-conferring behaviors. As a consequence of the multifactorial nature of drug abuse, the phenotypic expression is highly heterogeneous. Drug abuse is heterogeneous in terms of risk factors, gender distribution and expression, comorbid conditions, types and number of drugs of abuse, symptom expression, and

[1] The term "drug abuse" as used in this commentary refers broadly to several different but related concepts including drug abuse and drug dependence as defined by diagnostic criteria, as well as drug involvement, hazardous drug use, drug seeking behavior, and the like. While it is recognized that these concepts may not be interchangeable, the term drug abuse is used for the purposes of fluency. The term ''drug'' refers primarily to cannabis, cocaine, opiates, nicotine, but also includes the entire range of substances of abuse.

doi:10.1016/S0306-4603(06)00146-8

severity. The course of drug abuse is a dynamic one characterized by patterns of persistence and remittance, drug switching and drug combinations, and drug preferences. Drug abuse reflects developmental processes that unfold gradually over time, display continuity and discontinuity, and follow along multiple trajectories leading to similar or different "endpoints." Drug abuse is characterized by substantial individual differences with regard to age of onset and rate of progression from initial drug use to persistent use, abuse, and dependence.

Although contemporary theoretical models depict drug abuse as a heterogeneous and dynamic construct, this information has been comparatively less integrated into quantitative approaches to the study of drug abuse. Three examples illustrate this point. First, while it is well known that drug abusers often suffer from a range of psychiatric conditions, comorbidity is typically treated as a covariate to be "controlled" statistically when, alternatively, comorbidity may very well be an important feature of the outcome (or predictor) variable itself. Second, drug abuse is often characterized by substantial polysubstance involvement. Although marijuana abusers are likely to also be involved with nicotine and alcohol, marijuana abuse is conventionally operationalized in a dichotomous fashion with little attention to the nature and extent of polysubstance involvement. Furthermore, the diagnosis of marijuana dependence is a topic of debate that could be informed by alternative measures that more precisely reflect the characteristics of sustained marijuana involvement, such as cognitive impairment and "withdrawal behaviors." Third, extant research depicts drug abuse as involving cyclical patterns of harmful drug use, remittance, and relapse. Yet, rarely has the course of drug abuse been used to operationalize the drug abuse phenotype. In sum, much prior quantitative research has defined drug abuse in a superficial manner whereby potentially critical features of drug abuse have been overlooked.

A call for research on novel phenotypes takes on increasing importance in the context of molecular genetic studies where an imprecise case definition will greatly hamper the detection of risk-conferring genes and gene-by-environment interactive effects. Despite the real promise of molecular genetics, there has been limited success in reliably identifying specific susceptibility genes for drug abuse. Although this difficulty is often attributed to genetic heterogeneity, attaining greater clarity of the phenotypic heterogeneity of drug abuse looms large as a major challenge for the field. Indeed, most analytic approaches operationalize drug abuse as a dichotomous and static outcome, and consider as covariates (or even statistical error) factors that may represent critical clues about drug abuse risk and etiology. Ultimately, the successful identification of specific genes and related mechanisms, underlying physiologic systems, and other etiological processes hinges on precise and specific phenotypic definitions and greater understanding of how such phenotypes influence and are shaped by environmental factors, developmental course, and individual characteristics.

Faced with the scientific problem of drug abuse heterogeneity, in 2003, NIDA launched a series of initiatives in an attempt to articulate the nature of drug abuse heterogeneity and brainstorm ways (both conceptual and methodological) to identify more homogenous and precise phenotypic indicators of underlying genetic and environmental risk. In 2003, NIDA convened a small scientific workshop and subsequently issued a Request for Applications (RFA) focusing on this subject. A portfolio of grants was created, with the lead investigators meeting yearly to discuss progress and opportunities for collaboration. Through the Addictions 2006 conference and in partnership with Elsevier and Addictive Behaviors, NIDA is now initiating more widespread dissemination and public discussion of scientific information on this topic.