Addictive Behaviors 53 (2016) 132–140

Contents lists available at ScienceDirect

Addictive Behaviors

Psychometric modeling of abuse and dependence symptoms across six illicit substances indicates novel dimensions of misuse

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HIGHLIGHTS

- The liability to misuse illicit substance is drug class specific.
- There is no evidence to support a general liability for illicit substance misuse.
- We identified dimensions capturing propensity toward specific misuse symptoms.

ARTICLE INFO

Article history:
Received 26 March 2015
Received in revised form 14 October 2015
Accepted 16 October 2015
Available online 17 October 2015

Keywords:
Cannabis
Cocaine
Dependence
DSM
Opioids
Factor analysis

ABSTRACT

Aims: This study explored the factor structure of DSM III-R/IV symptoms for substance abuse and dependence across six illicit substance categories in a population-based sample of males.
Method: DSM III-R/IV drug abuse and dependence symptoms for cannabis, sedatives, stimulants, cocaine, opioids and hallucinogens from 4179 males born 1940–1970 from the population-based Virginia Adult Twin Study of Psychiatric and Substance Use Disorders were analyzed. Confirmatory factor analyses tested specific hypotheses regarding the latent structure of substance misuse for a comprehensive battery of 13 misuse symptoms measured across six illicit substance categories (78 items).
Results: Among the models fit, the latent structure of substance misuse was best represented by a combination of substance-specific factors and misuse symptom-specific factors. We found no support for a general liability factor to illicit substance misuse.
Conclusions: Results indicate that liability to misuse illicit substances is drug class specific, with little evidence for a general liability factor. Additionally, unique dimensions capturing propensity toward specific misuse symptoms (e.g., tolerance, withdrawal) across substances were identified. While this finding requires independent replication, the possibility of symptom-specific misuse factors, present in multiple substances, raises the prospect of genetic, neurobiological and behavioral predispositions toward distinct, narrowly defined features of drug abuse and dependence.

1. Introduction

Effective treatment of substance use disorder (SUD) depends on accurate models and measurement of the underlying psychopathological phenotypes. The importance of this issue has prompted extensive research examining the latent structure of substance misuse characteristics in dialogue with the models implicit in DSM diagnostic categories. Such research recently led to revising the long-standing DSM model of separate substance-specific SUD diagnoses for abuse and dependence, combining both criteria into single substance-specific SUDs in DSM-5 (Hasin et al., 2013). This revision was supported by expert consensus that when considering substances individually, a single factor, known as *liability*, best explains the covariance between DSM abuse and dependence symptoms (Baillie & Teesson, 2010; Hartman et al., 2008; Lynskey & Agrawal, 2007; Langenbucher et al., 2004; Teesson, Lynskey, Manor, & Baillie, 2002; Swift, Hall, & Teesson, 2001; Nelson, Rehm, Ustun, Grant, & Chatterji, 1999; Feingold & Rounsaville, 1995; Morgenstern, Langenbucher, & Labouvie, 1994; Bryant, Rounsaville, & Babor, 1991). However, less research has jointly considered misuse

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http://dx.doi.org/10.1016/j.addbeh.2015.10.015
0306-4603/

symptoms across multiple substance categories to examine the possibility of general poly-substance liability and/or more complex latent structures.

Among studies jointly considering misuse across multiple substance classes, results have been equivocal, primarily due to differing methodologies and substantive aims. Contrasting our current psychometric approach of modeling the latent structure of substance misuse phenotypes, previous studies have generally employed biometric approaches to decompose misuse phenotype variance into genetic and environmental components. Results from such research, including previous analyses of the present sample (Kendler, Jacobson, Prescott, & Neale, 2003), have typically found a mix of substance-specific and general liability factors in both genetic and environmental risk (Tsuang et al., 1998; Vanyukov, 2012). This conclusion has not received universal support, however, as other studies have found distinct, but correlated, genetic and environmental influences for cannabis versus other illicit substances (i.e., cocaine, sedatives, stimulants, hallucinogens or opioids) (Agrawal, Neale, Prescott, & Kendler, 2004), as well as unique genetic liabilities toward illicit (cocaine and cannabis) versus licit (alcohol, nicotine and caffeine) substance dependence (Kendler, Myers, & Prescott, 2007). Moreover, studies of illicit drug abuse/dependence using categorical, rather than dimensional, latent variable models have suggested distinct patterns of substance misuse (e.g., cannabis-only, prescription drugs), with truly general poly-substance misuse occurring rarely (Agrawal, Lynskey, Madden, Bucholz, & Heath, 2007). Thus, while general liability to substance misuse has conceptual appeal and has received considerable empirical support, research on the topic has been inconclusive.

One major limitation of the studies described above is they rely on a count of dichotomous indicators to generate DSM diagnoses. For example, DSM V diagnosis of severe substance abuse requires at least 6 of 10 possible symptoms. This method may be sub-optimal because it assumes the symptoms function equivalently both within and between substances. Thus, all symptoms are implicitly assumed to be equally valid measures of SUD diagnosis, regardless of the substance in question. However, as shown by Gillespie et al. (Gillespie, Neale, Prescott, Aggen, & Kendler, 2007), identical symptoms measure different levels of liability across substances, suggesting that substance misuse symptoms do not function equivalently. Thus, condensing symptom data into binary diagnostic categories greatly decreases the amount of unique, relevant information compared to psychometric approaches directly modeling symptom-level data. The situation is only slightly improved in DSM-V, which sub-classifies SUDs into mild, moderate and severe. With symptom-level data it may be possible to identify novel latent dimensions of substance misuse, in addition to improved ability to adjudicate between substance-specific versus general misuse liability. Of particular interest, symptom-level data across a range of illicit substances allow the investigation of poly-substance liability to different misuse characteristics. For instance, there may exist a propensity to develop tolerance across multiple substances. The possibility of poly-substance liability was overlooked in previous analyses of the topic (e.g., Gillespie et al., 2007) which only investigated liability structures within one specific substance at a time and not across substances. Identification of liability factors for specific misuse symptoms has the potential to yield novel targets for studies of, e.g., genetic association, neural substrates, prevention or treatment.

In this article, we build on previous research exploring SUD liability by jointly analyzing 13 individual DSM III-R/IV abuse and dependence symptoms across six inclusive illicit substance categories. This approach addresses limitations associated with examining substance categories independently, as well as those due to collapsing symptom data into binary diagnoses. Specifically, the study has two primary aims. The first is to determine whether there are substance-specific and/or misuse symptom-specific liability factors underlying DSM SUD symptom data. Second, we test whether the general SUD liability factor identified in previous research using diagnostic categories represents an accurate model of DSM illicit substance misuse symptoms when examining symptom-level data.

2. Methods

2.1. Participants and measures

This study is based on data collected from Caucasian adult male twins in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD). Described in detail elsewhere (Kendler & Prescott, 2006), data came from a second wave of interviews between 1994 and 1998. Subjects were eligible for participation if they were successfully matched to birth records, a member of a multiple birth with at least one male, Caucasian, and born between 1940 and 1974 in Virginia, USA. Interviewers had a master's degree in a mental health-related field or a bachelor's degree in this area plus two years of clinical experience. Of 9417 eligible individuals for the first wave (1993–1996), 6814 (72.4%) completed the interview. The second interview was completed by 5629 individuals (82.6%). Complete drug initiation data were available from 4179 male subjects ranging in age from 20 to 58 years ($\mu =$ 36.9 yrs., $\sigma^2 = 9.1$ yrs). Unlike previous analyses (Gillespie et al., 2007), these data included an additional 1602 males from opposite-sex and incomplete twin pairs. As recruitment focused on males, analyses of females were relatively underpowered in this sample. This fact, combined with previous research indicating gender differences in substance liability factor structure (Palmer et al., 2012), led us to limit analyses to males only. Subjects were informed of the study's goals and provided informed consent. The project was approved by the Virginia Commonwealth University institutional review board.

The interview included assessments of lifetime drug use, abuse and dependence across six categories of substances using an adaptation of the Structured Clinical Interview (SCID) (Spitzer, Williams, & Gibbon, 1987). Categories (examples) included: cannabis (marijuana and hashish); sedatives (quaalude, Seconal and Valium); stimulants (speed, ecstasy and Ritalin); cocaine (intranasal and crack); opioids (heroin and morphine); and hallucinogens (LSD and PCP). For substances that could be obtained legally, we defined non-medical use as, 1) without a doctor's prescription, 2) in greater amounts or more often than prescribed, or 3) for any reason other than a doctor prescribed. For each substance, the abuse and dependence assessment comprised 13 symptoms listed in Table 1. Symptoms were structured this way to permit assignment of both DSM-III-R and DSM-IV diagnostic definitions. Initially, all 13 symptoms were measured on a three-point scale (definite/probable/no). Consistent with previous research in this sample (Gillespie et al., 2007), 'probable' responses were combined with 'definite' to minimize small cell optimization problems. The data were analyzed as dichotomous variables.

2.2. Statistical methods

We used Mplus V6.0 (Muthén & Muthén, 1998) to jointly model the diagnostic symptoms from the six substances. Specifically, the latent structure of SUD liability was modeled using confirmatory factor analysis. To handle twin clustering, we specified the "complex" analysis option, which implements a clustering corrected robust maximum likelihood estimator (Muthén & Satorra, 1995). This method uses a Huber/White/Sandwich clustered variance estimator to calculate standard errors (Huber, 1967; White, 1980), and has superior estimation properties for the analysis of dichotomous data with small cluster sizes (Muthén & Satorra, 1995), as observed here. Subjects not initiating use of a substance were considered missing for those symptoms.

2.2.1. Confirmatory factor analyses (CFAs)

A series of CFA models were fit to the symptom data for all six substances. Using CFA we were able to test specific hypotheses about the structure of factors underlying liability to SUD. Specifically, we